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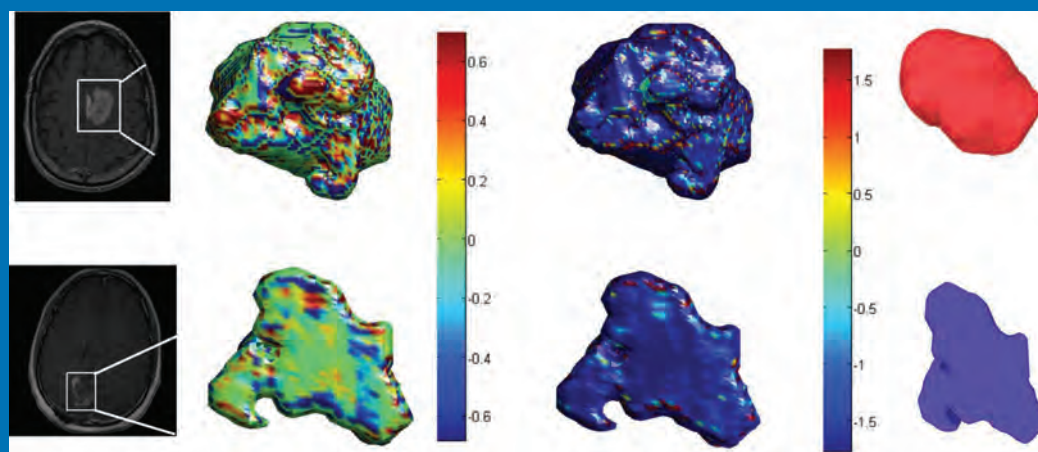
AMERICAN JOURNAL OF NEURORADIOLOGY

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THE JOURNAL OF DIAGNOSTIC AND
INTERVENTIONAL NEURORADIOLOGY

Differentiating brain tumor progression from pseudoprogression
Endoscopic third ventriculostomy evaluation with CISS
Transdural blood supply in cerebral arteriovenous malformations

Official Journal ASNR • ASFNR • ASHNR • ASPNR • ASSR



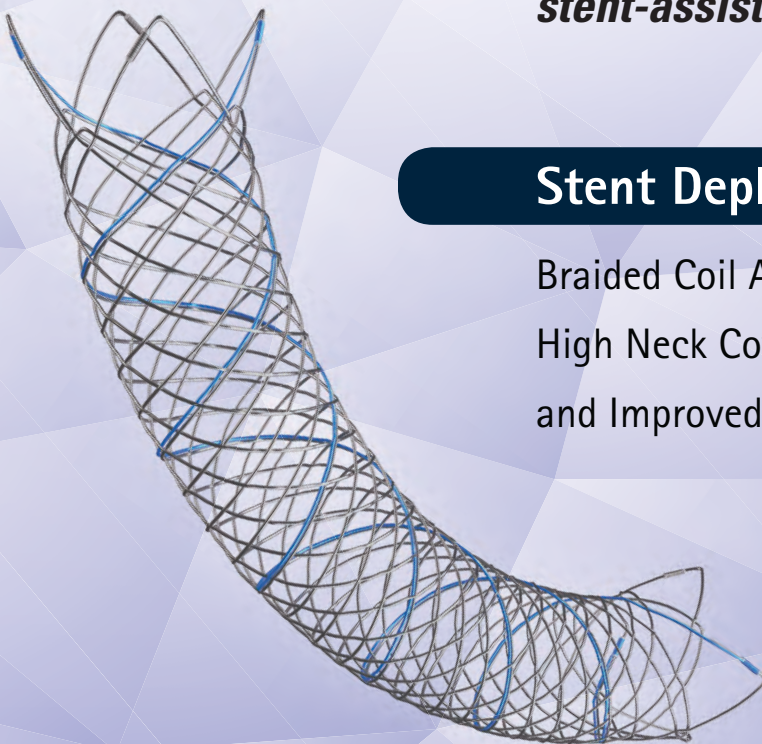


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LVIS[®]

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***The first and only stent with
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Braided Coil Assist Stents with
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Low-profile Visualized Intraluminal Support



INDICATIONS FOR USE:

The LVIS[®] and LVIS[®] Jr. devices are indicated for use with neurovascular embolization coils in patients ≥ 18 years of age for the treatment of wide-neck (neck width ≥ 4 mm or dome to neck ratio < 2) saccular intracranial aneurysms arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 4.5 mm.

Rx Only: Federal (USA) law restricts this device to sale by or on the order of a physician.

The HydroCoil[®] Embolic System (HES) and MicroPlex[®] Coil System (MCS) are intended for the endovascular embolization of intracranial aneurysms and other neurovascular abnormalities such as arteriovenous malformations and arteriovenous fistulae. The HES and MCS are also intended for vascular occlusion of blood vessels within the neurovascular system to permanently obstruct blood flow to an aneurysm or other vascular malformation and for arterial and venous embolizations in the peripheral vasculature.

The device should only be used by physicians who have undergone pre-clinical training in all aspects of HES/MCS procedures as prescribed by MicroVention.

A Complete Coil Portfolio

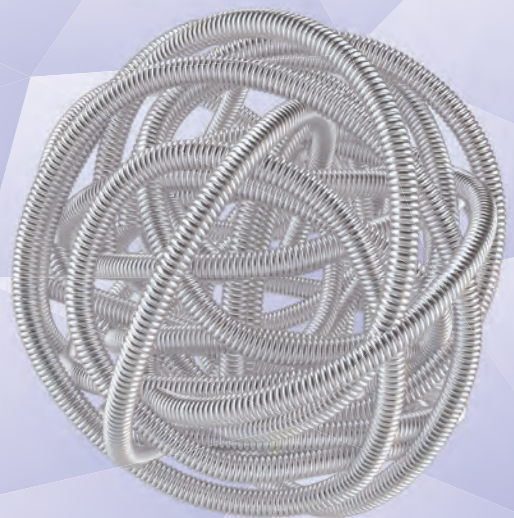
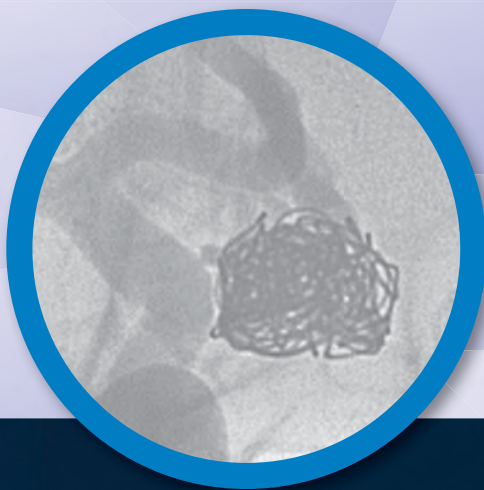
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MicroVention's comprehensive portfolio features clinically proven Hydrogel coils, which can be used exclusively or in combination with our trusted Platinum coils to treat a wide range of aneurysms and neurovascular lesions.

Breakthrough Hydrogel Technology

- Less Recurrence
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- More Progressive Occlusion

Compared to platinum coils with comparable safety¹



REFERENCES:

1. Taschner et al. Second-Generation Hydrogel Coils for the Endovascular Treatment of Intracranial Aneurysm; A Randomized Controlled Trial. 2018;49:00-00. DOI:10.1161/STROKEAHA.117.018707

For more information or a product demonstration,
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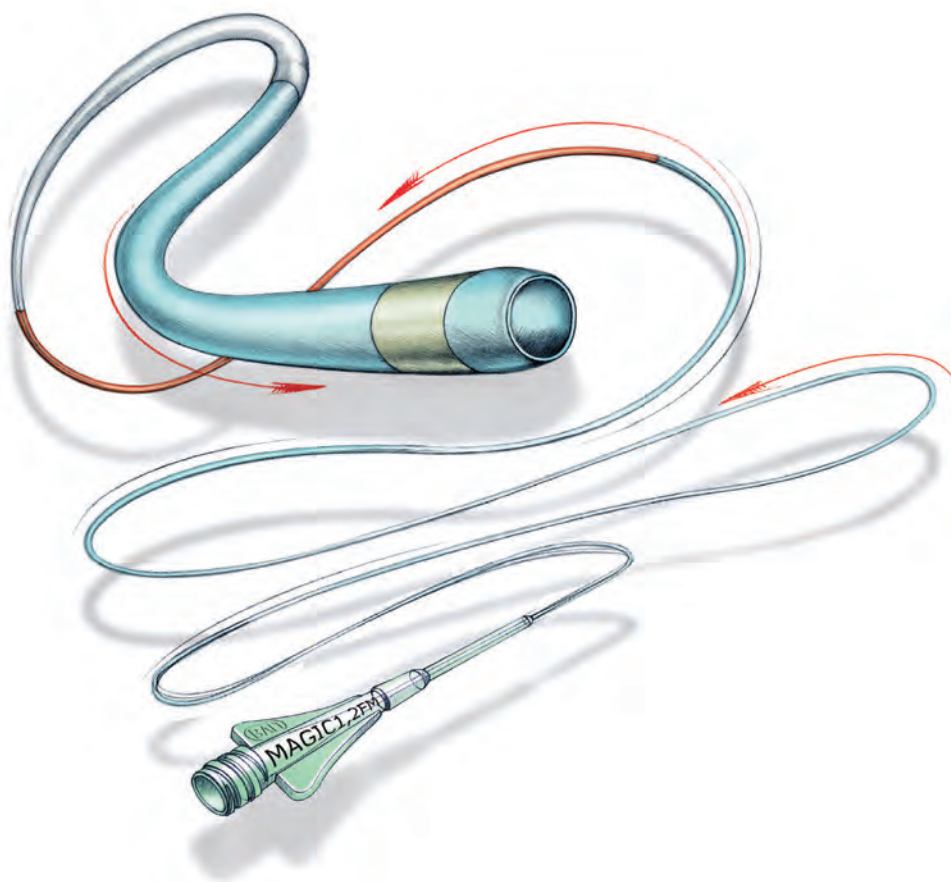
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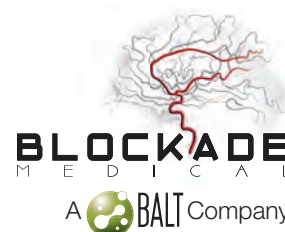
MAGIC catheters are designed for general intravascular use. They may be used for the controlled, selective regional infusion of therapeutic agents or embolic materials into vessels.¹

1. Magic Catheters IFU – Ind 19

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Now you have **24 hours** to make a lifetime of difference in stroke patients like Nora



The Trevo Retriever is the only device cleared to **reduce disability in stroke patients up to 24 hours** from time last seen well.

For more information, visit strykerneurovascular.com/trevo24hours

Trevo[®] XP
PROVUE RETRIEVER

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AXS Infinity LS™ Plus Long Sheath

See package insert for complete indications, contraindications, warnings and instructions for use.

INDICATIONS FOR USE

The AXS Infinity LS Plus Long Sheath is indicated for the introduction of interventional devices into the peripheral, coronary, and neuro vasculature.

RX ONLY

CONTRAINDICATIONS

There are no known contraindications.

POTENTIAL ADVERSE EVENTS

- Acute vessel occlusion
- Air embolism
- Death
- Distal embolization
- Emboli
- False aneurysm formation
- Hematoma or hemorrhage at the puncture site
- Infection
- Intracranial hemorrhage
- Ischemia
- Neurological deficit including stroke
- Vessel spasm, thrombosis, dissection or perforation

WARNINGS

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Stryker Neurovascular representative.

For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

1. Do not re-sterilize or reuse, intended for single use only. Re-sterilization and/or reuse may result in cross contamination and/or reduced performance.
2. When the long sheath is exposed to the vascular system, it should be manipulated while under high-quality fluoroscopic observation. Do not advance or retract the long sheath if resistance is met during manipulation; determine the cause of the resistance before proceeding.

PRECAUTIONS

1. Store in a cool, dry, dark place.
2. Do not use kinked, damaged, or opened devices.
3. Use the device prior to the "Use By" date specified on the package.
4. Exposure to temperatures above 54°C (130°F) may damage device. Do not autoclave.
5. Torquing or moving the device against resistance may result in damage to the vessel or device.
6. Maintain a constant infusion of appropriate flush solution.
7. If flow through the device becomes restricted, do not attempt to clear the lumen by infusion. Remove and replace the device.
8. Examine the device to verify functionality and to ensure that its size and shape are suitable for the specific procedure for which it is to be used.
9. The AXS Infinity LS Plus Long Sheath should be used only by physicians trained in percutaneous procedures and/or interventional techniques.
10. Do not use if labeling is incomplete or illegible.

AXS Vecta™ 71 Aspiration Catheter

See package insert for complete indications, contraindications, warnings and instructions for use.

INDICATIONS FOR USE

The AXS Vecta™ Aspiration System, including the AXS Vecta 71 Aspiration Catheter, Aspiration Tubing Set, and VC-701 Cliq Aspirator Pump, is indicated in the revascularization of patients with acute ischemic stroke secondary to intracranial large vessel occlusive disease (within the internal carotid, middle cerebral – M1 and M2 segments, basilar, and vertebral arteries) within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who failed IV t-PA therapy are candidates for treatment.

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Scout is a trademark of InNeuroCo, Inc.

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Trevo® XP ProVue Retrievers

See package insert for complete indications, complications, warnings, and instructions for use.

INDICATIONS FOR USE

1. The Trevo Retriever is indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion, and smaller core infarcts who have first received intravenous tissue plasminogen activator (IV t-PA). Endovascular therapy with the device should start within 6 hours of symptom onset.
2. The Trevo Retriever is intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke within 8 hours of symptom onset. Patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy are candidates for treatment.
3. The Trevo Retriever is indicated for use to restore blood flow in the neurovasculature by removing thrombus for the treatment of acute ischemic stroke to reduce disability in patients with a persistent, proximal anterior circulation, large vessel occlusion of the internal carotid artery (ICA) or middle cerebral artery (MCA)-M1 segments with smaller core infarcts (0-50cc for age < 80 years, 0-20cc for age ≥ 80 years). Endovascular therapy with the device should start within 6-24 hours of time last seen well in patients who are ineligible for intravenous tissue plasminogen activator (IV t-PA) or who fail IV t-PA therapy.

COMPLICATIONS

Procedures requiring percutaneous catheter introduction should not be attempted by physicians unfamiliar with possible complications which may occur during or after the procedure. Possible complications include, but are not limited to, the following: air embolism; hematoma or hemorrhage at puncture site; infection; distal embolization; pain/headache; vessel spasm, thrombosis, dissection, or perforation; emboli; acute occlusion; ischemia; intracranial hemorrhage; false aneurysm formation; neurological deficits including stroke; and death.

COMPATIBILITY

3x20mm retrievers are compatible with Trevo® Pro 14 Microcatheters (REF 90231) and Trevo® Pro 18 Microcatheters (REF 90238). 4x20mm retrievers are compatible with Trevo® Pro 18 Microcatheters (REF 90238). 4x30mm retrievers are compatible with Excelsior® XT-27™ Microcatheters (150cm x 6cm straight REF 275081) and Trevo® Pro 18 Microcatheters (REF 90238). 6x25mm Retrievers are compatible with Excelsior® XT-27™ Microcatheters (150cm x 6cm straight REF 275081). Recommended minimum vessel ID for all Retriever sizes is 2.5mm. Compatibility of the Retriever with other microcatheters has not been established. Performance of the Retriever device may be impacted if a different microcatheter is used.

Balloon Guide Catheters (such as Merc® Balloon Guide Catheter and FlowGate® Balloon Guide Catheter) are recommended for use during thrombus removal procedures.

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RX ONLY

DEVICE DESCRIPTION

The AXS Vecta Aspiration System consists of the **AXS Vecta 71** Aspiration Catheter, the Aspiration Tubing Set, and the VC 701 Cliq Aspirator Pump. The AXS Vecta 71 Aspiration Catheter is a single lumen, flexible, variable stiffness catheter. It has a radiopaque marker band on the distal end and a Luer hub at the proximal end. The AXS Vecta 71 Aspiration Catheter shaft has a lubricious coating at the distal end to reduce friction during use. The Scout Introducer may be used in conjunction with the AXS Vecta 71 Aspiration Catheter to facilitate in the introduction of the AXS Vecta 71 Aspiration Catheter into distal vasculature and aid in navigation to distal anatomy. The Scout Introducer has a lubricious coating at the distal end to reduce friction during use. The inner lumen of the AXS Vecta 71 Aspiration Catheters is compatible with the Scout Introducer, guide wires and micro catheters. The inner lumen of the Scout Introducer is compatible with guide wires and micro catheters of an outer diameter of less than 0.044in. Each package includes one AXS Vecta 71 Aspiration Catheter, one Scout Introducer, one hemostasis valve, and two peel-away introducers. Dimensions of the AXS Vecta 71 Aspiration Catheter and Scout Introducer are included on the individual device label. The AXS Vecta 71 Aspiration Catheters are available in 3 different lengths, the device configurations including the length of the Scout packaged with each catheter and the recommended microcatheter length is presented in the table below.

Catheter part number	INC-11129-115	INC-11129-125	INC-11129-132
Catheter inner diameter (in)	0.071	0.071	0.071
Distal catheter outer diameter (in)	0.082	0.082	0.082
Catheter working length (cm)	115	125	132
Scout Introducer length (cm)	133	143	150
Recommended compatible microcatheter length (cm)	150	160	160
Recommended compatible microcatheter outer diameter (in)	0.044 max	0.044 max	0.044 max
Recommended compatible guidewire outer diameter (in)	0.038 max	0.038 max	0.038 max

The AXS Vecta Aspiration System is recommended for use in the following vessel size ranges based on non-clinical testing:

AXS Vecta 71 Aspiration Catheter	Vessel size (mm)
INC-11129-115	2-4
INC-11129-125	2-4
INC-11129-132	2-4

CONTRAINDICATIONS

The AXS Vecta 71 Aspiration Catheter has not been evaluated for use in the coronary vasculature. Do not use automated high-pressure contrast injection equipment with the AXS Vecta 71 Aspiration Catheter because it may damage the device.

POTENTIAL ADVERSE EVENTS

- Acute vessel occlusion
- Air embolism
- Allergic reaction and anaphylaxis from contrast media
- Arteriovenous fistula
- Death
- Device malfunction
- Distal embolization
- Emboli
- False aneurysm formation
- Hematoma or hemorrhage at the puncture site
- Inability to completely remove thrombus
- Infection
- Intracranial hemorrhage
- Ischemia
- Kidney damage from contrast media
- Neurological deficit including stroke
- Risks associated with angiographic and fluoroscopic radiation including but not limited to: alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia
- Vessel spasm, thrombosis, dissection or perforation

Retrievers are compatible with the Abbott Vascular DOC® Guide Wire Extension (REF 22260). Retrievers are compatible with Boston Scientific Rotating Hemostatic Valve (REF 421242).

SPECIFIC WARNINGS FOR INDICATION 1

- The safety and effectiveness of the Trevo Retrievers in reducing disability has not been established in patients with large core infarcts (i.e. ASPECTS ≤ 7). There may be increased risks, such as intracerebral hemorrhage, in these patients.
- The safety and effectiveness of the Trevo Retrievers in reducing disability has not been established or evaluated in patients with occlusions in the posterior circulation (e.g., basilar or vertebral arteries) or for more distal occlusions in the anterior circulation.

SPECIFIC WARNINGS FOR INDICATION 2

- To reduce risk of vessel damage, take care to appropriately size Retriever to vessel diameter at intended site of deployment.

SPECIFIC WARNINGS FOR INDICATION 3

- The safety and effectiveness of the Trevo Retrievers in reducing disability has not been established in patients with large core infarcts (i.e. ASPECTS ≤ 7). There may be increased risks, such as intracerebral hemorrhage, in these patients.
- The safety and effectiveness of the Trevo Retrievers in reducing disability has not been established or evaluated in patients with occlusions in the posterior circulation (e.g., basilar or vertebral arteries) or for more distal occlusions in the anterior circulation.
- Users should validate their imaging software analysis techniques to ensure robust and consistent results for assessing core infarct size.

WARNINGS APPLIED TO ALL INDICATIONS

- Administration of IV t-PA should be within the FDA-approved window (within 3 hours of stroke symptom onset).
 - Do to reduce risk of vessel damage, adhere to the following recommendations:
 - Do not perform more than six (6) retrieval attempts in same vessel using Retriever devices.
 - Maintain Retriever position in vessel when removing or exchanging Microcatheter.
- To reduce risk of kinking/fracture, adhere to the following recommendations:
 - Immediately after unsheathing Retriever, position Microcatheter tip marker just proximal to shaped section. Maintain Microcatheter tip marker just proximal to shaped section of Retriever during manipulation and withdrawal.
 - Do not rotate or torque Retriever.
 - Use caution when passing Retriever through stented arteries.
- The Retriever is a delicate instrument and should be handled carefully. Before use and when possible during procedure, inspect device carefully for damage. Do not use a device that shows signs of damage. Damage may prevent device from functioning and may cause complications.
- Do not advance or withdraw Retriever against resistance or significant vasospasm. Moving or torquing device against resistance or significant vasospasm may result in damage to vessel or device. Assess cause of resistance using fluoroscopy and if needed resheath the device to withdraw.

WARNINGS

Contents supplied STERILE using an ethylene oxide (EO) process. Do not use if sterile barrier is damaged. If damage is found, call your Stryker representative.

For single use only. Do not reuse, reprocess or resterilize. Reuse, reprocessing or resterilization may compromise the structural integrity of the device and/or lead to device failure which, in turn, may result in patient injury, illness or death. Reuse, reprocessing or resterilization may also create a risk of contamination of the device and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness or death of the patient.

After use, dispose of product and packaging in accordance with hospital, administrative and/or local government policy.

1. The AXS Vecta 71 Aspiration Catheter has not been evaluated for more than one (1) clot retrieval attempt.
2. The AXS Vecta 71 Aspiration Catheter was evaluated for an average duration of direct aspiration of 4 minutes.
3. This product is intended for single use only, do not re-sterilize or reuse. Re-sterilization and/or reuse may result in cross contamination and/or reduced performance.
4. When the catheter is exposed to the vascular system, it should be manipulated while under high-quality fluoroscopic observation. Do not advance or retract the catheter if resistance is met during manipulation; determine the cause of the resistance before proceeding.
5. Operators should take all necessary precautions to limit x-radiation doses to patients and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying x-ray technical factors where possible.

PRECAUTIONS

1. Store in a cool, dry, dark place.
2. Do not use kinked, damaged, or opened devices.
3. Use the device prior to the "Use By" date specified on the package.
4. Exposure to temperatures above 54°C (130°F) may damage device. Do not autoclave.
5. Torquing or moving the device against resistance may result in damage to the vessel or device.
6. Maintain a constant infusion of appropriate flush solution.
7. If flow through the device becomes restricted, do not attempt to clear the lumen by infusion. Remove and replace the device.
8. Examine the device to verify functionality and to ensure that its size and shape are suitable for the specific procedure for which it is to be used.
9. The AXS Vecta Aspiration System should be used only by physicians trained in percutaneous procedures and/or interventional techniques.
10. The Scout Introducer should be used with a guidewire and microcatheter inserted when in vasculature.
11. If using the AXS Vecta Aspiration System for thrombectomy, monitor the canister fluid level and replace the canister if the fill level reaches 75% of the canister volume.
12. Administration of anticoagulants and antiplatelets should be suspended until 24 hours post-treatment. Medical management and acute post stroke care should follow the American Stroke Association (ASA) guidelines.
13. Any neurological determination should be evaluated by urgent CT scan and other evaluations as indicated according to investigator/hospital best practice.
14. As in all surgical interventions, monitoring of intra-procedural blood loss is recommended so that appropriate management may be instituted.
15. Limit the usage of the AXS Vecta 71 Aspiration Catheter to arteries greater than the catheter's outer diameter.
16. Excessive aspiration with the distal tip of the AXS Vecta 71 Aspiration Catheter covered by the vessel wall may cause vessel injury. Carefully investigate location of the distal tip under fluoroscopy prior to aspiration.
17. There is an inherent risk with the use of angiography and fluoroscopy.
18. When transporting the VC-701 Cliq pump, utilize the pump handle.
19. Do not use if labeling is incomplete or illegible.



Stryker Neurovascular
47900 Bayside Parkway
Fremont, CA 94538

strykerneurovascular.com

Date of Release: SEP/2018
EX_EN_US

- If Retriever is difficult to withdraw from the vessel, do not torque Retriever. Advance Microcatheter distally, gently pull Retriever back into Microcatheter, and remove Retriever and Microcatheter as a unit. If undue resistance is met when withdrawing the Retriever into the Microcatheter, consider extending the Retriever using the Abbott Vascular DOC guidewire extension (REF 22260) so that the Microcatheter can be exchanged for a larger diameter catheter such as a DAC® Catheter. Gently withdraw the Retriever into the larger diameter catheter.
- Administer anti-coagulation and anti-platelet medications per standard institutional guidelines.
- Users should take all necessary precautions to limit x-radiation doses to patients and themselves by using sufficient shielding, reducing fluoroscopy times, and modifying X-ray technical factors where possible.

PRECAUTIONS

- Prescription only – device restricted to use by or on order of a physician.
- Store in cool, dry, dark place.
- Do not use open or damaged packages.
- Use by "Use By" date.
- Exposure to temperatures above 54°C (130°F) may damage device and accessories. Do not autoclave.
- Do not expose Retriever to solvents.
- Use Retriever in conjunction with fluoroscopic visualization and proper anti-coagulation agents.
- To prevent thrombus formation and contrast media crystal formation, maintain a constant infusion of appropriate flush solution between guide catheter and Microcatheter and between Microcatheter and Retriever or guidewire.
- Do not attach a torque device to the shaped proximal end of DOC® Compatible Retriever. Damage may occur, preventing ability to attach DOC® Guide Wire Extension.

DOC is a trademark of Abbott Laboratories.



Stryker Neurovascular
47900 Bayside Parkway
Fremont, CA 94538

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Date of Release: APR/2018
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2019 Candidate Information and Requirements

ASNR and AJNR are pleased once again to join efforts with other imaging-related journals that have training programs on editorial aspects of publishing for trainees or junior staff (3–5 years after training), including Radiology (Olmsted fellowship), AJR (Figley and Rogers fellowships), JACR (Bruce J. Hillman fellowship), and Radiologia.

GOALS

- Increase interest in editorial and publication-related activities in younger individuals.
- Increase understanding and participation in the AJNR review process.
- Incorporate into AJNR's Editorial Board younger individuals who have previous experience in the review and publication process.
- Fill a specific need in neuroradiology not offered by other similar fellowships.
- Increase the relationship between “new” generation of neuroradiologists and more established individuals.
- Increase visibility of AJNR among younger neuroradiologists.

ACTIVITIES OF THE FELLOWSHIP

- Serve as Editorial Fellow for one year. This individual will be listed on the masthead as such.
- Review at least one manuscript per month for 12 months. Evaluate all review articles submitted to AJNR.
- Learn how electronic manuscript review systems work.
- Be involved in the final decision of selected manuscripts together with the Editor-in-Chief.
- Participate in all monthly Senior Editor telephone conference calls.
- Participate in all meetings of the Editors during the annual meetings of ASNR and RSNA and the Radiology Editors Forum as per candidate's availability. The Foundation of the ASNR will provide \$2000 funding for this activity.
- Evaluate progress and adjust program to specific needs in annual meeting or telephone conference with the Editor-in-Chief.
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- Be an “in-training” or member of ASNR in any other category.

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- Include a short letter of intent with statement of goals and desired research project. CV must be included.
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- Applications should be received by March 1, 2019 and sent to Ms. Karen Halm, AJNR Managing Editor, electronically at khalm@asnr.org.

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Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities. NSF may result in fatal or debilitating fibrosis affecting the skin, muscle and internal organs.

- The risk for NSF appears highest among patients with:
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 - Acute kidney injury.
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DOTAREM® (gadoterate meglumine) injection is a prescription gadolinium-based contrast agent indicated for intravenous use with magnetic resonance imaging (MRI) in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier (BBB) and/or abnormal vascularity.

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History of clinically important hypersensitivity reactions to DOTAREM.

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References: 1. Dotarem [package insert]. Princeton, NJ: Guerbet LLC; Aug 2018. 2. Maravilla K et al. Comparison of Gadoterate Meglumine and Gadobutrol in the Diagnosis of Primary Brain Tumors: A Double-Blind Randomized Controlled Intraindividual Crossover Study (the REMIND Study). 2017 June 29. doi: 10.3174/ajnr.A5316. [Epub ahead of print]. 3. de Kerviler E et al. Adverse reactions to gadoterate meglumine: review of over 25 years of clinical use and more than 50 million doses. Invest Radiol 2016;51:544–51 CrossRef Medline. 4. Endrikat J et al. Safety of gadobutrol: results from 42 clinical phase II to IV studies and postmarketing surveillance after 29 million applications. Invest Radiol 2016;51: 537–43 CrossRef Medline. 5. Port M et al. Efficiency, thermodynamic and kinetic stability of marketed gadolinium chelates and their possible clinical consequences: a critical review. Biometals. 2008;21:469–90. 6. Frenzel T et al. Stability of gadolinium-based magnetic resonance imaging contrast agents in human serum at 37°C. Invest Radiol. 2008;43:817–828.

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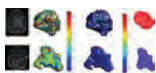
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Color maps visualizing the significant local features on an enhancing lesion region for a tumor progression case (upper row) and a pseudoprogression case (lower row). The total curvature measure is shown in left column, whereas the sharpness measure is shown in the middle column. In the right column, surface-rendering for the 2 cases shows the compactness global feature that was discriminative by the classifier. The pseudoprogression mass is more elliptic, whereas the tumor appears to be more compact.



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Evidence-Based Medicine Level 1



Evidence-Based Medicine Level 2



Title: Perito Moreno Glacier. This is one of 48 glaciers in the Southern Patagonia Icefield in Argentina, the second largest contiguous ice field in the world. Unlike most glaciers in Patagonia that are receding due to climate change, the Perito Moreno glacier grows as much each year as it loses, keeping it in equilibrium. The glacier is 3 miles wide, rises approximately 74 meters above Lago Argentino, and extends 170 meters below the water surface.

Momin Muzaffar, MD, Neuroradiology, Dupage Medical Group, Lisle, Illinois

Gadolinium and Multiple Sclerosis: Vessels, Barriers of the Brain, and Glymphatics

C. Saade, R. Bou-Fakhredin, D.M. Yousem, K. Asmar, L. Naffaa, and F. El-Merhi



ABSTRACT

SUMMARY: The pathogenesis of multiple sclerosis is characterized by a cascade of pathobiologic events, ranging from focal lymphocytic infiltration and microglia activation to demyelination and axonal degeneration. MS has several of the hallmarks of an inflammatory autoimmune disorder, including breakdown of the BBB. Gadolinium-enhanced MR imaging is currently the reference standard to detect active inflammatory lesions in MS. Knowledge of the patterns and mechanisms of contrast enhancement is vital to limit the radiologic differential diagnosis in the staging and evaluation of MS lesion activity. The aim of this review was the following: 1) to outline the pathophysiology of the effect of lymphocyte-driven inflammation in MS, 2) to describe the effects of gadolinium on the BBB and glymphatic system, and 3) to describe gadolinium enhancement patterns and artifacts that can mimic lesions in MS.

ABBREVIATIONS: Gd³⁺ = gadolinium; MTR = magnetization transfer ratio

MR imaging is used as paraclinical supporting evidence of MS and has become an established tool for disease monitoring.¹ It is used to guide treatment by identifying poor responders during follow-up of lesions in the white matter tracts and gray matter,² which is important given that MS is a chronic disease. Technically, challenges remain in standardizing MR imaging scanner and contrast media protocols to better characterize and follow lesions during disease progression.

Gadolinium enhancement is used to depict the early inflammatory phase of MS lesions, which is primarily dependent on 2 key conditions: First, there must be sufficient inflammation surrounding the MS lesion, and, second, the time lapse between gadolinium (Gd³⁺) injection and image acquisition allows the Gd³⁺ molecule to traverse the disrupted BBB and glymphatic system into the lesions (See On-line Appendix for more on Gadolinium enhancement).³ The aim of this review was the following: 1) to outline the pathophysiology of lymphocyte-driven inflammation

in MS, 2) to describe the effects of Gd³⁺ on the BBB and glymphatic system, and 3) to describe Gd³⁺ enhancement patterns and artifacts that can obscure the detection of MS plaques.

Lymphocyte-Driven Inflammation and Microglial Activation

Lymphocyte-driven inflammation and microglial activation play central roles in the pathophysiology of MS. The inflammatory plaques characteristic of MS comprise a wide variation of immunologic and pathologic features.⁴

At the early stages of MS, acute plaques are a common finding. They typically consist of robust inflammatory infiltration with demyelination throughout the lesion.⁵ The inflammatory components at this stage are mainly T-lymphocytes, monocytes, and macrophages, and their influx is centered around vessels (perivascular cuffing). Foamy macrophages can also be found distributed throughout the lesion because they contribute to active stripping of myelin from axons.⁴ Even though the axon itself is usually spared, it is common to find extensive axonal injury in these lesions, and despite prominent glial reactivity, dense glial scarring is not typical.

When MS plaques become chronic, the lesions are predominantly hypocellular with obvious glial scarring and loss of myelin.

The inflammatory progression of MS can be clarified by a recent typing of MS lesions based on the pattern of leukocyte markers, myelin proteins, immunoglobulin, and complement proteins present in the lesions. Pattern 1 has predominant T-cell and macrophage inflammatory content. Pattern 2 has T-cell and macrophage infiltration with immunoglobulin and myelin degradation products in the macrophages. Pattern 3 has obvious oligodendro-

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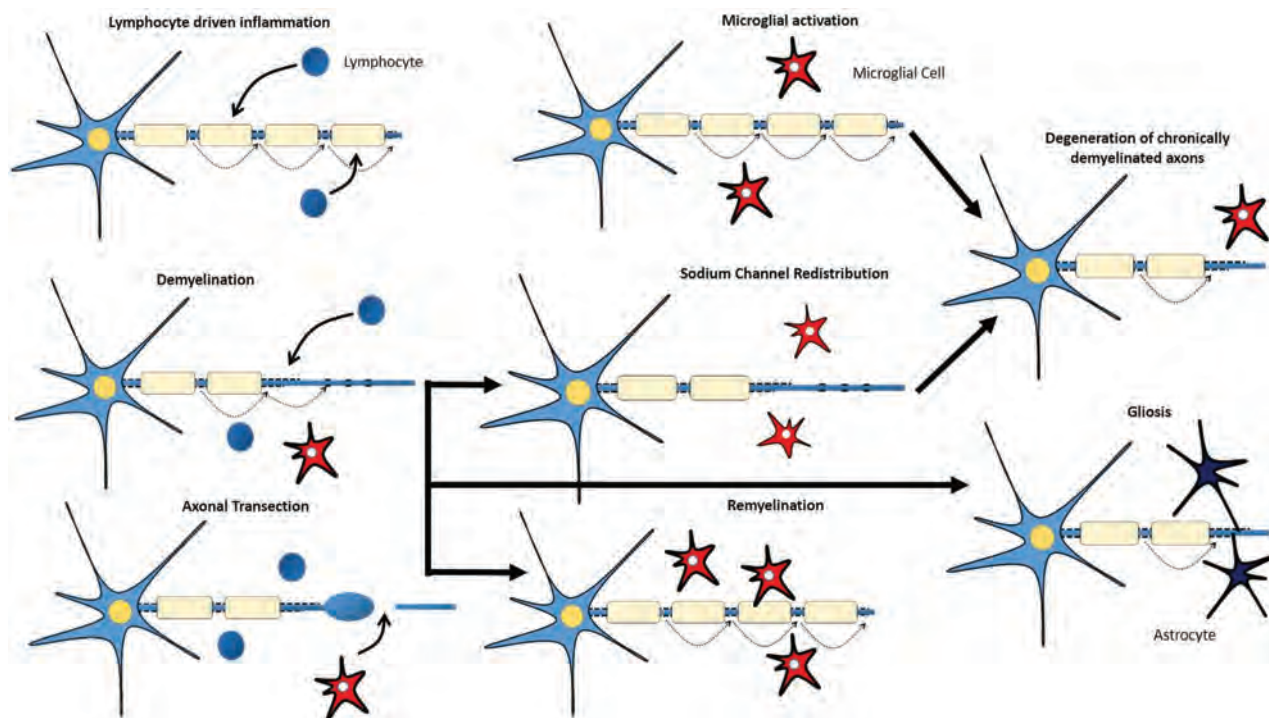


FIG 1. Lymphocyte-driven inflammation induces conduction blocks in structurally intact axons, drives demyelination, and induces transection of axons (with consequent conduction block) within acute lesions. Activated microglial cells might contribute to the repair mechanisms that lead to remyelination or to the degeneration of axons. Redistribution of sodium channels along demyelinated axons could restore conduction. Astrocytic activation and proliferation (gliosis) might impede repair.

cyte loss at the active edge of the lesion with loss of myelin-associated glycoprotein. Pattern 4 has oligodendrocyte dystrophy and absence of remyelination.⁶

The pathogenesis of MS is still a poorly understood mechanism. One hypothesis states that the initial event during plaque genesis is an early intrinsic oligodendrocyte injury that leads to the inflammatory damage associated with MS. This hypothesis seems to be supported, to a certain extent, by a study⁷ that found that the tissue immediately adjacent to lesion borders showed microscopic evidence of cellular injury without the presence of immune infiltration. It is well-established that MS is an immune-mediated destruction of CNS components.

Role of T-Lymphocytes in MS

The presence of lymphocytes in MS suggests an antigen-specific targeting of myelin in this disease. T-cells isolated from patients with MS have been shown to react to a variety of antigens of myelin origin like myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein, and myelin oligodendrocytic basic protein.⁸⁻¹² In addition, many nonmyelin antigens and neuronal antigens have also been described. The exact mechanism causing the T-cells to become abnormally activated is still elusive, but molecular mimicry has been suspected. Another culprit is interleukin 17. Interleukin 17-secreting cells were found in the CSF of a patient with MS,¹³ and the percentage of interleukin 17 producing memory CD4 T-cells was elevated in the peripheral blood of patients with MS.¹⁴ Interleukin 17 gene expression is also elevated in lesions of patients with MS, thus suggesting a high association between this interleukin and MS pathogenesis, especially with the lymphocyte T helper 17 being a critical mediator of

the immune destruction of myelin and axons in MS.¹⁵ In addition, T helper 17 cells have been shown to cross the BBB more efficiently than other T-cells, and the presence of interleukin 17-secreting CD4 T-cells has been shown to be capable of causing damage to the BBB,¹⁶ which contributes to the influx of inflammatory cells into the brain.

In response to inflammation, injury, and axonal degeneration, microglial cells, which represent the macrophages resident in the CNS parenchyma, become activated.¹⁷ When activated, these microglial cells can adopt diverse phenotypes, which can be benign, protective, or contributory to neurodegeneration (Fig 1).^{18,19} The pathogenesis of MS is characterized by not only lymphocyte-driven inflammation and microglial activation but also demyelination, remyelination, axonal degeneration, and gliotic response.

Demyelination and Remyelination. Demyelination is a hallmark of MS and occurs in GM and WM lesions (Fig 1). The inflammatory process, characterized by a breakdown in the BBB, inflammatory cell infiltrates, and production of immune-soluble mediators and harmful inflammatory enzymes, can lead to the development of acute demyelinating lesions. Acute demyelination is the main determinant for the conduction block that creates the acute neurologic deficit. Additionally, demyelinated axons can become hyperexcitable and spontaneously generate impulses that translate into the positive symptoms of MS.¹⁸

The most valuable role of remyelination could be to ensure axonal survival for the long term rather than the immediate restoration of nerve conduction (Fig 1). Low levels of remyelination are seen in most patients with MS.²⁰ Oligodendrocyte precursors are available even in chronic lesions of patients with progressive

MS, suggesting that their availability is not the limiting factor for remyelination.²¹ Therefore, several reasons for remyelination failure might exist, including recurrent demyelination in previously remyelinated areas.¹⁸

Axonal Degeneration and Neuronal Damage. Axonal loss can occur acutely in new inflammatory lesions but also across time in chronic, demyelinated lesions (Fig 1).¹ Mechanisms that link inflammation to axonal loss include neuronal energy deficit or the loss of myelin trophic support.^{20,22} CD8-positive T-cells are suspects in the immune-mediated axonal damage witnessed in MS, possibly via the release of cytotoxic granules, induction of apoptosis (activating surface receptors like Fas), or release of cytokines like tumor necrosis factor- α . The innate immune system also seems to play a role via the toll-like receptors.^{23,24} Autoantibodies have also been linked to axonal injury in MS.²⁵ The axon in this situation is at high risk of irreversible damage because higher energy demands on demyelinated axons and glutamate-mediated excitotoxicity are a consequence of immune injury to myelin.²⁶

Gliotic Response. The gliotic response is the process of hypertrophy and proliferation of astrocytes seen within and at the margins of inflammatory demyelinating lesions and also in normal-appearing WM (Fig 1). It is generally thought to be secondary to neuronal damage and apoptosis of oligodendrocytes²⁷ and to contribute to irreversible (chronic) symptoms.¹⁸

T2-weighted sequences, whether true T2-weighted or FLAIR sequences, are useful for identifying the number and size of WM lesions, but often they cannot determine the activity level of a plaque in and of itself.²⁸ T1-weighted imaging without contrast helps detect late MS lesions that appear hypointense on MR imaging and demonstrate irreversible axonal pathology.²⁸ T1-weighted sequences with Gd³⁺ detect BBB breakdown, which occurs with active inflammation.

The current diagnostic criteria of MS are based on the detection of CNS lesions demonstrating dissemination in space and time. Several criteria aim to quantify the parameters involved in the dissemination in space and time. The 2005 McDonald criteria reported a sensitivity and specificity of 77% and 90%, respectively.²⁹ The newly revised 2010 McDonald criteria demonstrated sensitivity and specificity of 100% and 86%, respectively, for children older than 11 years of age with symptoms inconsistent with acute disseminated encephalomyelitis.³⁰ The Swanton criteria for dissemination in space reported a sensitivity and specificity of 71% and 86%, respectively.³¹ In Europe, radiologists have adopted the Magnetic Resonance Imaging in MS modification with the following changes: 1) Optic neuritis is added to 4 locations in McDonald criteria, 2) ≥ 3 periventricular lesions are required, 3) cortical and juxtacortical lesions are considered qualifying, and 4) dissemination in time does not need to be asymptomatic or symptomatic, and any new lesion or enhancing/nonenhancing lesions in the same study qualify.

Gadolinium Effects

BBB. Gadolinium distribution into the neural tissue is complex because it occurs by a variety of mechanisms. To ensure adequate oxygen delivery to the highly metabolically active neurons, the capillary network of the brain is dense. A unique distinguishing

feature of the brain microvasculature is the presence of tight junctions between the adjacent endothelial cells lining the capillaries. The BBB exists at all levels of the vascular tree within the CNS, including the penetrating arteries and arterioles, the dense capillary bed, the postcapillary venules, and the draining venules and veins.^{32,33} Although each vascular segment needs to maintain tight barrier properties to insulate the neural tissue from the blood, there are specializations within the vascular bed that are crucial for BBB function.

The BBB is a multicellular vascular structure that separates the CNS from the peripheral blood circulation. It is regulated by the interchange among the main compartments of the CNS, brain, CSF, and blood by a combination of physical and functional mechanisms. There are 4 main interfaces in the BBB: 1) the BBB proper at the level of the cerebral endothelial cells that allows highly lipophilic solutes such as caffeine to pass the BBB, 2) the blood-CSF barrier at the epithelial cells of the choroid plexuses within the 4 cerebral ventricles, 3) the pia arachnoid, and 4) an additional barrier interface present only in the early brain development between the CSF and the brain interstitial fluid (Fig 2). BBB dysfunction can lead to ion dysregulation, altered signaling homeostasis, and entry of immune cells and molecules into the CNS, processes that lead to neuronal dysfunction and degeneration.³³

Blood supply to both WM and GM occurs with the primary vessels crossing the pia mater into the GM. However, in patients with MS, capillary density is relatively maintained, but with decreased cerebral blood flow resulting from numerous string vessels.³⁴ String vessels are thin connective tissue strands, remnants of capillaries, with no endothelial cells, because they do not carry blood. Whether string vessels are the cause or effect of GM hypoperfusion and eventual brain atrophy is unknown. Another potential hypothesis is that inflammatory processes can result in microvascular damage by different mechanisms: Cytotoxic T-cells may recognize antigens on endothelial cells and activate a clotting cascade, which, in turn, leads to thrombosis.³⁵ Additionally, evidence³⁶ suggests that parenchymal plaques may initially be associated with capillaries and arterioles in an attempt to seal microvascular leakage, especially during inflammation. Finally, in advanced stages of inflammation, the pressure exerted by the growing perivascular amyloid deposits constricts the microvessel, leaving dysfunctional capillary stumps and string vessels.

Glymphatic System. An indirect mechanism of Gd³⁺ distribution occurs via the glymphatic system, which is a highly polarized macroscopic system of convective fluid fluxes with rapid interchange of CSF and interstitial fluid. This exchange is facilitated by a convective influx of CSF along the periaxonal space. CSF, from the subarachnoid space, is driven into the Virchow-Robin perivascular spaces by a combination of arterial pulsatility, slow vasomotion, respiration, and CSF pressure gradients. The loose fibrous matrix of the perivascular space can be viewed as a low-resistance highway for CSF influx. The subsequent transport of CSF into the dense and complex brain parenchyma is facilitated by astrocytic aquaporin-4 water channels expressed in a highly polarized manner in astrocytic end-feet that ensheath the brain vasculature.³⁷⁻³⁹ CSF movement into the parenchyma drives convective interstitial fluid fluxes within the tissue toward the

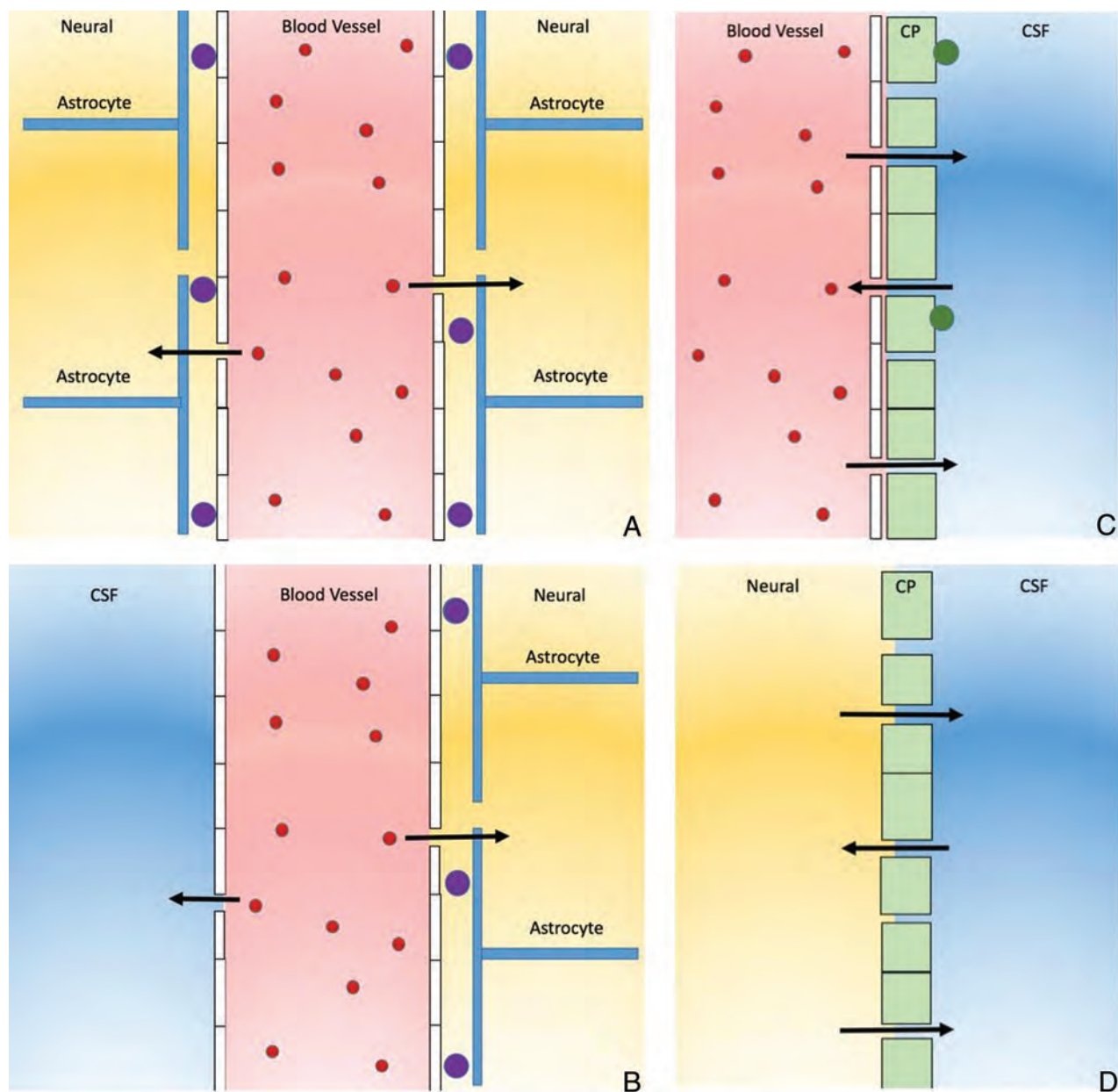


FIG 2. The 4 main interfaces of the blood-brain barrier. *A*, The blood-brain barrier proper is formed by tight junctions between the endothelial cells of the cerebral vasculature. It is thought that pericytes (purple circles) are sufficient to induce some barrier characteristics in endothelial cells, while astrocytes are able to maintain the integrity of the blood-brain barrier postnatally. *B*, The outer CSF-brain barrier and the level of the pia arachnoid are formed by tight junctions between endothelial cells of the arachnoid vessels. *C*, The blood-CSF barrier is formed by tight junctions between epithelial cells of the choroid plexus (CP) (note that the plexus vasculature is fenestrated). Resident epiplexus (green circles) immune cells are present on the CSF-surface of the plexus epithelium. *D*, The inner CSF-brain barrier, present only in early development, is formed by strap junctions between the neuroepithelial cells lining the ventricular surfaces. In the adult, this barrier is no longer present.

perivascular spaces surrounding the large deep veins. The interstitial fluid is then collected in the perivascular space from where it drains out of the brain and toward the cervical venous system. The glymphatic system provides a paravascular, transparenchymal outflow passage, which helps remove brain metabolites⁴⁰ such as amyloid β and inulin⁴¹ found in the CSF. The paravascular space comprises the compartment between the pia mater and glia limitans, which encompasses the vascular wall of the leptomeningeal vein. The paravascular space however, is in direct contact with the extracellular space and the subarachnoid space of the leptomeningeal artery. The inflow of CSF in the paravascular space is along

the arteries and exits through the veins, where it is mixed with interstitial fluid.⁴²

The clearance of excess metabolites is essential for tissue homeostasis⁴¹ and is mediated by the CSF-interstitial fluid exchange pathway. Furthermore, studies on rodent brains have demonstrated that the primary, most rapid glymphatic inflow occurs at the level of the hypothalamus, olfactory tract, retrosplenial cortex, pons, amygdala, cerebellum, and hippocampus.⁴³ The glymphatic system is also dependent on the intensity by which the pulse is generated throughout the smooth-muscle cells of the arteries. Particular to arteries, pulsation that is often generated by

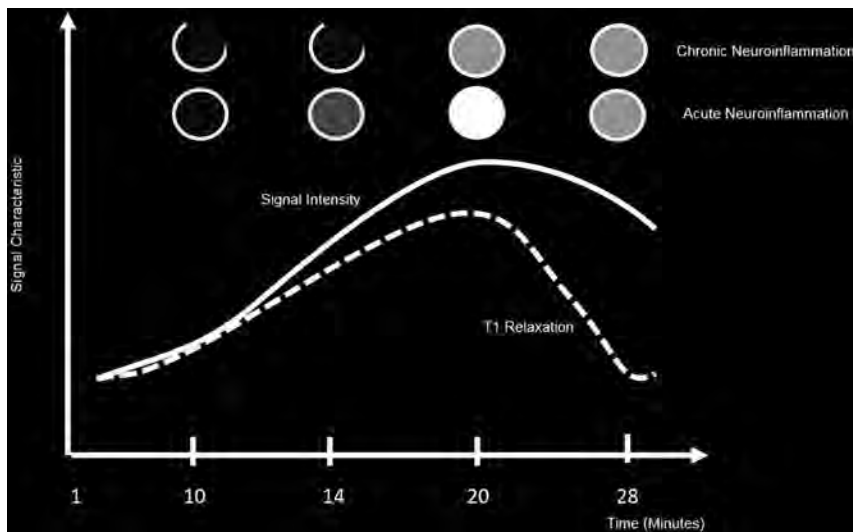


FIG 3. Enhancement patterns of lesions across time depicting signal intensity versus T1 relaxation times of acute and chronic MS lesions.

smooth-muscle cells creates pulse waves along the whole length of the pial artery and penetrating arteries diving into the brain from the cortical surface.^{38,44} It has been shown that adrenergic agonists such as dobutamine increase the pulsatile effect significantly when administered to mice and result in a larger amount of CSF penetration into the parenchyma.^{32,41} The opposite effect was obtained when arterial pulsatility was dampened by internal carotid artery ligation. Additionally, the reduction of pulse waves decreased CSF-interstitial fluid exchange.³⁸ This feature suggests that glymphatic activity, at least in part, is driven by arterial pulsatility and explains why perivascular influx occurs preferentially around pulsating arteries and not cerebral veins.

The parameters that aid in the facilitation of flow in the glymphatic system mainly include cell volume, pulsatility, astrocytic aquaporin-4 channels, water channel positions,⁴³ and sleep state.⁴¹ Studies have shown that for one to fully understand the glymphatic system, small-molecular-weight tracers need to be administered to penetrate the cortical and basal arteries to reach the capillaries and, finally, interstitial compartments. This method will provide a clear pathway for the paravascular space in the glymphatic system that could be detected by different imaging techniques.⁴³ Studies have shown that tracers injected into the paravascular space are only evident along the arteries and not veins and are characterized as being bidirectional, depending of the site of injection. Moreover, large tracers do not penetrate the paravascular space, and their flow is affected by the aquaporin-4 and pulsation mechanism.⁴²

The glymphatic system has been implicated in the discovery of deposition of Gd^{3+} in the dentate nucleus.⁴⁵ Eide and Ringstad⁴⁰ evaluated patients who had Gd^{3+} administrations in the subarachnoid space with MR imaging. Four hours after Gd^{3+} administration in the subarachnoid space, both the cortical GM and WM of the brain demonstrated increased signal intensity and the Gd^{3+} was surmised to enter the human brain through the glymphatic system. Naganawa et al⁴⁶ evaluated the brain MR imaging of 27 subjects who had been administered Gd^{3+} 4 hours prior. On

the postcontrast FLAIR image, the subarachnoid and perivascular spaces showed increased signal intensity, subsequent to Gd^{3+} transfer to the subarachnoid and perivascular spaces. These results demonstrate that intravenously administered Gd^{3+} can be transported through the glymphatic system to reach the brain. However, the association between the hyperintensity of the dentate nucleus and the Gd^{3+} transported through the glymphatic system is still unclear. The glymphatic system transports all low-molecular-weight materials passively, and both the linear and macrocyclic Gd^{3+} is transported in the same way.⁴⁵ However, the signal intensity of the dentate nucleus varies according to the type of administered Gd^{3+} .^{45,47} In addition, the distribution

of Gd^{3+} cannot be explained by passive transportation. The accumulation of Gd^{3+} in the brain is probably due, to some extent, to the glymphatic system, but the association between the glymphatic system and hyperintensity of the dentate nucleus remains unclear and controversial.⁴⁷

The impact of double and triple doses of Gd^{3+} has been investigated to determine lesion activity and active plaque numbers. Gasperini et al⁴⁸ compared the number and volume of MS lesions when the patient was administered double and triple doses of gadolinium. The volume of lesion enhancement with a triple dose was higher compared with the double dose (1.9 versus 1.7 mL). However, they concluded that the double dose provided similar sensitivity with lower cost and improved safety than triple dose studies for MS detection. Additionally, in a recent study,⁴⁹ it was concluded that macrocyclic Gd^{3+} deposition is reduced but not completely eliminated when macrocyclic Gd^{3+} is used compared with linear agents. Thus, in light of the previous studies, double and triple doses of Gd^{3+} pose greater risk than benefit to the patient in MS imaging.

Enhancement Patterns and Lesion Characteristics

The cause of the enhancement in MS is inflammation, which most often is limited to perivenular inflammation; there is no neovascularity and no angiogenesis. Therefore, enhancement of MS plaques may be faint, the lesions usually do not produce any perilesional vasogenic edema, and the enhancing rim is either thin and often incomplete or solidly enhancing.⁵⁰ Additionally, enhancement may not occur when there is a low level of inflammation. The degree of enhancement of MS lesions is an indicator of the degree of active inflammation and distinguishes between old and new lesions by identifying areas of active BBB breakdown (Fig 3).⁵¹

MR imaging has revealed that these lesions tend to undergo a series of changes with time, and they disappear within <6 months.⁵² Moreover, most enhancing lesions tend to show a nodular enhancement pattern. The remaining lesions show a complete or incomplete ringlike enhancement pattern. There are no

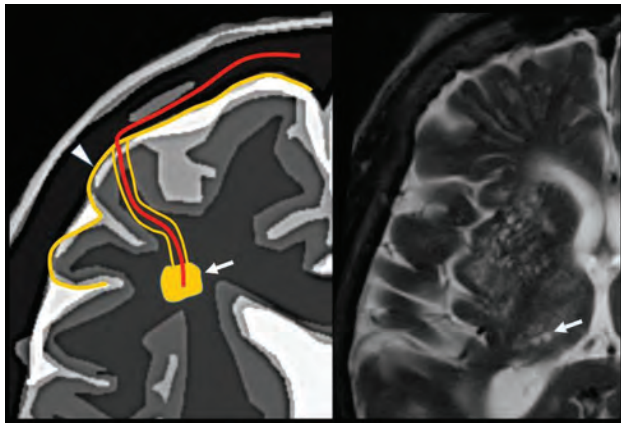


FIG 4. Pathophysiology of the vascular pattern. The picture features the mural and/or endoluminal microvascular lesion that induces the ischemic lesion of the parenchyma. Arrowhead indicates perivascular inflammation. Image modified with permission from Martorell et al.⁵⁶

histologic differences between these 2 distinct types of enhancement patterns,^{50,53,54} and the differences may be due to the lesion size and/or the timing of scanning after Gd^{3+} administration, which reflects the capability of Gd^{3+} to fill the lesion but not the surrounding normal tissue.^{48,53,54}

Several studies^{48,52} have established a correlation between enhancement pattern and the magnetization transfer ratio (MTR). During MTR, magnetization is transferred from the mobile proton pool to the immobile one. The resulting signal density in the mobile pool gives a signal reduction. It allows subcategorization of MS lesions into those with very low MTR such as demyelinating lesions and slightly low MTR as in edematous lesions. Its major advantage is that it is a sensitive parameter to quantify the integrity of myelinated WM (both demyelinated and remyelinated tissue) in the absence of axonal loss.⁵⁵ Additionally, it has been suggested that the nodular enhancing lesions have the highest MTR, while ringlike enhancing lesions have the lowest MTR. Nevertheless, lesion enhancement can depend on many other factors, including the dosage of contrast agent, the time from injection to imaging, the magnitude of BBB abnormalities, magnetic field strength, concurrent steroid use, and the MR imaging pulse sequence parameters used between each study.

Basic Pathophysiology. One possible mechanism of damage to the WM is through the involvement of a cerebral venule or an arteriole, which provides the blood supply of the parenchyma that depends on the vasculature.⁵⁶ White matter microvascular disease involves a broad range of conditions such as infection, hypoxia-ischemia, atherosclerosis, granulomatous or nongranulomatous inflammation, among others. Radiologically, it can manifest as focal lesions in the WM or in paravascular spaces. It may have a noninfectious inflammatory etiology (as is the case of MS), an atypical infectious etiology, a metabolic etiology, or a traumatic etiology (diffuse axonal injury).

Types. The differential diagnosis of multiple hyperintense punctate images in the white matter on T2-weighted sequences is manifold, and many of these entities must be excluded to make the diagnosis of MS. On the basis of several semiological elements, 3

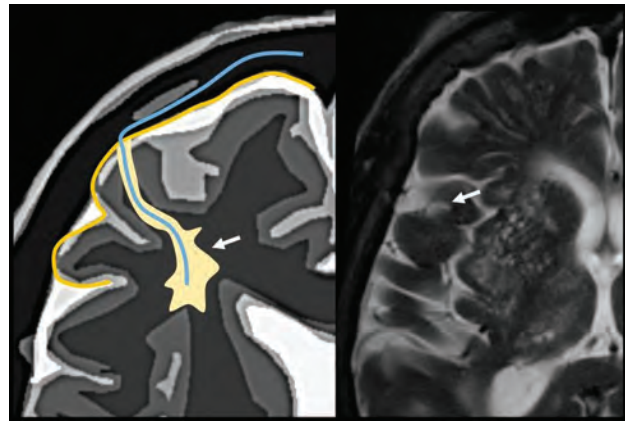


FIG 5. Pathophysiology of the perivascular pattern, the arrows represent perivascular inflammation from the perivascular space. The picture features a perivascular pathologic process and the adjacent parenchymal lesion. The demyelinating layer is caused by perivascular inflammation in a patient with multiple sclerosis. Image modified with permission from Martorell et al.⁵⁶

main patterns can be identified. The first is a vascular pattern, which is caused by an arteriolar lesion and is the most prevalent, seen in the elderly with atherosclerotic risk factors (leukoaraiosis) (Fig 4). The second is a perivascular pattern, which is caused by perivascular inflammation.⁵⁷ The paradigm of this pattern is MS, for which autoimmune perivascular inflammation has been implicated as the etiology of the demyelination (Fig 5). The third is a nonspecific pattern,⁵⁸ which is also usually caused by microvascular disease.

Distribution and Location. Hyperintense punctate foci in the WM may present with a predominantly supratentorial, infratentorial, or mixed distribution.⁵⁶ The presence of lesions with a supratentorial distribution suggests small-vessel disease as a first option, which favors a vascular pattern. The concurrent finding of striatocapsular or deep GM lacunes also supports this diagnosis, as does hemosiderin deposition in hypertension-related GM lesions. A lesion is regarded as periventricular when it is in contact or virtually in contact with the ependymal surface of the ventricle.⁵⁹ Infratentorial lesions can have either a peripheral or central location closer to the brain stem or fourth ventricle. A peripheral lesion is typically associated with a perivascular pattern, whereas a central lesion is generally associated with a vascular pattern.⁵⁶

In the past decade, the focus in MS research has switched from WM to GM involvement.⁶⁰ Unfortunately, cortical lesions (juxtacortical, intracortical, and subpial GM lesions) remain difficult to detect without high-resolution MR imaging, using a standard field strength. The most likely reason for the difficulty is their relatively small size.⁶¹ Moreover, the difference in pathologic substrate, anatomic paucity of myelin in the cortex generating little MR imaging contrast on demyelination, and partial volume effects from adjacent CSF and WM probably play a role. Many in vivo studies have shown improved detection using higher magnetic field strengths up to 7T.⁶² The implementation of 7T MR imaging has resulted in an increased detection of cortical (enhancing) lesions in patients with MS, compared with the lower 3T and 1.5T MR imaging systems.⁶³ Although the first results with 7T seem promising, several questions still remain to be answered.

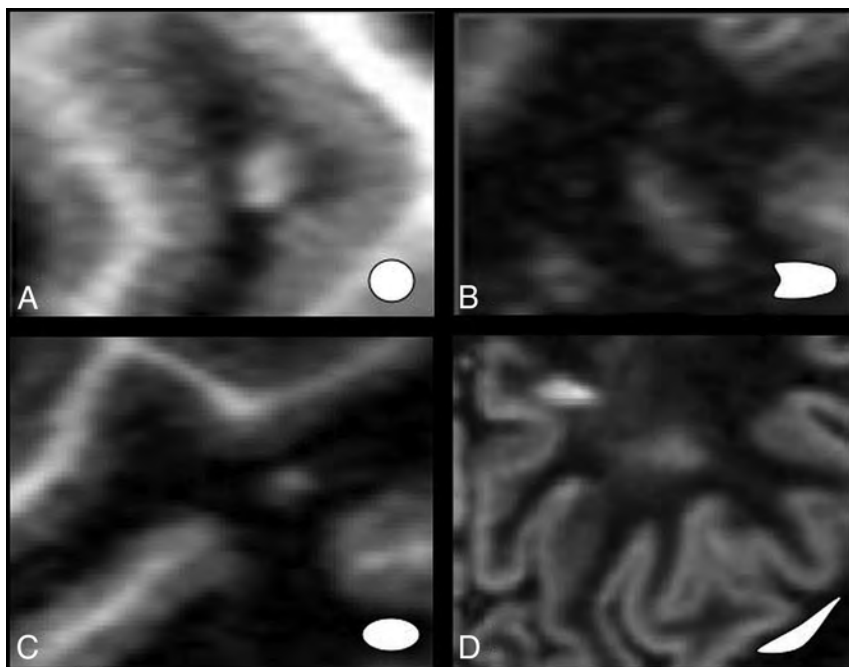


FIG 6. Types of lesion patterns: specific (A and B) versus nonspecific (C and D).

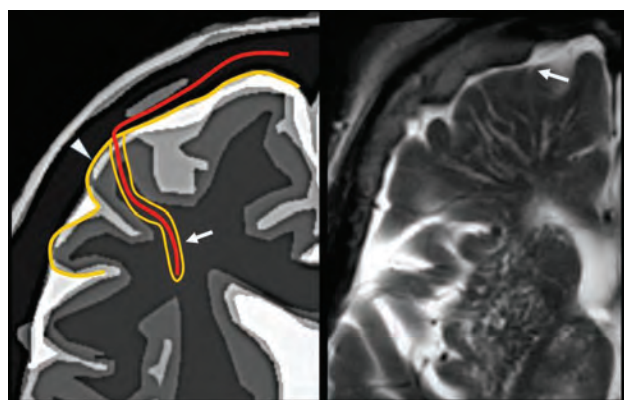


FIG 7. Periaxonal space of the pial arterioles is surrounded by 1 leptomeningeal layer that separates it from the subpial space (arrow). The periaxonal space of lenticulostriated arterioles is surrounded by 2 leptomeningeal layers that separate it from the subpial space (arrowhead). Image modified with permission from Martorell et al.⁵⁶

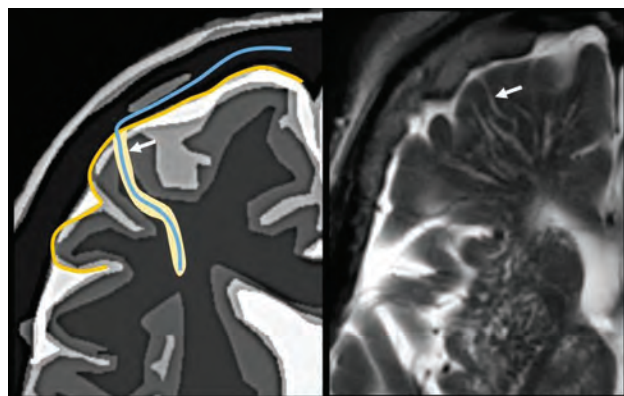


FIG 8. Perivascular space. Communication with the subpial space (arrow). Image modified with permission from Martorell et al.⁵⁶

Morphology, Size, and Changes with Time. Lesions can be of several shapes: oval or fusiform and punctate, linear, nodular, or round (Fig 6). Punctate, roundish, and amorphous lesions are nonspecific. On the other hand, oval or fusiform lesions may have a distribution parallel to the cerebral microcirculation, and they have a perivascular pattern. Oval or fusiform periventricular lesions in a radial pattern are a common feature of MS. They are known as Dawson fingers. The confluence of these lesions makes up a ridgelike configuration, which is also associated with MS.⁵⁶

Localization of an isolated lesion of >10–15 mm is suggestive of a perivascular pattern. Smaller lesions are nonspecific and can be indicative of either a microvascular or a perivascular lesion.⁵⁶ With time, lesion shape changes from round punctate to oval or fusiform.

Leptomeningeal Enhancement. Meningeal inflammation is rapidly becoming an area of focus in histopathologic findings in multiple sclerosis.⁶⁴ Meningeal inflammation is a consequence of the long-term disease processes of MS. Recent studies^{65,66} have found that 3T imaging demonstrated minimal amounts of leptomeningeal enhancement compared with 7T.⁶⁴ Additionally, there was an association with reduced cortical gray matter volumes, which may represent blood-meningeal barrier breakdown near sites of meningeal inflammation.

Artifact-Mimicking Lesions

Perivascular Spaces. The perivascular space surrounds the wall of arteries and arterioles and veins and venules communicating with the subarachnoid space along the intraparenchymatous course of the vessels. The superficial or cortical arterioles are surrounded by 1 layer of leptomeninges that separates the vascular surface from the periaxonal space (Fig 7). The pia mater limits the parenchymal surface of this area. The perivascular space of the penetrating arterioles of the basal ganglia is constrained by the 2 layers of leptomeninges that border their endothelium. There is a direct communication of the superficial and deep perivascular space with the subpial space, with no leptomeningeal layers separating them (Fig 8).^{67,68} Fortunately, the advent of FLAIR scanning has nearly eliminated any confusion between perivascular spaces which, like CSF, are dark on FLAIR scans, versus MS plaques, which are bright on FLAIR. Only “black holes” of complete myelin loss are dark on FLAIR.

CONCLUSIONS

Understanding the pathophysiology of lymphocyte-driven inflammation in MS, lesion enhancement patterns, the effect of Gd³⁺ on the BBB, and the glymphatic system as well as lesion mimics is pivotal in this debilitating autoimmune disease. By understanding the imaging variations that determine the radiologic

differential diagnosis, one can make a more accurate and timely diagnosis of MS. These concepts explain the variable appearance of the MS lesions in space and time.

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REFERENCES

- Rocca MA, Absinta M, Filippi M. The role of advanced magnetic resonance imaging techniques in primary progressive MS. *J Neurol* 2012;259:611–21 CrossRef Medline
- Río J, Castelló J, Rovira A, et al. Measures in the first year of therapy predict the response to interferon beta in MS. *Mult Scler* 2009;15:848–53 CrossRef Medline
- Bou Fakhredin R, Saade C, Kerek R, et al. Imaging in multiple sclerosis: a new spin on lesions. *J Med Imaging Radiat Oncol* 2016;60:577–86 CrossRef Medline
- Wu GF, Alvarez E. The immunopathophysiology of multiple sclerosis. *Neurol Clin* 2011;29:257–78 CrossRef Medline
- Love S, Louis DN, Ellison DW. *Greenfield's Neuropathology*. 8th ed. London: Hodder Arnold; 2008
- Keegan M, König F, McClelland R, et al. Relation between humoral pathological changes in multiple sclerosis and response to therapeutic plasma exchange. *Lancet* 2005;366:579–82 CrossRef Medline
- Henderson AP, Barnett MH, Parratt JD, et al. Multiple sclerosis: distribution of inflammatory cells in newly forming lesions. *Ann Neurol* 2009;66:739–53 CrossRef Medline
- de Rosbo NK, Kaye JF, Eisenstein M, et al. The myelin-associated oligodendrocytic basic protein region MOBP15–36 encompasses the immunodominant major encephalitogenic epitope(s) for SJL/J mice and predicted epitope(s) for multiple sclerosis-associated HLA-DRB1*1501. *J Immunol* 2004;173:1426–35 CrossRef Medline
- Greer JM, Csurhes PA, Cameron KD, et al. Increased immunoreactivity to two overlapping peptides of myelin proteolipid protein in multiple sclerosis. *Brain* 1997;120(Pt 8):1447–60 CrossRef Medline
- Pette M, Fujita K, Wilkinson D, et al. Myelin autoreactivity in multiple sclerosis: recognition of myelin basic protein in the context of HLA-DR2 products by T lymphocytes of multiple-sclerosis patients and healthy donors. *Proc Natl Acad Sci U S A* 1990;87:7968–72 CrossRef Medline
- Valli A, Sette A, Kappos L, et al. Binding of myelin basic protein peptides to human histocompatibility leukocyte antigen class II molecules and their recognition by T cells from multiple sclerosis patients. *J Clin Invest* 1993;91:616–28 CrossRef Medline
- Zhang J, Markovic-Plese S, Lacet B, et al. Increased frequency of interleukin 2-responsive T cells specific for myelin basic protein and proteolipid protein in peripheral blood and cerebrospinal fluid of patients with multiple sclerosis. *J Exp Med* 1994;179:973–84 CrossRef Medline
- Brucklacher-Waldert V, Stuermer K, Kolster M, et al. Phenotypical and functional characterization of T helper 17 cells in multiple sclerosis. *Brain* 2009;132(Pt 12):3329–41 CrossRef Medline
- Durelli L, Conti L, Clerico M, et al. T-helper 17 cells expand in multiple sclerosis and are inhibited by interferon-beta. *Ann Neurol* 2009;65:499–509 CrossRef Medline
- Tzartos JS, Friese MA, Craner MJ, et al. Interleukin-17 production in central nervous system-infiltrating T cells and glial cells is associated with active disease in multiple sclerosis. *Am J Pathol* 2008;172:146–55 CrossRef Medline
- Kebir H, Kreyenborg K, Ifergan I, et al. Human TH17 lymphocytes promote blood-brain barrier disruption and central nervous system inflammation. *Nat Med* 2007;13:1173–75 CrossRef Medline
- Perry VH, Nicoll JA, Holmes C. Microglia in neurodegenerative disease. *Nat Rev Neurol* 2010;6:193–201
- Bodini B, Cercignani M, Toosy A, et al. A novel approach with “skel-etonised MTR” measures tract-specific microstructural changes in early primary progressive MS. *Hum Brain Mapp* 2014;35:723–33 CrossRef Medline
- Broom KA, Anthony DC, Blamire AM, et al. MRI reveals that early changes in cerebral blood volume precede blood-brain barrier breakdown and overt pathology in MS-like lesions in rat brain. *J Cereb Blood Flow Metab* 2005;25:204–16 CrossRef Medline
- Lassmann H. Relapsing-remitting and primary progressive MS have the same cause(s): the neuropathologist's view, 1. *Mult Scler* 2013;19:266–67 CrossRef Medline
- Karthikeyan K, Mahat MY, Chandrasekaran S, et al. Bioanalytical method development, validation and quantification of dorsomorphin in rat plasma by LC-MS/MS. *Biomed Chromatogr* 2013;27:1018–26 Medline
- Campbell JL, Le Blanc JC. Peptide and protein drug analysis by MS: challenges and opportunities for the discovery environment. *Bioanalysis* 2011;3:645–57 CrossRef Medline
- Fernández M, Montalbán X, Comabella M. Orchestrating innate immune responses in multiple sclerosis: molecular players. *J Neuroimmunol* 2010;225:5–12 CrossRef Medline
- Sloane JA, Batt C, Ma Y, et al. Hyaluronan blocks oligodendrocyte progenitor maturation and remyelination through TLR2. *Proc Natl Acad Sci U S A* 2010;107:11555–60 CrossRef Medline
- Mathey EK, Derfuss T, Storch MK, et al. Neurofascin as a novel target for autoantibody-mediated axonal injury. *J Exp Med* 2007;204:2363–72 CrossRef Medline
- Mahad DJ, Ziabreva I, Campbell G, et al. Mitochondrial changes within axons in multiple sclerosis. *Brain* 2009;132(Pt 5):1161–74 CrossRef Medline
- Scott P. New breakthroughs involving oligodendrocytes and stem cells, and their impact on multiple sclerosis. *Microreviews in Cell and Molecular Biology* 2012;1. <https://undergradsciencejournals.okstate.edu/index.php/MRCMB/article/view/1987>. Accessed February 5, 2018
- Mallik S, Samson RS, Wheeler-Kingshott CA, et al. Imaging outcomes for trials of remyelination in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2014;85:1396–404 CrossRef Medline
- Swanton JK, Fernando K, Dalton CM, et al. Modification of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. *J Neurol Neurosurg Psychiatry* 2006;77:830–33 CrossRef Medline
- Geurts JJ, Calabrese M, Fisher E, et al. Measurement and clinical effect of grey matter pathology in multiple sclerosis. *Lancet Neurol* 2012;11:1082–92 CrossRef Medline
- Lorentzen J, Grey MJ, Crone C, et al. Distinguishing active from passive components of ankle plantar flexor stiffness in stroke, spinal cord injury and multiple sclerosis. *Clin Neurophysiol* 2010;121:1939–51 CrossRef Medline
- Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. *Nat Med* 2013;19:1584–96 CrossRef Medline
- Goriely A, Geers MG, Holzapfel GA, et al. Mechanics of the brain: perspectives, challenges, and opportunities. *Biomech Model Mechanobiol* 2015;14:931–65 CrossRef Medline
- Yasuda T, Fukumura K, Sato Y, et al. Effects of detraining after blood flow-restricted low-intensity training on muscle size and strength in older adults. *Aging Clin Exp Res* 2014;26:561–64 CrossRef Medline
- Bammer R, Augustin M, Strasser-Fuchs S, et al. Magnetic resonance diffusion tensor imaging for characterizing diffuse and focal white matter abnormalities in multiple sclerosis. *Magn Reson Med* 2000;44:583–91 CrossRef Medline
- Enzinger C, Barkhof F, Ciccarelli O, et al; MAGNIMS study group. Nonconventional MRI and microstructural cerebral changes in multiple sclerosis. *Nat Rev Neurol* 2015;11:676–86 CrossRef Medline
- Lucchinetti CF, Popescu BF, Bunyan RF, et al. Inflammatory cortical demyelination in early multiple sclerosis. *N Engl J Med* 2011;365:2188–97 CrossRef Medline

38. Iliff JJ, Goldman SA, Nedergaard M. **Implications of the discovery of brain lymphatic pathways.** *Lancet Neurol* 2015;14:977–79 [CrossRef Medline](#)
39. Chaitanya GV, Omura S, Sato F, et al. **Inflammation induces neuro-lymphatic protein expression in multiple sclerosis brain neurovasculature.** *J Neuroinflammation* 2013;10:895 [CrossRef Medline](#)
40. Eide PK, Ringstad G. **MRI with intrathecal MRI gadolinium contrast medium administration: a possible method to assess glymphatic function in human brain.** *Acta Radiol Open* 2015;4:2058460115609635 [Medline](#)
41. Jessen NA, Munk AS, Lundgaard I, et al. **The glymphatic system: a beginner's guide.** *Neurochem Res* 2015;40:2583–99 [CrossRef Medline](#)
42. Bakker EN, Bacskaï BJ, Arbel-Ornath M, et al. **Lymphatic clearance of the brain: perivascular, paravascular and significance for neurodegenerative diseases.** *Cell Mol Neurobiol* 2016;36:181–94 [CrossRef Medline](#)
43. Ratner V, Zhu L, Kolesov I, et al. **Optimal-mass-transfer-based estimation of glymphatic transport in living brain.** *Proc SPIE Int Soc Opt Eng* 2015;9413 [CrossRef Medline](#)
44. Bilston LE, Stoodley MA, Fletcher DF. **The influence of the relative timing of arterial and subarachnoid space pulse waves on spinal perivascular cerebrospinal fluid flow as a possible factor in syrinx development.** *J Neurosurg* 2010;112:808–13 [CrossRef Medline](#)
45. Kanda T, Nakai Y, Oba H, et al. **Gadolinium deposition in the brain.** *Magn Reson Imaging* 2016;34:1346–50 [CrossRef Medline](#)
46. Naganawa S, Nakane T, Kawai H, et al. **Gd-based contrast enhancement of the perivascular spaces in the basal ganglia.** *Magn Reson Med Sci* 2017;16:61–65 [CrossRef Medline](#)
47. Ramalho M, Ramalho J, Burke LM, et al. **Gadolinium retention and toxicity: an update.** *Adv Chronic Kidney Dis* 2017;24:138–46 [CrossRef Medline](#)
48. Gasperini C, Paolillo A, Rovaris M, et al. **A comparison of the sensitivity of MRI after double-and triple-dose Gd-DTPA for detecting enhancing lesions in multiple sclerosis.** *Magn Reson Imaging* 2000;18:761–63
49. McDonald RJ, McDonald JS, Kallmes DF, et al. **Gadolinium deposition in human brain tissues after contrast-enhanced MR imaging in adult patients without intracranial abnormalities.** *Radiology* 2017;285:546–54 [CrossRef Medline](#)
50. Smirniotopoulos JG, Murphy FM, Rushing EJ, et al. **Patterns of contrast enhancement in the brain and meninges.** *Radiographics* 2007;27:525–51 [CrossRef Medline](#)
51. Gaitán MI, Shea CD, Evangelou IE, et al. **Evolution of the blood-brain barrier in newly forming multiple sclerosis lesions.** *Ann Neurol* 2011;70:22–29 [CrossRef Medline](#)
52. Tintore M, Rovira A. **MRI criteria distinguishing seropositive NMO spectrum disorder from MS.** *Neurology* 2013;80:1336 [CrossRef Medline](#)
53. Davis PC, Bravo O, Gehrke M, et al. **Development and validation of an LC-MS/MS method for the determination of quetiapine and four related metabolites in human plasma.** *J Pharm Biomed Anal* 2010;51:1113–19 [CrossRef Medline](#)
54. Yin H, Davis T, Porter NA. **Simultaneous analysis of multiple lipid oxidation products in vivo by liquid chromatographic-mass spectrometry (LC-MS).** *Methods Mol Biol* 2010;610:375–86 [CrossRef Medline](#)
55. Fischer M, Kunkel A, Buback P, et al. **How reliable is the classification of cognitive impairment across different criteria in early and late stages of multiple sclerosis?** *J Neurol Sci* 2014;343:91–99 [CrossRef Medline](#)
56. Medrano Martorell S, Cuadrado Blázquez M, García Figueredo D, et al. **Hyperintense punctiform images in the white matter: a diagnostic approach [in Spanish].** *Radiología* 2012;54:321–35 [CrossRef Medline](#)
57. Ge Y, Law M, Johnson G, et al. **Dynamic susceptibility contrast perfusion MR imaging of multiple sclerosis lesions: characterizing hemodynamic impairment and inflammatory activity.** *AJNR Am J Neuroradiol* 2005;26:1539–47 [Medline](#)
58. González-Quintanilla V, Oterino A, Toriello M, et al. **Cluster-tic syndrome as the initial manifestation of multiple sclerosis.** *J Headache Pain* 2012;13:425–29 [CrossRef Medline](#)
59. Takao H, Abe O, Yamasue H, et al. **Gray and white matter asymmetries in healthy individuals aged 21–29 years: a voxel-based morphometry and diffusion tensor imaging study.** *Hum Brain Mapp* 2011;32:1762–73 [CrossRef Medline](#)
60. Kilsdonk ID, Barkhof F, Wattjes MP. **2010 revisions to McDonald criteria for diagnosis of multiple sclerosis: impact of 3-Tesla magnetic resonance imaging.** *Ann Neurol* 2011;70:182–83 [CrossRef Medline](#)
61. Seewann A, Vrenken H, Kooi EJ, et al. **Imaging the tip of the iceberg: visualization of cortical lesions in multiple sclerosis.** *Mult Scler* 2011;17:1202–10 [CrossRef Medline](#)
62. Grabner G, Dal-Bianco A, Scherthaner M, et al. **Analysis of multiple sclerosis lesions using a fusion of 3.0 T FLAIR and 7.0 T SWI phase: FLAIR SWI.** *J Magn Reson Imaging* 2011;33:543–49 [CrossRef Medline](#)
63. de Graaf WL, Kilsdonk ID, Lopez-Soriano A, et al. **Clinical application of multi-contrast 7-T MR imaging in multiple sclerosis: increased lesion detection compared to 3 T confined to grey matter.** *Eur Radiol* 2013;23:528–40 [CrossRef Medline](#)
64. Harrison AM, das Nair R, Moss-Morris R. **Operationalising cognitive fatigability in multiple sclerosis: a Gordian knot that can be cut?** *Mult Scler* 2017;23:1682–96 [CrossRef Medline](#)
65. Patejdl R, Penner IK, Noack TK, et al. **Multiple sclerosis and fatigue: a review on the contribution of inflammation and immune-mediated neurodegeneration.** *Autoimmun Rev* 2016;15:210–20 [CrossRef Medline](#)
66. Absinta M, Cortese IC, Vuolo L, et al. **Leptomeningeal gadolinium enhancement across the spectrum of chronic neuroinflammatory diseases.** *Neurology* 2017;88:1439–44 [CrossRef Medline](#)
67. Kwee RM, Kwee TC. **Virchow-Robin spaces at MR imaging.** *Radiographics* 2007;27:1071–86 [CrossRef Medline](#)
68. Pollock H, Hutchings M, Weller RO, et al. **Perivascular spaces in the basal ganglia of the human brain: their relationship to lacunes.** *J Anat* 1997;191(Pt 3):337–46 [CrossRef Medline](#)

Perspectives on Neuroradiology Medical Expert Testimony: Fact and Fiction

 D.M. Yousem,  G.H. Zoarski,  A.S. Mark, and  E.S. Schwartz

ABSTRACT

SUMMARY: There are numerous misconceptions about serving as a medical malpractice expert witness. By maintaining an objective perspective based in the unbiased interpretation of the images provided (for both sides of the conflict), one can best serve society as a whole. Most cases for which a neuroradiology expert is recruited are the following: 1) not with the radiologist as a defendant, 2) resolved without court testimony, and 3) short-lived if frivolous. One can learn much about medicine, our nonradiology colleagues, and the litigation process by participating as an expert witness.

ABBREVIATION: ACR = American College of Radiology

This article provides multiple perspectives on the issues of serving as a medicolegal expert witness from the standpoint of a diagnostic neuroradiologist in academia (D.M.Y.), interventional neuroradiologist (G.H.Z.), private practice neuroradiologist (A.S.M.), and pediatric neuroradiologist (E.S.S.). When serving as an expert witness at a trial, one may be required to establish 3 of the 4 components of a legitimate malpractice case: 1) the standard of care for practice; 2) causation, ie, that the negligent act led to the damages; and 3) the damages leading from the negligent act. The fourth component, “duty,” in which a doctor-patient relationship is established, is rarely brought up outside the anonymous “curbside consult” or teleradiology preliminary reports. The American College of Radiology (ACR) has published practice parameters for expert witnesses regarding qualifications, responsibilities, and requisites¹ and recommends that its members sign an “ACR Expert Witness Affirmation Statement,” which describes the principles of appropriate behavior as an expert witness.²

How Are You Selected to Be an Expert Witness?

Most neuroradiologists have the opportunity to serve as expert witnesses. Two previous publications noted that of American Society of Neuroradiology member respondents to an on-line survey, 43.6%–44.1% had served as expert witnesses in neuroradiology, including nearly 71% of those older than 50 years of age.^{3,4} However, most (59.4%) of those who stated they had served as expert witnesses had served in fewer than 5 cases.⁴

Before assuming the position of Director of Neuroradiology at Johns Hopkins in 1998, I had never served as an expert witness. However, shortly after arriving at Hopkins, I began to get calls from malpractice lawyers searching for neuroradiology expert witnesses. I assumed that they Googled “Johns Hopkins Neuroradiology” or were referred via the Hopkins hospital operator (“Can you connect me to the Director of Neuroradiology, please?”). I have no idea why I became “targeted” as a reviewer.

During the past 20 years, I have now served in depositions and/or trial testimony on 50 medical malpractice cases, 1 capital murder trial, 5 personal injury cases (3 motor vehicle collisions, 1 carbon monoxide in the home, and 1 mold in the workplace), and 5 product liability trials (3 from the pharmaceutical industry). For every case that went to deposition or trial, there have been 2–3 that I have reviewed that were dropped or never heard from again.

Gregg H. Zoarski’s Perspective. I first served as an expert witness in 1994, merely 2 years after completing my fellowship in neuroradiology. The trial that resulted was memorable for the courtroom drama that evolved when the jury foreman had a seizure during my testimony; both defendants moved for a retrial on the basis of bias that might have resulted from my rendering care to

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Dr Yousem also wishes to disclose that he met his wife serving as an expert witness for her.

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the foreman. The circumstances brought about a settlement the next morning.

Since 1994, I have served as an expert witness for both plaintiffs and defendants in numerous cases throughout the United States. Depositions are common; trial appearances are rather rare, occurring typically only once or perhaps twice a year. With the high cost of pursuing a medical negligence case to its resolution, it is not surprising that calls from “ambulance chasers” or other disreputable firms are nearly nonexistent. On the contrary, most plaintiffs and defense firms that have sought my opinion are looking for a truthful expert analysis and opinion regarding the issues of the case. Furthermore, it has struck me that most of the firms with which I have interacted view their clients’ best interest and well-being as a priority.

Alexander S. Mark’s Perspective. I have been contacted by attorneys on both sides of the case approximately 20 times in the past 20 years. Having initially practiced in a large tertiary care semi-academic hospital, I have also been named in 5 law suits during that time (as “collateral damage” when other physicians were sued). Fortunately, all these cases were dismissed. I am grateful to the experts hired by my attorneys in each case.

I view my role as an expert witness as one of public service, trying to strongly discourage any frivolous suit regardless of the damages sustained. I offer an opinion based on the findings of the studies provided in the clinical context at the time.

Erin S. Schwartz’s Perspective. Assuming that the contact was related to the relative paucity of pediatric neuroradiologists, I was approached to serve as an expert witness immediately out of fellowship and continue to be sought out periodically. I have served as an expert witness approximately 50 times during almost 20 years.

Testifying for Plaintiffs or Defendants Only?

Many physicians are uncomfortable about testifying “against their brethren” as a plaintiff expert witness. However, the definition of “brethren” may be extended to neuroradiologists, radiologists in general, neuroscience clinicians, or all physicians. The survey of American Society of Neuroradiology members found that 69.7% (324 of 465) are willing to testify for both plaintiff and defendant firms,³ and most professional organizations encourage an egalitarian view of serving in the name of justice rather than on one side or the other.^{1,5} Others may restrict their expert witness testimony to physicians outside their geographic area to ensure that they do not alienate their referrers or compatriots at the state radiologic society.

Of the 50 cases for which I have served as a medical malpractice expert witness, I have testified on behalf of the plaintiff in 27 and the defendant in 23. Of the nonmedical malpractice cases, I have testified in 5 cases for the plaintiff and 5 for the defendant. It seems that most people who have negative attitudes about plaintiff malpractice expert witnesses believe they should be shunned. The nuance is that I never feel like I am testifying “for” or “against” anyone. I see myself as part of the investigative process, and I am testifying for the truth in the case. There are many cases in which a lawyer will ask my opinion, get it, say “thank you,” and never talk to me again, asking me to return the materials. I am not

offended, and if they find another person with a reasonable opposing opinion to mine, then that is part of the justice system.

Gregg H. Zoarski’s Perspective. While limiting testimony to defense work only may simply result from a physician’s heartfelt discomfort with testifying against another physician, such practice will certainly be exploited by the plaintiff’s counsel in an attempt to discredit the witness. Whether plaintiff or defendant, the parties involved in a malpractice action should always have access to fair and unbiased analysis of the care that was rendered, as well as damages. Furthermore, a lack of readily available and unbiased experts could ultimately drive plaintiffs’ attorneys to rely on a less impartial pool of experts, who might have a lower threshold for supporting claims regarding standard of care and causation (ie, “hired guns”). On the other hand, it is common for experts to decline plaintiffs’ cases in which the defendants are in geographic or social proximity or likely to fall within their circle of practice. It is important to consider who you would want as a plaintiff’s expert in a malpractice action in which you were a defendant. Ideally that would be someone with considerable experience and perspective in the issues involved, rather than a less-qualified individual. In many instances, including a multitude of matters in which I have been contacted to review a case from a plaintiff’s attorney, the matter was not filed or, if already in suit, sometimes not pursued as a result of a qualified expert’s opinion that there was not a breach in the standard of care and/or a lack of causation.

Alexander S. Mark’s Perspective. I try to review the case without knowledge of which side the attorney is representing, even though this is not always easy because some lawyers only represent plaintiffs or vice versa. I do not exclude cases on the basis of which side is contacting me.

Erin S. Schwartz’s Perspective. My experience has been similar to Dr Yousem’s comments, including having been contacted by many attorneys to provide an “informal” opinion without being formally declared as their expert, and our contact was limited to that single interaction.

Technique

One of the reasons that I testify for both plaintiffs and defendants is that I do blinded reviews. This means that I do not know whether the law firm that contacts me is a plaintiff or defense firm. I usually ask that I review the cases with only the history provided to the radiologist on the referral slip at the time of the review. Quite often this elicits the response that there is no claim against the radiologist, but I still read the case blinded to the issues of the case. I give the reading verbally, and I do not take notes because these notes are “discoverable” by the attorneys and may not accurately reflect my opinions on the case. Sometimes the lawyers hear my interpretation and say, “Thank you. Send me your bill.” Sometimes they say, “Thank you. Would you now like to hear the issues on the case?” Sometimes they say, “Thank you. Please send us a report in writing.” Sometimes they say, “Actually, I am more interested in the paranasal sinuses than the brain.” Sometimes they say, “Can you quantify the brain damages? We are consulting you for the damage assessment of the brain/spine/neck.”

I have made it my modus operandi that if the legal firm, in

their e-mail invitation to serve as an expert witness, gives background on the issues that their side wants addressed or other information that might bias me, I refer the case to another colleague. If they start to tell me something about the case on the phone, I usually say, "Stop. I'd prefer to read the case blinded to any information except what was provided to the radiologist at the time of the examination. After I give you my blinded interpretation, we can discuss the issues you want addressed. Just send me the images."

By having this policy in place, I can honestly say in deposition 3 years later (after I have forgotten everything about the case "between-hand") that I did a blinded review as per my convention.

Of course, this means that I may be contacted by plaintiff or defense teams without bias. Frankly, I do not remember whether a firm represents one or the other if they recontact me for a different case in the future. That is the benefit of having a poor memory for these things.

Gregg H. Zoarski's Perspective. Once contacted by a law firm, it is impossible to erase the knowledge that the matter under consideration is somehow related to litigation. Some will claim that this knowledge alone raises the level of scrutiny that an expert may dedicate to their review of the imaging and records. In a radiology matter, an expert for either side may assume the presence of a missed finding and search "harder" and longer" than they typically might in the usual clinical setting. The next level of bias can arise when an attorney relates the facts of the case, the outcomes, and his or her legal opinion to the expert during an initial conversation. Like Dr Yousem, I will always stop an attorney from telling me about a case (to avoid bias). I will then review the imaging studies and contact the attorney to discuss the findings or, at other times, record my findings on a dated memo with the note that my findings and opinions were based simply on review of the imaging and formulated before reviewing records or correspondence.

Alexander S. Mark's Perspective. Similar to Dr. Yousem, I also try to learn from other people's mistakes.

Erin S. Schwartz's Perspective. Similar to Dr. Yousem, my practice is to review the imaging studies without, or at least before, review of the medical records and formal radiologist interpretation. The imaging findings are the findings—and whether I am consulted by the defense or plaintiff teams does not impact my interpretation.

Who Are the Defendants?

Another assumption made is that when you are serving as an expert witness, you are testifying for or against your colleagues in radiology. That is not my experience at all. Of the 50 medical malpractice cases in which I have been deposed or testified in court, radiologists were named in the suit in only 14 (28%). If one adds in the other 10 nonmalpractice cases, the 14 constitute 23.3% of my expert opinion volume. Of these 60 cases, I testified on the plaintiff's side in 9 cases (15%) in which a radiologist was a defendant and in 5 cases (8.3%) on behalf of a radiologist defendant.

Who are the most common nonradiologist defendants? Most were neurosurgeons (18/36), obstetricians (5/36), head and neck surgeons (5/36), and emergency department physicians (4/36).

Gregg H. Zoarski's Perspective. Most cases in which I have been involved have been matters of causation. In other words, what do the imaging studies show and are the findings related to the alleged injuries? Overall, the defendants in most cases that I have reviewed involve spine surgeons, neurologists, and emergency department physicians and are related to the outcome of spinal surgery, hypoxic brain injury, or a failure to diagnose and treat acute stroke in a timely fashion. While I may provide standard-of-care opinions in these matters, some states are restrictive with regard to the training and practice requirements to qualify as a standard-of-care expert. I do review a number of cases that involve standard of care in radiology or neurointervention; however, these are perhaps approximately 25% of my volume. Those cases typically involve allegations of damages caused by a missed finding or improper performance of a neurovascular or spinal intervention. Many of those involve the failure to detect and report a brain aneurysm or related findings such as subarachnoid hemorrhage or a small intracranial or head and neck tumor.

Alexander S. Mark's Perspective. I prefer not to testify against colleagues in my community. If I think that malpractice has been committed, I mention it to the attorney and suggest that they find another expert. I strongly discourage pursuing a claim if I think it has no merit, regardless of the outcome. I have not always been successful, and on 1 occasion, I was hired 2 years later by the opposing party.

Erin S. Schwartz's Perspective. As a pediatric neuroradiologist, most cases on which I am asked to serve as an expert witness involve so called "bad baby" cases, in which the request of the radiology expert is to assist with confirmation that the pattern of brain injury is indeed that typically associated with hypoxic-ischemic injury and to suggest the time interval when the injury most likely occurred. More commonly, I am contacted by attorneys representing a hospital or an obstetrician/obstetrical group but have been retained by the plaintiff's attorneys as well. Rarely, I have served as an expert in criminal matters, relating to abusive head trauma. Only once have I been asked by attorneys representing a radiologist to determine whether the radiology interpretation of a scan met the standard of care, and that was regarding the interpretation of a fetal brain MR imaging though I suspect I will be seeing more of these as use of fetal MR imaging proliferates.

What Type of Cases Are Involved?

When separating the cases into brain, spine, and head and neck, one finds that most ($n = 28$) are from the brain followed by the spine ($n = 15$) and the head and neck ($n = 7$). Of the brain cases, most were related to hypoxic-ischemic events ($n = 11$) and missed hemorrhages ($n = 10$). The spine cases were dominated by the results of and complications after surgery for degenerative disease ($n = 11$). In fact, of the 50 cases, many were related to surgical procedures ($n = 14$).

Of the 14 cases in which radiologists were named, 3 involved delayed diagnosis of aneurysm or subarachnoid hemorrhage and 2 involved delayed diagnosis of stroke. The remaining 9 cases did not have a theme.

Alexander S. Mark's Perspective. I have not participated in enough cases across the years to be able to come up with mean-

ingful statistical trends. The cases range from missed tumors, optic neuritis, and other miscellaneous conditions.

Erin S. Schwartz's Perspective. The overwhelming majority of my cases are related to the suspicion of perinatal hypoxic-ischemic injury; rarely, cases have involved perinatal spinal cord injury, alleged wrong-site brain surgery, and trauma.

Outcome of the Cases

As an expert witness, you are often not privy to the outcome of cases in which you provide an opinion, even those in which you are deposed. Often the cases are settled, but the settlement agreement prohibits disclosure of the sum of money exchanged. Additionally, the defense team will often settle a case for a low amount of money and call it a "win" because of avoidance of court costs. In some states (eg, California), if the amount settled is less than \$30,000, the report is not counted as a settlement against the individual physician as part of the accumulated totals that result in public disclosure. Thus, it is difficult to determine "winners" except in cases that go to trial. For the 15 cases in which I testified at trial, 6 were plaintiff verdicts, 7 were defendant verdicts, and 2 were declared mistrials and subsequently settled out of court.

Of course, for every case that goes to deposition or trial there are, on average in my estimation, 3–4 that never come to that in part because they are determined to be frivolous (by the plaintiffs' lawyers) or are dropped (on behalf of the defendants) or are settled beforehand because the issues are so obvious.

Gregg H. Zoarski's Perspective. It is my experience that matters that I have reviewed for the plaintiff are much more likely to proceed to deposition than defense matters, which are frequently resolved before or early along the discovery timeline. Approximately one-half of the plaintiffs' matters I have reviewed have gone to deposition. This is certainly because claims are researched and reviewed internally by good plaintiff firms, which typically employ paralegals and nurses specifically for that purpose, before reaching out to expert witnesses. Moreover, the need for a witness with particular expertise may not even be evident before the initiation of discovery. Defense firms, on the other hand, tend to be reactive and will often designate an expert witness as soon as possible after receiving a claim or even on receiving notice of a pending claim. Some defense claims that I review are not yet even in suit. Often a defense matter is resolved via settlement before my deposition, particularly when a legitimate standard-of-care claim is raised by the plaintiffs, causation is clear, and the only matter at issue is the amount of damages.

Alexander S. Mark's Perspective. I agree with Dr Yousem. I do not always receive follow-up, and the results may be covered by confidentiality agreements. Most of the time, I felt that my testimony contributed to providing a balanced perspective on the case. Only a very small number of cases end up in a trial. Most are settled.

Erin S. Schwartz's Perspective. In my experience, approximately 1 in every 10–20 cases reaches deposition and even fewer go to trial, typically due to cases settling, and I am not notified of the outcome.

DISCUSSION

Although most radiology societies and the American Medical Association advocate for physicians to perform expert witness review, like peer review for quality improvement, in an unbiased objective manner, there is a stigma associated with engaging in medicolegal testimony. This is particularly true under several conditions: 1) only serving on one side or the other, refusing to testify on behalf (usually) of plaintiffs or defendants ("hired guns"); 2) advertising one's services blatantly; 3) gouging the law firms/insurance companies with exorbitant fees; 4) taking positions at odds with convention; and 5) deriving a large proportion of one's income from experts' fees. Case law has established that it is reasonable for lawyers to receive information from experts on the following: 1) the percentage of gross income derived from expert witness testimony, 2) the cases in which they have testified in the previous 5 years in a manner that counsel can find such testimony in court documents, and 3) the name of the insurance company for testimony in personal injury cases in the previous 10 years.^{6,7} Most law firms prefer an expert who is actively engaged in the practice for which they are opining. In fact, some jurisdictions look askance at experts that show income from testimony that exceeds 30% of their annual total compensation. "Professional experts" who are no longer in the practice of medicine but who are available for medicolegal testimony may be challenged if they are not up-to-date on the standard of care currently practiced (or at the time of the incident occurrence).

Most expert witnesses will say that they find medicolegal testimony a learning experience. This derives from several factors: 1) identifying one's own blind spots; 2) learning some medicine beyond radiology through the issues discussed by the clinical experts; 3) understanding the litigation process, especially how slowly it moves through the system; 4) understanding how often cases are settled even if duty, breach of standard of care, causation, and damages are not firmly established because of the expense of litigating a case; and 5) learning how to use the correct terms so as to best portray your opinions. On the latter point, malpractice cases are civil cases in which the legal teams must show that the preponderance of evidence supports their claims. In that regard, the medicolegal expert is expected to testify at a level of "more likely than not." Therefore, one does not have to be absolutely certain that the mass is a tumor rather than an aneurysm: One merely has to believe that given the evidence, it is more likely to be a neoplasm. That assuredness is not necessarily how we practice medicine. We want to be 99% sure that we do not send a neurosurgeon in to biopsy a mass and find that it is an aneurysm.

The other epiphany one experiences as an expert witness is the dangers that other professions face in practicing medicine: knowing when to deliver a fetus in distress, whether to operate on someone who already has a myelomalacic spinal cord, which studies are absolutely needed before intervening on vascular cases, and how rapidly an emergency department patient must be triaged and treated. These are sometimes decisions that determine a good outcome versus a "negligence" case. The neuroradiology expert may be testifying on the extent of CNS injury in such cases, but seeing how precarious the situation may be when clinicians are making judgments in the practice of medicine can be eye-opening.

One also sees that there are just as many cases that are absolutely egregious as frivolous. The frivolous ones, because of the cost of litigation, often are dropped quickly. The egregious ones often proceed to court because the potential financial rewards to the plaintiff may be dramatic when presented to a jury. Most cases brought to trial have definite justification, and the expert witness is the key to enlightening the jury about the complex medical issues.

Final Comments

Gregg H. Zoarski's Perspective. Beyond developing an opinion regarding the issues of standard of care, causation, and damages as any particular matter may require, an expert witness assumes a valuable role as a teacher. The "class" includes attorneys on both sides of the matter as well as the parties and perhaps even other experts reviewing the matter. Maintaining this role avoids advocating for either the plaintiff or defense, and ultimately, if the matter proceeds to trial, the judge and jury join the classroom and rely on the education you provide to reach some very important decisions.

Alexander S. Mark's Perspective. I have found that the lawyers who consult me as an expert witness will usually follow my advice and not pursue frivolous lawsuits even when something was missed, as long as it did not result in an injury or if it did not change the outcome.

Erin S. Schwartz's Perspective. When called on to provide expertise regarding the neuroimaging features in pediatric patients, expert witnesses would do well to remember that the brains of premature and full-term infants are not simply small adult brains and

that the findings in perinatal hypoxic-ischemic injury do not necessarily have the same etiologies or follow the same temporal and imaging evolution as those from arterial thrombosis or embolism in older children and adults. Our opinions must be evidence-based and consistent, regardless of who hires us.

Disclosures: David M. Yousem—*UNRELATED: Expert Testimony*: medicolegal work; *Payment for Lectures Including Service on Speakers Bureaus*: ACR Education Center; *Royalties*: Elsevier for 5 books; *Travel/Accommodations/Meeting Expenses Unrelated to Activities Listed*: Radiological Society of North America 2018 as an awardee. Gregg H. Zoarski—*UNRELATED: Expert Testimony*: various, *Comments*: none specifically on behalf of medical product or pharmaceutical manufacturers. Erin S. Schwartz—*UNRELATED: Expert Testimony*: numerous legal firms.

REFERENCES

1. ACR Practice Parameter on the Physician Expert Witness in Radiology and Radiation Oncology. <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/ExpertWitness.pdf>. Accessed April 17, 2018
2. ACR Expert Witness Affirmation Statement. [http://appcenter.acr.org/ewa/\(S\(w0eqgug5hlj2tkcdhoyj2c4\)\)/default.aspx?ewa=true](http://appcenter.acr.org/ewa/(S(w0eqgug5hlj2tkcdhoyj2c4))/default.aspx?ewa=true). Accessed April 17, 2018
3. Pereira NP, Lewin JS, Yousem KP, et al. **Expert witnesses: neuroradiologists' perspectives.** *J Am Coll Radiol* 2014;11:984–88 CrossRef Medline
4. Pereira NP, Lewin JS, Yousem KP, et al. **Attitudes about medical malpractice: an American Society of Neuroradiology survey.** *AJNR Am J Neuroradiol* 2014;35:638–43 CrossRef Medline
5. AMA. Code of Medical Ethics Opinion 9.7.1. <https://www.ama-assn.org/delivering-care/medical-testimony>. Accessed April 17, 2018
6. Behler v. Hanlon, 199 F.R.D. 553 (D. Md. 2001)
7. Gutheil TG, Simon RI, Simpson S. **Attorneys' requests for complete tax records from opposing expert witnesses: some approaches to the problem.** *J Am Acad Psychiatry Law* 2006;34:518–22 Medline

The Top 20 Most Prolific Authors in the *American Journal of Neuroradiology*: What Is Their Impact?

J.H. Huntley, J. Pakpoor, and D.M. Yousem

ABSTRACT

BACKGROUND AND PURPOSE: Many articles that are relevant to patient care but published in radiology journals may escape notice by clinicians. We sought to determine how often the 20 most prolific *American Journal of Neuroradiology* (AJNR) authors from 2013 to 2017 published in clinical journals and the extent to which their articles were disseminated into the clinical literature.

MATERIALS AND METHODS: We counted all authors' first- or senior-authored articles in the AJNR from 2013 to 2017 to identify the 20 most prolific authors in AJNR. We searched for these 20 authors' total articles from 2013 to 2017 to determine which were published in radiology or clinical journals and the number of citations received from radiology and clinical journals. Authors were sorted into quartiles according to these metrics, and other descriptive statistics were performed.

RESULTS: The top 20 AJNR authors contributed to 1463 articles during 5 years, including 711 (48.6%) in radiology and 752 (51.4%) in clinical journals. These articles were cited 15,857 times, including 4659 (29.3%) by articles in radiology journals. The more prolific authors published in clinical journals more often (Spearman $\rho = 0.65$, $P = .002$) and were cited more ($\rho = 0.42$, $P = .07$). Articles published in clinical journals were cited more often (mean, 12.3 clinical, 9.3 radiology general versus 8.7 in AJNR), and whether published in radiology or clinical journals, they were cited more frequently by clinical journals.

CONCLUSIONS: Regardless of where it is published, radiology research is disseminating into the clinical realm. Radiology articles published in clinical journals are cited more often than those published in radiology journals.

ABBREVIATIONS: AJNR = *American Journal of Neuroradiology*

The Impact Factors of many radiology journals have increased during the past decade, especially among cardiac imaging and neuroradiology journals.¹ Because of this growth, researchers in radiology may think that publishing their best material in radiology journals is sufficient to reach the wider medical community. A possible drawback of publishing one's articles solely in the radiology literature, however, is that the journals may be outside the routine purview of referring clinicians not in academia and so may have limited influence in broader patient care settings.

For example, how would a private practice general practitioner learn about the appropriateness criteria for MR neurography published in the *American Journal of Neuroradiology* (AJNR)? Such an article may totally escape notice by nonradiologists.

Nonetheless, its message is actually more apropos to the clinical literature. When radiologists exclusively submit articles to their own journals, could they be reducing the impact of their work? A better method may be for radiology researchers to consider whether their work is more relevant to radiologists or nonradiologists and to publish their work in an appropriate journal.

Because neuroradiology is one of the fastest growing fields in imaging science, we sought to evaluate the publishing characteristics of the top 20 contributors to the AJNR, as a sample from one of the most popular clinically focused journals of the specialty. We set out to answer the following questions: 1) To what extent are these neuroradiology authors publishing articles only in radiology journals? 2) Are these articles in radiology journals being cited only by radiologists in radiology journals, or do they disseminate into the clinical literature? 3) Are radiology articles published in clinical journals cited more than those published in radiology journals? 4) How, if at all, do the publishing characteristics of the more prolific of these top 20 authors (ie, the ultraprolific) differ from those of the less prolific in the AJNR top 20? and 5) How do the top 20 authors differ from the next 20 AJNR authors (numbers 21–40) in terms of education/training, funding, and country of origin?

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Table 1: The top 20 AJNR authors sorted into quartiles according to 3 metrics^a

	≥75% (No.) (%)	50%–74% (No.) (%)	25%–49% (No.) (%)	<25% (No.) (%)
Articles published in radiology journals	6 (30)	7 (35)	7 (35)	0 (0)
First or senior author				
All articles (radiology and nonradiology)	1 (5)	12 (60)	6 (30)	1 (5)
Articles in radiology journals	5 (25)	12 (60)	3 (15)	0 (0)
Articles in nonradiology journals	0 (0)	8 (40)	8 (40)	4 (20)
Articles in AJNR	11 (55)	6 (30)	3 (15)	0 (0)
Cited by articles published in radiology journals				
All articles (radiology and nonradiology)	0 (0)	2 (10)	12 (60)	6 (30)
Articles in radiology journals	0 (0)	7 (35)	12 (60)	1 (5)
Articles in nonradiology journals	0 (0)	1 (5)	6 (30)	13 (65)
Articles in AJNR	1 (5)	5 (25)	13 (65)	1 (5)

^a The top 20 authors were sorted into 4 quartiles (≥75%, 50%–74%, 25%–49%, <25%) based on 3 metrics: the percentage of their articles that appeared in radiology journals, the percentage of their articles for which they were first or senior author, and the percentage of citations they received from articles in radiology journals. We determined the latter 2 metrics using all of the top 20 authors' articles, only their articles in radiology journals, only their articles in nonradiology journals, and only their articles in AJNR.

MATERIALS AND METHODS

This study did not comprise human subject research and therefore did not require institutional review board approval.

Data Collection

We extracted author information from all articles published in the AJNR (www.ajnr.org) between January 1, 2013, and December 31, 2017. Only original research articles (including clinical trials) and review articles were included in this study. We then totaled each author's first- and senior-authored publications in AJNR to determine the top 20 most prolific first/senior AJNR authors. Google searches of author names were performed to establish each author's primary institution, education/training (MD versus PhD versus MD, PhD), and country of origin (United States versus non-United States). We also determined the next 20 (numbers 21–40) AJNR authors and extracted the same data for them as well.

Next, we used PubMed (www.pubmed.gov) to search the MEDLINE data base for all articles published by these 20 authors in any journal between January 1, 2013, and December 31, 2017. For each article, we extracted the complete author list, year of publication, and publishing journal. For the articles in the AJNR from both the top 20 authors and authors 21–40, we also recorded whether each study was funded by the US government, funded by an entity other than the US government, or not funded at all. We then determined how many of these articles were published in a radiology (diagnostic or interventional) or clinical/nonradiology journal and whether the top 20 AJNR authors in question were in the first, last, or middle position of the author list. Journals on the Scimago Journal and Country Rank Web site (scimagojr.com) under the Radiology, Nuclear Medicine, and Imaging categories (<https://www.scimagojr.com/journalrank.php>) that focused primarily on radiology and imaging topics were considered to be radiology journals for analysis purposes.

On April 4, 2018, we used the Web of Science² to identify the citation counts of articles authored by the top 20 AJNR contributors and determined whether the citing articles were published in a radiology or nonradiology journal. In instances in which an article was not available on Web of Science, Google Scholar was used instead (91/1463, 6.2% of articles). The Scopus citations data base³ was queried to extract self-citation data for each of the top 20

AJNR authors as well as the h-index of each of the top 20 AJNR authors and AJNR authors 21–40.

In instances in which authors had similar names or an author used differing attributions (eg, middle initial or an accented letter), we considered the topic and field of the article, the publishing journal, and the author's institution to determine the author identity and remove duplicates when applicable.

Data Analysis

Descriptive statistics were performed using R, Version 3.4.4⁴ and Excel 2016 (Microsoft, Redmond, Washington). Spearman rank correlation tests were performed when examining the relationship of 2 variables, and Mann-Whitney *U* tests were used when determining whether 2 samples differed significantly. All tests were performed at 95% confidence ($\alpha = .05$).

We sorted individual authors into sets of quartiles (≥75%, 50%–74%, 25%–49%, <25%) according to 3 separate metrics based on their published articles: 1) the proportion of their articles published in radiology journals, 2) the proportion of citations their articles received from articles in radiology journals, and 3) the proportion of their articles in which they were the first or senior author. For each author, we calculated the second and third metrics for the following: 1) all articles, 2) articles published in radiology journals, 3) articles published in nonradiology journals, and 4) articles published in the AJNR (Table 1). When analyzing publications of individual authors, articles in which >1 of the top 20 authors appeared on the author list were included in each author's respective set of publications (ie, if 2 of the top 20 authors were authors on the same article, that article would be included in analyses of both authors).

We also evaluated how the more prolific top 20 authors compared with the less prolific top 20 authors. In 1 analysis, we ran a correlation test between each author's total number of published articles and the average number of times their articles were cited. In another analysis, we performed a correlation test between each author's total number of published articles and the percentage of his or her articles published in clinical (nonradiology) journals.

Last, we calculated the following 5 values for all 20 authors collectively: 1) the average number of citations each article received; 2) the average number of citations from articles in radiology journals per article; 3) among articles published in radiology journals, the percentage of citations from articles also in radiology journals; 4) among articles published in AJNR, the percentage of citations from articles in radiology journals; and 5) among articles published in nonradiology journals, the percentage of citations from articles in radiology journals.

RESULTS

RESULTS

Descriptive Statistics

The top 20 authors published 218 unique articles in AJNR between January 1, 2013, and December 31, 2017 as first or senior

authors, occupying 252 first or last author positions for an average of 2.52 articles per author per year (total 5-year range, 8–30). They represented about 0.8% of all *AJNR* authors yet occupied 6.8% of first or senior author positions of all *AJNR* articles during that time. The top 20 authors included contributors from the Mayo Clinic (4 authors), Duke University (2 authors), Stanford University (2 authors), and 12 other institutions (Table 2). Of the top 20 authors, 17 had an MD degree only (or equivalent in their country), 1 had a PhD degree only, and 2 had MD, PhDs. Thirteen (65%) of these authors had a primary affiliation with an institution in the United States. The next 20 authors (numbers 21–40 in the *AJNR*), in comparison, included more authors with a PhD degree. Included in this group were 13 authors with an MD only, 1 with a PhD only, and 6 with both an MD and PhD. Twelve (60%) of this group of authors were primarily affiliated with an institution in the United States.

Top 20 Authors' Articles in All (Radiology and Nonradiology/Clinical) Journals

In all journals from 2013 to 2017, the top 20 authors contributed to 1463 unique original investigations, including clinical trials, or reviews (occupying 1724 authorship positions), with 711 (48.6%) in radiology journals and 752 (51.4%) in nonradiology journals. These articles were cited by 15,857 articles in total (mean citations per article, 10.8; median, 4), 4659 (29.4%) of which were in radi-

ology journals and 11,198 (70.6%) in nonradiology journals. Articles in clinical journals were cited an average of 12.3 times per article. The distribution of citations is highly skewed to the right (Pearson skewness coefficient = 0.49). More than half (52.8%) of articles were cited ≤ 4 times, and those cited ≤ 40 times accounted for $>95\%$ of all published articles (Figure). One article was cited 1283 times, accounting for 8.1% of all citations. While review articles accounted for only 19.3% (280/1463) of articles, they were cited significantly more, on average, than original investigations when clinical trials were not included (13.5 versus 8.0, $P < .001$). Only 124 articles detailing clinical trials were included in the dataset. These articles were cited an average of 29.1 times each, largely due to a select few articles being very highly cited. Nevertheless, clinical trial articles did not receive a significantly different number of citations, on average, than review articles ($P = .85$). On the other hand, clinical trial articles did receive a significantly higher number of citations than non-review, non-clinical trial original investigations ($P < .001$).

There was a positive correlation between the total number of articles an author published and the average number of times their articles were cited (Spearman $\rho = 0.42$, $P = .07$). More prolific authors were significantly more likely to publish in non-radiology journals ($\rho = 0.65$, $P = .002$) and to publish a smaller proportion of their articles in *AJNR* ($\rho = -0.86$, $P < .001$). The top 10 *AJNR* authors had an average h-index of 37.5 ± 14.3 (range, 43), whereas authors 11–20 had an average h-index of 32.4 ± 18.0 (range, 48) ($P = .43$). The top 20 *AJNR* authors did not have a significantly different average h-index than *AJNR* authors 21–40 (mean, 35.0 ± 16.1 versus mean, 34.2 ± 17.7) ($P = .79$). Only 8.3% of the citations from the top 20 authors were self-citations.

Six of the top 20 authors (30%) published at least 75% of their articles in radiology journals, 7 (35%) published between 50% and 74% of their articles in radiology journals, and 7 (35%) published between 25% and 49% of their articles in radiology journals. No author published $<25\%$ of their articles in radiology journals (Table 1).

When considering articles that the top 20 authors published in all journals (radiology and nonradiology), no author received $\geq 75\%$ of their citations from articles in radiology journals (ie, at least 25% of the articles that cited them were in nonradiology journals). Only 2 authors (10%) received 50%–74% of their cita-

tions from articles in radiology journals, with most (12/20, 60%) receiving 25%–49% of their citations from articles in radiology journals. The remainder (6/20, 30%) received $<25\%$ of their citations from articles in radiology journals (Table 1).

Only 1 top 20 author (5%) was first or senior author for $\geq 75\%$ of his or her articles. Most authors (12/20, 60%) were first or senior author for 50%–74% of their articles, while nearly all the rest (6/20, 30%) were first or senior author for 25%–49% of their articles. One author (5%) was the first or senior author for $<25\%$ of his or her articles (Table 1).

Table 2: Primary affiliations of the top 20 *AJNR* authors

Institution	No. of Authors
Mayo Clinic	4
Duke University	2
Stanford University	2
George Washington University	1
Harvard University	1
Hofstra University	1
Johns Hopkins University	1
Seoul National University	1
University at Buffalo	1
University of Amsterdam	1
University of Montréal	1
University of Paris-Sud	1
University of Reims Champagne-Ardenne	1
University of Toronto	1
Uppsala University	1

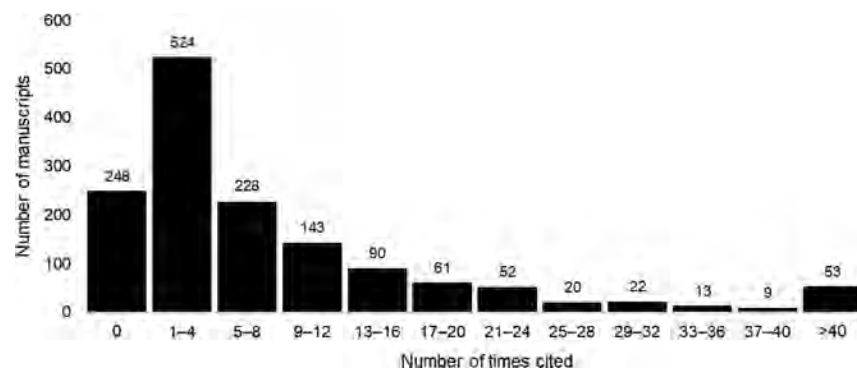


FIGURE. A histogram of how many times all articles from the top 20 *AJNR* authors were cited. Most (52.8%) articles were cited ≤ 4 times, and 17.0% were not cited at all. Articles that were cited >40 times are combined into a single bin.

Top 20 Authors' Articles in Radiology Journals

The 711 articles published in radiology journals were cited 6577 times in total (mean citations per article, 9.3). When we considered only his or her articles published in radiology journals, no author (0%) received at least 75% of their citations from articles in radiology journals, 7 (35%) received between 50% and 74% of their citations from articles in radiology journals, 12 (60%) received between 25% and 49% of their citations from articles in radiology journals, and only 1 (5%) received <25% of their citations from articles in radiology journals (Table 1).

Most interesting, articles published in radiology journals received slightly fewer citations, on average, than articles published in clinical, nonradiology journals (9.3 versus 12.3, $P = .16$), albeit not to a significant degree.

Top 20 Authors' Articles in AJNR

The top 20 AJNR authors contributed as first, middle, or senior author to a total of 272 unique original investigations or reviews in AJNR during the study period. These articles were cited a total of 2364 times (mean citations per article, 8.7). When we considered only the articles published in AJNR, 1 author (5%) received at least 75% of his or her citations from articles in radiology journals, 5 (25%) received between 50% and 74% of their citations from articles in radiology journals, 13 (65%) received between 25% and 49% of their citations from articles in radiology journals, and only 1 (5%) received <25% of his or her citations from articles in radiology journals (Table 1).

When we considered studies from the top 20 authors, roughly one-third (84/272, 30.9%) recorded receiving funding only by the US government (28/272, 10.3%), by some entity other than the US government (46/272, 16.9%), or by both the US government and some other entity (10/272, 3.7%). Funded studies of the top 20 authors received significantly more citations than unfunded studies (11.5 versus 7.4, $P < .001$). In comparison, a higher percentage of studies from AJNR authors 21–40 received funding; of these 34.0% (66/194) of funded studies, 15.5% (30/194) were funded only by the US government; 12.4% (24/194), only by an entity other than the US government; and 6.2% (12/194), by both the US government and some other entity.

Additional Analyses for All Top 20 Authors

The top 20 AJNR authors received an average of 10.8 (median, 4) citations per article during the study period. Of the 10.8 citations per article, only 3.2 (29.4%) were from articles in radiology journals. When we considered only the articles from these authors published in a radiology journal, however, 43.0% of the citations received were from articles also in radiology journals. Articles that were published in nonradiology journals received only 19.7% of their citations from articles published in radiology journals. For articles published in AJNR, 41.2% of the citations received were from articles in radiology journals. In summary, most of the citations that the top 20 AJNR authors received for their publications in any journal, in radiology journals, in nonradiology journals, and in the AJNR were from articles in clinical, nonradiology journals.

DISCUSSION

In this study, we identified several interesting features about the publishing characteristics of the top 20 most prolific authors in AJNR from 2013 to 2017. Overall, these authors averaged between 2 and 3 articles published in AJNR per year as first or senior author, with the most prolific author publishing nearly 4 times as many articles as the twentieth most prolific author (30 articles versus 8 articles). When we considered all articles written by these authors, nearly half (48.6%) were published in radiology journals and half (51.4%) in nonradiology journals. More than half of the authors, however, published more than half of their articles in radiology journals and received less than half of their citations from articles in radiology journals. Finally, we found that most of these top authors were first or senior authors on more than half of their articles published in all journals (radiology and nonradiology).

One of our most interesting analyses revealed that when the top 20 authors published in radiology journals, they were cited by articles in radiology journals more than twice as often as when they published in nonradiology journals (43.0% versus 19.7%). This disparity in citations between publishing in radiology and nonradiology journals may suggest that radiology researchers who produce articles with high clinical relevance should be publishing in nonradiology journals if they want to capture the attention of clinicians more broadly. We note, however, that all articles in radiology journals, clinical (nonradiology) journals, and AJNR specifically were cited more often by articles in clinical journals than in radiology journals. Therefore, even if radiology researchers continue to publish exclusively or primarily in radiology journals, their message will still be distributed to clinicians—though perhaps not as widely as if their work appeared in a nonradiology journal. In any case, the radiologist's message is getting out.

Comparing the publishing habits of the more prolific top 20 AJNR authors with those of the less prolific top 20 authors showed that more prolific authors are cited more often on average ($p = 0.42$, $P = .07$). This finding may simply result from publishing more often. If authors publish more often, they are more likely to produce a "hit" that boosts the average number of times they are cited.^{5,6} While these data indicate that the more prolific authors among the top 20 are cited more often than the less prolific ones, our h-index analyses suggest that the top 20 as a group are roughly equal to authors 21–40 on this metric. Thus, there may be 2 broad categories of authors at play: One is very prolific overall and, as expected, publishes a smaller proportion of their articles in AJNR, and the other is less prolific overall and publishes a larger proportion of their articles in AJNR. Authors in these 2 categories seem to be interspersed throughout the top 40 authorship ranks in AJNR so that the authors with the highest number of AJNR publications are not simply ultraprolific researchers who publish a small proportion of their articles in AJNR, nor are they only researchers who publish a large proportion of their articles in AJNR—there is a mix of the 2.

We also found that authors who are more prolific overall published a significantly higher proportion of their articles outside of radiology journals ($p = 0.65$, $P = .002$). One explanation for this finding may be that when the top neuroradiology researchers publish outside of radiology, their work tends to appear in higher

impact journals.⁷ If the most proliferative authors we analyzed publish in high-impact nonradiology journals more commonly than the less proliferative authors, they would likely receive more citations on average. While we did not assess the Impact Factors of the journals in which the top 20 *AJNR* authors published, we did find that articles published in nonradiology journals were cited slightly more often overall than articles published in radiology journals and in the *AJNR* specifically (12.3 versus 9.3 versus 8.7).

Radiology is becoming a more interdisciplinary field. A study published in 2006 compared articles in 3 large radiology journals during 2 periods (1992–1993 and 2002–2003), finding that primary authors were less likely to be radiologists.⁸ Our findings in this study corroborate this notion of increasing diversification in radiology: The top 20 *AJNR* authors published nearly half of their articles from 2013 to 2017 in radiology journals, leaving the other half distributed primarily across clinical journals. Another study that analyzed where radiologists publish similarly found that roughly one-third of articles with a radiologist as a first author were published in nonradiology journals.⁷ If this publishing pattern is consistent among radiology researchers in general, there is a sizable body of radiology literature that appears outside radiology journals. In fact, Lehman et al (2014)⁹ found that nearly 90% of articles about intracranial imaging of uncommon diseases appeared in clinical publications. This phenomenon is not unique to radiology; researchers publishing in journals outside their “core” field have been described in several other fields as well, including occupational therapy,¹⁰ medical informatics,¹¹ family medicine,¹² and nephrology.¹³ This evidence all points to the same conclusion: Because radiology research is increasingly being published in journals that aim to reach the broader medical community, radiologists may wish to also regularly include nonradiology journals in their reading.

Several limiting factors may have influenced our findings. First, articles published earlier in the study period had more time to be cited by other authors,¹⁴ but this applied to all 20 top authors and we stopped looking at articles published after December 31, 2017. Some articles were also published less than a year before the data analysis. While this likely resulted in articles being cited less often than if we had chosen an earlier timeframe, we expect our other findings to be largely unaffected. Another study that analyzed citation counts of immunology and surgical journals found that a median of 17.6% of articles in immunology journals were uncited and a median of 32.8% of articles in surgical journals were uncited.¹⁵ In comparison, 17.0% of the articles we analyzed were uncited. These authors also found a median citation count for original articles (3 for immunology articles and 1 for surgical articles) that is comparable with what we found (4 for all articles). We also did not adjust our results for self-citation. We did, however, determine that the self-citation rate among the top 20 authors was roughly 8%—a relatively low rate¹⁶ of self-citation that is unlikely to significantly impact our conclusions. The type of article that each author published most frequently may have also affected our results. Because reviews tend to be cited more often than original investigations¹⁷ (in our data, 13.5 versus 8.0, $P < .001$), authors who write more reviews would likely receive more citations than authors who do not write as many.

CONCLUSIONS

The top 20 *AJNR* authors publish nearly equally in radiology and nonradiology journals. Their work, however, is cited more commonly by articles in clinical journals than by articles in radiology journals, no matter where that original article was published. A radiology article published in a clinical journal tends to have more citations than one published in a radiology journal and the *AJNR*. This suggests that dissemination of radiology research in the clinical realm is progressing.

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REFERENCES

1. Rosenkrantz AB, Ayoola A. **The Impact Factor of radiological journals: associations with journal content and other characteristics over a recent 12-year period.** *Acad Radiol* 2016;23:661–68 [CrossRef Medline](#)
2. Thomson Reuters. Web of Science. <https://www.webofknowledge.com/>. Accessed June 15, 2018
3. Scopus. <https://www.scopus.com/>. Accessed June 20, 2018
4. R Core Team. R: A Language and Environment for Statistical Computing. <https://www.R-project.org/>. Accessed June 15, 2018
5. Michalska-Smith MJ, Allesina S. **And, not or: quality, quantity in scientific publishing.** *PLoS One* 2017;12:e0178074 [CrossRef Medline](#)
6. Sandström U, van den Besselaar P. **Quantity and/or quality? The importance of publishing many papers.** *PLoS One* 2016;11:e0166149 [CrossRef Medline](#)
7. Yun EJ, Yoon DY, Kim BY, et al. **Where do radiologists publish their work? A comparative analysis of publications by radiologists in nonradiology journals in 2000 and 2010.** *AJR Am J Roentgenol* 2013; 200:W560–65 [CrossRef Medline](#)
8. Ray CE Jr, Gupta R, Blackwell J. **Changes in the American interventional radiology literature: comparison over a 10-year time period.** *Cardiovasc Intervent Radiol* 2006;29:599–604 [CrossRef Medline](#)
9. Lehman VT, Doolittle DA, Hunt CH, et al. **Intracranial imaging of uncommon diseases is more frequently reported in clinical publications than in radiology publications.** *AJNR Am J Neuroradiol* 2014;35:45–48 [CrossRef Medline](#)
10. Reed KL. **Mapping the literature of occupational therapy.** *Bull Med Libr Assoc* 1999;87:298–304 [Medline](#)
11. Sittig DF. **Identifying a core set of medical informatics serials: an analysis using the MEDLINE database.** *Bull Med Libr Assoc* 1996;84: 200–04 [Medline](#)
12. Ingram TG. **A cross-sectional analysis of family medicine publications in the indexed medical literature.** *Fam Med* 1992;24:303–06 [Medline](#)
13. Garg AX, Iansavichus AV, Kastner M, et al. **Lost in publication: half of all renal practice evidence is published in non-renal journals.** *Kidney Int* 2006;70:1995–2005 [CrossRef Medline](#)
14. Royle S. The Great Curve: Citation distributions. *Quantixed*. September 25, 2015. <https://quantixed.org/2015/09/25/the-great-curve-citation-distributions/>. Accessed May 1, 2018
15. Weale AR, Bailey M, Lear PA. **The level of non-citation of articles within a journal as a measure of quality: a comparison to the Impact Factor.** *BMC Med Res Methodol* 2004;4:14 [CrossRef Medline](#)
16. Clarivate Analytics. Journal Self-citation in the Journal Citation Reports: Science Fiction (2002). <https://clarivate.com/essays/journal-self-citation-jcr/>. Accessed June 15, 2018
17. Bhandari M, Busse J, Devereaux PJ, et al. **Factors associated with citation rates in the orthopedic literature.** *Can J Surg* 2007;50: 119–23 [Medline](#)

Shape Features of the Lesion Habitat to Differentiate Brain Tumor Progression from Pseudoprogression on Routine Multiparametric MRI: A Multisite Study

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ABSTRACT

BACKGROUND AND PURPOSE: Differentiating pseudoprogression, a radiation-induced treatment effect, from tumor progression on imaging is a substantial challenge in glioblastoma management. Unfortunately, guidelines set by the Response Assessment in Neuro-Oncology criteria are based solely on bidirectional diametric measurements of enhancement observed on T1WI and T2WI/FLAIR scans. We hypothesized that quantitative 3D shape features of the enhancing lesion on T1WI, and T2WI/FLAIR hyperintensities (together called the lesion habitat) can more comprehensively capture pathophysiologic differences across pseudoprogression and tumor recurrence, not appreciable on diametric measurements alone.

MATERIALS AND METHODS: A total of 105 glioblastoma studies from 2 institutions were analyzed, consisting of a training ($n = 59$) and an independent test ($n = 46$) cohort. For every study, expert delineation of the lesion habitat (T1WI enhancing lesion and T2WI/FLAIR hyperintense perilesional region) was obtained, followed by extraction of 30 shape features capturing 14 “global” contour characteristics and 16 “local” curvature measures for every habitat region. Feature selection was used to identify most discriminative features on the training cohort, which were evaluated on the test cohort using a support vector machine classifier.

RESULTS: The top 2 most discriminative features were identified as local features capturing total curvature of the enhancing lesion and curvedness of the T2WI/FLAIR hyperintense perilesional region. Using top features from the training cohort (training accuracy = 91.5%), we obtained an accuracy of 90.2% on the test set in distinguishing pseudoprogression from tumor progression.

CONCLUSIONS: Our preliminary results suggest that 3D shape attributes from the lesion habitat can differentially express across pseudoprogression and tumor progression and could be used to distinguish these radiographically similar pathologies.

ABBREVIATIONS: C = curvedness; Gd = gadolinium; K_T = measure of the total curvature; PsP = pseudoprogression; RANO = Response Assessment in Neuro-Oncology; S = sharpness; SI = shape index; SVM = support vector machine; TP = tumor progression

The treatment of malignant brain tumors relies heavily on surgical resection and chemoradiation therapy, followed by at least 6 months of adjuvant temozolomide.¹ This treatment regi-

men has been shown to improve overall prognosis in patients with brain tumors. However, a significant challenge postchemoradiation is the presence of radiation-induced side effects, such as pseudoprogression (PsP), which mimic the appearance of tumor progression on posttreatment MR imaging. PsP is an early-delayed benign treatment effect that occurs in approximately one-third of all malignant brain tumors and often stabilizes without further treatment.² In the absence of reliable imaging tools to distinguish PsP from tumor progression,³ patients are typically kept on a “wait-and-watch” protocol, causing increased patient anxiety regarding their disease outcome and, in some cases, leading to un-

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necessary surgical interventions in patients with PsP with risks of morbidity. There is hence a significant clinical need to accurately differentiate PsP from true progression to improve patients' treatment management.

The Response Assessment in Neuro-Oncology (RANO) criteria⁴ are the currently established criteria for posttreatment response assessment in malignant glioblastomas. The most recent RANO criteria uses semiquantitative bidirectional diametric measurements of enhancing tumor on gadolinium contrast-enhanced T1WI and T2/FLAIR changes to stratify posttreatment lesions as PsP or tumor progression. However, these semiquantitative measurements result in interreader variability⁵ and overestimation of lesion volume,⁶ confounding reliable differentiation of PsP from tumor progression. Advanced imaging modalities such as perfusion imaging,⁷ MR spectroscopy,⁸ and diffusion-weighted imaging⁹ have shown some promise in distinguishing tumor progression from posttreatment radiation effects. They, however, are limited in clinical applicability because they are not universally available and are often difficult to reproduce.¹⁰

Recently, "radiomics" (computational feature extraction approaches) have been used in conjunction with routinely available MR imaging sequences for survival prediction and response assessment in brain tumors.^{11,12} These radiomic approaches capture higher order quantitative measurements (eg, co-occurrence matrix homogeneity, neighboring gray-level dependence matrix) for modeling macro- and microscale textural and morphologic attributes within the lesion area and drawing associations of these features with clinical outcomes. While a few studies^{13,14} have explored distinguishing radiation necrosis (a delayed radiation-induced effect) from tumor recurrence using radiomic texture analysis, relatively little work has focused on distinguishing PsP from brain tumor recurrence, potentially on account of the poorly understood pathophysiology of PsP.^{3,15}

Histopathologically, tumor progression is characterized by the presence of tumor cells, increased cellularity, and vascular proliferation and is known to morphologically alter white matter structure in complex ways due to infiltration, displacement, and blood-brain barrier disruption.¹⁶ Furthermore, some studies have linked the presence of tumor progression with corpus callosum involvement and subependymal spread on MR imaging.¹⁷ Evidence also suggests that a pronounced local inflammatory tissue response may develop in patients with PsP due to inherent and radiation therapy-induced capillary permeability, leading to more pronounced peritumoral brain edema.¹⁸ These changes in the pathophysiology of tumor progression and PsP are likely seen as morphometric changes in the lesion enhancement on T1-weighted MR imaging as well as perilesional T2WI/FLAIR hyperintensities but may not be appreciable using bidirectional measurements obtained from the RANO criteria alone.

In this work, we attempted to evaluate the role of 3D shape features in enhancing lesion and perilesional regions on T1WI and T2WI/FLAIR hyperintensities to improve the differentiation of PsP from tumor progression on routine MR imaging. We hypothesized that uneven tumor growth due to irregular and aggressive tumor infiltration will likely induce shape and surface differences in both the enhancing lesion and the T2WI/FLAIR hyperintense perilesional components¹⁸⁻²⁰ (together called the

"lesion habitat"); and the radiomic shape differences in the lesion habitat will likely be different between tumor progression and PsP on routine gadolinium-enhanced T1WI (Gd-T1WI), T2WI, and FLAIR. To our knowledge, this is the first attempt at distinguishing PsP from tumor progression through jointly interrogating shape features of intratumoral and peritumoral regions from posttreatment MR imaging. We first define a tumor habitat²¹ by delineating 2 compartments for every posttreatment lesion: a hyperintense enhancing lesion on Gd-T1WI, and T2WI/FLAIR hyperintense perilesional components constituting both edema and the nonenhancing lesion. We then compute changes in "local" surface and "global" shape radiomic features individually from each of these delineated enhancing lesion and T2WI/FLAIR hyperintense perilesional regions to capture morphometric differences between tumor progression and PsP. We then identify the most differentiating features from each compartment obtained on the training cohort and evaluate their efficacy on the test cohort. Additionally, we also consider features combined across both compartments of the lesion habitat to distinguish PsP and tumor progression.

MATERIALS AND METHODS

Study Population

This institutional review board-approved and Health Insurance Portability and Accountability Act-compliant study comprised independent training and test cohorts of patients with glioblastoma from 2 different institutions: Cleveland Clinic and Dana-Farber/Brigham and Women's Cancer Center. The 2 cohorts were identified by performing a retrospective review of all patients with brain tumors who underwent chemoradiation treatment using the Stupp protocol at the respective institutions and had an enhancing lesion within 3 months of treatment. Patients who were prescribed bevacizumab or any other treatment after receiving the standard-of-care treatment were excluded from the study. The training cohort consisted of 59 MR images obtained from the Cleveland Clinic, where 38 tumor-progression cases and 21 PsP cases were confirmed for disease presence using the criteria provided below. All 59 cases in the training cohort were *IDH* wild-type and were acquired from a 1.5T scanner. The testing cohort was obtained from Dana-Farber/Brigham and Women's Cancer Center and included 46 cases in which 33 tumor progression cases and 13 PsP cases were confirmed for disease presence using criteria similar to that used for the training cohort. Informed consent was obtained for all patients involved in the study. Forty-two cases in the test cohort were *IDH* wild-type, whereas the remaining 4 were *IDH* mutant. For T2WI and FLAIR scans, slice thickness was 4 mm; slice gap, 0.8 mm; and FOV, 210 mm, whereas for MPRAGE, the volumetric acquisition had a voxel size of $1 \times 1 \times 1$ mm. The acquisition matrices for T2, FLAIR, and MPRAGE scans were 224×320 , 168×256 , and 256×256 , respectively.

Table 1 summarizes the demographics for this study population.

Confirmation for Disease Presence

Our inclusion criteria consisted of the following: 1) patients treated with standard-of-care chemoradiation with no additional follow-up treatment; 2) availability of all 3 routine MR imaging sequences (Gd-T1WI, T2WI, FLAIR); 3) MR images with diag-

Table 1: Summary of study population across the training and test cohorts

Characteristic	Training	Testing
No. of patients	59	46
Women	20	16
Men	39	30
Mean age (yr)	60.6	55.6
Age range (yr)	26–74	25–76

nostic image quality as determined by collaborating radiologists; and 4) patients with posttreatment enhancing lesions with >5 mm of rim enhancement and the availability of diagnostic reads of the lesion as belonging to PsP or tumor progression following disease confirmation. Confirmation for progression or pseudoprogession was obtained by either histologic analysis in some cases or follow-up imaging. Continued enhancing tumor size increase on follow-up MR imaging within the subsequent 6-month period was considered progression, while reduction in tumor size or growth within the subsequent 6-month period was considered pseudoprogession.

Preprocessing

For every patient study, the 3 MR imaging sequences, Gd-T1WI, T2WI, and FLAIR, were coregistered to a T1-weighted brain atlas (Montreal Neurological Institute 152) using 3D Slicer (<http://www.slicer.org>). Registering every study to an average standard brain atlas allowed us to perform reliable cross-patient shape analyses across the 2 sites. Bias field correction was then conducted using a nonparametric nonuniform intensity normalization technique.²² Skull stripping was finally performed via the skull-stripping module in 3D Slicer.²³

Segmentation of Lesion Habitat

Segments were conducted for every MR imaging slice with >5 mm of rim enhancement as recognized by an expert radiologist (V.S.). Every lesion was annotated into 2 regions: an enhancing lesion and a T2WI/FLAIR hyperintense perilesional component. T1WI scans were used to delineate the enhancing lesion, while both T2WI and FLAIR scans were used to annotate the T2WI/FLAIR hyperintense perilesional compartment. Scans were manually annotated across contiguous slices by 2 experienced board-certified neuroradiologists with >10 years of experience, V.H. and V.S. (1 for each site), via a hand-annotation tool in 3D Slicer. All segmentations of MR images were conducted on a standard desktop computer, with 24 GB RAM, and GT 730 GPU (NVIDIA, Santa Clara, California), with a Cintiq 22HD touchscreen monitor (Wacom, Saitama, Japan).

Feature Extraction

Global Features. Fourteen global shape features were extracted from the enhancing lesion and T2WI/FLAIR hyperintense perilesional compartments for each subject. These features aim to characterize the global contour of the ROI, such as volume (number of voxels in the ROI), major and minor axes (longest and shortest diameters of the shape), and elongation (ratio between major and minor axes of the ROI). Extracted features are based on an Insight Segmentation and Registration Toolkit (ITK) implementation

(www.itk.org). Descriptions of the 14 global shape features are provided in the On-line Table and Appendix.

Local Features. The local features were mainly derived from curvature measures computed for the surface of every 3D segmented compartment (enhancing lesion or T2WI/FLAIR hyperintense perilesional regions) on a voxel basis. An isosurface is first constructed from each 3D compartment, followed by computing the first and second fundamental forms of the surface. Gaussian and mean curvatures are computed from these fundamental forms for each voxel.²⁴ Four measures that capture the local curvature changes are then derived from Gaussian and mean curvatures: curvedness (C), sharpness (S), shape index (SI), and total curvature (K_T).

For each segmented compartment, the mean, median, kurtosis, and SD of curvedness, shape index, sharpness, and total curvature were extracted (ie, a total of 16 local features were extracted per compartment per subject). Computations were implemented using in-house software implemented in Matlab R2016a platform (MathWorks, Natick, Massachusetts). A detailed description of the local features is provided in the On-line Table and the Appendix.

Feature Selection and Classification

A sequential feed-forward feature-selection algorithm²⁵ was used so that only a subset of the top discriminative features is automatically selected for classification, and at each iteration, an additional feature is sequentially included in the feature set. The scheme starts from an empty feature vector and then gradually adds features that are most discriminative between the 2 groups until there is no improvement in the prediction. The selection algorithm was used along with a support vector machine (SVM) classifier,²⁶ a robust machine-learning classifier that is commonly used for classification of biomedical data. In this work, we used a nonlinear radial basis function kernel within the SVM. To avoid training bias, we used a 4-fold cross-validation scheme within the training set, in which 3 folds were used for training and the fourth fold was held out for testing. The experiment was run 100 times, and the features that appeared most frequently across all runs were identified as the top discriminative features within the training cohort. Top performing features were then used within the independent test cohort for distinguishing PsP from tumor progression. Specifically, we used the following experiments:

Experiment 1: Distinguishing PsP from Tumor Progression Using the Shape Features of the Enhancing Lesion Alone. Local and global features extracted from the lesion compartment (30 in total) were used to train an SVM classifier. The top 5 features chosen by the classifier across the 100 runs were identified as the most discriminative subset from a total of 30 features for the enhancing lesion regions and used within the independent test set to distinguish PsP from tumor progression.

Experiment 2: Distinguishing PsP from Tumor Progression Using T2WI/FLAIR Hyperintense Perilesional Shape Features Alone. Local and global features extracted from the T2WI/FLAIR hyperintense perilesional compartment (30 in total) were used to train an SVM classifier. The top 5 features selected by the classifier across the 100 runs were identified as the most discriminative

subset from a total of 30 features extracted from T2WI/FLAIR hyperintense perilesional regions and used within the independent test set for distinguishing PsP from tumor progression.

Experiment 3: Distinguishing PsP from Tumor Progression Using Integrated Tumor Habitat Shape Features. All 60 features extracted from both the enhancing lesion and T2WI/FLAIR hyperintense perilesional compartments were used in conjunction to train an SVM classifier. The top 5 features selected by the classifier from both enhancing lesion and T2WI/FLAIR hyperintense perilesional features across 100 runs of cross-validation were identified as the most discriminative from the 60 features extracted across the lesion habitat and used within the independent test set to distinguish PsP from tumor progression.

Statistical Analysis

Statistical analysis was performed using a nonparametric Wilcoxon signed ranked test to further evaluate whether there are significant differences in PsP and tumor progression, across the top performing features that were selected by the classifier.

Evaluating Variability of Top Shape Radiomic Features across the 2 Sites

To test the variability of the top features selected by the classifier across the 2 sites, we computed their correlation coefficients between the training and testing sets across true progression and PsP. The correlation coefficients were computed for every feature, separately for every class (PsP or tumor progression) across the 2 sites, with high correlation values reflecting less variability across features across the 2 sites and low values reflecting more variability.

Table 2: Statistically significant features using the Wilcoxon rank sum test for the training cohort

Compartment	Feature	P Value
Enhancing lesion	SD of S	.05
Enhancing lesion	Roundness	.0057
Enhancing lesion	Compactness	.00027
T2WI/FLAIR hyperintense perilesion	Minor axis length	.02

RESULTS

Experiment 1: Distinguishing PsP from Tumor Progression Using Enhancing Lesion Shape Features Alone

Classification in the Training Cohort. Following SVM classification using shape features of the enhancing lesion alone, the following 5 features were identified as the top discriminative features between tumor progression (TP) and PsP cases: 3 global features constituting roundness (0.5 ± 0.16 TP, 0.33 ± 0.15 PsP), eccentricity (0.8 ± 0.1 TP, 0.912 ± 0.08 PsP), and compactness (0.3 ± 0.2 TP, 0.1 ± 0.24 PsP) and 2 local features including the mean of K_T (0.11 ± 0.01 TP, 0.09 ± 0.01 PsP), and the SD of S (4 ± 2 TP, 1 ± 0.9 PsP). Adding additional features to this subset did not improve the classification accuracy. Three of the top 5 features, compactness, roundness, and the SD of S, also were statistically significantly different between PsP and tumor progression (Table 2). Figure 1 demonstrates color maps of the enhancing lesion subcompartment of a tumor progression case and a PsP case, reflecting 3 of the top discriminative local and global features. Using the shape features of the enhancing lesion within the SVM classifier, we correctly classified 50 of 59 subjects (accuracy = 84.75%). Five of the misclassified cases were tumor progression, while the other 4 were PsP.

Classification in the Test Cohort. When we applied the top 5 discriminative features obtained on the training set for enhancing lesions to the test set ($n = 41$, 29 tumor progression cases and 12 PsP cases), the classifier missed 3 tumor progression cases and 4 PsP cases (accuracy = 83%).

Experiment 2: Distinguishing PsP from Tumor Progression Using the T2WI/FLAIR Hyperintense Perilesional Shape Features Alone

Classification in the Training Cohort. For the T2WI/FLAIR hyperintense perilesional regions, the top 5 discriminative shape features as identified by the SVM classifier were the following: 2 global features constituting the elongation shape factor ($0.29 \pm$

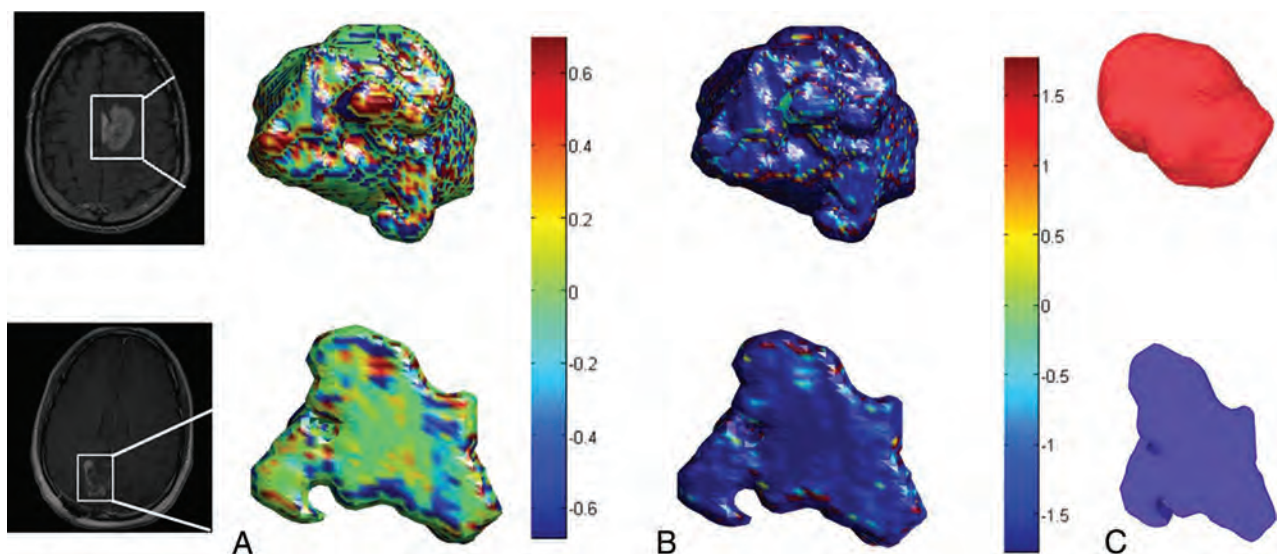


FIG1. Color maps visualizing the significant local features on an enhancing lesion region for a TP case (upper row) and a PsP case (lower row). The K_T measure is shown in A, whereas the S measure is shown in B. C, Surface-rendering for the 2 cases shows the compactness global feature that was discriminative by the classifier. The PsP mass is more elliptic, whereas the tumor appears to be more compact.

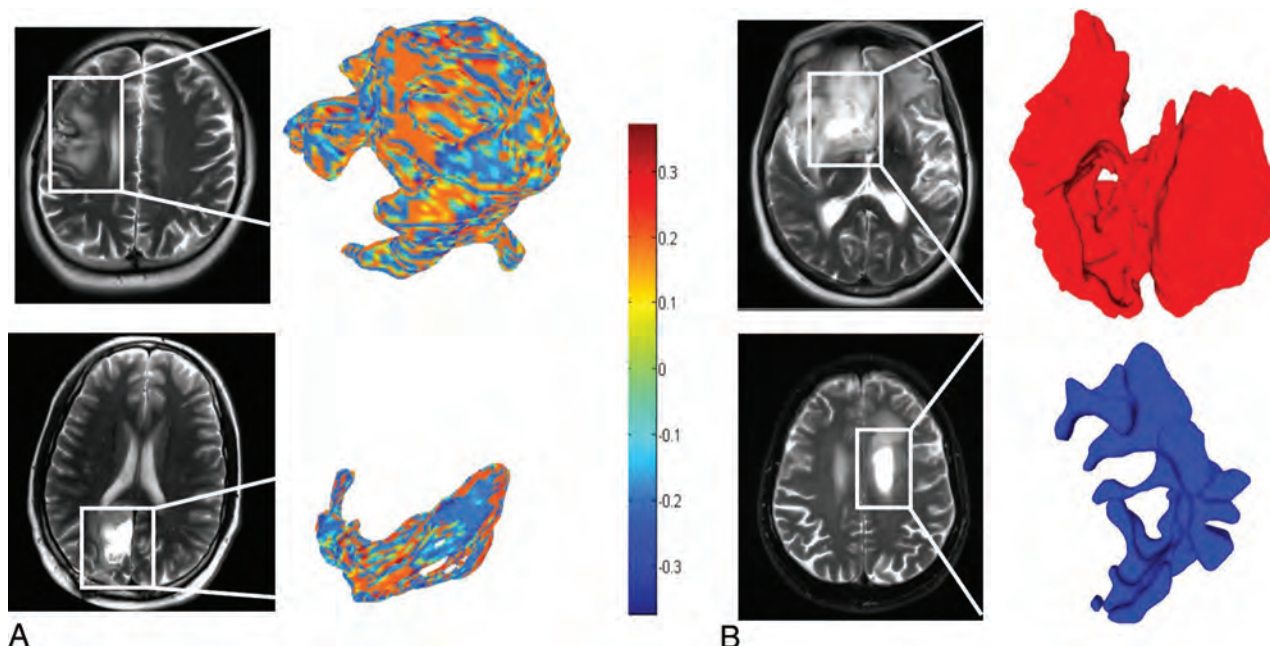


FIG 2. A, Color maps visualizing a significant local feature (shape index) on a peritumoral region for a tumor progression case (*upper row*) and a PsP case (*lower row*). B, Surface-rendering for 2 other cases that visualize the elongation shape factor feature as a discriminative feature between tumor progression and PsP. The higher elongation shown in the *lower row* for the PsP case is aligned with the previous findings reporting a rather elongated and elliptic shape of benign masses.³¹

Table 3: Experiments conducted on the training and testing cohorts and the corresponding classifier performance

Compartment	Features	Training	Testing
Enhancing lesion	Mean of K_T , SD of S, roundness, eccentricity, compactness	38 TP, 21 PsP: Accuracy = 84.75%	29 TP, 12 PsP: Accuracy = 83%
T2WI/FLAIR hyperintense perilesion	Median of C, median of S, median of SI, minor axis length, elongation shape factor	38 TP, 21 PsP: Accuracy = 88.14%	33 TP, 13 PsP: Accuracy = 82.6%
Lesion habitat	Lesion: Mean of K_T , roundness, eccentricity T2WI/FLAIR hyperintense Perilesion: median of C, elongation shape factor	38 TP, 21 PsP: Accuracy = 91.5%	29 TP, 12 PsP: Accuracy = 90.2%

0.2 TP, 0.6 ± 0.43 PsP) and minor axis length (0.5 ± 0.23 TP, 0.4 ± 0.24 PsP) and 3 local features including a median of S (0.1 ± 0.03 TP, 0.09 ± 0.01 PsP), a median of C (0.05 ± 0.03 TP, 0.03 ± 0.03 PsP), and a median of SI (0.05 ± 0.01 TP, 0.03 ± 0.01 PsP). These features correctly classified 52 of 59 patients (accuracy = 88.14%), with 4 PsP cases and 3 tumor progression cases misclassified. Minor axis length was statistically significant as well (Table 2). Figure 2 demonstrates the SI and the elongation shape factor features for T2WI/FLAIR hyperintense perilesional areas of both a TP and a PsP case.

Classification in the Test Cohort. Of the 46 test studies that included the T2WI/FLAIR hyperintense perilesional compartment, the top 5 features obtained by the classifier from the T2WI/FLAIR hyperintense perilesional areas as identified on the training set correctly classified 27 of the 33 subjects with tumor progression, as well as 11 of the 13 PsP cases (accuracy = 82.6%).

Experiment 3: Distinguishing PsP from Tumor Progression Using Integrated Lesion Habitat Features

Classification in the Training Cohort. When integrating shape and surface features from the enhancing lesion as well as the T2WI/FLAIR hyperintense perilesional regions within an SVM classifier, we selected a set of top 5 features from the training set. The top 5 features included the T2WI/FLAIR elongation shape

factor of the perilesion, and the median of C as well as the mean of K_T , roundness, and eccentricity of the enhancing lesion. These top features correctly identified 54 of 59 subjects (accuracy = 91.5%), with 2 tumor progression and 3 PsP cases misclassified. A summary of the top discriminative features for all the 3 experiments is provided in Table 3.

Classification in the Test Cohort. Using integrated top features from both enhancing lesion and T2WI/FLAIR hyperintense perilesional areas (5 in total across both compartments) on the test cases resulted in 37 of the 41 cases being correctly classified (accuracy = 90.2%). All 29 tumor-progression cases were correctly classified, and 8 of 12 PsP cases were correctly classified, suggesting that including T2WI/FLAIR hyperintense perilesional shape features along with the enhancing lesion shape features improved the performance of the classifier.

Evaluating Variability of Top Shape Radiomic Features across the 2 Sites

The On-line Figure shows boxplots for the top 3 features (SD of S of the enhancing lesion and T2WI/FLAIR median of C and median of S of the hyperintense perilesion) for both true progression and PsP classes across the 2 cohorts. The correlation coefficients for the lesion SD of S for both true progression and PsP across the 2 sites were 0.88 and 0.77, respectively, whereas they were 0.75 and

0.81 for T2WI/FLAIR median of C of the hyperintense perilesion and 0.9 and 0.775 for T2WI/FLAIR median of S of the hyperintense perilesion. These relatively high values of correlation coefficients between the 2 sites for both groups seem to suggest low variability across the 2 sites (Cleveland Clinic and Dana-Farber/Brigham and Women's Cancer Center) for the best performing features.

DISCUSSION

Distinguishing tumor progression from PsP is currently one of the greatest clinical challenges in neuro-oncology.² We present the first approach at assessing the effectiveness of 3D shape and surface radiomic features extracted from the tumor habitat (enhancing lesion and T2WI/FLAIR hyperintense perilesional regions) to differentiate tumor progression from PsP on conventional MR images (Gd-T1WI, T2WI, FLAIR). Our work was based on the rationale that there are observable 3D shape and surface irregularities encountered on the enhancing lesion as well as the perilesional boundaries in patients with tumor recurrence (potentially due to aggressive tumor infiltration and disruption) compared with those with benign pseudoprogression, which will likely have more regular boundaries.^{16,19,20}

Multiple experiments were conducted, including using shape features from the enhancing lesion alone and from T2WI/FLAIR hyperintense perilesional areas alone and finally using the feature set of both compartments for distinguishing tumor progression from PsP. Results summarized in Table 3 suggest that using the integrated set of features from the lesion habitat provided the best classification accuracies in distinguishing PsP from tumor progression. When we used integrated shape features from the lesion habitat, classification accuracies were improved for both training and testing cohorts, with significant improvement in the test cohort (90.2% accuracy versus 83% for the lesion alone and 82.6% for T2WI/FLAIR hyperintense perilesion). One hundred percent sensitivity was obtained for identifying tumor progression cases for the test cohort, and only 2 cases of 38 in the training cohort were misclassified. A study has previously suggested the presence of more defined peritumoral edema in patients with PsP due to local inflammatory tissue response caused by inherent and radiation therapy-induced capillary permeability.¹⁸ These changes are likely seen as changes in shape features in the perilesional compartment contributing to improved distinction of PsP from tumor progression.

For the global radiomic features, minor axis length and the elongation shape factor of T2WI/FLAIR hyperintense perilesional areas were the most discriminative between tumor progression and PsP. The elongation shape factor had higher values in PsP, which agree with previous findings that benign masses tend to be more elongated and elliptic than tumor-progression cases.^{20,27} The discriminative features of the enhancing lesion compartment (eccentricity, roundness, and compactness) also agree with previous findings that emphasized the anisotropic, irregular structure of lesion regions in tumor progression compared with a rather elliptic shape of benign brain masses.²⁰ This finding was supported by the higher eccentricity values of PsP cases (ie, more elliptic and elongated) than tumor progression cases shown in our results. Our reported findings in global shape differences between

tumor progression and PsP are also supported by findings in breast tumors that aimed at quantifying tumor boundaries using various shape descriptors (eg, compactness, moments) for tumor classification.^{27,28} Other studies showed that measures of circularity (ie, roundness), size, and irregularity could distinguish primary glioblastomas and metastases.^{16,29}

Surface features measuring local curvatures showed higher dominance in the enhancing lesion and in T2WI/FLAIR hyperintense perilesional regions of tumor progression cases (Fig 1). This could be attributed to tumors tending to alter the structure of white matter through infiltration and disruption, which eventually causes many shape irregularities leading to notable tumor surface changes.¹⁶ A study on local curvature analysis for classifying breast tumors similarly demonstrated that malignant tumor masses had more variations in their local curvature measures than benign masses.³⁰

The stability analysis of the top features showed relatively high values of correlation coefficients of the top features across the 2 sites for tumor progression and PsP. This finding suggests that the most discriminative shape features of PsP versus tumor progression are also likely stable across the 2 sites.

This study, however, has its limitations. The results reported are preliminary because our training and testing cohorts were limited to a relatively small sample size. A large independent multisite validation should be performed to further validate our findings. While the training and test data within the respective sites were largely consistent, the potential variability introduced due to differences in imaging sequence parameters (ie, slice thickness, scanner) across the training and test sets was not explicitly studied in this work and will be a part of a future study. Additionally, the cohorts included in this study did not have information regarding the administration of steroids posttreatment; hence, this could not be studied. The ground truth for most of the studies was obtained from follow-up imaging scans and lacked histologic confirmation.

While this study is preliminary, the top features identified in the training cohort (an overall accuracy of 91.5%) seemed to perform well in the independent cohort, with an accuracy of 90.2%. Future studies will involve a large-scale validation of these findings to create a "lockdown" classifier by identifying the most discriminative and stable features using data cohorts from multiple institutions.

Future work will also focus on integrating the most discriminative shape features with radiomic texture features¹³ as well as other clinical parameters (age, sex, Karnofsky performance score) and investigating their performance in distinguishing PsP from tumor progression.

CONCLUSIONS

The results presented suggest that a combination of local surface and global shape attributes from the enhancing lesion and T2WI/FLAIR hyperintense perilesional areas (lesion habitat) from routinely acquired MR images could improve the distinction of PsP from tumor progression over using features from enhancing lesions or T2WI/FLAIR hyperintense perilesional regions alone.

Disclosures: Virginia Hill—UNRELATED: Consultancy: Google, Comments: Google asked me radiology questions for 30 minutes, and I will be paid \$75; OTHER RELATIONSHIPS: Some of my coworkers and I are in discussions with Enlitic to embark on a joint research project automating detection of head CT emergencies. This has nothing to do with this article. Manmeet Aahluwalia—UNRELATED: Consultancy: Monteris Medical, AstraZeneca, Bristol-Myers Squibb, Abbvie, Varian Medical Systems, Flatiron, CBT Pharmaceuticals, Incyte; Grants/Grants Pending: Novartis, Bristol-Myers Squibb, AstraZeneca, NovoCure, Pharmacyclics, Incyte, Abbvie, Merck; Stock/Stock Options: MimiVax, Doctible.

REFERENCES

- Wick W, Chinot OL, Bendszus M, et al. Evaluation of pseudoprogression rates and tumor progression patterns in a phase III trial of bevacizumab plus radiotherapy/temozolomide for newly diagnosed glioblastoma. *Neuro Oncol* 2016;18:1434–41 CrossRef Medline
- Clarke JL, Chang S. Pseudoprogression and pseudoresponse: challenges in brain tumor imaging. *Curr Neurol Neurosci Rep* 2009;9:241–46 CrossRef Medline
- Parvez K, Parvez A, Zadeh G. The diagnosis and treatment of pseudoprogression, radiation necrosis and brain tumor recurrence. *Int J Mol Sci* 2014;15:11832–46 CrossRef Medline
- Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology working group. *J Clin Oncol* 2010;28:1963–72 CrossRef Medline
- Provenzale JM, Ison C, DeLong D. Bidimensional measurements in brain tumors: assessment of interobserver variability. *AJR Am J Roentgenol* 2009;193:W515–22 CrossRef Medline
- Dempsey MF, Condon BR, Hadley DM. Measurement of tumor “size” in recurrent malignant glioma: 1D, 2D, or 3D? *AJNR Am J Neuroradiol* 2005;26:770–76 Medline
- Mitsuya K, Nakasu Y, Horiguchi S, et al. Perfusion weighted magnetic resonance imaging to distinguish the recurrence of metastatic brain tumors from radiation necrosis after stereotactic radiosurgery. *J Neurooncol* 2010;99:81–88 CrossRef Medline
- Elias AE, Carlos RC, Smith EA, et al. MR spectroscopy using normalized and non-normalized metabolite ratios for differentiating recurrent brain tumor from radiation injury. *Acad Radiol* 2011;18:1101–08 CrossRef Medline
- Asao C, Korogi Y, Kitajima M, et al. Diffusion-weighted imaging of radiation-induced brain injury for differentiation from tumor recurrence. *AJNR Am J Neuroradiol* 2005;26:1455–60 Medline
- Brandsma D, Stalpers L, Taal W, et al. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol* 2008;9:453–61 CrossRef Medline
- Kickingereder P, Burth S, Wick A, et al. Radiomic profiling of glioblastoma: identifying an imaging predictor of patient survival with improved performance over established clinical and radiologic risk models. *Radiology* 2016;280:880–89 CrossRef Medline
- Yang D, Rao G, Martinez J, et al. Evaluation of tumor-derived MRI-texture features for discrimination of molecular subtypes and prediction of 12-month survival status in glioblastoma. *Med Phys* 2015;42:6725–35 CrossRef Medline
- Tiwari P, Prasanna P, Wolansky L, et al. Computer-extracted texture features to distinguish cerebral radionecrosis from recurrent brain tumors on multiparametric MRI: a feasibility study. *AJNR Am J Neuroradiol* 2016;37:2231–36 CrossRef Medline
- Zhang Z, Yang J, Ho A, et al. A predictive model for distinguishing radiation necrosis from tumor progression after gamma knife radiosurgery based on radiomic features from MR images. *Eur Radiol* 2018;28:2255–63 CrossRef Medline
- Ellingson BM, Chung C, Pope WB, et al. Pseudoprogression, radionecrosis, inflammation or true tumor progression? Challenges associated with glioblastoma response assessment in an evolving therapeutic landscape. *J Neurooncol* 2017;134:495–504 CrossRef Medline
- Goldberg-Zimring D, Talos IF, Bhagwat JG, et al. Statistical validation of brain tumor shape approximation via spherical harmonics for image-guided neurosurgery. *Acad Radiol* 2005;12:459–66 CrossRef Medline
- Kumar AJ, Leeds NE, Fuller GN, et al. Malignant gliomas: MR imaging spectrum of radiation therapy-and chemotherapy-induced necrosis of the brain after treatment. *Radiology* 2000;217:377–84 CrossRef Medline
- Brandes AA, Tosoni A, Spagnoli F, et al. Disease progression or pseudoprogression after concomitant radiochemotherapy treatment: pitfalls in neurooncology. *Neuro Oncol* 2008;10:361–67 CrossRef Medline
- Bharath K, Kurtek S, Rao A, et al. Radiologic image-based statistical shape analysis of brain tumors. *Journal of the Royal Statistical Society: Series C (Applied Statistics)*. Accessed January 29, 2018
- Wu P, Xie K, Zheng Y, et al. Brain tumors classification based on 3D shape. In: Jin D, Lin S, eds. *Advances in Future Computer and Control Systems*. Berlin: Springer; 2012;160:277–83
- Gatenby RA, Grove O, Gillies RJ. Quantitative imaging in cancer evolution and ecology. *Radiology* 2013;269:8–15 CrossRef Medline
- Tustison NJ, Avants BB, Cook PA, et al. N4ITK: improved N3 bias correction. *IEEE Trans Med Imaging* 2010;29:1310–20 CrossRef Medline
- Tao X, Chang MC. A skull stripping method using deformable surface and tissue classification. In: *Medical Imaging: Image Processing*. Ohio: International Society for Optics and Photonics; 2010;7623:76233L
- Pienaar R, Fischl B, Caviness V, et al. A methodology for analyzing curvature in the developing brain from preterm to adult. *Int J Imaging Syst Technol* 2008;18:42–68 CrossRef Medline
- Marcano-Cedeno A, Quintanilla-Domínguez J, Cortina-Januchs MG, et al. Feature selection using sequential forward selection and classification applying artificial metaplasticity neural network. In: *Proceedings of the Annual Conference of the Institute of Electrical and Electronics Engineers Industrial Electronics Society*. Glendale, Arizona; November 7–10, 2010;2845–50
- Guyon I, Weston J, Barnhill S, et al. Gene selection for cancer classification using support vector machines. *Machine Learning* 2002;46:389–422 CrossRef
- Chen Y, Gunawan E, Low KS, et al. Effect of lesion morphology on microwave signature in 2-D ultra-wideband breast imaging. *IEEE Trans Biomed Eng* 2008;55:2011–21 CrossRef Medline
- Tsui PH, Liao YY, Chang CC, et al. Classification of benign and malignant breast tumors by 2-D analysis based on contour description and scatterer characterization. *IEEE Trans Med Imaging* 2010;29:513–22 CrossRef Medline
- Zacharakis EI, Wang S, Chawla S, et al. Classification of brain tumor type and grade using MRI texture and shape in a machine learning scheme. *Magn Reson Med* 2009;62:1609–18 CrossRef Medline
- Lee J, Nishikawa RM, Reiser I, et al. Local curvature analysis for classifying breast tumors: preliminary analysis in dedicated breast CT. *Med Phys* 2015;42:5479–89 Medline

Synthesizing a Contrast-Enhancement Map in Patients with High-Grade Gliomas Based on a Postcontrast MR Imaging Quantification Only

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ABSTRACT

BACKGROUND AND PURPOSE: Administration of a gadolinium-based contrast agent is an important diagnostic biomarker for blood-brain barrier damage. In clinical use, detection is based on subjective comparison of native and postgadolinium-based contrast agent T1-weighted images. Quantitative MR imaging studies have suggested a relation between the longitudinal relaxation rate and proton-density in the brain parenchyma, which is disturbed by gadolinium-based contrast agents. This discrepancy can be used to synthesize a contrast-enhancement map based solely on the postgadolinium-based contrast agent acquisition. The aim of this study was to compare synthetic enhancement maps with subtraction maps of native and postgadolinium-based contrast agent images.

MATERIALS AND METHODS: For 14 patients with high-grade gliomas, quantitative MR imaging was performed before and after gadolinium-based contrast agent administration. The quantification sequence was multidynamic and multiecho, with a scan time of 6 minutes. The 2 image stacks were coregistered using in-plane transformation. The longitudinal relaxation maps were subtracted and correlated with the synthetic longitudinal relaxation enhancement maps on the basis of the postgadolinium-based contrast agent images only. ROIs were drawn for tumor delineation.

RESULTS: Linear regression of the subtraction and synthetic longitudinal relaxation enhancement maps showed a slope of 1.02 ± 0.19 and an intercept of 0.05 ± 0.12 . The Pearson correlation coefficient was 0.861 ± 0.059 , and the coefficient of variation was 0.18 ± 0.04 . On average, a volume of 1.71 ± 1.28 mL of low-intensity enhancement was detected in the synthetic enhancement maps outside the borders of the drawn ROI.

CONCLUSIONS: The study shows that there was a good correlation between subtraction longitudinal relaxation enhancement maps and synthetic longitudinal relaxation enhancement maps in patients with high-grade gliomas. The method may improve the sensitivity and objectivity for the detection of gadolinium-based contrast agent enhancement.

ABBREVIATIONS: dR₁ = R₁ enhancement; GBCA = gadolinium-based contrast agent; PD = proton-density; R₁ = longitudinal relaxation rate; R₂ = transverse relaxation rate

The clinical use of gadolinium-based contrast agents (GBCAs) is a diagnostic biomarker for detecting blood-brain barrier damage, a frequent finding in high-grade gliomas. In clinical practice, a native T1-weighted image is acquired to depict the baseline, followed by administration of a gadolinium-based contrast agent. After 5–10 minutes, the T1-weighted acquisition is repeated to show potential leakage of gadolinium-based contrast

agent into the brain parenchyma, visible as signal enhancement. Typically, the resulting images are shown juxtaposed, and contrast enhancement is estimated by a subjective visual evaluation of the pre- and postcontrast images.

A challenge when using conventional T1-weighted images is that the signal intensity has an arbitrary scale, affected by scanner imperfections such as B₁ inhomogeneity and coil sensitivity. These prohibit the use of quantitative measures of actual GBCA uptake, which is reported to add value to the assessment and prediction of the outcome of patients with high-grade gliomas.^{1,2} Even though contrast enhancement is an important feature when assessing high-grade gliomas, these tumors are also known to infiltrate into the peritumoral edema.³ Tumor infiltration is difficult to detect visually with conventional MR images, and quantitative measurements may therefore add information.

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Table 1: Overview of patient details

Patient Sex	Age (yr)	WHO 2007
Male	68	Glioblastoma IV
Female	57	Glioblastoma IV
Male	63	Anaplastic oligodendroglioma III
Female	58	Glioblastoma
Male	69	Glioblastoma
Male	71	Glioblastoma
Male	65	Gliosarcoma
Female	65	Anaplastic oligodendroglioma
Female	45	Glioblastoma
Male	65	Glioblastoma
Male	79	Glioblastoma
Male	45	Glioblastoma
Male	72	Glioblastoma
Male	74	Glioblastoma

Note:—WHO indicates World Health Organization.

Recent developments in MR imaging quantification of the longitudinal relaxation rate (R_1), transverse relaxation rate (R_2), and proton-density (PD) have resulted in sequences that can simultaneously measure these physical properties in a reasonable scan time.^{4–8} The advantage of MR imaging quantification is that R_1 , R_2 , and PD are measured on an absolute scale and are independent of MR imaging scanner settings and imperfections. The multiple parameters can be plotted as a parametric space, where each tissue type has a characteristic range of coordinates.^{9–11} The uptake of GBCA, however, selectively increases the R_1 (or, equivalently, decreases the longitudinal T1 relaxation time, where $T1 = 1/R_1$) in comparison with unenhanced tissue, without affecting the PD. Therefore, it is possible to estimate the relative increase in R_1 relaxation in a post-GBCA acquisition by taking its PD values and calculating the expected native R_1 values on the basis of the predetermined relation of native R_1 –PD coordinates of gray matter and white matter. Subtraction of the measured R_1 values and the calculated native R_1 values provides an estimate of the R_1 enhancement map without actually acquiring the native R_1 values. This procedure can synthesize an absolute R_1 enhancement map solely from the post-GBCA acquisition.

The purpose of this study was to create synthetic contrast-enhancement images based on a post-GBCA acquisition only and to correlate these with subtraction contrast-enhancement maps in patients with high-grade gliomas. An ROI assessment was performed to get an indication of the sensitivity of the approach.

MATERIALS AND METHODS

Subjects

For this prospective study, 14 patients with typical radiologic images of high-grade gliomas were included. Patient details are provided in Table 1. The mean age was 64 ± 10 years. Patients were examined at baseline before the operations and oncologic treatment. The diagnosis was confirmed after surgery with histopathologic analysis. The regional ethics review board approved the study under approval number 2011/406–31. Written informed consent was obtained from all patients.

MR Imaging Quantification Sequence

The multiecho, multidynamic sequence to retrieve R_1 , R_2 , and PD maps has been described previously.⁷ Acquisition details are the following: FOV = 220×180 , 24 slices, voxel size = $0.43 \times 0.43 \times$

5 mm (gap = 1 mm). Eight images per slice were measured with TE = 22 or 95 ms; and TI = 170, 670, 1840, or 3840 ms at a TR of 4000 ms. The MR imaging scanner was a 750 3T system (GE Healthcare, Milwaukee, Wisconsin, with Magnetic Resonance Image Compilation), using the 32-channel head coil. The scan time was 5 minutes and 55 seconds. The sequence was obtained both before and after GBCA injection, with a delay time after injection of about 10 minutes.

R_1 Enhancement Calculation

As shown by West et al,¹² the mean position of native cortical gray matter is at $R_1 = 0.77$ seconds^{−1} with PD at 86.88% and the mean position of native white matter is at $R_1 = 1.38$ seconds^{−1} with PD at 65.60% at 3T. All partial volumes of GM and WM between the mean positions are approximately linear. If one assumes a linear relationship, every 1% change of the PD value is associated with a 0.029 second^{−1} change in the R_1 value. All measured R_1 and PD combinations in the post-GBCA acquisition were projected onto the line between the gray matter and white matter coordinates. R_1 enhancement was then calculated as the measured R_1 value minus the estimated native R_1 value. A minimum threshold of 0.2 seconds^{−1} was applied to suppress 95% of the noisy background.

For comparison, subtraction R_1 enhancement maps were calculated by performing manual coregistration of the native R_1 maps using in-plane transformation (rotation and translation) and subtracting the native R_1 maps from the post-GBCA R_1 maps.

Synthetic T1-Weighted Images

Synthetic T1-weighted images were reconstructed on the basis of the measured R_1 , R_2 , and PD maps. The expected signal strength, S , in a synthetic T1-weighted image is calculated according to $S = PD \times [1 - \exp(-R_1 \times TR) \times \exp(-R_2 \times TE)]$. The TE was set to 10 ms; the TR was set to 500 ms. Calculation and visualization of the quantitative maps and synthetic T1-weighted images were performed with SyMRI 8.0 (SyntheticMR, Linköping, Sweden).

ROI Placement

Synthetic T1-weighted images were transferred to the software MeVisLab 2.7 (MeVis Medical Solutions, Bremen, Germany), and ROIs were drawn by 1 neuroradiologist (I.B.), blinded to the clinical information, on the synthetic post-GBCA T1-weighted images to delineate the contrast-enhancing part of the tumor. Care was taken to include the entire enhancing part of the tumor inside the drawn ROI line.

Statistical Analysis

Linear regression analysis was used to estimate the slope and intercept of the synthetic R_1 enhancement maps as a function of the subtraction R_1 enhancement maps for each subject. The Pearson correlation coefficient was applied to estimate the correlation per subject. The coefficient of variation was calculated as the SD of the difference in synthetic and subtraction R_1 enhancement maps divided by the mean of the post-GBCA R_1 map, also per subject. For all analyses, only voxels that had a R_1 enhancement (dR_1) of >0.2 seconds^{−1} were included to avoid a large number of voxels at (0,0), which would bias the intercept. No measures were obtained to suppress residual coregistration artifacts in the subtraction R_1

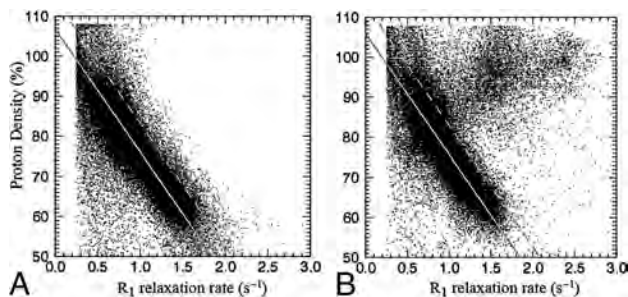


FIG 1. A, Measured proton-density values as a function of R_1 relaxation rate values of a slice of a brain of a patient with glioma grade IV before administration of GBCA (at 3T). The *solid line* traverses the average position of gray matter and white matter, indicating the predetermined, linear relationship between R_1 and PD for the native brain parenchyma. The *dotted line* indicates a threshold of 0.2 seconds⁻¹ from the *solid line*. B, PD and R_1 of the same slice after GBCA administration in which the present glioma exhibits enhancement. Some R_1 values are substantially increased above the dotted *threshold line*. The estimated R_1 enhancement corresponds to the measured R_1 value minus the corresponding R_1 value on the predetermined *solid line*.

enhancement maps. The mean and SD for all subjects were calculated using all individual slopes, intercepts, Pearson correlation coefficients, and coefficients of variation. For the ROI analysis, all pixels in the images touched by the ROI lines were selectively analyzed for R_1 enhancement using mean and SD. The ROI lines were expanded by 1 and 2 mm using region-growing to make an analysis on an ROI volume with a larger margin around the tumor.

RESULTS

The parametric representation of R_1 enhancement due to GBCA is illustrated in Fig 1. In Fig 1A, the R_1 and PD values of a slice of a brain are plotted before GBCA administration. It can be clearly seen that the relation between R_1 and PD for the entire brain parenchyma is approximately linear, as indicated by the gray line. In Fig 1B, the same slice is depicted after GBCA administration. The R_1 values within an enhancing part of the tumor have shifted to much higher values, substantially beyond the normal, native R_1 -PD combinations. The rest of the brain remains largely unchanged. The synthetic R_1 enhancement map is calculated using the difference of post-GBCA R_1 values and the estimated native R_1 values on the predetermined line. In Fig 2, the same slice of the brain is shown. Synthetic T1-weighted images (A and B) are generated using the R_1 , R_2 , and PD maps of the quantification sequence. The enhancement due to administration of GBCA is clearly visible on the T1-weighted images, as well as on the R_1 maps (C and D). The native R_1 maps are coregistered to the post-GBCA R_1 maps to obtain the subtraction R_1 enhancement (E). High-intensity enhancement corresponds to a dR_1 in the range of 1.5–2.5 seconds⁻¹. The diffuse signals throughout the entire volume are due to imperfect image coregistration of the anatomic details. In Fig 2F, the synthetic R_1 enhancement map, based on the post-GBCA acquisition only, is shown. Linear regression of the subtraction and synthetic R_1 enhancement maps on all patients showed a mean slope of 1.02 ± 0.19 and mean intercept of 0.05 ± 0.12 . Statistically, the unity line at intercept zero could not be ruled out. The mean Pearson correlation coefficient of all patients was 0.861 ± 0.059 . The mean coefficient of variation of

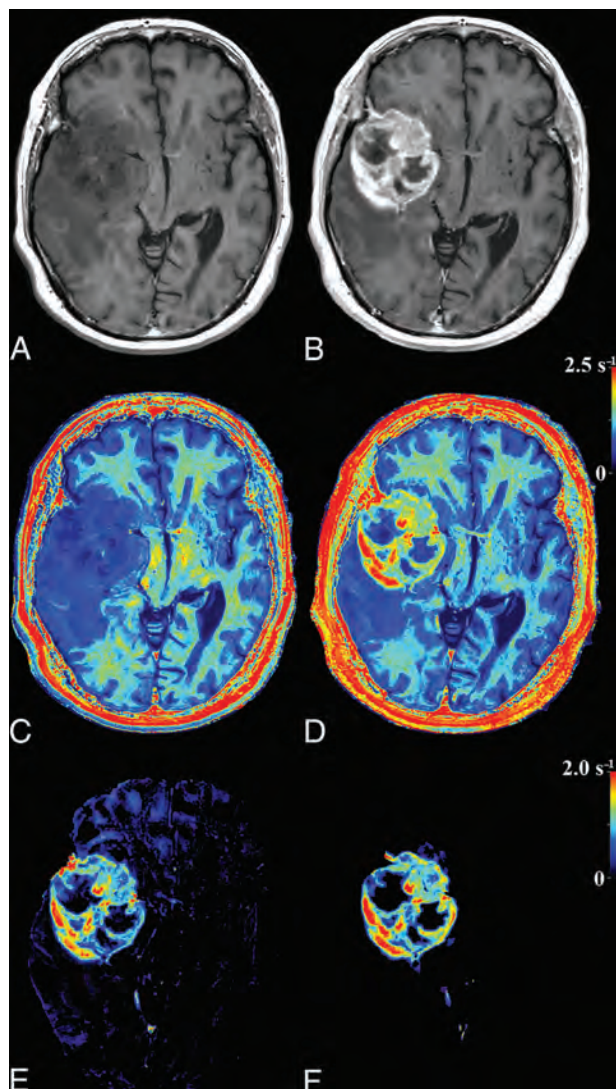


FIG 2. Images of the same slice as in Fig 1: synthetic T1-weighted imaging using native data (A), synthetic T1-weighted imaging using post-GBCA data (B), the native R_1 map (C), the post-GBCA R_1 map (D), the difference map of the coregistered native map (E), and the post-GBCA R_1 synthetic-difference map based on the post-GBCA acquisition only (F).

all patients was 0.18 ± 0.04 . In Fig 3, a 2D histogram is plotted of the detected R_1 enhancement using subtraction of the native and post-GBCA R_1 maps as a function of synthetic R_1 maps for all included patients.

In Fig 4, the tumor in Fig 2 is zoomed-in. The native and post-GBCA T1-weighted images are shown as well as the ROI drawn by the radiologist. In Fig 4D, the synthetic R_1 enhancement map is shown as a green overlay where full color corresponds to a dR_1 of 1 seconds⁻¹. At various places, low-intensity enhancement in the range 0.2–0.5 seconds⁻¹ is observable outside the high-intensity enhancing tumor and drawn ROI. On average for all patients, 35.8% of the pixels touched by the drawn ROI lines had values above 0.2 seconds⁻¹ for the synthetic R_1 enhancement map and even 50.3% for the subtraction R_1 enhancement map. When the ROI line was expanded with an additional margin of 1 or 2 mm, this percentage reduced to 8.0/17.4% and 2.3/8.6%, respectively (Table 2).

In 10 of 14 patients, >1 mL of tissue was found in the synthetic R_1 enhancement images with an enhancement of $>0.2 \text{ seconds}^{-1}$ outside the drawn ROI. The mean additional tumor volume for all patients was $1.71 \pm 1.28 \text{ mL}$, with a maximum of 4.3 mL. In comparison, the mean tumor volume within the ROIs was $63.5 \pm 44.4 \text{ mL}$ (range, 9–134 mL). More examples of the synthetic R_1 -enhancement maps are provided in Fig 5.

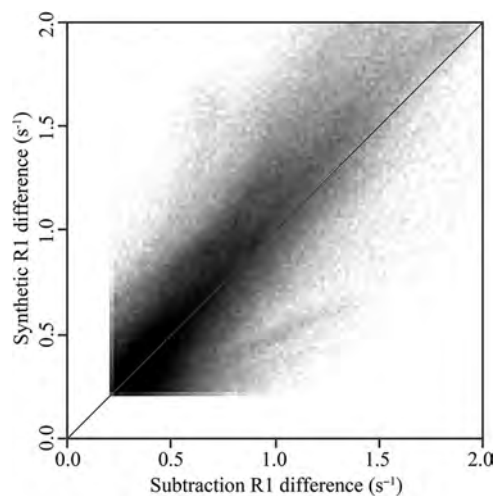


FIG 3. 2D histogram of the R_1 enhancement found using the subtraction of native and post-GBCA R_1 maps as a function of the synthetic R_1 enhancement, based on the post-GBCA acquisition only, of all included patients. The black and white intensity in the plot is proportional to the number of times an x, y coordinate occurred. The diagonal line indicates equivalence.

DISCUSSION

Detection of GBCA enhancement is an important clinical biomarker, which generally is used in a qualitative manner because a native T1-weighted image is subjectively compared with the post-GBCA T1-weighted image by the radiologist. Fortunately, quantitative MR imaging, including measurement of the absolute R_1 relaxation rates, is increasingly available and clinically supported.¹³ Some reports exist on the application of quantitative MR imaging to gliomas.^{14–16} The use of R_1 maps is expected to be more sensitive than conventional T1-weighted imaging. As observed in Fig 1, the increase of the R_1 of enhancing tumors is on the order of 2 seconds^{-1} , starting at a native value of about 0.5 seconds^{-1} . This corresponds to a relative increase of 400%. A conventional T1-weighted TSE image, on the other hand, is an exponentially saturated image, proportional to $1 - \exp(-R_1 \times TR)$. The relative increase of signal strength in a T1-weighted image, using the same R_1 values and a TR of 500 ms, is only 220%. The true advantage of R_1 mapping, however, is that these maps are not obscured by PD, B_1 , and coil-sensitivity differences.

Accurately measuring the quantitative R_1 enhancement due to GBCA administration in clinical practice, however, is still challenging due to patient motion. Patients tend to change position between acquisitions, and image subtraction requires robust, enhancement-independent image coregistration.¹⁷ Especially, subtle, low-intensity enhancement areas at the edges of a high-intensity tumor are easily corrupted by residual anatomic detail (Fig 2E). The lack of confidence in such areas generally results in ignoring them, which can have an impact on treatment and outcome.^{18,19} Our study shows that quantitative R_1 enhancement can be found using the post-GBCA acquisition only, removing the

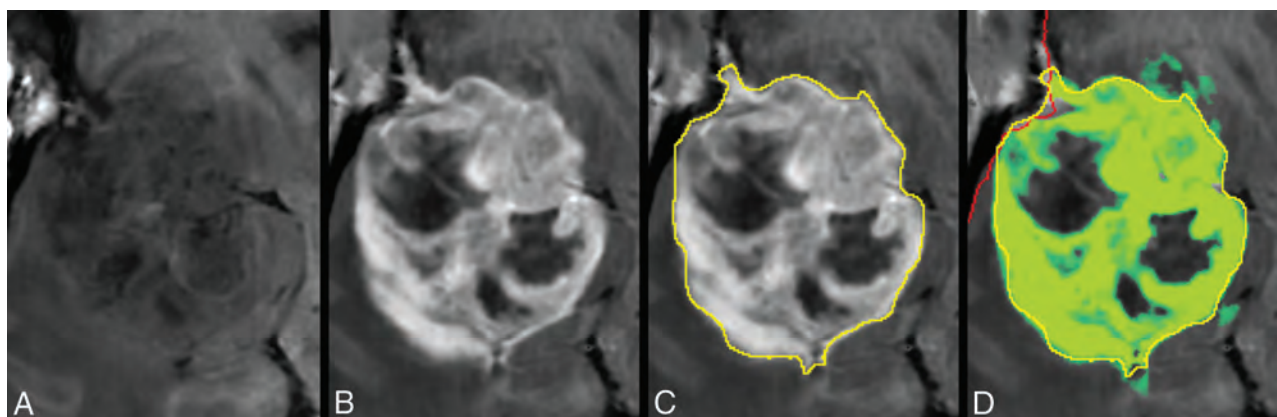


FIG 4. Zoomed part around the tumor displayed in Fig 2. Synthetic T1-weighted imaging using native data (A), synthetic T1-weighted imaging using post-GBCA data (B), the ROI line as drawn by a neuroradiologist to encapsulate the border of the enhancing tumor (C). D, Synthetic R_1 enhancement map shown as a green overlay on the synthetic T1-weighted image in which full color corresponds to $dR_1 = 1.0 \text{ seconds}^{-1}$. The minimum enhancement was set at $dR_1 = 0.2 \text{ seconds}^{-1}$. Some low-intensity enhancement is visible outside the yellow ROI. The red line indicates the edge of the intracranial volume.

Table 2: Observed R_1 enhancement of the pixels of the ROI line drawn by a neuroradiologist to encapsulate the enhancing tumor, as a percentage of all values above $dR_1 = 0.2 \text{ seconds}^{-1}$, the mean dR_1 , and the mean dR_1 of all values of $>0.2 \text{ seconds}^{-1}$ ^a

	$dR_1 > 0.2 \text{ s}^{-1}$ (%)		Mean dR_1 (s^{-1})		Mean dR_1 ($>0.2 \text{ s}^{-1}$ only) (s^{-1})	
	Synthetic	Subtraction	Synthetic	Subtraction	Synthetic	Subtraction
On ROI line	35.8 ± 14.3	50.3 ± 10.2	0.19 ± 0.09	0.27 ± 0.08	0.48 ± 0.12	0.46 ± 0.11
+ 1 mm	8.0 ± 5.8	17.4 ± 9.0	0.03 ± 0.02	0.08 ± 0.05	0.35 ± 0.08	0.37 ± 0.12
+ 2 mm	2.3 ± 1.5	8.6 ± 4.9	0.01 ± 0.01	0.04 ± 0.04	0.32 ± 0.15	0.37 ± 0.17

^a Results are listed for the R_1 difference generated by synthesizing the R_1 difference map and subtraction of the pre- and post-GBCA R_1 maps. Two more ROI lines were created at 1- and 2-mm outward to analyze the results if a larger margin around the enhancing tumor had been drawn.

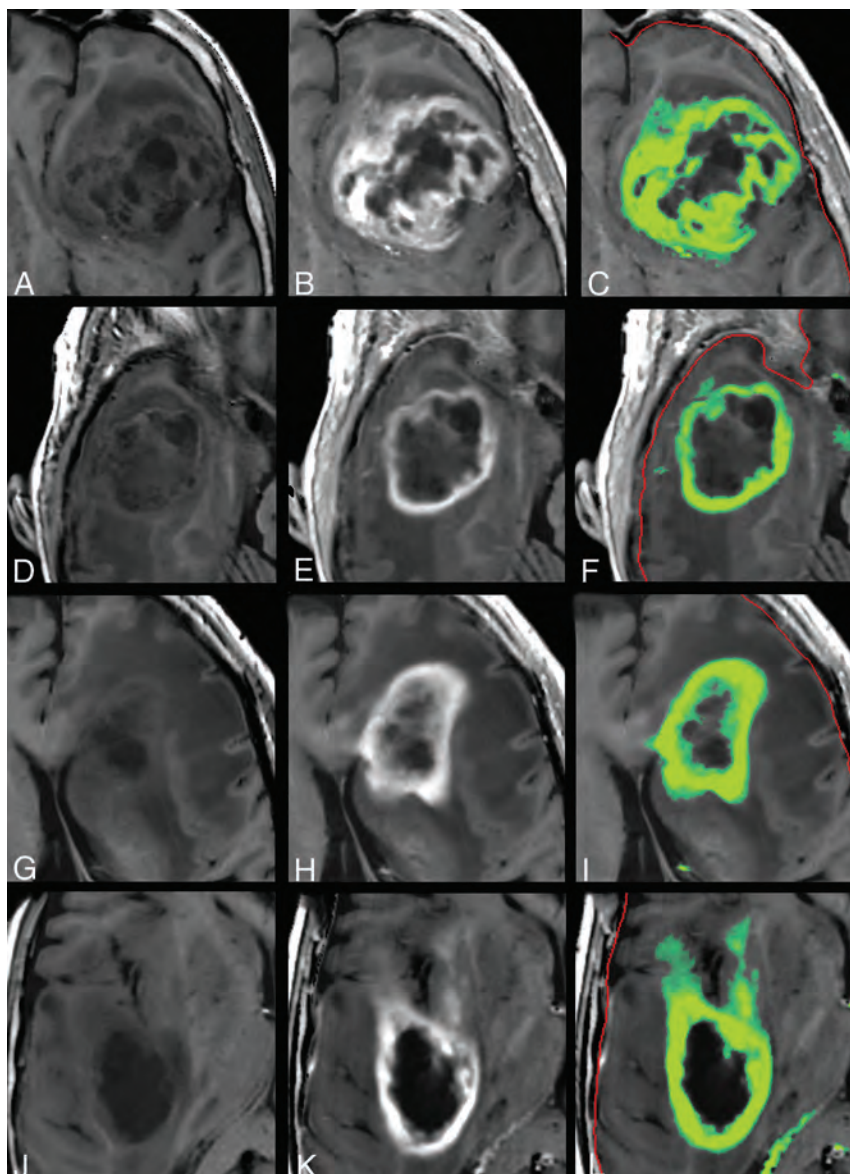


FIG 5. Other examples of the synthetic R_1 enhancement map and low-intensity enhancement at the edges of high-intensity enhancement in gliomas. *Left:* native synthetic T1-weighted image. *Center:* post-GBCA synthetic T1-weighted image. *Right:* synthetic R_1 enhancement map as a green overlay. The color indicates a range of dR_1 of 0.2–1.0 seconds⁻¹. The red line indicates the edge of the intracranial volume.

image coregistration issue entirely. Linear regression between our proposed method and image subtraction was observed to be very close to unity (slope of 1.02, intercept of 0.05). This opens the opportunity to objectively measure R_1 enhancement without the acquisition of the native R_1 maps. The removal of image coregistration issues may improve the sensitivity of low-enhancement areas and allow an objective threshold for tumor delineation.

To illustrate the perception of a radiologist, we drew ROIs to encapsulate the enhancing part of the tumor. For our 14 subjects, 36% of the pixels touched by the ROI line had dR_1 values above the chosen threshold of 0.2 seconds⁻¹, with a mean enhancement of 0.48 seconds⁻¹. For the subtraction R_1 -enhancement map, it was 50%, with similar mean enhancement. This indicates that the perception of the trained eye to determine R_1 enhancement is on the order of 0.2–0.5 seconds⁻¹, corresponding to 10%–25% of

the maximum enhancement. Further studies, with more readers are required to verify this value, but it shows that low-intensity enhancement in a T1-weighted image is easily rated as nonenhancing, which can affect the diagnosis.^{20,21} It is well-known that high-grade gliomas infiltrate into the peritumoral edema,^{3,16} which can be detected with higher sensitivity using diffusion²² or a multiparametric approach.²³ In our study, the application of an additional peritumoral margin of 1 or 2 mm rapidly reduced the number of pixels above the threshold as well as the mean dR_1 on the ROI line. For those pixels that did have values above 0.2 seconds⁻¹, however, the mean dR_1 was 0.3–0.4 seconds⁻¹, indicating that the enhancement was highly localized. Examples are shown in Figs 4 and 5. Low-intensity enhancement at the tumor edges is not distributed equally on all sides; it occurs mainly in a limited number of focal areas. In a previous study, we showed a gradient of R_1 relaxation at the edge of enhancing tumors.¹⁶ The current study indicates that the detected gradient was likely to be a composition of no-gradient areas and high-gradient areas.

A limitation of this study is the small number of patients and the use of a specific pathology. It can be speculated that synthetic R_1 enhancement maps can be generated for all cases of GBCA infiltration, but general use is yet to be confirmed. Furthermore, synthetic R_1 enhancement may have other causes than the presence of GBCA, for example, a hematoma or fatty tissue. A larger study would be required to assess the potential implications on diagnostic confidence

in the neuroradiology assessment. Secondary reactions due to radiation therapy treatment, which may mimic tumor growth,²⁴ were not investigated. No biopsy data were available to confirm a relation with the synthetic low-intensity R_1 enhancement and actual tumor infiltration. Larger clinical studies are required to validate our approach and assess the impact of its potential use.

A technical limitation was our assumption of a fixed R_1 –PD relation for the entire brain. This may seem rather coarse, but our study showed that it worked remarkably well. The reason is that the relative increase of R_1 due to GBCA administration is so large, nearly an order of magnitude larger than the normal variation within brain tissue from the R_1 –PD line. These large GBCA enhancements are typical for clinical routine because the contrast difference in conventional T1-weighted images is not linear and is relatively weak compared with an R_1 map. Possibly, quantitative

MR imaging may therefore permit using lower doses of GBCA. Our proposed synthetic R_1 enhancement approach may, in some cases, allow omitting the native T1-weighted images, which would result in a considerable examination time gain. Even if omission proves impossible, the quantitative enhancement measurement may still provide a more objective and sensitive input for drawing the margin around gliomas, especially considering the low-intensity enhancement areas.

CONCLUSIONS

Our study shows that it is possible to synthesize an R_1 -enhancement map in patients with high-grade gliomas on the basis of a post-GBCA MR imaging quantification sequence only. A good correlation with subtraction R_1 -enhancement maps was found. The method may improve the sensitivity and objectivity for enhancement detection, especially for areas with low-intensity enhancement.

Disclosures: Marcel Warntjes—UNRELATED: Employment: SyntheticMR AB, Comments: part-time employment at SyntheticMR AB; Stock/Stock Options: SyntheticMR AB.

REFERENCES

- Ellingson BM, Bendszus M, Sorensen AG, et al. **Emerging techniques and technologies in brain tumor imaging.** *Neuro Oncol* 2014; 16(Suppl 7):vii12–23 [CrossRef Medline](#)
- Ellingson BM, Harris RJ, Woodworth KL. **Baseline pretreatment contrast enhancing tumor volume including central necrosis is a prognostic factor in recurrent glioblastoma: evidence from single- and multicenter trials.** *Neuro Oncol* 2017;19:89–98 [CrossRef Medline](#)
- Claes A, Idema AJ, Wesseling P. **Diffuse glioma growth: a guerilla war.** *Acta Neuropathol* 2007;114:443–58 [CrossRef Medline](#)
- Zhu DC, Penn RD. **Full-brain T1 mapping through inversion recovery fast spin echo imaging with time-efficient slice ordering.** *Magn Reson Med* 2005;54:725–31 [CrossRef Medline](#)
- Neeb H, Zilles K, Shah NJ. **A new method for fast quantitative mapping of absolute water content in vivo.** *Neuroimage* 2006;31:1156–68 [CrossRef Medline](#)
- Deoni SC, Peters TM, Rutt BK. **High-resolution T1 and T2 mapping of the brain in a clinically acceptable time with DESPOT1 and DESPOT2.** *Magn Reson Med* 2005;53:237–41 [CrossRef Medline](#)
- Warntjes JB, Leinhard OD, West J, et al. **Rapid magnetic resonance quantification on the brain: optimization for clinical usage.** *Magn Reson Med* 2008;60:320–29 [CrossRef Medline](#)
- Ma D, Gulani V, Seiberlich N, et al. **Magnetic resonance fingerprinting.** *Nature* 2013;495:187–92 [CrossRef Medline](#)
- Alfano B, Brunetti A, Arpaia M, et al. **Multiparametric display of spin-echo data from MR studies of brain.** *J Magn Reson Imaging* 1995;5:217–25 [CrossRef Medline](#)
- Warntjes JB, Engström M, Tisell A, et al. **Brain characterization using normalized quantitative magnetic resonance imaging.** *PLoS One* 2013;8:e70864 [CrossRef Medline](#)
- Engström M, Warntjes JB, Tisell A, et al. **Multi-parametric representation of voxel-based quantitative magnetic resonance imaging.** *PLoS One* 2014;9:e111688 [CrossRef Medline](#)
- West J, Blystad I, Engström M, et al. **Application of quantitative MRI for brain tissue segmentation at 1.5 T and 3.0 T field strengths.** *PLoS One* 2013;8:e74795 [CrossRef Medline](#)
- Tanenbaum LN, Tsiouris AJ, Johnson AN, et al. **Synthetic MRI for clinical neuroimaging: results of the Magnetic Resonance Image Compilation (MAGiC) prospective, multicenter, multireader trial.** *AJNR Am J Neuroradiol* 2017;38:1103–10 [CrossRef Medline](#)
- Müller A, Jurcoane A, Kebir S, et al. **Quantitative T1-mapping detects cloudy-enhancing tumor compartments predicting outcome of patients with glioblastoma.** *Cancer Med* 2017;6:89–99 [CrossRef Medline](#)
- Lescher S, Jurcoane A, Veit A, et al. **Quantitative T1 and T2 mapping in recurrent glioblastomas under bevacizumab: earlier detection of tumor progression compared to conventional MRI.** *Neuroradiology* 2015;57:11–20 [CrossRef Medline](#)
- Blystad I, Warntjes JBM, Smedby Ö, et al. **Quantitative MRI for analysis of peritumoral edema in malignant gliomas.** *PLoS One* 2017;12:e0177135 [CrossRef Medline](#)
- Ellingson BM, Kim HJ, Woodworth DC, et al. **Recurrent glioblastoma treated with bevacizumab: contrast-enhanced T1-weighted subtraction maps improve tumor delineation and aid prediction of survival in a multicenter clinical trial.** *Radiology* 2014;271:200–10 [CrossRef Medline](#)
- Grabowski MM, Recinos PF, Nowacki AS, et al. **Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma.** *J Neurosurg* 2014;121:1115–23 [CrossRef Medline](#)
- Chaichana KL, Jusue-Torres I, Navarro-Ramirez R, et al. **Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma.** *Neuro Oncol* 2014;16:113–22 [CrossRef Medline](#)
- Eisele SC, Wen PY, Lee EQ. **Assessment of brain tumor response: RANO and its offspring.** *Curr Treat Options Oncol* 2016;17:35 [CrossRef Medline Medline](#)
- Shiroishi MS, Boxerman JL, Pope WB. **Physiologic MRI for assessment of response to therapy and prognosis in glioblastoma.** *Neuro Oncol* 2016;18:467–78 [CrossRef Medline](#)
- Lemercier P, Paz Maya S, Patrie JT, et al. **Gradient of apparent diffusion coefficient values in peritumoral edema helps in differentiation of glioblastoma from solitary metastatic lesions.** *AJR Am J Roentgenol* 2014;203:163–69 [CrossRef Medline](#)
- Akbari H, Macyszyn L, Da X, et al. **Imaging surrogates of infiltration obtained via multiparametric imaging pattern analysis predict subsequent location of recurrence of glioblastoma.** *Neurosurgery* 2016; 78:572–80 [CrossRef Medline](#)
- Hygino da Cruz LC Jr, Rodriguez I, Domingues RC, et al. **Pseudoprogession and pseudoresponse: imaging challenges in the assessment of posttreatment glioma.** *AJNR Am J Neuroradiol* 2011;32: 1978–85 [CrossRef Medline](#)

MRI Evidence of Altered Callosal Sodium in Mild Traumatic Brain Injury

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ABSTRACT

BACKGROUND AND PURPOSE: Mild traumatic brain injury is a leading cause of death and disability worldwide with 42 million cases reported annually, increasing the need to understand the underlying pathophysiology because this could help guide the development of targeted therapy. White matter, particularly the corpus callosum, is susceptible to injury. Animal models suggest stretch-induced mechanoporation of the axonal membrane resulting in ionic shifts and altered sodium ion distribution. The purpose of this study was to compare the distribution of total sodium concentration in the corpus callosum between patients with mild traumatic brain injury and controls using sodium (^{23}Na) MR imaging.

MATERIALS AND METHODS: Eleven patients with a history of mild traumatic brain injury and 10 age- and sex-matched controls underwent sodium (^{23}Na) MR imaging using a 3T scanner. Total sodium concentration was measured in the genu, body, and splenium of the corpus callosum with 5-mm ROIs; total sodium concentration of the genu-to-splenium ratio was calculated and compared between patients and controls.

RESULTS: Higher total sodium concentration in the genu (49.28 versus 43.29 mmol/L, $P = .01$) and lower total sodium concentration in the splenium (which was not statistically significant; 38.35 versus 44.06 mmol/L, $P = .08$) was seen in patients with mild traumatic brain injury compared with controls. The ratio of genu total sodium concentration to splenium total sodium concentration was also higher in patients with mild traumatic brain injury (1.3 versus 1.01, $P = .001$).

CONCLUSIONS: Complex differences are seen in callosal total sodium concentration in symptomatic patients with mild traumatic brain injury, supporting the notion of ionic dysfunction in the pathogenesis of mild traumatic brain injury. The total sodium concentration appears to be altered beyond the immediate postinjury phase, and further work is needed to understand the relationship to persistent symptoms and outcome.

ABBREVIATIONS: CC = corpus callosum; mTBI = mild traumatic brain injury; TSC = total sodium concentration

Mild traumatic brain injury (mTBI) is the leading cause of death and disability in the United States and worldwide, with approximately 42 million cases annually.¹ Patients may have a complex array of symptoms, including cognitive disturbance, headache, and visual impairment, and there is a critical need to

gain further insight into the pathophysiology underlying the injury. It is known that sodium is critical to cellular homeostasis, which maintains fluid volume in the intracellular and extracellular compartments, maintains resting potential across membranes, and triggers action potential. Mild TBI causes mechanical injury to axons, resulting in widespread membrane depolarizations and activation of cellular ionic cascades, thereby causing disruption of sodium homeostasis.²⁻⁴ There is a resultant increase in intracellular sodium, which lowers the threshold for membrane depolarization.⁴⁻⁸ White matter is known to be susceptible to injury in mTBI relating to acceleration, deceleration, and rotational forces.^{8,9} In particular, the corpus callosum (CC) is at specific risk due to axon density, transverse orientation, and connection of the 2 cerebral hemispheres, which can experience opposing forces during complex head injury.² It is known from the biomechanical literature that quantitative stress measures such as principal strain, strain

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rate,¹⁰ and von Mises stress¹¹ are highest in and around the CC. Because the CC is a group of anatomic tracts that integrate information across cerebral hemispheres, patients with mTBI tend to experience deficits in integrative functions (cognitive slowing, confusion, difficulty with complex tasks) rather than focal neurologic deficits.

Noninvasive imaging of brain sodium on clinical MR imaging scanners is very challenging due to low signal-to-noise ratio. Recent advances in technologies achieved at our site, such as coil design, data acquisition, and sodium quantification, now allow us to study ionic changes noninvasively at clinical field strengths of 3T or higher.^{12–16} The purpose of this pilot study was to measure total sodium concentration (TSC) in the CC in patients with mTBI using sodium (²³Na) MRI and to compare TSC and its spatial distribution across the CC with that in healthy controls.

MATERIALS AND METHODS

The study was performed under approval by the institutional review board. Informed consent was obtained from each of the subjects studied.

Human Subjects and Clinical Assessments

Eleven patients (5 men and 6 women; age range, 19–70 years) with a history of mTBI (as defined by the American Congress of Rehabilitation Medicine⁹) and 10 age- and sex-matched healthy controls were prospectively recruited for sodium (²³Na) MRI. Review of clinical charts was performed for pertinent clinical history and assessment, including postconcussive symptoms, neurologic examination, and scores on the Standardized Assessment of Concussion.

MR Imaging Acquisition

Sodium (²³Na) MRI scans were performed on a clinical 3T scanner (Magnetom Prisma; Siemens, Erlangen, Germany) with a custom-built 8-channel dual-tuned (¹H-²³Na) transmit/receive head array coil.¹³ The twisted projection imaging pulse sequence^{15,17} was applied to a 3D volume covering the whole head (FOV = 220 mm, matrix size = 64, 3D isotropic, nominal resolution = 3.44 mm, rectangular radiofrequency pulse duration = 0.5 ms, TE/TR = 0.3/100 ms, flip angle = 90°, rings = 28, *P* [key parameter] = .4, projections = 1595, averages = 4, TA [time of acquisition] = 10.6 minutes). This scheme of data acquisition produced a typically high SNR of 55 in gray matter, 35 in white matter, and 57 in CSF in the square-root of the sum-of-squares sodium image of healthy controls before the correction for coil sensitivities. A magnetization-prepared rapid acquisition of gradient echo ¹H-MR imaging pulse sequence was performed for structural imaging of the brain (FOV = 256 × 216 mm², matrix size = 384 × 324, slice thickness = 1 mm at 144 slices, TE/TR = 3.56/2,220 ms, acceleration factor = 3, TA = 4.6 minutes).

Image Preprocessing

Sodium images were corrected for intensity inhomogeneity relating to the array coil by dividing by a low-resolution version of the images reconstructed from the *k*-space center of an optimally selected diameter of 9.0/FOV.¹⁸ Normalization was then accomplished with conversion of image intensity into sodium concen-

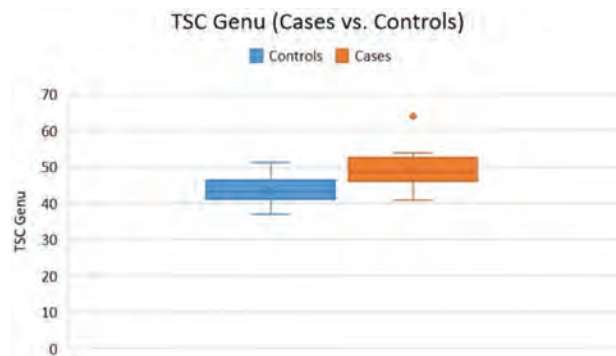


FIG 1. The TSC of the genu was higher in patients with mTBI compared with controls ($P = .01$).

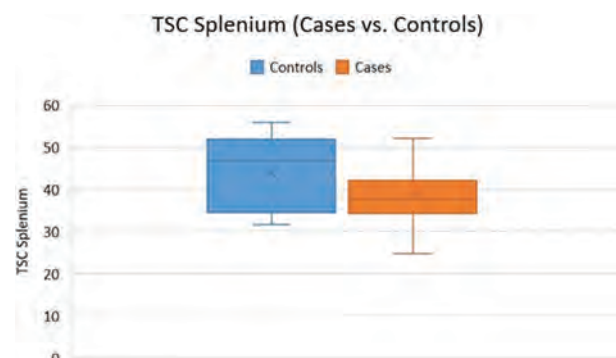


FIG 2. The TSC in the splenium was lower in patients with mTBI compared with controls ($P = .08$).

tration in millimoles per liter on a pixel-by-pixel basis through a 2-point linear calibration¹⁶ with a noise-only background region set at 0 mmol/L and an ROI within the posterior chamber of the ocular globe set at a known (previously established) human vitreous sodium concentration of 145 mmol/L.^{19,20}

ROI Analysis

Circular ROIs of 5-mm in diameter were placed by 2 reviewers (1 research associate specifically working on neuroimaging and 1 neuroradiologist with >10 years of experience) in consensus in the genu, body, and splenium of the CC. A small-sized ROI was chosen to avoid volume averaging. The mean TSC was compared between subjects with mTBI and controls using a 2-tailed Student *t* test and a significance level of .05.

For further assessment of the TSC spatial distribution across the corpus callosum, a TSC ratio of genu to splenium was calculated and compared between patients and controls. A TSC color map was created using MR Viewer software (MRI Research Lab, Mayo Clinic and Foundation) (<https://cortechsolutions.com/emse/software/mr-viewer/>).

RESULTS

Five men and six women with an age range 19–70 years and a history of mTBI were studied, with an average time since injury of 16 weeks. All patients were symptomatic at assessment. Ten of 11 subjects with mTBI had formal clinical assessments at our institution. One subject declined this assessment.

All of the 10 patients who underwent clinical assessment were symptomatic at time of imaging (detailed in the On-line Table).

Of note, most patients reported headaches, sleep disturbances, dizziness, decreased concentration, and an average Standardized Assessment of Concussion score of 27.5 (highest Standardized Assessment of Concussion score = 30, normal score ≥ 25).²¹

The mean TSC in the genu, body, and splenium of the CC in patients with mTBI was 49.28 ± 0.51 mmol/L, 46.04 ± 0.43 mmol/L, and 38.35 ± 0.36 mmol/L, respectively, compared with 43.29 ± 0.46 mmol/L, 45.25 ± 0.38 mmol/L, and 44.06 ± 0.46 mmol/L in controls. There were statistically significant differences between patients with mTBI and controls with respect to the callosal TSC in the genu (49.28 versus 43.29 mmol/L, $P = .01$)

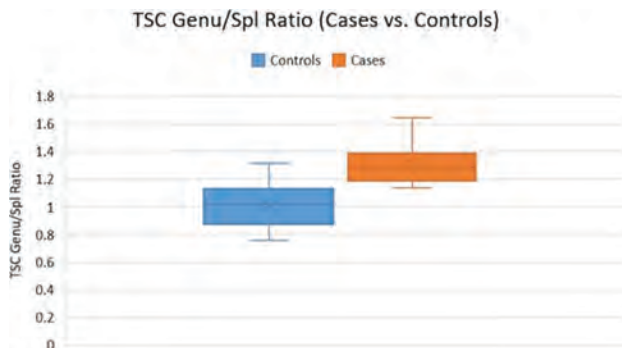


FIG 3. The TSC of the genu/splenium ratio was higher in patients compared with controls ($P = .001$).

(Fig 1). No significant differences in the average TSC were found between patients and controls in the body ($P = .32$) and splenium of the corpus callosum ($P = .08$) (Fig 2).

The average ratio (genu/splenium) was 1.3 in patients and 1.01 in controls ($P = .001$) (Fig 3).

DISCUSSION

The results of this investigation show differences in the callosal TSC between a small group of symptomatic patients with mTBI and age- and sex-matched healthy controls. Differences in the TSC between study groups varied depending on the location within the CC, with higher genu TSC and a trend that did not reach statistical significance of lower splenial TSC in patients with mTBI (Fig 4).

The findings corroborate a growing body of literature that underscores the importance of cytosolic sodium as a marker of tissue injury after trauma. In mTBI, twisting and stretching of axons results in mechanical disruption of membranes, altered function of voltage-gated sodium channels and sodium-potassium adenosine triphosphatase,^{4,5,22} and changed regulation of the expression of sodium channels,^{6,7} with potential persistent sodium abnormality.

It is not fully clear what caused the change of TSC in the CC: TSC has contributions from both intracellular and extracellular compartments, and derangements in either of these compart-

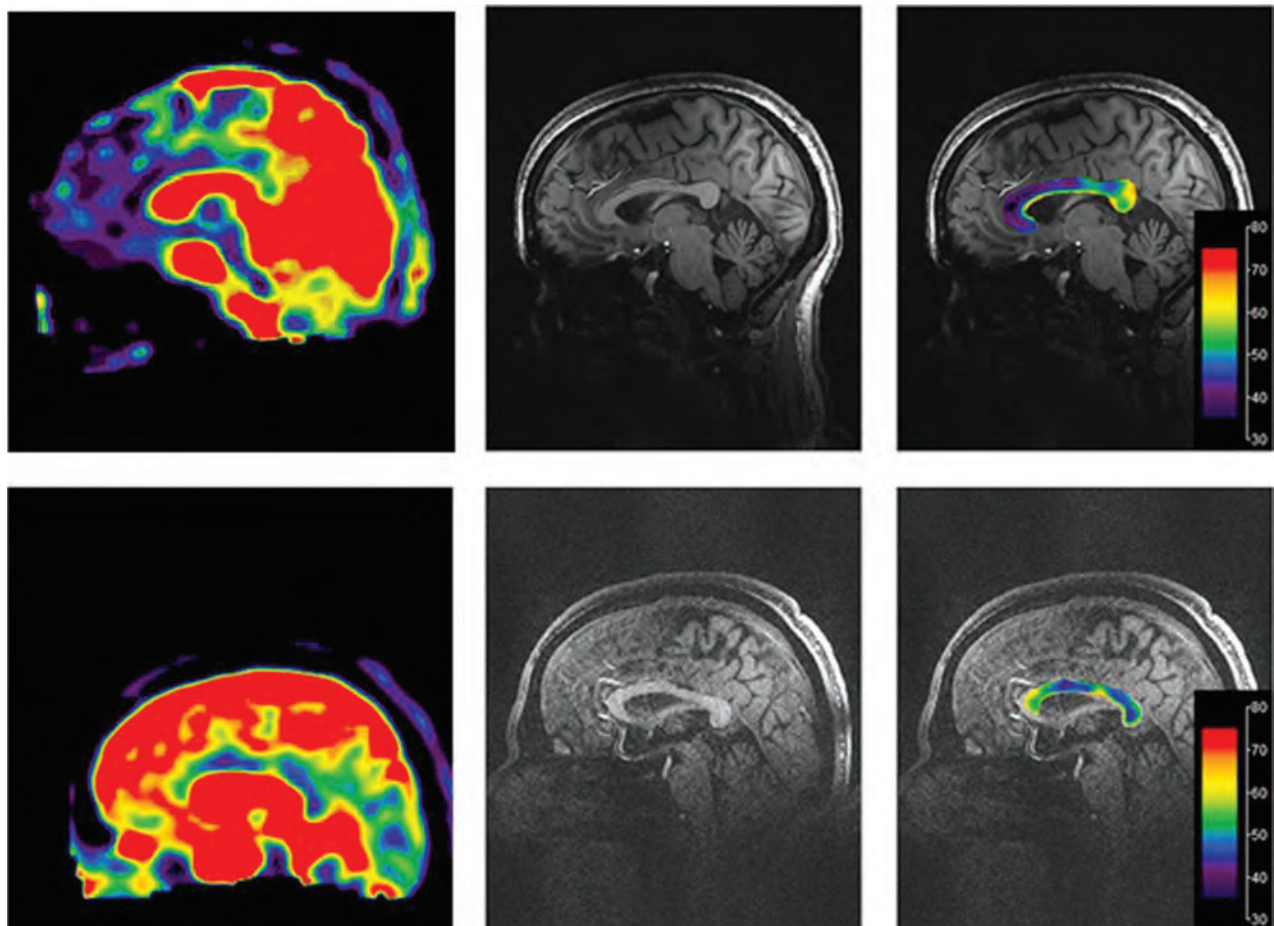


FIG 4. The TSC heat color map of the corpus callosum superimposed on a midline MPAGE image in a control subject (top) and a patient with mTBI (bottom) shows that the TSC is higher in the genu and lower in the splenium in the patient with mTBI.

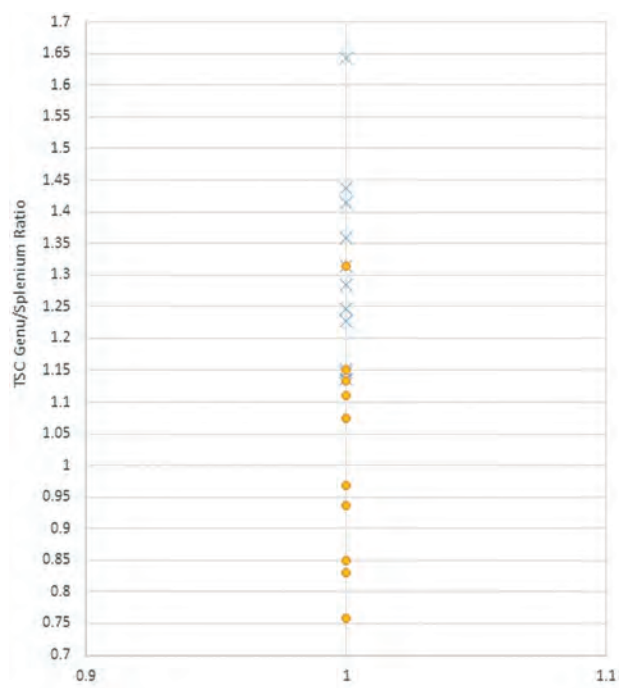


FIG 5. TSC genu/splenium ratio in patients with mTBI (X) and controls (O).

ments could contribute to the altered TSC. Because the extracellular compartment rapidly equilibrates with a larger plasma sodium pool, changes in intracellular sodium concentration could certainly affect TSC measures.^{23,24} Alterations in the relative size of the compartments would also be expected to affect TSC measurements. Work is currently underway to attempt to estimate intracellular and extracellular contributions to the TSC signal.^{16,23,25,26}

Why injury may affect sodium differently across various parts of the CC is unclear. There is variable myelination across the CC,^{27–29} and expression of some specific voltage-gated sodium channels is known to track with myelination.³⁰ In addition, von Reyn et al³ demonstrated anatomic redistribution of voltage-gated sodium channels in the CC in an animal model of mTBI. These factors may contribute to anatomic differences in TSC across the CC after injury.

Many medications may affect sodium homeostasis. The most relevant ones were specifically screened and included in the chart review. Patient 5 was on the antidepressant escitalopram (selective serotonin reuptake inhibitor). There are a few recent reports of escitalopram causing a syndrome of inappropriate antidiuretic hormone secretion and hyponatremia. Our patient exhibited no signs of the syndrome of inappropriate antidiuretic hormone secretion and had normal serum chemistry values. Patient 3 was treated with lamotrigine, a central nervous system voltage-gated sodium channel blocker, for posttraumatic dystonia. In this subject, the TSC genu/splenium ratio among the mTBI group was the closest to that of the control cohort (Fig 5).

Limitations of this study include the small sample size; however, here we show proof of concept that TSC can be measured in vivo, noninvasively, on a clinical 3T scanner in subjects with mTBI after injury. This represents the first report we are aware of

suggesting sodium homeostasis abnormality in human subjects with mTBI using a noninvasive method. Already discussed is the need to estimate cellular compartmental contributions to the TSC to further elucidate ionic abnormalities in mTBI. This pilot work included a heterogeneous population of patients with respect to time since injury, history of prior mTBI, and medications that may affect the sodium balance. In this preliminary study, no T2WI/FLAIR was performed in these subjects.

CONCLUSIONS

This study shows complex differences in the TSC in the CC in symptomatic patients with mTBI compared with age- and sex-matched healthy controls. Specifically, the TSC in the genu of the CC was elevated. Further work is needed to understand the relationship between the TSC change and symptom resolution or outcome prediction.

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REFERENCES

- Gardner RC, Yaffe K. **Epidemiology of mild traumatic brain injury and neurodegenerative disease.** *Mol Cell Neurosci* 2015;66:75–80 CrossRef Medline
- Prins M, Greco T, Alexander D, et al. **The pathophysiology of traumatic brain injury at a glance.** *Dis Model Mech* 2013;6:1307–15 CrossRef Medline
- von Reyn CR, Mott RE, Siman R, et al. **Mechanisms of calpain mediated proteolysis of voltage gated sodium channel α -subunits following in vitro dynamic stretch injury.** *J Neurochem* 2012;121:793–805 CrossRef Medline
- Wolf JA, Stys PK, Lusardi T, et al. **Traumatic axonal injury induces calcium influx modulated by tetrodotoxin-sensitive sodium channels.** *J Neurosci* 2001;21:1923–30 CrossRef Medline
- Gardiner D. **Quantitative Analysis of Contactin-Associated Protein and Voltage-Gated Sodium Channel Isoform 1.6 Following Experimental Diffuse Traumatic Brain Injury** [Master of Science Thesis, Physiology]. Richmond: Virginia Commonwealth University; 2011
- Mao Q, Jia F, Zhang XH, et al. **The up-regulation of voltage-gated sodium channel Nav1.6 expression following fluid percussion traumatic brain injury in rats.** *Neurosurgery* 2010;66:1134–39; discussion 1139 CrossRef Medline
- Huang XJ, Mao Q, Lin Y, et al. **Expression of voltage-gated sodium channel Nav1.3 is associated with severity of traumatic brain injury in adult rats.** *J Neurotrauma* 2013;30:39–46 CrossRef Medline
- Huang XJ, Li WP, Lin Y, et al. **Blockage of the upregulation of voltage-gated sodium channel nav1.3 improves outcomes after experimental traumatic brain injury.** *J Neurotrauma* 2014;1:346–57 CrossRef Medline
- Ruff RM, Iverson GL, Barth JT, et al; NAN Policy and Planning Committee. **Recommendations for diagnosing a mild traumatic brain injury: a National Academy of Neuropsychology education paper.** *Arch Clin Neuropsychol* 2009;24:3–10 CrossRef Medline
- McAllister TW, Ford JC, Ji S, et al. **Maximum principal strain and strain rate associated with concussion diagnosis correlates with changes in corpus callosum white matter indices.** *Ann Biomed Eng* 2012;40:127–40 CrossRef Medline
- Patton DA, McIntosh AS, Kleiven S. **The biomechanical determinants of concussion: finite element simulations to investigate tis-**

- sue-level predictors of injury during sporting impacts to the unprotected head. *J Appl Biomech* 2015;31:264–68 [CrossRef Medline](#)
12. Wiggins GC, Brown R, Lakshmanan K. **High-performance radiofrequency coils for (23)Na MRI: brain and musculoskeletal applications.** *NMR Biomed* 2016;29:96–106 [CrossRef Medline](#)
 13. Lakshmanan K, Brown R, Madelin G, et al. **An eight-channel sodium/proton coil for brain MRI at 3 T.** *NMR Biomed* 2018;31:e3867 [CrossRef Medline](#)
 14. Qian Y, Zhao T, Wiggins GC, et al. **Sodium imaging of human brain at 7 T with 15-channel array coil.** *Magn Reson Med* 2012;68:1807–14 [CrossRef Medline](#)
 15. Qian Y, Stenger VA, Boada FE. **Parallel imaging with 3D TPI trajectory: SNR and acceleration benefits.** *Magn Reson Imaging* 2009;27:656–63 [CrossRef Medline](#)
 16. Qian Y, Panigrahy A, Laymon CM, et al. **Short-T2 imaging for quantifying concentration of sodium (23 Na) of bi-exponential T2 relaxation.** *Magn Reson Med* 2015;74:162–174 [CrossRef Medline](#)
 17. Boada FE, Shen GX, Chang SY, et al. **Spectrally weighted twisted projection imaging: reducing T2 signal attenuation effects in fast three-dimensional sodium imaging.** *Magn Reson Med* 1997;38:1022–28 [CrossRef Medline](#)
 18. Qian Y, Zhang Z, Stenger VA, et al. **Self-calibrated spiral SENSE.** *Magn Reson Med* 2004;52:688–92 [CrossRef Medline](#)
 19. Harrington MG, Salomon RM, Pogoda JM, et al. **Cerebrospinal fluid sodium rhythms.** *Cerebrospinal Fluid Res* 2010;7:3 [CrossRef Medline](#)
 20. Kokavec J, Min SH, Tan MH, et al. **Biochemical analysis of the living human vitreous.** *Clin Exp Ophthalmol* 2016;44:597–609 [CrossRef Medline](#)
 21. O'Neil B, Naunheim R, DeLorenzo R. **CT positive brain injury in mild TBI patients presenting with normal SAC scores.** *Mil Med* 2014;179:1250–53 [CrossRef Medline](#)
 22. Paling D, Solanky BS, Riemer F, et al. **Sodium accumulation is associated with disability and a progressive course in multiple sclerosis.** *Brain* 2013;136:2305–17 [CrossRef Medline](#)
 23. Madelin G, Kline R, Walvick R, et al. **A method for estimating intracellular sodium concentration and extracellular volume fraction in brain in vivo using sodium magnetic resonance imaging.** *Sci Rep* 2014;4:4763 [CrossRef Medline](#)
 24. Alessandri B, Doppenberg E, Zauner A, et al. **Cortical extracellular sodium transients after human head injury: an indicator of secondary brain damage?** *Acta Neurochir Suppl* 1998;71:237–40 [Medline](#)
 25. Fleysher L, Oesingmann N, Brown R, et al. **Noninvasive quantification of intracellular sodium in human brain using ultrahigh-field MRI.** *NMR Biomed* 2013;26:9–19 [CrossRef Medline](#)
 26. Mirkes C, Shajan G, Bause J, et al. **Triple-quantum-filtered sodium imaging at 9.4 Tesla.** *Magn Reson Med* 2016;75:1278–89 [CrossRef Medline](#)
 27. Knyazeva MG. **Splenium of corpus callosum: patterns of interhemispheric interaction in children and adults.** *Neural Plast* 2013;2013:639430 [CrossRef Medline](#)
 28. Dąmbska M, Wisniewski KE. *Normal and Pathologic Development of the Human Brain and Spinal Cord.* London: John Libbey; 1999
 29. Luders E, Thompson PM, Toga AW. **The development of the corpus callosum in the healthy human brain.** *J Neurosci* 2010;30:10985–90 [CrossRef Medline](#)
 30. Schafer DP, Custer AW, Shrager P, et al. **Early events in node of Ranvier formation during myelination and remyelination in the PNS.** *Neuron Glia Biol* 2006;2:69–79 [CrossRef Medline](#)

Differentiation of Hemorrhage from Iodine Using Spectral Detector CT: A Phantom Study

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ABSTRACT

BACKGROUND AND PURPOSE: Conventional CT often cannot distinguish hemorrhage from iodine extravasation following reperfusion therapy for acute ischemic stroke. We investigated the potential of spectral detector CT in differentiating these lesions.

MATERIALS AND METHODS: Centrifuged blood with increasing hematocrit (5%–85%) was used to model hemorrhage. Pure blood, blood-iodine mixtures (75/25, 50/50, and 25/75 ratios), and iodine solutions (0–14 mg I/mL) were scanned in a phantom with attenuation ranging from 12 to 75 HU on conventional imaging. Conventional and virtual noncontrast attenuation was compared and investigated for correlation with calculation of relative virtual noncontrast attenuation. Values for all investigated categories were compared using the Mann-Whitney *U* test. Sensitivity and specificity of virtual noncontrast, relative virtual noncontrast, conventional CT attenuation, and iodine quantification for hemorrhage detection were determined with receiver operating characteristic analysis.

RESULTS: Conventional image attenuation was not significantly different among all samples containing blood ($P > .05$), while virtual noncontrast attenuation showed a significant decrease with a decreasing blood component ($P < .01$) in all blood-iodine mixtures. Relative virtual noncontrast values were significantly different among all investigated categories ($P < .01$), with correct hemorrhagic component size estimation for all categories within a 95% confidence interval. Areas under the curve for hemorrhage detection were 0.97, 0.87, 0.29, and 0.16 for virtual noncontrast, relative virtual noncontrast, conventional CT attenuation, and iodine quantification, respectively. A ≥ 10 -HU virtual noncontrast, ≥ 20 -HU virtual noncontrast, $\geq 40\%$ relative virtual noncontrast, and combined ≥ 10 -HU virtual noncontrast and $\geq 40\%$ relative virtual noncontrast attenuation threshold had a sensitivity/specificity for detecting hemorrhage of 100%/23%, 89%/95%, 100%/82%, and 100%/100%, respectively.

CONCLUSIONS: Spectral detector CT can accurately differentiate blood from iodinated contrast in a phantom setting.

ABBREVIATIONS: ICH = intracranial hemorrhage; R-VNC = relative virtual noncontrast; SDCT = spectral detector CT; VNC = virtual noncontrast

Material with similar attenuation can be difficult to distinguish on conventional CT. A common clinical illustration of this problem is the differentiation of iodine from hemorrhage because both are hyperdense on conventional unenhanced CT. In patients with acute ischemic stroke, intra-arterial thrombolytic therapy has been shown to decrease morbidity and mortality.¹

However, it has also been reported that this increases the risk of intracranial hemorrhage (ICH), with reported frequencies of 10%–15% and mortality up to 83% for symptomatic ICH.^{2–7} Because of the disruption of the blood-brain barrier, contrast extravasation can occur during the procedure in 30%–50% of cases, impairing the detection of or the differentiation from ICH due to the overlap in density.^{5,8–11} As of this writing, unenhanced conventional CT is performed within 24 hours after treatment for the detection of complications. In case of unclear findings (eg, if differentiation between ICH and iodine extravasation is not possible), follow-up imaging may be performed. Hence, the ability to differentiate these 2 is highly desirable to avoid additional examinations and to ensure appropriate management.²

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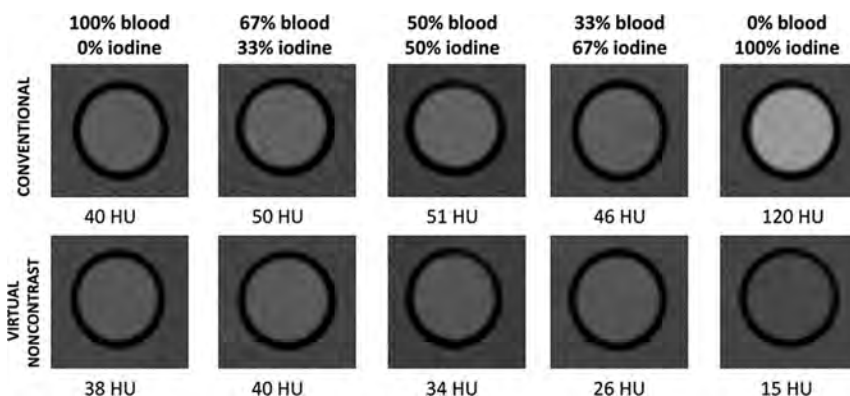


FIG 1. Comparison of the attenuation of diluted blood, iodine, and blood-iodine mixtures on conventional and virtual noncontrast images. There is an incremental decrease of VNC attenuation values with decreasing blood content, compared with conventional CT attenuation values.

Two major discriminators of attenuation within a voxel are the energy of the x-ray beam and the concentration of attenuating material in that voxel. The presence or concentration of each discriminator in that voxel therefore cannot be determined by performing a single attenuation measurement from a broad photon energy spectrum. However, in dual-energy CT, attenuation at different energies is registered. In single- and dual-source dual-energy Revolution CT, this is achieved using a fast-kilovolt(peak) switching x-ray source (GE Healthcare, Milwaukee, Wisconsin) or 2 x-ray sources and 2 detectors (Somatom Force, Siemens Healthineers, Forchheim, Germany), respectively. Spectral detector CT (SDCT) (IQon; Philips Healthcare, Best, the Netherlands) distinguishes low- and high-energy data at the level of the detector using a dual-layer detector. The bottom and top layer absorb high- and low-energy photons, respectively. The main advantage of the latter approach is that spectral data are collected without the need to prospectively choose a spectral scanning protocol or mode, as needed in other dual-energy CT approaches.

Previous studies have shown the potential of dual-energy CT for differentiating iodine from hemorrhage in clinical settings^{10,12-16}; however, no study has been performed using SDCT for this application nor has the sensitivity or specificity been determined in a phantom system.

In our study, we investigated the ability of SDCT to differentiate ICH from iodinated contrast in a phantom model.

MATERIALS AND METHODS

Image Acquisition

All scans were performed with a 464 Phantom (Gammex, Madison, Wisconsin) with a plastic 50-mL tube in its air cavity, filled with samples simulating hemorrhage (blood), diluted iodine, and a hemorrhage-iodine (blood-iodine) mixture. Each sample was scanned in the phantom with the following settings on the IQon SDCT scanner: 200 mAs, 120 kVp, pitch = 1, gantry rotation time = 330 ms, detector collimation = 64×0.625 mm, volume CT dose index = 18 mGy. Conventional CT images were reconstructed using an iterative reconstruction algorithm (iDose 4, Level 3; Philips Healthcare), while the spectral images were reconstructed using a spectral reconstruction algorithm (Spectral B, level 0). Reconstructed slice thickness was 3 mm. All scans were performed 3 times to account for interscan variability.

Sample Preparation

Previous studies have shown that the density of blood is primarily determined by the hemoglobin concentration.¹⁷ In turn, changes in hematocrit are reflected in the density of a hemorrhage seen on conventional CT.¹⁸ We collected discarded packed red blood cells and prepared samples to a range of 0%, 5%, 15%, 25%, 35%, 45%, 55%, 65%, 75%, and 85% hematocrit. The packed red blood cells were prepared using phosphate buffered saline to prevent cytotoxicity. Each sample was scanned with the protocol described above. Diluted iodine (Optiray 350, Ioversol; Mallinckrodt, St. Louis, Missouri) samples in

phosphate buffered saline, with concentrations ranging from 0 to 14 mg I/mL (0.00, 0.70, 1.40, 2.10, 2.80, 3.50, 4.20, 4.90, 5.60, 7.00, 14.00 mg I/mL) were scanned using the same protocol. We matched the iodine attenuation with the densities found for 85%, 75%, 65%, 55%, 45%, and 35% hematocrit to create iodine dilutions with matching densities (2.50, 2.10, 1.80, 1.40, 1.10, and 0.70 mg I/mL, respectively) at those hematocrit levels.

Blood-iodine mixtures with matching densities were scanned with following proportions: [2/3] blood + [1/3] iodine; + [1/2] blood + [1/2] iodine; [1/3] blood + [2/3] iodine.

Image Analysis

All image analysis was performed using the proprietary image viewer (Spectral Diagnostic Suite; Philips Healthcare) of the vendor. Each diluted blood, diluted iodine, and blood-iodine mixture sample was analyzed by placing a circular 2-cm² ROI centrally in the inserts. The attenuation on the conventional and virtual noncontrast (VNC) image (using VNC image) and iodine concentration (using the iodine density map) were measured within each ROI (Fig 1). Relative VNC (R-VNC) attenuation (%) is calculated using the following equation:

$$\text{R-VNC} = \frac{\text{Attenuation VNC}}{\text{Attenuation Conventional}} \times 100.$$

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 (IBM, Armonk, New York). Iodine-quantification measurements were compared with true iodine concentrations for correlation. Mean iodine quantification error (milligram/milliliter) was calculated and presented with a 95% confidence interval and Bland-Altman plot analysis. Attenuation in the conventional and VNC images was compared for correlation using the Pearson correlation. Attenuation on conventional images, VNC attenuation, and R-VNC are reported with 95% CIs for the investigated sample compositions (blood, [2/3] blood + [1/3] iodine; [1/2] blood + [1/2] iodine; [1/3] blood + [2/3] iodine, iodine) and compared by means of the Mann-Whitney *U* test. VNC attenuation for the samples containing blood was compared with the hematocrit in the samples for correlation. VNC attenuation, R-VNC attenuation, and attenuation on the conventional images were analyzed for sensitivity and speci-

ficity in detecting a hemorrhagic component. Receiver operating characteristic analysis was performed for conventional CT, VNC, R-VNC attenuation, and iodine quantification, and the corresponding areas under the curve with 95% CIs are reported. The difference among areas under the curve was assessed by the method of Hanley and McNeil.¹⁹ A *P* value < .05 was considered statistically significant.

RESULTS

Mean attenuation on the conventional and VNC images ($\pm$ 95% CI) for the pure blood samples was similar: respectively, 39.1 ± 31.5 – 46.7 HU and 39.1 ± 31.5 – 46.7 HU (Fig 2 and the Table). The blood-iodine mixtures, consisting of [2/3] blood + [1/3] iodine; [1/2] blood + [1/2] iodine; [1/3] blood + [2/3] iodine had almost identical attenuation values on conventional images: 49.48 ± 42.8 – 56.2 HU, 49.2 ± 41.7 – 56.7 HU, and 49.4 ± 42.2 – 56.6 HU, respectively. Meanwhile, the corresponding VNC attenuation values incrementally decreased with an increasing iodine fraction, measuring 40.4 ± 35.9 – 44.9 HU, 32.6 ± 28.6 – 36.6 HU, and 26.0 ± 23.3 – 28.6 HU, respectively.

Differences in attenuation on the conventional images among the different investigated compositions containing a blood component were not significant (*P* > .05). Conversely, VNC attenuation values were significantly different among samples containing 67% blood, 50% blood, and 33% blood, but not among samples consisting of 100% and 67% blood (*P* = .70).

Conventional and VNC attenuation correlated significantly

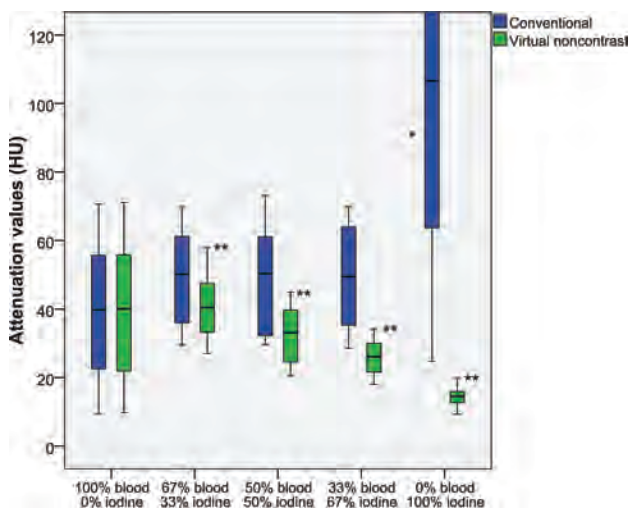


FIG 2. Attenuation values (HU) of diluted blood, blood-iodine mixtures, and diluted iodine on spectral detector CT conventional and virtual non-contrast images. There is a significant incremental decrease of VNC attenuation values with decreasing blood content. The asterisk indicates a significant difference of conventional CT attenuation compared with other compositions (*P* < .01); double asterisks, significant differences of VNC attenuation among these compositions (*P* < .01).

Attenuation values (HU) of diluted blood, blood-iodine mixtures, and diluted iodine on SDCT conventional and VNC images^a

	Conventional (HU)		VNC (HU)		R-VNC (%)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
100% blood–0% iodine	39.1	31.5–46.7	39.1	31.5–46.7	99.6	98.8–100.4
67% blood–33% iodine	49.5	42.8–56.2	40.4	35.9–44.9	82.8	79.5–86.1
50% blood–50% iodine	49.2	41.7–56.7	32.6	28.6–36.6	67.6	64.4–70.9
33% blood–67% iodine	49.4	42.2–56.6	26.0	23.3–28.6	54.3	50.6–58.0
0% blood–100% iodine	129.5	99.4–159.6	14.5	13.4–15.6	15.7	12.4–19.1

^a R-VNC attenuation (%) was calculated by comparing VNC attenuation with the attenuation on conventional CT for all investigated categories.

for all samples containing a blood component ($R^2 > 0.97$, *P* < .01). Correlation was highest for pure blood dilutions ($R^2 = 1.00$), followed by [2/3] blood + [1/3] iodine, [1/2] blood + [1/2] iodine mixtures, and it was lowest for samples containing [1/3] blood + [2/3] iodine ($R^2 = 0.97$).

Correlation between the hematocrit level in our samples and VNC attenuation was excellent ($R^2 = 0.97$, *P* < .01), while correlation with the attenuation on the conventional images was moderate, but still significant ($R^2 = 0.50$, *P* < .01) (Fig 3).

For the samples consisting only of diluted iodine, mean attenuation on conventional and VNC images ($\pm$ 95% CI) was 129.5 ± 99.4 – 159.6 HU and 14.5 ± 13.4 – 15.6 HU, respectively, which were both significantly different from other samples containing a blood component (*P* < .01) (Fig 2 and the Table). When one interprets these results, it is important to note that phosphate buffered saline has different attenuation properties from normal saline. The average attenuation of samples filled with only phosphate buffered saline was 8.5 and 8.3 HU on conventional and VNC images, respectively. Correlation between conventional and VNC attenuation for samples with pure iodine dilutions was not significant ($R^2 = 0.77$, *P* = .08).

The differences between R-VNC attenuation values of all compositions were significant (*P* < .01), as shown in Fig 4 and the Table. Mean R-VNC attenuation ($\pm$ 95% CI) for the pure blood, [2/3] blood – [1/3] iodine, [1/2] blood – [1/2] iodine, [1/3] blood – [2/3] iodine, and pure iodine was $99.59\% \pm 98.8\%$ – 100.4% , $82.8\% \pm 79.5\%$ – 86.1% , $67.6\% \pm 64.4\%$ – 70.9% , $54.3\% \pm 50.6\%$ – 58.0% , and $15.7\% \pm 12.4\%$ – 19.1% . There was no overlap within the 95% CI between R-VNC values for all compositions, contrary to VNC values in which all samples containing blood showed overlap.

There was a significant correlation between measured and true iodine concentrations ($R^2 > 0.99$, *P* < .01), with a mean iodine quantification error of -0.41 ± 0.31 – 0.50 mg/mL (Fig 5).

Receiver operating characteristic curve analysis for hemorrhagic-component detection showed a significant difference among areas under the curve (*P* < .01), being highest for VNC attenuation (0.97 ± 0.94 – 0.99 HU), followed by R-VNC attenuation (0.87 ± 0.77 – 0.97 HU) and attenuation in the conventional CT images (0.29 ± 0.16 – 0.41 HU), and lowest for iodine quantification (0.16 ± 0.06 – 0.25 HU) (Fig 6A); these differences were significant (*P* < .01). Using a threshold of ≥ 10 and ≥ 20 HU for VNC had a sensitivity/specificity of 100%/23% and 89%/95%, respectively. An R-VNC attenuation of $\geq 40\%$ had a sensitivity/specificity of 100%/82%. Conversely, using a threshold of ≥ 10 and ≥ 20 HU on the conventional CT images had a sensitivity/specificity of 100%/13% and 94%/15%, respectively (Fig 6).

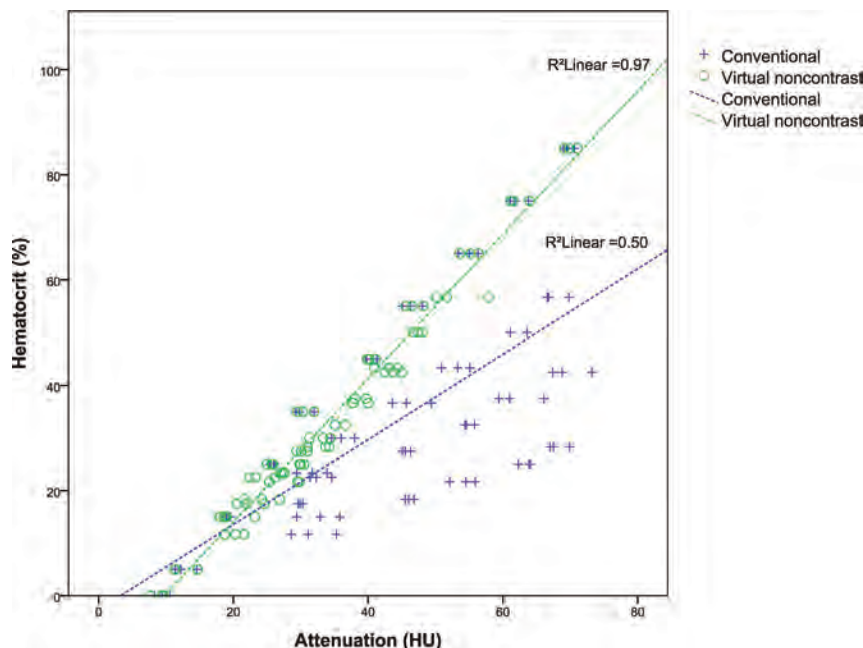


FIG 3. Correlation between the hematocrit in our dilutions and the attenuation in the conventional and VNC images.

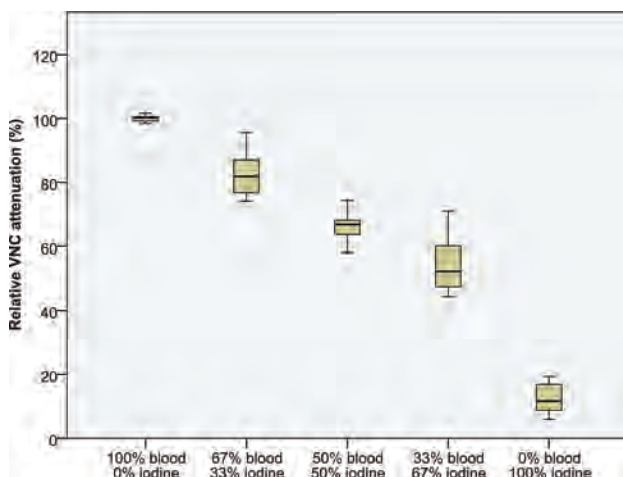


FIG 4. Relative VNC attenuation (%), by comparing VNC attenuation with the attenuation on conventional CT for all investigated categories (diluted blood, blood-iodine mixtures, and diluted iodine). R-VNC values among all compositions were significantly different ($P < .01$).

DISCUSSION

Our results show that SDCT has excellent diagnostic accuracy for differentiating blood from iodinated contrast in a phantom. We observed similar sensitivity and specificity (both $>90\%$) for hemorrhage detection using spectral dual-layer VNC images, compared with previous clinical studies that used single- or dual-source dual-energy CT.^{10,13,15} These studies used visual assessment by radiologists for classifying hyperdensities on “simulated” conventional head CT images as hemorrhage or iodine; hyperdensities visible on VNC images were classified as having a hemorrhagic component. Although typical ICHs are hyperdense (>50 HU), they can be associated with a lower density due to anticoagulation, the presence of CSF with arachnoid laceration, or severe anemia (eg, sickle cell anemia), which can complicate

subjective assessment.²⁰⁻²⁹ Our results show high accuracy by quantitative VNC assessment for blood detection, including low densities on conventional images (as low as 10 HU). By combining a ≥ 10 HU VNC and $\geq 40\%$ R-VNC cut-off, we observed a sensitivity and specificity of 100% for blood, including low densities and mixtures with iodine on conventional images (Fig 6).

Several authors have investigated the accuracy of SDCT for material decomposition, which allows iodine to be subtracted from an image. These studies have shown high accuracy for iodine-quantification and VNC attenuation values, though results vary. Our results show slightly lower iodine-quantification accuracy than recent publications, which can be explained by the extremely low iodine concentrations needed in our study, though results are still excellent.

We had results comparable with those of Pelgrim et al,³⁰ which showed a median

error of -0.6 mg/mL, while more recent studies showed differences ranging from -0.46 to 0.1 mg/mL.³¹ Regarding VNC, Duan et al³¹ showed good agreement between measured spectral detector VNC attenuation values and reference standards (-9.95 – 6.41 HU), confirmed by our study. Still, VNC inaccuracies can occur. When we incorporated a comparison of the attenuation between VNC and conventional images, small inaccuracies of true VNC values can be negated, which can explain the excellent results of R-VNC in our study for hemorrhage detection (100% sensitivity and 82% specificity) and size estimation (Figs 4 and 5).

Clinical studies using SDCT differentiating iodine from blood in skull imaging have been rare. As of this writing, the authors found only a pilot study from Cho et al,³² showing that spectral data analysis can be helpful in discriminating ICH from contrast enhancement in intracranial malignancies. Regarding the detection of hemorrhage, a recent study of Nute et al³³ used single-source dual-energy CT for distinguishing ICH from calcification in a phantom model with densities from 40 to 100 HU, resulting in an accuracy of $>90\%$.

There are several limitations to our study. First, our results are without clinical data because this was not within the scope of our investigation. Our goal was to investigate in a phantom setting. Second, our hemorrhage dilutions were prepared with phosphate buffered saline to prevent red blood cell hemolysis, but this could potentially bias the attenuation characteristics of blood and iodine in our results: Phosphate buffered saline is not representative of brain tissue in a clinical setting. Third, our mixtures were homogeneously mixed for optimal spectral analysis, which may not always be the case in a clinical setting. Last, we used a relatively large 2-cm^2 ROI for our measurements, so our results could not be affected by spatial resolution and partial volume limitations. This might not always be feasible in patients if the size of the clinical ROI is small.

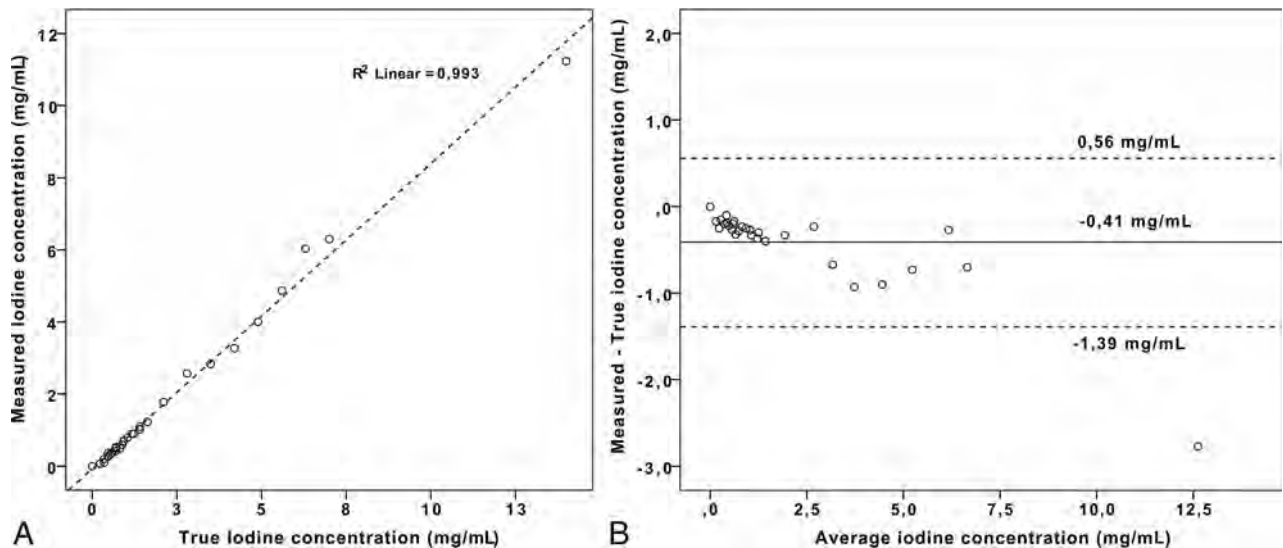


FIG 5. Results of the iodine quantification measurements by comparison of measured-to-true iodine concentrations (A) and errors in iodine quantification measurements by a Bland-Altman plot (B). A, Correlation between measured and true iodine concentrations is excellent ($R^2 > 0.99$, $P < .01$). B, Mean iodine quantification error ($\pm$ 95% CI) was -0.41 ± 0.31 – 0.50 mg/mL.

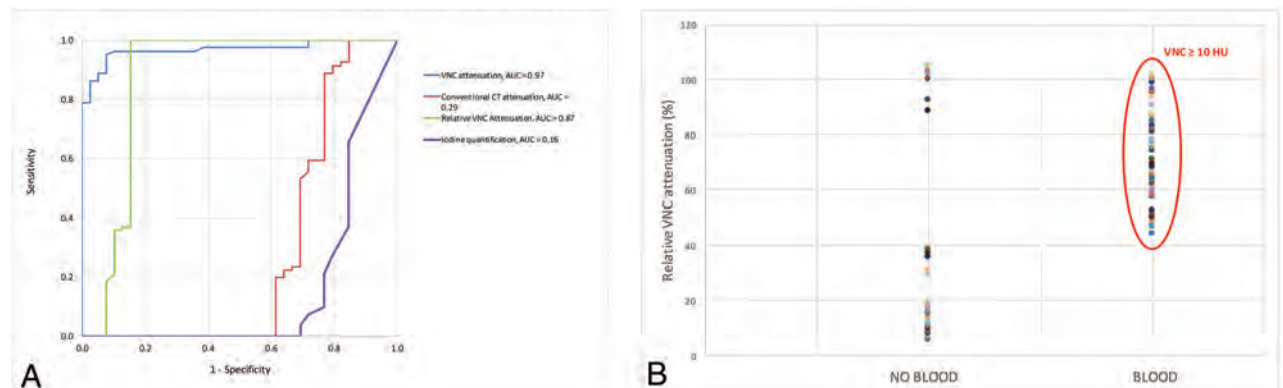


FIG 6. Performance of conventional CT attenuation, virtual noncontrast attenuation, and relative VNC attenuation for the detection of blood. A, Receiver operating characteristic curve analysis shows the highest area under the curve for VNC (0.97 ± 0.94 – 0.99), followed by R-VNC attenuation (0.87 ± 0.77 – 0.97) and attenuation in the conventional CT images (0.29 ± 0.16 – 0.41), and the area under the curve was lowest for iodine quantification (0.16 ± 0.06 – 0.25). B, When we combined a $\geq 40\%$ R-VNC (dashed line) and ≥ 10 HU VNC cutoff, there is 100% differentiation between blood-containing (diluted blood and blood-iodine mixtures) and diluted iodine samples.

CONCLUSIONS

Our results show that the added spectral information of SDCT has high sensitivity and specificity in detecting blood and can accurately estimate hemorrhagic component size, including when mixed with iodine. This information could be of potential benefit in brain imaging for patients following reperfusion therapy in acute stroke.

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our existing Master Research Agreement. No direct funds were received*; *OTHER RELATIONSHIPS:* hospital grant from Philips regulated by Master Research Agreement, consisting of a Spectral Detector CT unit. David Jordan—*RELATED: Grant:* Philips Healthcare, *Comments:* The IQon CT scanner was provided to University Hospitals Cleveland Medical Center under a research agreement*; *UNRELATED: Payment for Lectures Including Service on Speakers Bureaus:* Medical Technology Management Institute/Herzing University, *Comments:* paid speaker for continuing education programs for medical physicists. Kai Roman Laukamp—*RELATED: Grant:* Philips Healthcare, *Comments:* Philips Healthcare provided partial funding*. *Money paid to the institution.

REFERENCES

1. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. **Tissue plasminogen activator for acute ischemic stroke.** *N Engl J Med* 1995;333:1581–87 [CrossRef Medline](#)
2. Mokin M, Kan P, Kass-Hout T, et al. **Intracerebral hemorrhage secondary to intravenous and endovascular intraarterial revascularization therapies in acute ischemic stroke: an update on risk factors, predictors, and management.** *Neurosurg Focus* 2012;32:E2 [CrossRef Medline](#)
3. Fiorelli M, Bastianello S, von Kummer R, et al. **Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European**

- Cooperative Acute Stroke Study I (ECASS I) cohort. *Stroke* 1999;30:2280–84 [CrossRef Medline](#)
4. Nakano S, Iseda T, Kawano H, et al. Parenchymal hyperdensity on computed tomography after intra-arterial reperfusion therapy for acute middle cerebral artery occlusion: incidence and clinical significance. *Stroke* 2001;32:2042–48 [CrossRef Medline](#)
5. Yoon W, Seo JJ, Kim JK, et al. Contrast enhancement and contrast extravasation on computed tomography after intra-arterial thrombolysis in patients with acute ischemic stroke. *Stroke* 2004;35:876–81 [CrossRef Medline](#)
6. Yedavalli V, Sammet S. Contrast extravasation versus hemorrhage after thrombectomy in patients with acute stroke. *J Neuroimaging* 2017;27:570–76 [CrossRef Medline](#)
7. Greer DM, Koroshetz WJ, Cullen S, et al. Magnetic resonance imaging improves detection of intracerebral hemorrhage over computed tomography after intra-arterial thrombolysis. *Stroke* 2004;35:491–95 [CrossRef Medline](#)
8. Jang YM, Lee DH, Kim HS, et al. The fate of high-density lesions on the non-contrast CT obtained immediately after intra-arterial thrombolysis in ischemic stroke patients. *Korean J Radiol* 2006;7:221–28 [CrossRef Medline](#)
9. Mericle RA, Lopes DK, Fronckowiak MD, et al. A grading scale to predict outcomes after intra-arterial thrombolysis for stroke complicated by contrast extravasation. *Neurosurgery* 2000;46:1307–14; discussion 14–15 [CrossRef Medline](#)
10. Gupta R, Phan CM, Leidecker C, et al. Evaluation of dual-energy CT for differentiating intracerebral hemorrhage from iodinated contrast material staining. *Radiology* 2010;257:205–11 [CrossRef Medline](#)
11. Yokogami K, Nakano S, Ohta H, et al. Prediction of hemorrhagic complications after thrombolytic therapy for middle cerebral artery occlusion: value of pre- and post-therapeutic computed tomographic findings and angiographic occlusive site. *Neurosurgery* 1996;39:1102–07 [CrossRef Medline](#)
12. Siddiqui FM, Bekker SV, Qureshi AI. Neuroimaging of hemorrhage and vascular defects. *Neurotherapeutics* 2011;8:28–38 [CrossRef Medline](#)
13. Tijssen MP, Hofman PA, Stadler AA, et al. The role of dual energy CT in differentiating between brain haemorrhage and contrast medium after mechanical revascularisation in acute ischaemic stroke. *Eur Radiol* 2014;24:834–40 [CrossRef Medline](#)
14. Nute JL, Le Roux L, Chandler AG, et al. Differentiation of low-attenuation intracranial hemorrhage and calcification using dual-energy computed tomography in a phantom system. *Invest Radiol* 2015;50:9–16 [CrossRef Medline](#)
15. Phan CM, Yoo AJ, Hirsch JA, et al. Differentiation of hemorrhage from iodinated contrast in different intracranial compartments using dual-energy head CT. *AJNR Am J Neuroradiol* 2012;33:1088–94 [CrossRef Medline](#)
16. Hu R, Padole A, Gupta R. Dual-energy computed tomographic applications for differentiation of intracranial hemorrhage, calcium, and iodine. *Neuroimaging Clin N Am* 2017;27:401–09 [CrossRef Medline](#)
17. New PF, Aronow S. Attenuation measurements of whole blood and blood fractions in computed tomography. *Radiology* 1976;121(3 Pt. 1):635–40 [CrossRef Medline](#)
18. Bergström M, Ericson K, Levander B, et al. Variation with time of the attenuation values of intracranial hematomas. *J Comput Assist Tomogr* 1977;1:57–63 [CrossRef Medline](#)
19. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143:29–36 [CrossRef Medline](#)
20. Grelat M, Madkouri R, Bousquet O. Acute isodense subdural hematoma on computed tomography scan—diagnostic and therapeutic trap: a case report. *J Med Case Rep* 2016;10:43 [CrossRef Medline](#)
21. Lee KS, Bae WK, Bae HG, et al. The computed tomographic attenuation and the age of subdural hematomas. *J Korean Med Sci* 1997;12:353–59 [CrossRef Medline](#)
22. Boyko OB, Cooper DF, Grossman CB. Contrast-enhanced CT of acute isodense subdural hematoma. *AJNR Am J Neuroradiol* 1991;12:341–43 [Medline](#)
23. Mendonça R, Lima TT, Dini LI, et al. Bilateral isodense epidural hematoma: case report. *Arq Neuropsiquiatr* 2005;63:862–63 [CrossRef Medline](#)
24. May PL, Miles JB. Acute isodense extradural haematoma. *Br J Neurosurg* 1989;3:221–24 [CrossRef Medline](#)
25. Rieth KG, Schwartz FT, Davis DO. Acute isodense epidural hematoma on computed tomography. *J Comput Assist Tomogr* 1979;3:691–93 [CrossRef Medline](#)
26. Harbury OL, Provenzale JM, Barboriak DP. Vertex epidural hematomas: imaging findings and diagnostic pitfalls. *Eur J Radiol* 2000;36:150–57 [CrossRef Medline](#)
27. Claes F, Verhagen CV, Verhagen WI, et al. Acute isodense intracerebral haematoma due to coagulopathy associated with prostate cancer. *Clin Neurol Neurosurg* 2007;109:520–22 [CrossRef Medline](#)
28. Kaufman HH, Singer JM, Sadhu VK, et al. Isodense acute subdural hematoma. *J Comput Assist Tomogr* 1980;4:557–59 [CrossRef Medline](#)
29. Thust SC, Burke C, Siddiqui A. Neuroimaging findings in sickle cell disease. *Br J Radiol* 2014;87:20130699 [CrossRef Medline](#)
30. Pelgrim GJ, van Hamersvelt RW, Willemink MJ, et al. Accuracy of iodine quantification using dual energy CT in latest generation dual source and dual layer CT. *Eur Radiol* 2017;27:3904–12 [CrossRef Medline](#)
31. Duan X, Arbique G, Guild J, et al. Technical note: quantitative accuracy evaluation for spectral images from a detector-based spectral CT scanner using an iodine phantom. *Med Phys* 2018;45:2048–53 [CrossRef Medline](#)
32. Cho SB, Baek HJ, Ryu KH, et al. Initial clinical experience with dual-layer detector spectral CT in patients with acute intracerebral haemorrhage: a single-centre pilot study. *PLoS One* 2017;12:e0186024 [CrossRef Medline](#)
33. Nute JL, Jacobsen MC, Chandler A, et al. Dual-energy computed tomography for the characterization of intracranial hemorrhage and calcification: a systematic approach in a phantom system. *Invest Radiol* 2017;52:30–41 [CrossRef Medline](#)

Abnormal Cerebral Perfusion Profile in Older Adults with HIV-Associated Neurocognitive Disorder: Discriminative Power of Arterial Spin-Labeling

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ABSTRACT

BACKGROUND AND PURPOSE: The aging HIV-infected (HIV⁺) population has increased vascular comorbidities, including stroke, and increased cognitive deficits compared with the general population. Arterial spin-labeling is a technique to measure cerebral blood flow and is more sensitive than regional volume loss in assessing neurodegenerative diseases and cognitive aging. Previous studies have found global cerebral perfusion abnormalities in the HIV⁺ participants. In this study, we evaluated the specific regional pattern of CBF abnormalities in older HIV⁺ participants using quantitative whole-brain arterial spin-labeling.

MATERIALS AND METHODS: CBF data from the UCSF HIV Over 60 Cohort and the Alzheimer Disease Neuroimaging Initiative were retrospectively evaluated to identify 19 HIV⁺ older adults, all with plasma viral suppression (including 5 with HIV-associated neurocognitive disorder); 13 healthy, age-matched controls; and 19 participants with early mild cognitive impairment. CBF values were averaged by ROI and compared among the 3 groups using generalized linear models.

RESULTS: When we accounted for age, education, sex, and vascular risk factors, the HIV⁺ participants demonstrated alterations in regional cerebral perfusion, including hypoperfusion of bilateral temporal, parietal, and occipital brain regions compared with both clinically healthy participants and those with mild cognitive impairment. Arterial spin-labeling showed reasonable test characteristics in distinguishing those with HIV-associated neurocognitive disorder from healthy controls and participants with mild cognitive impairment.

CONCLUSIONS: This study found specific CBF patterns associated with HIV status despite viral suppression—data that should animate further investigations into the pathobiologic basis of vascular and cognitive abnormalities in HIV-associated neurocognitive disorders.

ABBREVIATIONS: ADNI = Alzheimer Disease Neuroimaging Initiative cohort; ASL = arterial spin-labeling; GLMnet = generalized linear model via penalized maximum likelihood; HAND = HIV-associated neurocognitive disorders; HC = healthy controls; HIV⁺ = HIV-infected; MCI = mild cognitive impairment; MND = mild neurologic disorder; MND = mild neurocognitive disorder

By 2013, >25% of the HIV-infected (HIV⁺) population in the United States was older than 55 years of age, a number projected to double by 2045.¹ In this same population, the prevalence of HIV-associated neurocognitive disorders (HAND) in the United States may be up to 50%, despite access to antiretroviral therapy.² Cerebrovascular risk factors are prevalent in the aging

HIV⁺ population. These individuals face increased vascular comorbidities, including stroke, as well as cognitive deficits above those of the general population.^{3,4} While the pathobiologic basis of vascular and cognitive abnormalities in HAND is unclear,⁵ studies implicate injury to the neurovascular endothelium because HIV itself can induce endothelial dysfunction and capillary loss.⁶ Indeed, virally suppressed HIV⁺ participants have gene-expression profiles suggesting neurovascular endothelial dysfunction.⁷⁻⁹ In this context, neuroimaging studies of HIV⁺ participants consistently demonstrated increased white matter intensities¹⁰⁻¹² as well as altered cerebrovascular reactivity and autoregulation.^{13,14} Given that small-vessel ischemic disease is associated with reduced cerebral perfusion across time¹⁵ and hypoperfusion acts as precursor to volume loss in other neurodegenerative diseases,^{16,17} several investigators have found global cerebral perfusion abnormalities in the HIV⁺ population.¹⁸⁻²¹ The current study evaluated the specific regional pattern of CBF abnormalities in older HIV⁺ virally suppressed

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Sample size and demographic characteristics of the cohort

	HIV ⁺	HC	MCI
No. of participants	19	13	19
HAND-MND diagnosis	5	—	—
Age (mean) (minimum, maximum) (yr)	66.31 ± 3.09 (61, 72)	69.28 ± 4.73 (60, 74)	65.83 ± 4.19 (59, 74)
Years of education (mean)	16.74 ± 2.26	16.38 ± 2.69	16.47 ± 2.93
Sex	18 M, 1 F	13 M, 0 F	19 M, 0 F
HIV variables			
CD4 count (mean) (cells/mm ³)	651.17 ± 223.98	—	—
CD4 nadir (mean)	208.65 ± 176.35	—	—
Years since diagnosis (mean)	21.5 ± 7	—	—
Undetectable viral load (% of participants)	100%	—	—
Cerebrovascular risk factors			
Myocardial infarct (No.) (%)	1 (5.2%)	0 (0%)	0 (0.0%)
Stroke (No.) (%)	0 (0%)	1 (7.7%)	0 (0.0%)
Diabetes (No.) (%)	2 (10.5%)	0 (0.0%)	0 (0.0%)
History of smoking (No.) (%)	10 (52.6%)	8 (61.5%)	8 (42.1%)
Hypertension history (No.) (%)	9 (47.3%)	4 (30.8%)	7 (36.8%)
Hypercholesterol history (No.) (%)	11 (57.9%)	11 (84.6%)	11 (57.9%)

Note: — indicates a variable which is inapplicable to the subject group.

participants using quantitative whole-brain arterial spin-labeling (ASL).

MATERIALS AND METHODS

Participants

This study was based on 19 available cross-sectional brain MRIs from older HIV⁺ individuals enrolled in a larger cohort study of cognition in HIV⁺ individuals older than 60 years of age (UCSF HIV Over 60 Cohort) that explored the relationship between HIV and aging.²² Five HIV⁺ participants in the study (26.3%) had mild neurocognitive disorder (MND) according to the Frascati criteria,²³ a HAND subcategory. To compare ASL scans from HIV⁺ participants and those with mild cognitive impairment (MCI),²⁴ we matched participants with MCI and healthy controls (HC) to the HIV participants by age, sex, and education (Table). The matched brain scans of HC and MCI participants were obtained as a part of the Alzheimer Disease Neuroimaging Initiative cohort (ADNI-2), which included ASL (inclusion/exclusion criteria at www.adni-info.org). Participants with MCI had Mini-Mental State Examination scores of >23; objective memory loss as shown on scores on delayed recall of the Wechsler Memory Scale Logical Memory II (0.5–1.5 SDs below the normal mean); a Clinical Dementia Rating scale score of 0.5 in preserved activities of daily living; and absence of dementia. All HC had Mini-Mental State Examination scores of >24 and Clinical Dementia Rating scale scores of 0. A *t* test was used to compare the distributions of age and education between those who were HIV⁺ and HC and between those who were HIV⁺ and participants with MCI, after checking that populations were normally distributed (Shapiro-Wilk test) and had the same variance (*F* test).

Cerebrovascular risk factors such as diabetes, hypertension, and hypercholesterolemia were identified through either self-report, medication list, or medical chart review and/or clinical data captured during the research visit. A 12-hour fasting serum level was obtained within 3 months of neuroimaging. Diabetes was defined as a fasting glucose level of >125 mg/dL or a current clinical diagnosis from medical history. “Hypertension” was defined as having a systolic blood pressure of >140 mm Hg or a diastolic blood pressure of >90 mm Hg; and

“hypercholesterolemia,” as having a fasting low-density lipoprotein level of >160 mg/dL, a total cholesterol level of >200 mg/dL, and/or a current clinical diagnosis from medical history. “Smoking history” was defined as total tobacco use of >100 cigarettes in a lifetime.

ASL Acquisition

ASL was performed on a 3T MR imaging machine from a single vendor (Magnetom Skyra; Siemens, Erlangen, Germany) using a pulsed ASL method (quantitative imaging of perfusion using a single subtraction [QUIPPS] II with thin-slice T1 periodic saturation) with echo-planar imaging.²⁵ Details of ASL data acquisition and processing are available on-line at adni.loni.usc.edu. Imaging parameters of the ASL scan used the ADNI-2 protocol: FOV = 256 mm, matrix = 64 × 64, TR = 3400 ms, TE = 12 ms, TI = 700 ms, total transit time of the spins (T2) = 1900 ms, tag thickness = 100 mm, tag-to-proximal slice gap = 25.4 mm, 24 axial slices, slice thickness = 4 mm, time lag between slices = 2.5 ms.

ASL Preprocessing

All ASL images were preprocessed using an extensively described pipeline.^{16,17} The ADNI investigator (D.T.) provided methods for quantitation of ASL data. Briefly, perfusion-weighted images were computed by taking the difference between the mean-tagged and the mean-untagged ASL images. The first untagged ASL image (providing a full relaxed MR imaging signal) was used as a reference image of the water density and used to calibrate the ASL signal for computing CBF and to estimate the transformation to coregister ASL and structural MR imaging.

Geometric Distortion-Correction and Structural-to-ASL Coregistration

To accomplish registration between CBF and structural MR imaging maps, we augmented linear transformation with 9 *df* based on normalized mutual information by a nonlinear registration approach based on total variance.²⁶

ASL Partial Volume Effect Correction

The analysis aimed to measure blood flow in primarily gray matter tissue. To correct for gray/white matter partial volume effects, we adjusted the scaled perfusion-weighted image intensities according to a linear model of gray and white matter contributions to the ASL signal and on the basis of probabilistic segmentation of gray and white matter densities in each MR imaging voxel. Adjustments were made assuming a constant ratio between gray and white matter perfusion, and the scaled reference image was adjusted assuming constant ratios between gray matter and water, white matter and water, and CSF and water.

Computation of CBF

The scaled distortion-corrected coregistered and partial volume-corrected perfusion-weighted images were normalized to the reference image to express the ASL signal in physical units of arterial water density as CBF (Milliliters/100 g $\times$ Minute).

Structural MR Imaging Acquisition

Structural MR imaging was also acquired within the ADNI-2 and ADNI Grand Opportunities protocols for registration purposes using a T1-weighted 3D MPRAGE sequence with the following acquisition parameters: TR = 2300 ms, TE = 2.98 ms, flip angle = 9°, FOV = 256 mm, resolution = $1.1 \times 1.1 \times 1.2$ mm³.

ROIs

FreeSurfer (surfer.nmr.mgh.harvard.edu) was used to generate anatomic ROI statistics for CBF and volume. Eighty-two brain regions from the left and right hemispheres were used in the analysis. Areas excluded from the analysis were the brain stem, corpus callosum, ventricles, CSF, cerebellum, choroid plexus, vessels, and optic chiasm, in both the left and right hemispheres. The left sensory cortex (postcentral gyrus) was considered a reference region where no changes were expected and was used to standardize the CBF values of the other brain regions. Moreover, CBF values were adjusted to account for volume differences among ROIs.

Statistical Analysis

Because the purpose of this study was to investigate a specific pattern in CBF impairment in HIV⁺ participants compared with HC and those with MCI, the CBF by brain regions and possible confounder factors were used as predictors of participant diagnosis (HIV⁺ versus HC and HIV⁺ versus MCI) under the hypothesis that if CBF in specific brain regions can be used to predict the participant diagnosis, the CBF pattern differs between HIV⁺ and HC (or MCI). All statistical analyses were performed in R (<http://www.r-project.org/>).²⁷ HC and participants with MCI were frequency matched to HIV⁺ participants as to age, sex, and education (2.5 SDs); however, age and education were still used in the analysis to adjust for any residual confounding.

The analyses were divided into 2 steps: 1) to create a predictive model to differentiate those HIV⁺ from HC (respectively MCI) based on CBF, and 2) to perform casual inference by identifying the key CBF brain regions that are different between the diagnostic groups. Because of these goals, the high dimensionality of the data (82 brain regions versus 32 participants), and the high degree of multicollinearity in the data, a generalized linear model via

penalized maximum likelihood (GLMnet),²⁸ was used to model the data. Given that our outcome variables were dichotomous (HIV⁺ versus HC and HIV⁺ versus MCI), the binomial family was used (logistic elastic net regression). This model uses a penalty value (L2 penalty term in the sum of squared error loss function) to shrink coefficients of correlated predictors toward each other. An additional parameter (α) combines the L1 penalty (number of zero coefficients) and L2 penalty terms. In the current modeling strategy, 10-fold cross-validation was used to optimize these 2 hyperparameters. Additionally, all predictors were centered and scaled in the analysis. Missing data were compared between groups and brain regions to ensure that imputation was acceptable.²⁹

For both analyses (HIV⁺ versus HC and HIV⁺ versus MCI), the data were resampled 500 times by bootstrapping to ensure stable parameter estimates from the GLMnet model. At each iteration of the bootstrap, the data were randomly split into a training and test set (60% and 40%, respectively) and a GLMnet model was fit using 10-fold cross-validation of the training set. The counts for each predictor, predictor coefficients, and accuracies of the model to predict participant classification on the left-out test set were collected at each iteration. Frequency bar charts of the accuracy, specificity, and sensitivity values were plotted.

Although elastic GLMnet regression does not generate a *P* value,³⁰ the mean coefficient value for each brain region and corresponding 95% confidence intervals can be calculated from the bootstrap coefficient distribution. Thus, these were used to compute the odds ratios associated with each brain region by exponentiating the mean coefficients identified in the GLMnet model. The interpretation of an OR > 1 is that an increase of CBF in the corresponding brain region resulted in an increase of the likelihood of being classified as an HIV⁺ participant. The ORs were plotted as dot-whisker plots to inspect how each brain region contributed to the ability of the model to distinguish HIV⁺ participants from controls. Visual explanation of the processing pipeline used to obtain the model coefficients is see in On-line Fig 1.

Effect of HAND Status on CBF

As stated in the Table, 5 participants with HAND (categorized as MND) were among the HIV⁺ participants. To study the effect of HAND diagnosis on the results of the GLMnet regression for all HIV⁺ participants' CBF (sensitivity analysis), a GLMnet model was computed and bootstrapped 50 times with the whole cohort and again excluding the 5 participants with HAND-MND. To study the differences between the 2 sets of models, the mean coefficients for each brain region and demographic predictor were computed for each technique (including or excluding participants with HAND-MND HIV⁺) and the differences in mean coefficients were compared with the SD associated with the corresponding predictor.

RESULTS

Participant Characteristics

Nineteen HIV⁺, 13 age- and education frequency-matched HC and 19 age- and education frequency-matched participants with MCI were included in these analyses (Table). For all participants,

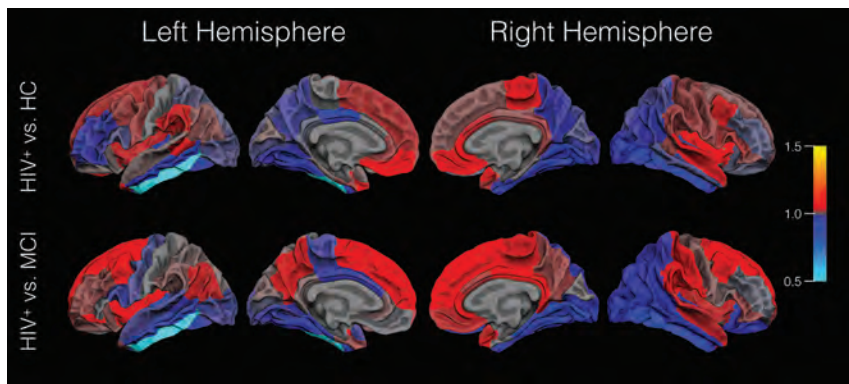


FIG1. Odds ratio from the GLMnet model averaged over 500 bootstrap iterations. Reductions in CBF in bilateral temporal, occipital, and posterior cingulate regions best distinguish HIV⁺ participants from HC (blue, hypoperfusion). This same pattern of reduced CBF distinguishes HIV⁺ from MCI, while the latter shows comparative reductions in frontal CBF (red, hyperperfusion in HIV⁺ participants relative to MCI).

age ranged from 59 to 74 years old, and education ranged from 12 to 21 years. All HIV⁺ participants had suppressed plasma HIV RNA levels. There were 98% male participants in the whole cohort (Table). The HIV⁺ group included 5 participants with HAND-MND meeting the criteria for MND, and 14 cognitively healthy HIV⁺ participants. No participants met the criteria for HIV-associated dementia or asymptomatic neurocognitive impairment. Cardiovascular and cerebrovascular risk factors were present within the HIV⁺ group in proportions similar to those in the HC and MCI groups (Table).

ROI CBF Alterations

Odds ratios from the GLMnet analysis were evaluated for 82 brain regions. Figure 1 shows the whole-brain patterns of CBF changes in each diagnostic group (HIV⁺, HC, MCI). Cold colors reflect hypoperfusion used to accurately distinguish HIV⁺ participants from the second group (HC or participants with MCI). Hot colors reflect relative hyperperfusion in HIV⁺ participants compared with the second group. HIV⁺ participants are distinguished by bilateral occipital, posterior cingulate, and bilateral temporal lobe hypoperfusion relative to HC. Compared with those with MCI, HIV⁺ participants are distinguished by a pattern of bilateral temporal, posterior cingulate, and occipital hypoperfusion and bilateral frontoinsular hyperperfusion. The complete dataset of regional odds ratios is shown in Fig 2.

Performances of the Elastic Net Regression

The elastic net regression performed prediction of HIV⁺ versus HC with a median accuracy of 0.75, a median sensitivity of 0.87, and a median specificity of 0.57; and a prediction of HIV⁺ versus MCI with a median accuracy of 0.73, a median sensitivity of 0.75, and a median specificity of 0.71. The frequency distributions of accuracy, sensitivity, and specificity over the bootstrap are shown in Fig 3.

Effect of HAND Status on CBF

On-line Fig 2 shows the difference of mean coefficients in the GLMnet models for regional CBF when including or excluding HAND-MND from HIV⁺ participants (gray bars) compared with the SD associated with the corresponding predictor (black

lines) for the 2 models (HIV⁺ versus HC and HIV⁺ versus MCI). A difference in mean coefficients smaller than the associated SD was observed for all brain regions and for both models, suggesting that the presence of participants with HAND-MND was not driving CBF abnormalities in specific regions or predictors for HIV⁺ compared with HC or participants with MCI.

DISCUSSION

We demonstrate a significant effect of HIV⁺ status on regional CBF compared with age-, sex-, and education-matched controls. Based on prior work,¹⁸⁻²¹ our primary hypothesis was that a pattern of regional cerebral hypoperfusion in HIV

despite plasma viral suppression would discriminate HIV⁺ participants from HIV-negative participants and from those with MCI. Our data suggest a pattern of hypoperfusion in HIV that involves bilateral temporal and occipital regions previously noted to be affected by longitudinal volumetric reductions²² in a larger sample of the same cohort (UCSF HIV Over 60 Cohort). Moreover, regional cortical thickness reductions in temporal and occipital regions were related to poor neuropsychological performance in other cohorts of treated virally suppressed HIV⁺ participants.³¹ Most important, given volume correction as part of our data, our findings cannot be explained by structural variations in these participants; the reduction in CBF reflects perfusion within volumes rather than the effects of volume loss. These data and distribution of abnormalities are in keeping with a prior ASL analysis that was restricted to a limited set of brain slices.¹⁸ These results suggested that an older cohort of HIV⁺ participants demonstrated a CBF profile that might suggest the diagnosis of HAND rather than MCI.

Few studies have evaluated quantitative CBF changes in viral-suppressed HIV⁺ participants. Ances et al¹⁸ evaluated mostly untreated HIV⁺ participants with ASL without whole-brain coverage due to technical limitations of the available ASL technology at the time. Nonetheless, they found reduced CBF in bilateral occipital volumes and the lenticular nucleus. This prior work represents a profile of a different population, primarily of a young age and detectable viral load. More recently, Su et al²³ evaluated mean gray matter CBF using whole-brain ROIs, demonstrating reduced CBF in HIV⁺ participants on antiretroviral therapy. Most important, the current study includes assessment of the vascular comorbidities that often accompany HIV⁺ status.³² In our study, HIV⁺ participants demonstrated similar rates of smoking, hypertension, and hypercholesterolemia compared with matched healthy controls and participants with MCI, though 2 HIV⁺ participants had a history of diabetes.

As the HIV⁺ population reaches geriatric age, differentiating HAND from early-stage Alzheimer disease has become a pressing HIV concern.²⁴ HIV-infected elders have higher rates of meeting the criteria for MCI, an intermediate state between typical cognitive aging and dementia in HIV-uninfected patient populations.³³ Comprehensive cognitive testing may discriminate the cognitive

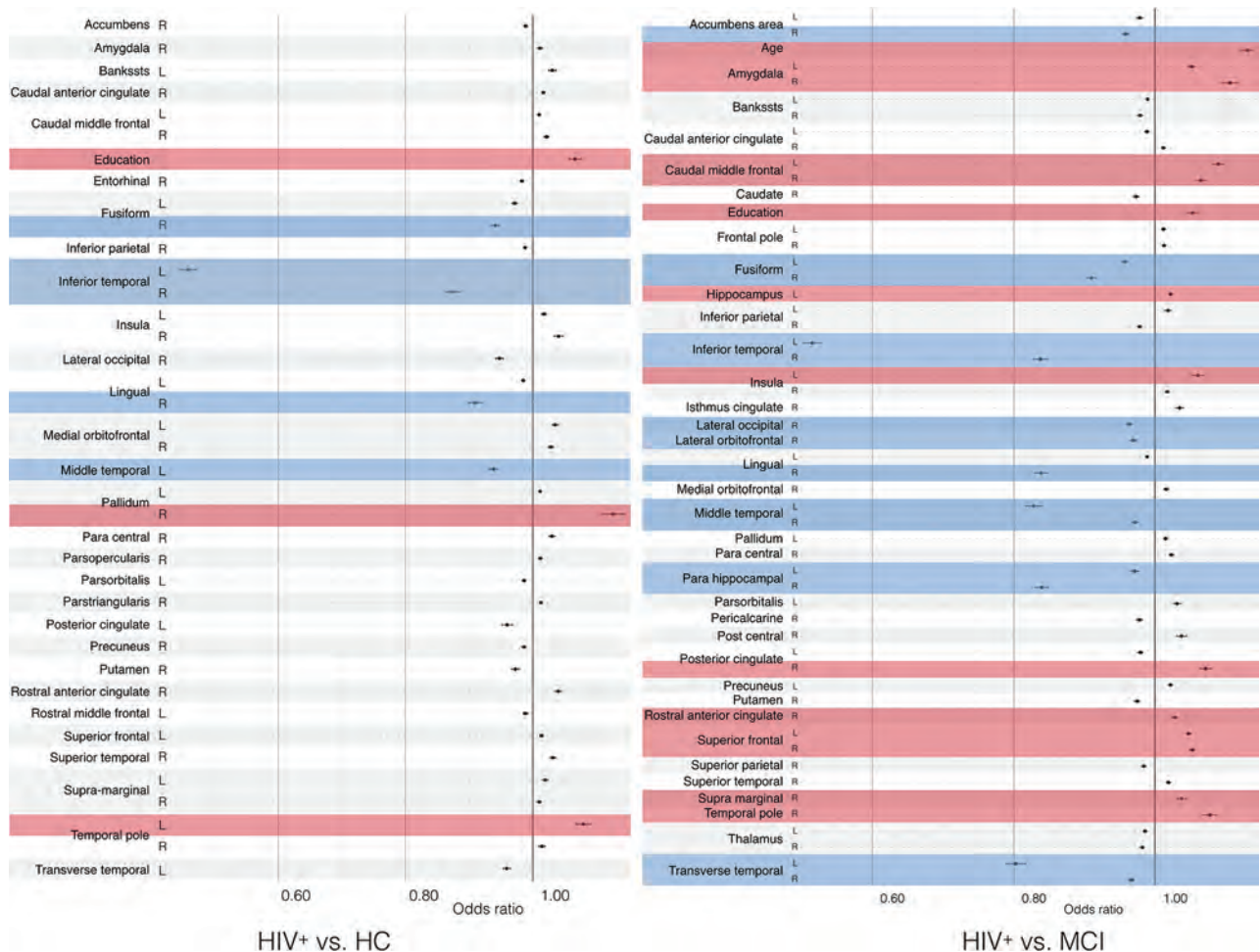


FIG 2. Odds ratios for each brain region and confounding factors in the GLMnet model, obtained by exponentiating the model coefficients averaged over a bootstrap (500 iterations). The regions used in the model in >25% bootstrap iterations are highlighted in blue for the region hypoperfused in HIV⁺ participants and in red for regions hyperperfused in HIV⁺ participants compared with HC or those with MCI. HIV⁺ participants demonstrate relative hypoperfusion in bilateral temporal and occipital regions and relative frontoinsular hyperperfusion.

phenotypes of mild HAND from those of MCI due to Alzheimer disease with reasonable accuracy.²⁴ Here we evaluated whether CBF measurements may add specificity to the evaluation of cognitive symptoms in elderly HIV⁺ participants. Our data suggest that CBF differences more accurately distinguish HIV⁺ participants from HC compared with HIV⁺ participants from those with MCI. Given temporal and parietal CBF changes within the Alzheimer disease spectrum,¹⁷ these findings are not surprising and explain the reduced sensitivity. However, when present, the abnormal CBF pattern in HIV⁺ participants is quite specific for the diagnosis of HIV⁺ compared with MCI. These findings suggest that ASL CBF measurements demonstrate appropriate test characteristics for a confirmatory study after neuropsychological evaluation in elderly HIV⁺ participants. Future work to evaluate the discriminative power of a combined cognitive and ASL CBF dataset is needed.

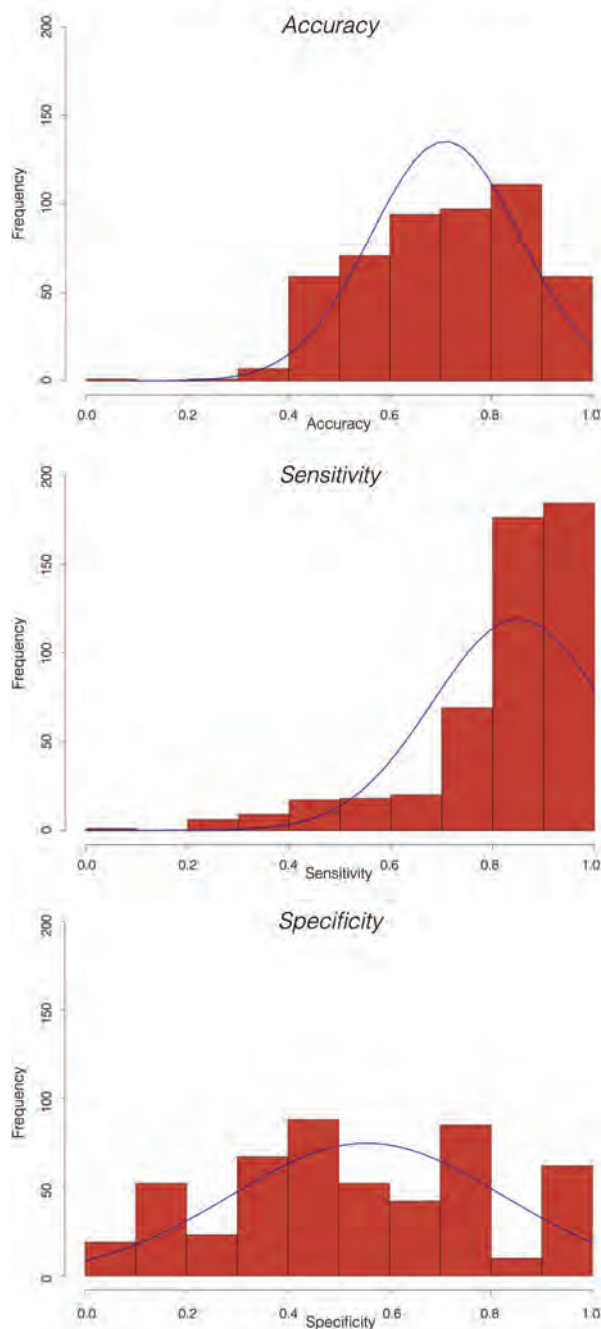
Sensitivity analyses were completed to examine whether CBF changes in patients with HAND-MND were driving CBF differences when comparing all HIV⁺ participants with other groups. We evaluated whether the HAND-MND subgroup showed regional CBF differences greater than the SD of all others by comparing the mean coefficients in the GLMnet analyses. Given that

the differences between the mean coefficients of each region between HAND-MND and others were much smaller compared with the SD, the presence of HAND-MND is unlikely to explain CBF abnormalities among all HIV⁺ participants.

The mechanisms for the observed CBF alterations within HIV⁺ participants remain an area of active investigation. While many mechanisms might explain the interactive effects of age and HIV on the CNS, data suggest that immune activation may induce and promote cerebrovascular inflammation.³⁴

Strengths of the current study include the comparison of our cohort of HIV⁺ participants with a comparable HIV-uninfected control group and MCI group, under uniforming imaging and analysis conditions i.e. using the same ASL sequence, scanner and scanning parameters and analysis pipeline. In the existing literature, CBF measurement techniques often vary considerably among different study cohorts.^{18,20,21} In addition, our analysis required no a priori hypothesis with regard to a specific region of abnormality. Another strength is the relative similarity of cerebrovascular risk factors between our HIV⁺ participants and comparison groups, a frequent confounder of studies of CBF and vascular disease in HIV. However, these results should be interpreted cautiously along with the limitations of the study. First, because of

Performance of GLMnet to classify HIV+ vs. HC over bootstrap (500 iterations)



Performance of GLMnet to classify HIV+ vs. MCI over bootstrap (500 iterations)

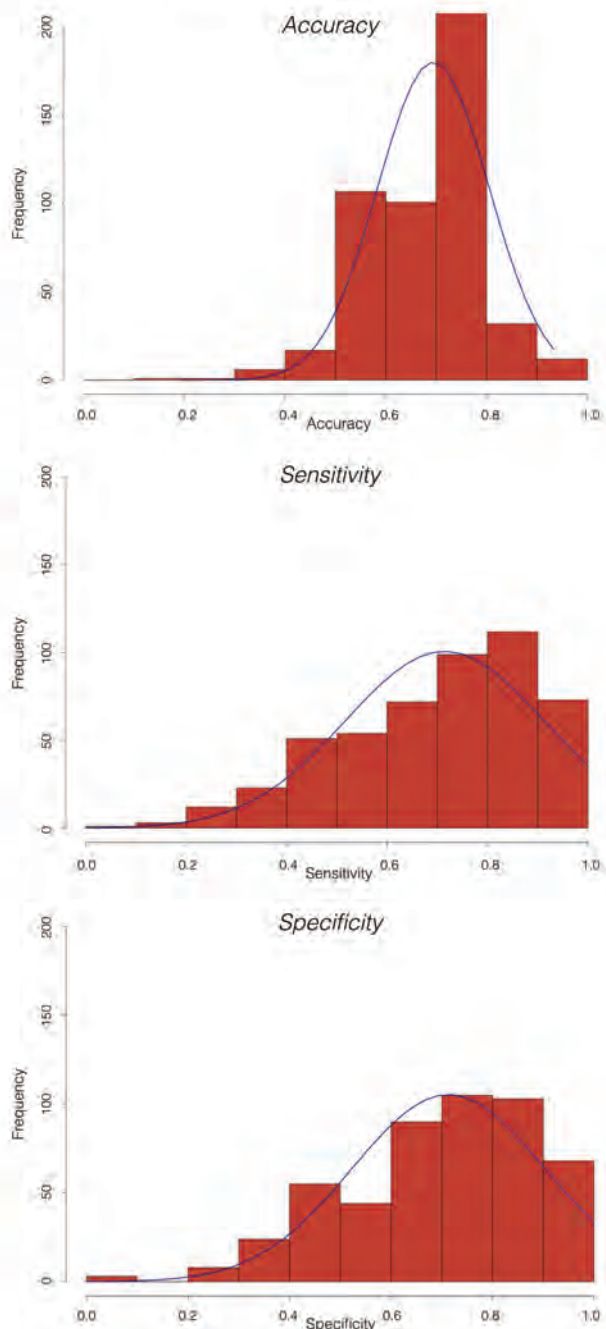


FIG 3. Histogram of the frequency distribution of accuracy, sensitivity, and specificity over the bootstrap (500 iterations) for the proposed GLMnet models.

the modest sample size, particularly in terms of uninfected controls, our findings are preliminary and need to be verified in a larger independent study. Second, this study presents an almost entirely male population, which is particularly challenging given data suggesting cerebrovascular risk in HIV may be higher in woman.³⁵ Finally, the age of HIV⁺ participants reflects frequent seroconversion before the generalization of combination antiretroviral therapy, and this finding may not be generalizable to younger post-antiretroviral therapy populations.

CONCLUSIONS

When we accounted for age, education, sex, and vascular risk factors, HIV⁺ participants demonstrated alterations in regional cerebral perfusion, including hypoperfusion of bilateral temporal, parietal, and occipital volumes compared with both clinically healthy individuals and those with MCI. Our data also add to previous reports that MR imaging-measured CBF has diagnostic ability in comparison with cognitive assessment in distinguishing HAND-MND from MCI.

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REFERENCES

- Hood JE, Golden MR, Hughes JP, et al. **Projected demographic composition of the United States population of people living with diagnosed HIV.** *AIDS Care* 2017;29:1543–50 CrossRef Medline
- Heaton RK, Clifford DB, Franklin DR Jr, et al; CHARTER Group. **HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study.** *Neurology* 2010;75:2087–96 CrossRef Medline
- Hasse B, Ledergerber B, Furrer H, et al; Swiss HIV Cohort Study. **Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study.** *Clin Infect Dis* 2011;53:1130–39 CrossRef Medline
- Chow FC. **HIV infection, vascular disease, and stroke.** *Semin Neurol* 2014;34:35–46 CrossRef Medline
- Hsue PY, Deeks SG, Hunt PW. **Immunologic basis of cardiovascular disease in HIV-infected adults.** *J Infect Dis* 2012;205(Suppl 3):S375–82 CrossRef Medline
- Silva JN, Poleskaya O, Wei HS, et al. **Chronic central nervous system expression of HIV-1 Tat leads to accelerated rarefaction of neo-cortical capillaries and loss of red blood cell velocity heterogeneity.** *Microcirculation* 2014;21:664–76 CrossRef Medline
- Jia P, Zhao Z, Hulgán T, et al; CHARTER Study Group. **Genome-wide association study of HIV-associated neurocognitive disorder (HAND): a CHARTER group study.** *Am J Med Genet B Neuropsychiatr Genet* 2017;174:413–26 CrossRef Medline
- Gelman BB, Chen T, Lisinichia JG, et al; National NeuroAIDS Tissue Consortium. **The National NeuroAIDS Tissue Consortium brain gene array: two types of HIV-associated neurocognitive impairment.** *PLoS One* 2012;7:e46178 CrossRef Medline
- Gelman BB. **Neuropathology of HAND with suppressive antiretroviral therapy: encephalitis and neurodegeneration reconsidered.** *Curr HIV/AIDS Rep* 2015;12:272–79 CrossRef Medline
- Nakamoto BK, Jahanshad N, McMurtray A, et al. **Cerebrovascular risk factors and brain microstructural abnormalities on diffusion tensor images in HIV-infected individuals.** *J Neurovirol* 2012;18:303–12 CrossRef Medline
- Watson C, Busovaca E, Foley JM, et al. **White matter hyperintensities correlate to cognition and fiber tract integrity in older adults with HIV.** *J Neurovirol* 2017;23:422–29 CrossRef Medline
- Su T, Wit FW, Caan MW, et al; AGEHIV Cohort Study. **White matter hyperintensities in relation to cognition in HIV-infected men with sustained suppressed viral load on combination antiretroviral therapy.** *AIDS* 2016;30:2329–39 CrossRef Medline
- Chow FC, Boscardin WJ, Mills C, et al. **Cerebral vasoreactivity is impaired in treated, virally suppressed HIV-infected individuals.** *AIDS* 2016;30:45–55 CrossRef Medline
- Chow FC, Li Y, Hu Y, et al. **Relationship between HIV infection, antiretroviral therapy, inflammatory markers, and cerebrovascular endothelial function among adults in urban China.** *J Acquir Immune Defic Syndr* 2017;74:339–46 CrossRef Medline
- van der Veen PH, Muller M, Vincken KL, et al; SMART Study Group. **Longitudinal relationship between cerebral small-vessel disease and cerebral blood flow: the second manifestations of arterial disease-magnetic resonance study.** *Stroke* 2015;46:1233–38 CrossRef Medline
- Mattsson N, Tosun D, Insel PS, et al; Alzheimer's Disease Neuroimaging Initiative. **Association of brain amyloid- β with cerebral perfusion and structure in Alzheimer's disease and mild cognitive impairment.** *Brain* 2014;137:1550–61 CrossRef Medline
- Tosun D, Schuff N, Jagust W, et al; Alzheimer's Disease Neuroimaging Initiative. **Discriminative power of arterial spin labeling magnetic resonance imaging and 18F-fluorodeoxyglucose positron emission tomography changes for amyloid- β -positive subjects in the Alzheimer's disease continuum.** *Neurodegener Dis* 2016;16:87–94 CrossRef Medline
- Ances BM, Sisti D, Vaida F, et al; HNRC group. **Resting cerebral blood flow: a potential biomarker of the effects of HIV in the brain.** *Neurology* 2009;73:702–08 CrossRef Medline
- Su T, Mutsaerts HJ, Caan MW, et al; AGEHIV Cohort Study. **Cerebral blood flow and cognitive function in HIV-infected men with sustained suppressed viremia on combination antiretroviral therapy.** *AIDS* 2017;31:847–56 CrossRef Medline
- Towgood KJ, Pitkanen M, Kulasegaram R, et al. **Regional cerebral blood flow and FDG uptake in asymptomatic HIV-1 men.** *Hum Brain Mapp* 2013;34:2484–93 CrossRef Medline
- Sen S, An H, Menezes P, et al. **Increased cortical cerebral blood flow in asymptomatic human immunodeficiency virus-infected subjects.** *J Stroke Cerebrovasc Dis* 2016;25:1891–95 CrossRef Medline
- Clifford KM, Samboju V, Cobigo Y, et al. **Progressive brain atrophy despite persistent viral suppression in HIV patients older than 60 years.** *J Acquir Immune Defic Syndr* 2017;76:289–97 CrossRef Medline
- Antinori A, Arendt G, Becker JT, et al. **Updated research nosology for HIV-associated neurocognitive disorders.** *Neurology* 2007;69:1789–99 CrossRef Medline
- Milanini B, Valcour V. **Differentiating HIV-associated neurocognitive disorders from Alzheimer's disease: an emerging issue in geriatric NeuroHIV.** *Curr HIV/AIDS Rep* 2017;14:123–32 CrossRef Medline
- Luh WM, Wong EC, Bandettini PA, et al. **QUIPSS II with thin-slice T1 ρ periodic saturation: a method for improving accuracy of quantitative perfusion imaging using pulsed arterial spin labeling.** *Magn Reson Med* 1999;41:1246–54 Medline
- Tao R, Fletcher PT, Gerber S, et al. **A variational image-based approach to the correction of susceptibility artifacts in the alignment of diffusion weighted and structural MRI.** *Inf Process Med Imaging* 2009;21:664–75 Medline
- R Development Core Team. **R foundation for statistical computing.** <https://www.r-project.org/>.
- Friedman J, Hastie T, Tibshirani R. **Regularization paths for generalized linear models via coordinate descent.** *J Stat Softw* 2010;33:1–22 Medline
- van Buuren S, Groothuis-Oudshoorn K. **MICE: multivariate imputation by chained equations in R.** *J Stat Softw* 2011;45: <https://www.jstatsoft.org/article/view/v045i03>.
- Frigessi A, Bühlmann P, Glad IK, et al. **Statistical Analysis for High-Dimensional Data: The Abel Symposium 2014.** New York: Springer; 2016
- Sanford R, Fernandez Cruz AL, Scott SC, et al. **Regionally specific brain volumetric and cortical thickness changes in HIV-infected patients in the HAART era.** *J Acquir Immune Defic Syndr* 2017;74:563–70 CrossRef Medline
- Kendall CE, Wong J, Taljaard M, et al. **A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario.** *BMC Public Health* 2014;14:161 CrossRef Medline
- Sheppard DP, Iudicello JE, Bondi MW, et al. **Elevated rates of mild cognitive impairment in HIV disease.** *J Neurovirol* 2015;21:576–84 CrossRef Medline
- Hong S, Banks WA. **Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications.** *Brain Behav Immun* 2015;45:1–12 CrossRef Medline
- Chow FC, Regan S, Zanni MV, et al. **Elevated ischemic stroke risk among women living with HIV infection.** *AIDS* 2018;32:59–67 CrossRef Medline

Diffusional Kurtosis along the Corticospinal Tract in Adult Normal Pressure Hydrocephalus

 B. Ades-Aron,  S. Yeager,  N. Miskin,  E. Fieremans,  A. George, and  J. Golomb



ABSTRACT

BACKGROUND AND PURPOSE: Normal Pressure Hydrocephalus is a reversible form of dementia characterized by enlarged ventricles, which can deform and cause disruptions to adjacent white matter fibers. The purpose of this work was to examine how diffusion and kurtosis parameters vary along the corticospinal tract and determine where along this path microstructure is compromised in patients diagnosed with normal pressure hydrocephalus. We hypothesized that disruption of the corticospinal tract from ventricular enlargement can be measured using diffusion MR imaging and this will be quantified in periventricular regions.

MATERIALS AND METHODS: We developed a method to analyze diffusion parameters at discrete points along neural tracts. We then used diffusion MR imaging data from patients with Alzheimer disease and healthy controls to compare whether diffusion along the corticospinal tract differs from that of patients with normal pressure hydrocephalus.

RESULTS: We found that diffusion parameters can differentiate patients with normal pressure hydrocephalus from those with Alzheimer disease and healthy controls: Axial diffusion, axial kurtosis, and the axonal water fraction were found to differ significantly across groups ($P < .05$) in an area located close to the superior internal capsule and corona radiata but below the cortex.

CONCLUSIONS: A lower axonal water fraction indicates a lower axonal density in the corticospinal tract, which may indicate permanent damage. Lower axial kurtosis may imply that axons are being more aligned due to compression.

ABBREVIATIONS: AD = axial diffusivity; AK = axial kurtosis; AUC = area under the receiver operating characteristic curve; AWF = axonal water fraction; CST = corticospinal tract; FA = fractional anisotropy; NPH = normal pressure hydrocephalus

The most widely accepted treatment for normal pressure hydrocephalus (NPH) symptoms is ventriculoperitoneal shunt placement, which can result in profound symptom amelioration, predominantly gait impairment.¹ Despite the well-established clinical features and the requisite cardinal radiologic feature of dilated ventricles, the mechanisms relating ventricular enlargement to clinical deficits and how fluid-dynamic alterations in

CSF post-shunt placement lead to gait improvement are poorly understood.

Previous studies using structural or functional imaging have indicated that mechanical compression of corticospinal white matter due to ventricular enlargement is responsible for gait disturbances commonly associated with NPH.^{2,3} Diffusional kurtosis imaging quantifies the contribution of non-Gaussian diffusion effects, such as the presence of microstructure in the brain.^{4,5} The white matter tract integrity⁶ model is a method that relates diffusional kurtosis imaging-compatible metrics to white matter microstructure by partitioning water into an intra-axonal compartment and an extra-axonal compartment and computing the axonal water fraction (AWF), which is sensitive to demyelination and axonal atrophy.⁷⁻⁹ These biomarkers may be used to represent the pathology occurring at the mesoscopic scale.

The corticospinal tract (CST) is altered by mechanical deformation resulting from ventricular enlargement, and we hypothesized that this compression can be measured using a combination of diffusion MR imaging and tractography of the CST. Here, we examined how diffusion and kurtosis parameters vary along the corticospinal tract and determined where, along this path, micro-

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Table 1: Key demographic information

	No. of Subjects	Age (Range) (Mean) (yr)	Male/Female Ratio
NPH	23	58–87 (76.9)	13:10
Alzheimer disease	10	56–81 (74.9)	5:5
Controls	11	60–87 (75)	6:5

structure is compromised in patients diagnosed with NPH. We localized pathology in NPH using an along-tract analysis of diffusion to determine whether this method can differentiate patients with NPH from those with Alzheimer disease and healthy controls and to study whether diffusion biomarkers can assess cell damage due to ventricular expansion. We studied patients with Alzheimer disease in addition to controls due to common radiologic features such as ventriculomegaly and the relatively common (31%–75%) comorbidity of the 2 diseases.¹⁰ We further investigated the relationship between CST injury and the presence of leukoaraiosis in NPH. We expect that in NPH, CST disruption would be maximal in the periventricular regions deformed by the enlarged lateral ventricles and not at sites distant to these locations.

MATERIALS AND METHODS

Demographics and Clinical Data

This retrospective, anonymized, single-center study was approved by the institutional review board with a waiver of consent and was Health Insurance Portability and Accountability Act-compliant. Demographics of the 3 patient groups (total $n = 44$) are given in Table 1. The 3 groups did not statistically differ in demographic characteristics.

Patients with NPH were selected from a pool of patients with enlarged ventricles and gait impairment referred to the New York University Adult Hydrocephalus Evaluation Program and evaluated by a neurologist (J.G.) with 25 years of experience. These patients all exhibited a characteristic dyspraxic gait, variable degrees of cognitive impairment, and symptoms of overactive bladder. From the initial chart review of patients with NPH from January 2003 through December 2014 ($n = 624$), we selected patients who fulfilled the following requirements: 1) completed a high-volume lumbar puncture or lumbar drain that resulted in convincing clinical improvement (clinician [J.G.] and the family's subjective impression of gait improvement), ($n = 101$); 2) the availability of preoperative 3T MR imaging acquired locally, which included a high-resolution MPAGE sequence as well as diffusion images appropriate for diffusional kurtosis imaging analysis ($n = 20$); and 3) free of comorbidities such as cerebrovascular disease, coexisting intracranial mass lesions, or prior craniectomy identified by a neuroradiologist (A.G.). The final sample size was 14; however, 9 additional subjects scanned after December 2014 were identified from a review of 125 cases and were included in the study after having been found to meet criteria 2 and 3. Most excluded from the study failed to meet criterion 1. The full population of 23 subjects with clinical presentations of NPH evaluated in this study responded positively to shunt surgery as evaluated by a neurologist (J.G.). Of the 23 patients with hydrocephalus included in the study, 15 demonstrated a risk of hypertension, 7 patients had diabetes, 10 had hyperlipidemia, 3 had coronary artery disease, and 7 tested negative for any cardiovas-

cular risk factors. Ten patients demonstrated comorbidities for ≥ 2 the risk factors listed above.

Control subjects were recruited retrospectively from the New York University Alzheimer Disease Center to undergo a full clinical research evaluation per Uniform Data Set procedures for Alzheimer Disease Centers,¹¹ and a brain MR imaging, including high-resolution MPAGE and the appropriate diffusion MR imaging protocol. Healthy control subjects had no evidence of dementia or mild cognitive impairment and had a Clinical Dementia Rating global score of 0. Subjects with Alzheimer disease were given a diagnosis based on the *Diagnostic and Statistical Manual of Mental Disorders*¹² and the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer Disease and Related Disorders Association criteria for probable Alzheimer disease¹³ and a Clinical Dementia Rating of ≥ 0.5 (range, 0.5–2.0) and were not deemed to have any medical, neurologic, or psychiatric conditions that could otherwise account for the dementia. The 3 groups did not statistically differ in demographic characteristics (Table 1). Due to the sensitivity of the diffusion MR imaging metrics in general to age,¹⁴ age was included as a covariate in all analyses.

MR Imaging Acquisition and Image Processing

MR images were acquired on a 3T Tim Trio system (Siemens, Erlangen, Germany). Patients with NPH were scanned before ventricular shunt placement. The MR imaging protocol included 3D T1-weighted imaging for anatomic reference using an MPAGE sequence and diffusion imaging with 3 b-values (0, 1000, 2000 s/mm²) along 60 diffusion-encoding directions using a single-shot twice-refocused echo-planar sequence. Data were acquired in an $88 \times 80 \times 30$ matrix with 2.6×2.6 mm resolution and 5-mm slice thickness. Diffusion-weighted MR images were preprocessed by denoising using a Gaussian smoothing kernel, followed by motion and eddy current correction using the FMRIB Software Library (FSL; <http://www.fmrib.ox.ac.uk/fsl>) and then the kurtosis tensor was fitted using a constrained weighted linear least-squares fit using in-house software¹⁵ written in Matlab (MathWorks, Natick, Massachusetts). The kurtosis tensors were then used to derive the diffusional kurtosis imaging-acquired parametric maps of mean diffusivity, axial diffusivity (AD), radial diffusivity, fractional anisotropy (FA), mean kurtosis, axial kurtosis (AK), and radial kurtosis. The axonal water fraction (ie, the ratio of intra-axonal water to intra-plus-extra-axonal water) was computed in addition to standard diffusion and kurtosis measures based on a 2-compartment model of neuronal tissue.⁷

Along-Tract Analysis

Tracts were generated using MRtrix (github.com/MRtrix3/mrtrix3) by manually placing seed ROIs in the cerebral peduncles and in the precentral gyrus of each subject. Streamline propagation was constrained using an FA value of 0.2 and a maximum angle of 45°. Streamlines were reoriented to begin at the brain stem and stretch cephalad toward the precentral gyrus. They were then truncated at the middle cerebellar peduncle and pial surface to ensure that tracts from different subjects could be compared without individual anatomy biasing results. To prevent partial volume effects from potentially biasing the analysis, we excluded

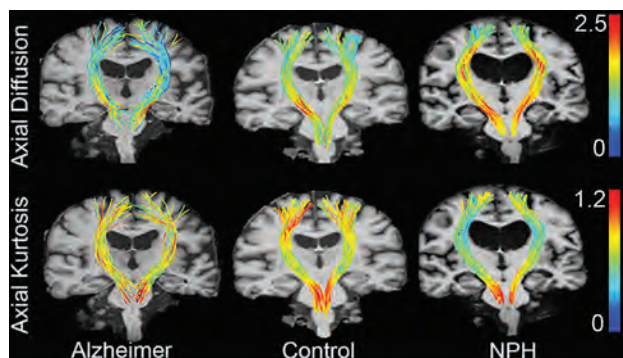


FIG 1. Axial diffusion and axial kurtosis overlaid onto the corticospinal tract as a scalar value and represented by a color: Red indicates higher axial kurtosis or axial diffusivity, while blue indicates lower values. From left to right, we show sample tracts for patients with Alzheimer disease, healthy controls, and patients with hydrocephalus. Patients with NPH have much lower axial diffusion in periventricular regions than control groups and much greater axial kurtosis values in the same region next to the ventricles.

tracts that came close to or intersected with the lateral ventricles by creating an ROI of the lateral ventricles, dilating it by 1 voxel, and discarding any streamline that intersected this region.

Using Matlab, we normalized tracts using cubic spline interpolation so that the same anatomy occurred at the same distance along the tract for each subject, and vertices were relocated so that there were exactly 100 vertices per streamline along the entire tract, similar to the methods used in Colby et al.¹⁶ The cerebral peduncles were constrained to exist at 25% of the distance from the middle cerebellar peduncle, and the anterior end of the precentral gyrus was constrained to 95%. Parametric diffusion, kurtosis, and white matter tract integrity maps were resampled onto tract vertices as scalar values. Figure 1 provides a qualitative demonstration of axial diffusion and axial kurtosis mapped into the corticospinal tract of a representative sample of a patient with Alzheimer disease, a healthy control, and a patient with hydrocephalus.

Periventricular white matter lesions were segmented for each subject based on T1 hypointensities and FLAIR hyperintensities from FreeSurfer parcellation of T1-weighted MPRAGE images (<http://surfer.nmr.mgh.harvard.edu>), followed by a nonlinear warp to a common space computed using the FMRIB Nonlinear Registration Tool (FNIRT; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT>). These segmentations were used to create leukoaraiosis probability maps to help visualize the location where this pathology is most likely to occur for patients with NPH, patients with Alzheimer disease, and healthy controls and to determine whether leukoaraiosis has a local impact on microstructural pathology associated with NPH.

Statistical Methods

One-way ANCOVA with age as a covariate was used to compare differences between patients with NPH and those with Alzheimer disease, those with NPH and healthy controls, and patients with Alzheimer disease and healthy controls at each point along the CST. A Bonferroni correction for multiple comparisons was used to correct for the presence of the 3 groups. The paired-samples *t* test was used to test for differences across hemispheres. Receiver operating characteristic curves were used to test the diagnostic

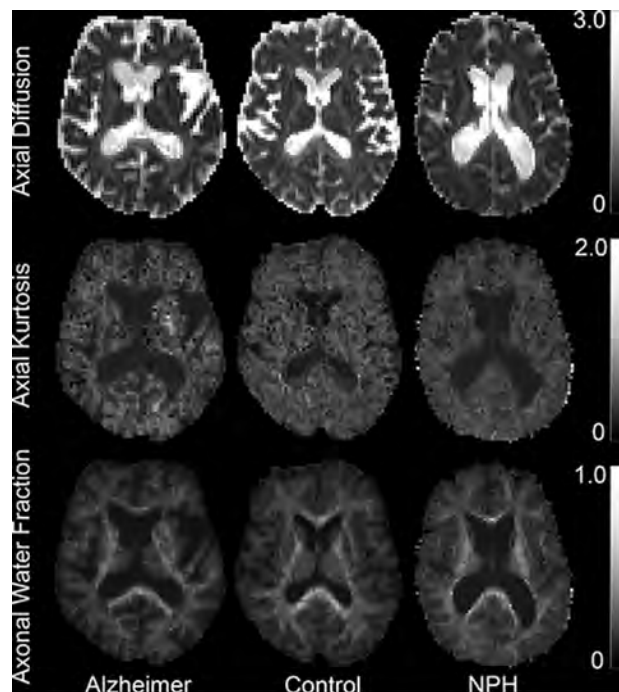


FIG 2. Sample parametric maps for patients with Alzheimer disease, healthy controls, and those with normal pressure hydrocephalus to qualitatively demonstrate values that are being mapped to the CST. From upper to lower, the maps show values for axial diffusivity, axial kurtosis, and axonal water fraction.

accuracy using the area under the receiver operating characteristic curve (AUC) of each diffusion metric and to determine the ones to best differentiate among study groups. One-way ANCOVA controlling for age was used to test for group differences in periventricular leukoaraiosis.

RESULTS

Along-Tract Analysis

Diffusion and kurtosis measures were computed for each subject and then sampled onto the corticospinal tract. Of all diffusion parameters examined during this study, axial diffusivity, axial kurtosis, and the axonal water fraction were found to differentiate subject groups with the greatest level of accuracy. Figure 2 shows sample parametric maps of AD, AK, and AWF to demonstrate the quality of these parameters. Values along the CST were averaged for each hemisphere separately, and groups were compared at each vertex for each diffusion parameter. Axial diffusivity differs significantly across groups ($P < .05$) between 65% and 85% of the distance along the tract; this area is located superior to the internal capsule but below the cortex. On-line Fig 1 provides a reference image to demonstrate the anatomic location where group differences may occur. Figure 3A plots the axial diffusion as a function of the distance on the tract from the superior end of the brain stem.

Axial kurtosis demonstrates the largest difference among groups both in terms of P values $< .05$ and in the number of significant voxels. Figure 3B shows the change in axial kurtosis, which significantly differs ($P < .05$) between groups from 50% to 90% of the distance along the CST. Figure 3C shows the change in the along-tract AWF, which significantly differs ($P < .05$) across

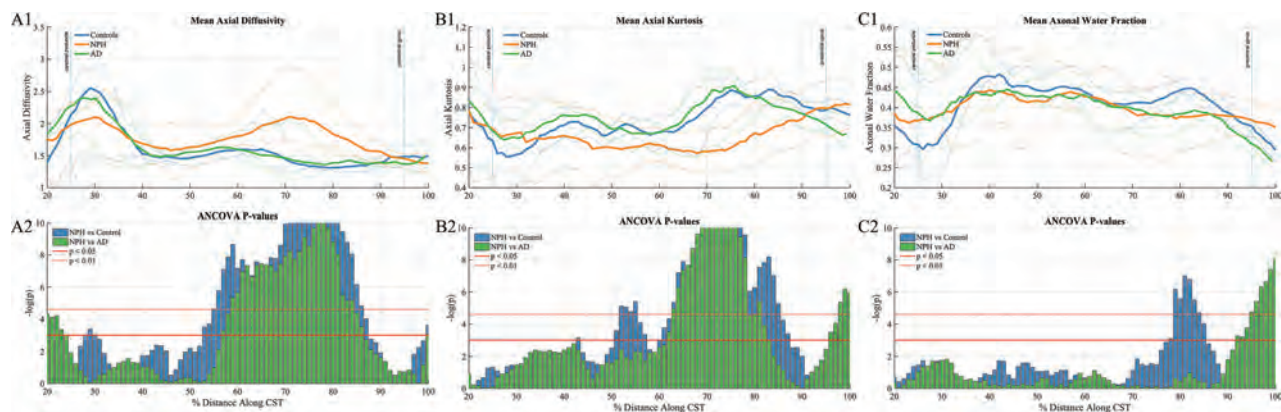


FIG 3. A: Along-tract group differences in axial diffusivity among patient groups. A1: Axial diffusion at each point along the CST in the right hemisphere. A2: ANCOVA *F*-test results show a significant difference between the NPH group and the Alzheimer and control groups at distances between 56% and 88%. B: Along-tract group differences in axial kurtosis among patient groups. B1: Axial kurtosis at each point along the CST in the right hemisphere. B2: ANCOVA *F*-test results show a significant difference between the NPH group and the Alzheimer and control groups at distances between 50% and 90%. C: Along-tract group differences in the axonal water fraction among patient groups. C1: Axonal water fraction at each point along the CST in the right hemisphere. C2: ANCOVA *F*-test results show a significant difference between the NPH group and the Alzheimer and control groups at distances between 67% and 86%.

Table 2: Values measured in the corona radiata, located at 70%–75% of the distance along the CST^a

	NC (n = 11) (Mean)	Alzheimer Disease (n = 10) (Mean)	NPH (n = 23) (Mean)	NPH vs Alzheimer Disease		NPH vs NC		Alzheimer Disease vs NC	
				<i>P</i> Value	AUC	<i>P</i> Value	AUC	<i>P</i> Value	AUC
FA	0.44 ± 0.07	0.39 ± 0.05	0.51 ± 0.10	0.01 ^b	0.88	0.04	0.76	0.12	0.76
MD	0.88 ± 0.05	0.89 ± 0.06	1.30 ± 0.37	0.02 ^b	0.87	<0.01 ^b	0.94	0.80	0.79
RD	0.67 ± 0.05	0.69 ± 0.07	0.93 ± 0.37	0.18	0.65	0.04 ^b	0.76	0.53	0.84
AD	1.30 ± 0.08	1.26 ± 0.07	2.04 ± 0.39	<0.01 ^c	0.96	<0.01 ^c	1.0	0.60	0.51
MK	1.08 ± 0.09	1.04 ± 0.09	0.99 ± 0.19	0.94	0.52	0.35	0.73	0.66	0.82
RK	1.40 ± 0.14	1.19 ± 0.22	1.54 ± 0.42	0.03	0.82	0.34	0.62	0.10	0.82
AK	0.86 ± 0.07	0.97 ± 0.06	0.63 ± 0.11	<0.01 ^c	0.97	<0.01 ^c	0.98	0.11	0.67
AWF	0.42 ± 0.02	0.39 ± 0.03	0.38 ± 0.07	0.88	0.66	0.22	0.74	0.12	0.86

Note:—MD indicates mean diffusivity; RD, radial diffusivity; MK, mean kurtosis; RK, radial kurtosis; NC, healthy controls.

^a Values for the left and right hemispheres did not differ significantly (paired sample *t* test) and were averaged.

^b *P* < .05.

^c *P* < .01.

groups in areas correlating with changes that occur in AK (between 67% and 86%).

Table 2 shows the mean and SD for all diffusion parameters analyzed during this study, as well as the results of receiver operating characteristic analysis in the periventricular region and AUC values for each metric at a tract distance of 75%. Seventy-five percent marks the approximate location of the corona radiata in each patient. This region was chosen because it is part of the region with the largest difference among all diffusion parameters among groups. Axial diffusivity showed the highest AUC with a value of 1.0. We also found significant differences between the NPH and Alzheimer groups in FA values, which agree with measurements made in literature.¹⁷ In addition to increased AD and FA in those with NPH compared with control groups, MD was also found to be significantly increased and AK and RK were found to be significantly decreased. AUC values (NPH versus controls) for mean diffusivity, AD, and AK were 0.94, 1.0, and 0.98, respectively, indicating that these parameters had the highest performance in differentiating those with NPH from controls.

Relationship with Leukoaraiosis

The extent of leukoaraiosis was significantly greater in patients with NPH (*P* < .05), with volumes greater than either the Alzheimer

group or the healthy control group. Figure 4 provides leukoaraiosis probability maps for each patient group, describing the extent to which leukoaraiosis may be affecting the corticospinal tract.

DISCUSSION

This study measured the microstructural properties of the CST in the 3 patient cohorts; the AUC findings here suggest that AD and AK can be used as markers for a clinical diagnosis of NPH in the presence of a confusing radiologic presentation. We found that pathology in NPH is located in the upper periventricular part of the CST, extending from the superior corona radiata to the posterior internal capsule. The most striking results were found in AD, AK, and AWF parameters. AD values were found to be higher in NPH than in Alzheimer and control groups up to a factor of 2, while AK and AWF were found to be lower by up to 45% and 21%, respectively, in the periventricular regions. The results found here also agree well with the work of other groups who have previously compared kurtosis measurements in white matter between those with NPH and controls. Kamiya et al¹⁷ found that in the internal capsule through the corona radiata regions, FA, mean diffusivity, and AD were significantly increased in those with NPH compared with controls, while mean kurtosis was decreased compared with

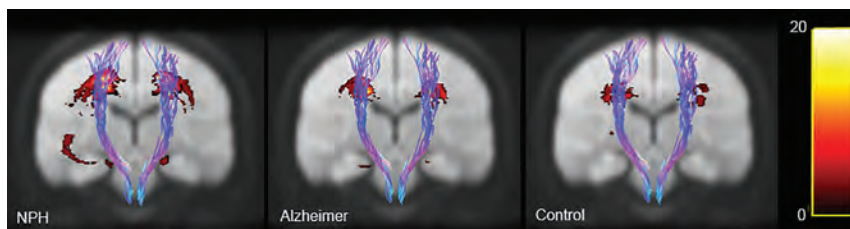


FIG 4. Leukoaraiosis heat maps. Yellow areas show regions where patients are most likely to have leukoaraiosis. Probability maps are shown on top of the 1-mm brain of the Montreal Neurological Institute 152 space.

the control group. We found very similar results for these particular diffusion parameters (Table 2), which helps provide confidence in the accuracy of this analysis.

These measurements have implications for the relative structure of periventricular white matter tract microarchitecture in NPH. Other studies have hypothesized that the white matter in NPH may be compressed due to mechanical pressure caused by ventricular dilation.^{18,19} This is consistent with our observation that an increase in axial diffusivity is seen in regions near the ventricle in patients with NPH. In particular, we found group differences in the corona radiata, where though several major white matter tracts are known to cross, evidence of motor neurons responsible for limb control have been identified¹⁹ in addition to motor neurons related to bladder control,²⁰ both of which are known to become impaired in NPH.

Increased axial diffusivity in patients with hydrocephalus compared with healthy controls and patients with Alzheimer disease implies more diffusion and coherent fiber alignment in the direction parallel to axon orientation, which may mean that NPH causes tracts to be more aligned in regions near the ventricles due to ventricular expansion. Increased diffusion also has the potential to be caused by local edema²¹; however, the indication that it is measuring fiber coherence is supported by increased FA values provided in Table 2. We also saw decreased axial kurtosis in patients with NPH, implying a decrease in microstructural complexity and a decrease in barriers to diffusion in the direction parallel to axonal orientation. Evidence suggests that up to a certain point, white matter changes in NPH are believed to be reversible, but permanent atrophy of the white matter can develop.²² Decreased axonal water fraction values imply a smaller fraction of axons in each voxel; this means that even though fibers are more tightly aligned in NPH due to ventricular expansion, the packing density of these fibers has decreased. While AWF is significantly decreased in those with NPH compared with controls, it does not differ from that of Alzheimer disease. This may relate to some of the similarities seen between the 2 types of dementia or that atrophy in the region of decreased AWF is related to increased ventricular size. Decreased AWF may imply that mechanical pressure on periventricular axons leads to atrophy and permanent damage to the CST or that these fibers may be decreasing in diameter.

Cerebral white matter changes are associated with aging as well as cerebrovascular risk factors and have a high prevalence in patients with hydrocephalus.²³ In our previous work,²⁴ we found a strong correlation between the presence of leukoaraiosis and diffusion parameters within ROIs in the internal capsule. Figure 4 quantifies the likelihood of each patient population having leu-

koaraiosis at any location in the brain. It is possible that mechanical stress on the brain is the cause of both changes observed in diffusion measurements as well as the presence of white matter lesions visible in the brains of diseased patient groups. However, our results indicate an independent NPH effect because even when the analysis is limited to where leukoaraiosis is shared (Table 2), we still see a significant difference in dif-

fusion and kurtosis values. This suggests that differences in diffusion and kurtosis measures cannot be due to the presence of leukoaraiosis alone.

In the future, this study should be expanded to include control populations with ventricles with sizes comparable to those in the NPH group. Furthermore, while we hypothesize that ventricular expansion may lead to permanent cell damage in the CST, this is only a possible explanation of our findings. This should be explored in follow-up studies examining postoperative kurtosis in patients who improve following shunt operations. The small size of the Alzheimer disease and healthy control populations potentially limits the reproducibility of this study. Future longitudinal analysis of NPH, AD, and healthy control populations will help provide certainty in the precision of the results presented here.

CONCLUSIONS

The along-tract analysis performed here provides a unique perspective on the localization of pathology in hydrocephalus. Examining the brain along its constituent tracts, rather than simply averaging all the data within them allows a better understanding of the mechanics of deformations occurring in the brain in hydrocephalus.

This study demonstrates that normal pressure hydrocephalus can be characterized by decreased axial kurtosis and increased axial diffusivity as well as a decreased axonal water fraction in the cortical spinal tract. The findings suggest that these measures can be used as diagnostic markers to help differentiate those with NPH and Alzheimer disease and healthy subjects, as reflected by axial kurtosis and diffusivity measures, at a specific periventricular region of the corticospinal tract. Axonal water fraction deficits may reflect microstructural damage. We hope to use these features in isolation and in combination with other distinct features as diagnostic as well as prognostic features of NPH that will help determine patient management in a noninvasive manner.

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REFERENCES

1. Adams RD, Fisher CM, Hakim S, et al. **Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure: a treatable syndrome.** *N Engl J Med* 1965;273:117–26 [CrossRef Medline](#)
2. Tarnaris A, Kitchen ND, Watkins LD. **Noninvasive biomarkers in normal pressure hydrocephalus: evidence for the role of neuroimaging.** *J Neurosurg* 2009;110:837–51 [CrossRef Medline](#)
3. Bradley WG. **Normal pressure hydrocephalus: new concepts on etiology and diagnosis.** *AJNR Am J Neuroradiol* 2000;21:1586–90 [Medline](#)
4. Jensen JH, Helpert JA. **MRI quantification of non-Gaussian water diffusion by kurtosis analysis.** *NMR Biomed* 2010;23:698–710 [CrossRef Medline](#)
5. Jensen JH, Helpert JA, Ramani A, et al. **Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging.** *Magn Reson Med* 2005;53:1432–40 [CrossRef Medline](#)
6. Fieremans E, Jensen JH, Helpert JA. **White matter characterization with diffusional kurtosis imaging.** *Neuroimage* 2011;58:177–88 [CrossRef Medline](#)
7. Fieremans E, Benitez A, Jensen JH, et al. **Novel white matter tract integrity metrics sensitive to Alzheimer disease progression.** *AJNR Am J Neuroradiol* 2013;34:2105–12 [CrossRef Medline](#)
8. Jelescu IO, Zurek M, Winters KV, et al. **In vivo quantification of demyelination and recovery using compartment-specific diffusion MRI metrics validated by electron microscopy.** *Neuroimage* 2016;132:104–14 [CrossRef Medline](#)
9. Benitez A, Fieremans E, Jensen JH, et al. **White matter tract integrity metrics reflect the vulnerability of late-myelinating tracts in Alzheimer's disease.** *Neuroimage Clin* 2014;4:64–71 [CrossRef Medline](#)
10. Golomb J, Wisoff J, Miller DC, et al. **Alzheimer's disease comorbidity in normal pressure hydrocephalus: prevalence and shunt response.** *J Neurol Neurosurg Psychiatry* 2000;68:778–81 [CrossRef Medline](#)
11. Morris JC, Weintraub S, Chui HC, et al. **The Uniform Data Set (UDS): clinical and cognitive variables and descriptive data from Alzheimer Disease Centers.** *Alzheimer Dis Assoc Disord* 2006;20:2101–06 [CrossRef Medline](#)
12. Gmitrowicz A, Kucharska A. **Developmental disorders in the fourth edition of the American classification: Diagnostic and Statistical Manual of Mental Disorders (DSM IV: optional book)** [in Polish]. *Psychiatr Pol* 1994;28:509–21 [Medline](#)
13. McKhann G, Drachman D, Folstein M, et al. **Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease.** *Neurology* 1984;34:939–44 [CrossRef Medline](#)
14. Sullivan EV, Pfefferbaum A. **Diffusion tensor imaging and aging.** *Neurosci Biobehav Rev* 2006;30:749–61 [CrossRef Medline](#)
15. Veraart J, Rajan J, Peeters RR, et al. **Comprehensive framework for accurate diffusion MRI parameter estimation.** *Magn Reson Med* 2013;70:972–84 [CrossRef Medline](#)
16. Colby JB, Soderberg L, Lebel C, et al. **Along-tract statistics allow for enhanced tractography analysis.** *Neuroimage* 2012;59:3227–42 [CrossRef Medline](#)
17. Kamiya K, Kamagata K, Miyajima M, et al. **Diffusional kurtosis imaging in idiopathic normal pressure hydrocephalus: correlation with severity of cognitive impairment.** *Magn Reson Med Sci* 2016;15:316–23 [CrossRef Medline](#)
18. Nakanishi A, Fukunaga I, Hori M, et al. **Microstructural changes of the corticospinal tract in idiopathic normal pressure hydrocephalus: a comparison of diffusion tensor and diffusional kurtosis imaging.** *Neuroradiology* 2013;55:971–76 [CrossRef Medline](#)
19. Kim JS, Pope A. **Somatotopically located motor fibers in corona radiata: evidence from subcortical small infarcts.** *Neurology* 2005;64:1438–40 [CrossRef Medline](#)
20. Sakakibara R, Panicker J, Fowler CJ, et al. **Vascular incontinence: incontinence in the elderly due to ischemic white matter changes.** *Neurol Int* 2012;4:e13 [CrossRef Medline](#)
21. Ebisu T, Naruse S, Horikawa Y, et al. **Discrimination between different types of white matter edema with diffusion-weighted MR imaging.** *J Magn Reson Imaging* 1993;3:863–68 [CrossRef Medline](#)
22. Del Bigio MR. **Cellular damage and prevention in childhood hydrocephalus.** *Brain Pathol* 2004;14:317–24 [Medline](#)
23. Pantoni L, Garcia JH. **Pathogenesis of leukoaraiosis: a review.** *Stroke* 1997;28:652–59 [CrossRef Medline](#)
24. Serulle Y, Pawar RV, Eubig J, et al. **Diffusional kurtosis imaging in hydrocephalus.** *Magn Reson Imaging* 2015;33:531–36 [CrossRef Medline](#)

Does Phase-Contrast Imaging through the Cerebral Aqueduct Predict the Outcome of Lumbar CSF Drainage or Shunt Surgery in Patients with Suspected Adult Hydrocephalus?

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ABSTRACT

BACKGROUND AND PURPOSE: Radiologic imaging plays a key role in diagnosing chronic adult hydrocephalus, but its role in predicting prognosis is still controversial. We sought to evaluate the effectiveness of cardiac-gated phase-contrast MR imaging through the cerebral aqueduct in predicting the clinical response to diagnostic lumbar puncture/lumbar drainage and shunt surgery in suspected adult hydrocephalus.

MATERIALS AND METHODS: In this retrospective study, the phase-contrast MR imaging of 185 patients with suspected chronic adult hydrocephalus was evaluated using the CSF Flow software package. Decision-making for shunt placement was performed in this cohort on the basis of clinical assessment alone without the availability of quantitative phase-contrast MR imaging results. We recorded the response to lumbar puncture or lumbar drainage and shunt surgery using quantitative tests such as the Tinetti Test, the Timed Up and Go, and the Mini-Mental State Examination and qualitative measures of gait, urinary, and cognitive symptom improvement before and after lumbar puncture/lumbar drainage and shunt surgery. Quantitative analysis of phase-contrast MR imaging was compared with clinical outcome measures.

RESULTS: Both CSF stroke volume and flow rate overlapped between lumbar puncture/lumbar drainage responders and nonresponders. There was also a significant overlap between shunt responders and nonresponders. Aqueductal stroke volume or flow rate alone was a poor predictor of lumbar puncture/lumbar drainage and shunt surgery response. Quantitative clinical measures after lumbar puncture/lumbar drainage were better predictors of shunt response.

CONCLUSIONS: This study suggests that the results of phase-contrast MR imaging through the cerebral aqueduct alone should not be used to select patients for diagnostic or therapeutic CSF diversion.

ABBREVIATIONS: AQ-PCMR = aqueductal phase-contrast MRI; CAH = chronic adult hydrocephalus; LD = lumbar drainage; LP = lumbar puncture; MMSE = Mini-Mental State Examination; TUG = Timed Up and Go

Chronic adult hydrocephalus (CAH) is a stereotyped clinical disorder in which elderly patients present with components of a triad of gait instability, cognitive disturbance, and urinary incontinence and are found to have dilated ventricles on imaging. The syndrome encompasses a variety of conditions and includes

normal pressure hydrocephalus as defined by Adams et al. in 1965,¹ along with other sources of hydrocephalus such as idiopathic hydrocephalus, hydrocephalus secondary to subarachnoid hemorrhage or trauma, and communicating hydrocephalus attributable to compromised CSF dynamics, aqueductal stenosis, and compensated arrested hydrocephalus.^{2,3} CAH is one of the few reversible causes of dementia and is likely underdiagnosed, estimated to occur in up to 14% of patients in the nursing home setting.⁴ Surgical interventions such as ventriculoperitoneal or ventriculoatrial shunt can dramatically improve the symptoms from CAH.⁵ However, the clinical or radiologic diagnosis of CAH is challenging because gait, cognitive, and urinary abnormalities are common in the elderly population, and ventricular enlargement may alternatively be the result of atrophy or normal aging.⁶ Moreover, symptoms may become irreversible in long-standing CAH.⁷ Therefore, methods of predicting shunt outcomes have been the primary focus of research in this field.

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Indicates article with supplemental on-line tables.



Indicates article with supplemental on-line photos.

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Lumbar puncture (LP) or lumbar drainage (LD) trials are widely used in selecting patients with reversible CAH⁸ but are costly, invasive, and uncomfortable for patients. Furthermore, while LP and LD demonstrate a >90% positive predictive value, they are limited by a <20% negative predictive value, thereby posing a risk of excluding patients who might benefit from an operation.⁹ These challenges spurred attempts to develop noninvasive diagnostic techniques to better predict the effect of shunt surgery. One of the most widely used noninvasive techniques is cardiac-gated phase-contrast MR imaging through the cerebral aqueduct (AQ-PCMR). AQ-PCMR was initially reported as demonstrating 100% positive predictive value and 50% negative predictive value.¹⁰ Although subsequent studies reported overlap of the aqueductal CSF flow rate between shunt responders and nonresponders, they reported that patients with high aqueductal flow tended to improve after shunt surgery.^{8,11–13} This discrepancy between the initial report and subsequent reports may be driven by differences in scan processing and calibration.¹⁴ The symptoms of aqueductal stenosis have been shown to substantially overlap those of communicating CAH.¹⁵ At our institution (Johns Hopkins Hospital), patients with potential hydrocephalus undergo a standardized MR imaging study, including AQ-PCMR and high-spatial-resolution heavily T2-weighted (CISS) imaging. This protocol is performed primarily to exclude ventricular dilation due to aqueductal stenosis or other intraventricular obstructions that would contraindicate LP/LD due to risk of brain stem herniation.

Surgical decisions for the remaining cases (cases of nonobstructive CAH) at other centers are often based, at least in part, on the CSF flow rates or stroke volume through the cerebral aqueduct on AQ-PCMR, with the claim that the technique aids in distinguishing patients who will respond to shunting. Yet, there have been suggestions that AQ-PCMR is simply an epiphenomenon of ventricular dilation,¹⁶ and there have also been reports that AQ-PCMR does not aid in establishing a diagnosis or prognosis to the extent originally reported.^{11,17–19} Current practice guidelines from the American Academy of Neurology acknowledge the limitations of AQ-PCMR but suggest that the patients with higher aqueductal flow are more likely to respond to shunting.⁸

Due to controversy regarding the role of AQ-PCMR, quantitation of the results of this technique was not performed at initial imaging and has not been used in decision-making regarding shunt surgery at our institution. The aim of this study was to retrospectively perform quantitation of AQ-PCMR and to determine whether it would have predicted LP or shunt outcomes.

MATERIALS AND METHODS

Selecting Patients with Chronic Adult Hydrocephalus

A total of 185 patients (83 women and 102 men; median age, 73 years; age range, 41–89 years) who had undergone high-resolution MR imaging and AQ-PCMR to evaluate the patency of the cerebral aqueduct before diagnostic lumbar CSF removal and who were clinically evaluated at our center between March 2010 and August 2014 were included in this retrospective institutional review board–approved study.

Clinical Assessment and Diagnosis of Adult Hydrocephalus

All subjects had ventriculomegaly with an Evans index of ≥ 0.3 and had gait symptoms or exhibited Tinetti score deficits at the time of imaging. Patients with a visible obstruction within the ventricular system (24 subjects) were excluded. For each eligible study, the clinical chart was reviewed to collect the duration of symptoms and responses to LP/LD and shunt surgery measured by the Tinetti, Timed Up and Go (TUG), Mini-Mental State Examination (MMSE) scores and subjective reports. Overall symptom improvement after LP/LD was graded in 4 levels (significant improvement, marginal improvement, no improvement, and worsening). For patients who had undergone shunt surgeries, the Tinetti, MMSE, and TUG scores and subjective symptom improvement and changes in 3 categories (gait, urinary, and cognitive symptoms) were assessed up to 1 year after ventriculoatrial or ventriculoperitoneal shunt surgeries. Patients with continuous postsurgical complications such as shunt blockage or infection within the period of inspection were excluded. To account for possible shunt malfunctions or sub-optimal shunt settings, we selected the best outcome measures reported within a year of the operation. The preprocedural aqueductal stroke volume and flow rate measured by AQ-PCMR and Flow software (<http://www.tidam.fr/documentation>)²⁰ were compared among LP/LD, or shunt surgery responders and nonresponders.

MR Imaging Technique

All patients were examined with a 1.5T (Magnetom Avanto and Magnetom Espree; Siemens, Erlangen, Germany) or 3T (Magnetom Trio and Magnetom Verio; Siemens) MR imaging scanners with a 12-channel head coil. Flow images were acquired at the center of the cerebral aqueduct perpendicular to the CSF flow direction with a 2D fast cine phase-contrast MR imaging pulse sequence with retrospective peripheral gating. In the cine phase-contrast MR imaging, the through-plane velocity-encoding was in the craniocaudal direction. The sequence parameters were as follows: TR/TE, 51/6.4 ms; NEX, 2; slice thickness, 4 mm; FOV, 120 × 120 mm; pixel spacing, 0.375 mm; flip angle, 20°; and velocity encoding, 8–30 cm/s for the axial-oblique plane. Images were re-acquired with higher velocity-encoding parameters if they had aliasing artifacts. The cardiac cycle was partitioned into 32 segments. Depending on the patient's heart rate, the acquisition time was approximately 4–6 minutes for AQ-PCMR. Thin-section sagittal imaging with a CISS sequence used to evaluate possible aqueductal stenosis was obtained for all the samples. The sequence parameters were as follows: TR/TE, 6.16/2.85 ms; NEX, 2; slice thickness, 0.5 mm; FOV, 320 × 320 × 15 mm; pixel spacing, 0.5 mm; flip angle, 40°.

Aqueductal Flow Analysis

Data were analyzed using an image-processing software Flow with an optimized CSF flows segmentation algorithm, which automatically extracts the ROI at the level of the cerebral aqueduct.²⁰ The CSF flow profiles were generated versus the 32 segments of the cardiac cycle, and the integration of this curve provided the CSF cephalic and caudal stroke volume (in microliters) and flow rate (in milliliters/minute), which represented the CSF volume dis-

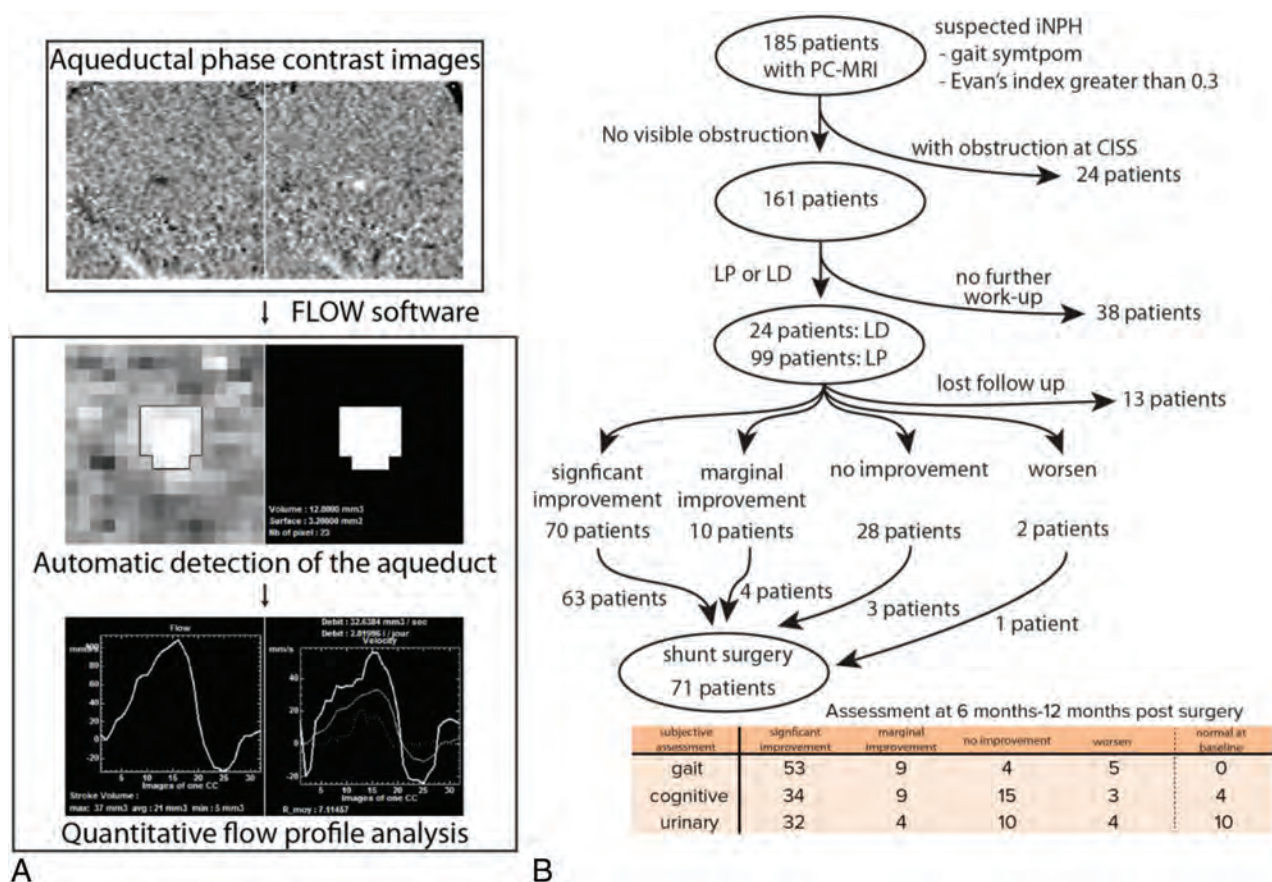


FIG 1. An overview of the AQ-PCMR image-processing pipeline and treatment flowchart of patients suspected of having CAH in this study. *A*, The phase-contrast MR imaging data acquired at the level of cerebral aqueduct are analyzed by Flow software to calculate the stroke volume and flow rate of each patient. *B*, One hundred eighty-five patients with gait abnormality and ventricular enlargement determined by the Evans index are included in this study. Depending on quantitative and subjective response to LP/LD, patients undergo shunt surgery. The shunt outcomes are determined within 12 months after surgery using both subjective assessment in 3 symptom categories and quantitative measurements such as the Tinetti, TUG, or MMSE scores.

placed in both directions through the considered ROI at the level of cerebral aqueduct. We averaged the cephalic and caudal flow rate and stroke volume.

Statistical Analysis

Statistical comparisons for all the analyses were performed by using R statistical and computing software (<http://www.r-project.org/>). Comparisons among Tinetti, TUG, and MMSE scores before and after LP/LD and/or shunt surgery were made using the Wilcoxon rank sum test. When comparing the improvement after LP/LD and the improvement after a shunt, we also used the Wilcoxon rank sum test. We used Pearson correlation tests to assess the relationship between improvements in hydrocephalus symptoms after LP/LD and after shunt. To analyze whether the aqueductal flow rate and stroke volume had prognostic or diagnostic value, we first divided patients into quartiles with an equal number of patients based on the Tinetti, TUG, or MMSE scores collected at baseline. We then compared the aqueductal flow rate (in milliliters/minute) and aqueductal stroke volume (in microliters) between each pair of these quartiles using ANOVA along with the Tukey Honest Significant Difference test. We repeated the same analysis using quartiles defined by the Tinetti, TUG, or MMSE score changes after LP/LD or shunt surgery. To compare LP/LD

or shunt responders and nonresponders, we defined “shunt response” by 3 criteria: subjective improvement, >20% improvement in TUG score, or >20% improvement in Tinetti score. The Wilcoxon rank sum test was used when comparing flow rate and stroke volume between LP/LD or shunt responders and nonresponders. We tested the likelihood of improvement after shunt surgery given improvement after LP/LD using the Fisher exact test. Finally, we used receiver operating characteristic analysis to find the cutoff values for the aqueductal flow rate and stroke volume that maximized sensitivity and specificity with respect to shunt outcomes.

RESULTS

The process of Flow software to survey the flow rate from AQ-PCMR is shown in Fig 1A.²⁰ Clinical assessment and AQ-PCMR results post-LP/LD and postshunt response work flow are shown in Fig 1B. One hundred eighty-five patients with suspected CAH symptoms with ventricular enlargement determined by the Evans index were evaluated for potential obstruction in the aqueductal system determined with high-resolution CISS images and AQ-PCMR. After we removed 24 patients with obstructions in the ventricular system, 123 patients underwent LP/LD. Seventy and

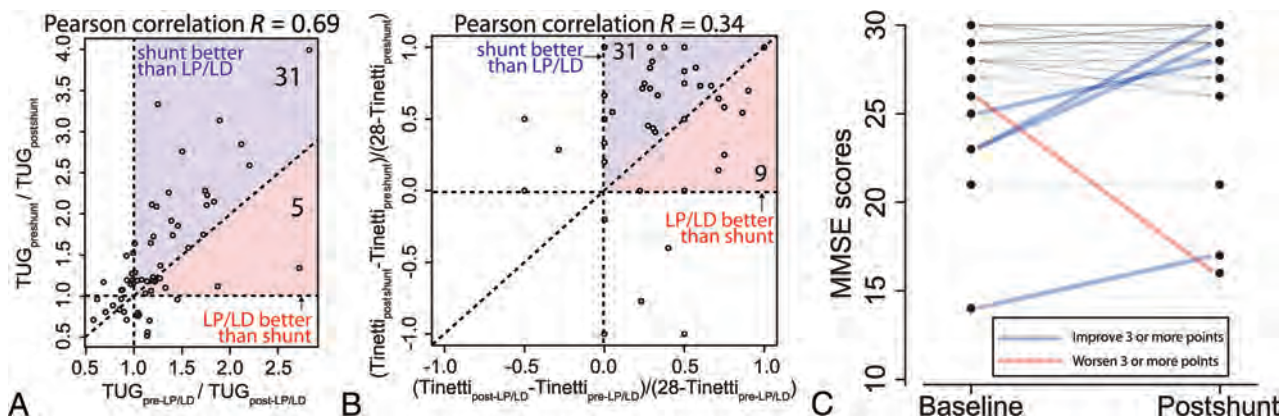


FIG 2. Quantitative assessment for LP/LD and shunt response. A, Comparison between the improvement in TUG scores after LP/LD (x-axis) and after shunt surgery (y-axis). Thirty-one patients show better improvement after shunt surgery than after LP/LD, whereas 5 patients show better improvement after LP/LD than after shunt surgery. B, Comparison between the improvement in the Tinetti score “deficit” after LP/LD (x-axis) and after shunt surgery (y-axis). Patients with a Tinetti score of 28 at baseline and 2 outliers (−1.4, 0.6) and (−1, −2) are not shown on this graph. Thirty-one patients show better improvement after shunt surgery than after LP/LD, whereas 9 patients show better improvement after LP/LD than after shunt surgery. C, Changes in the MMSE score after shunt surgery. Blue lines represent patients who improved, and red lines represent patients who worsened by ≥ 3 points in the MMSE test after shunt surgery.

10 patients showed significant and moderate symptom improvement after LP/LD, whereas 28 and 2 patients reported no improvement or worsening of symptoms, respectively. Most patients with significant improvement (88.2% of patients with significant improvement) but also some patients without symptom improvement (6% of patients with no improvement) after LP/LD underwent shunt surgery (Fig 1B). Both subjective and objective assessments after shunt surgery were performed. After the operation, 75%, 53%, and 52% of patients who had gait, urinary, or cognitive symptoms, respectively, reported significant improvement.

In addition to patients’ subjective reports, we surveyed quantitative assessments: Tinetti and TUG scores (before and after LP/LD and shunt surgery) and MMSE scores (before and after shunt surgery) (Fig 2). In our patient population, both LP/LD and shunt surgery significantly resulted in objective improvement in the TUG score (Fig 2A, paired Wilcoxon rank sum test; P values $< .001$ for LP/LD and $< .001$ for shunt surgery) and Tinetti score (Fig 2B, paired Wilcoxon rank sum test; P values $< .001$ for LP/LD and $< .001$ for shunt surgery). In contrast, MMSE scores did not show significant improvement after shunt surgery (Fig 2C, paired Wilcoxon rank sum test; P value = .74 for shunt surgery).

When we compared the improvement after LP/LD and the improvement after shunt surgery, shunt surgery resulted in significantly greater improvement than LP/LD in both Tinetti and TUG scores (Fig 2A, -B, paired Wilcoxon rank sum test; P values = .007 for the Tinetti Test and .001 for the TUG test). Nonetheless, both TUG and Tinetti scores showed positive correlations (Fig 2A, -B, Pearson correlation $R = 0.69$ and 0.34) between LP/LD response and shunt surgery, suggesting that the LP/LD could predict the responses to the shunt surgery quantitatively.

We next tested whether aqueductal CSF flow has a diagnostic or prognostic value. When they were divided into 4 quartiles based on Tinetti, TUG, and MMSE scores collected at baseline, there was no significant difference in the aqueductal flow rate and aqueductal stroke volume among quartiles (On-line Tables 1 and 2, upper 3 rows of each table). These quartiles did not demon-

strate any significant differences in Tinetti, TUG, and MMSE score changes after LP/LD or shunt surgery (On-line Tables 1 and 2, lower 5 rows of each table). When we divided subjects into LP/LD responders and nonresponders based on their subjective improvement, the flow rate and stroke volume of the responders and nonresponders overlapped (Fig 3A). Most interesting, a small number of patients within the LP nonresponder group had very high aqueductal flow rates. These patients exhibited significantly higher flow rates than the LP responder group (P value = .04). Likewise, TUG score improvement after LP/LD and shunt surgery showed a weak negative correlation with respect to stroke volume and flow rate (Fig 3B and On-line Fig 1B). We performed the same analyses for shunt surgery. Patients were divided into shunt responders and nonresponders based on the symptom relief after shunt surgery, and their aqueductal flow parameters were compared (On-line Fig 1A). Similar to the LP/LD response, the flow rate and stroke volume of the shunt responders and nonresponders overlapped. The difference between the 2 groups was not significantly different for both the aqueductal flow rate and stroke volume (P value = .35 and .38, respectively). There were 4 patients within the shunt responder group exhibiting higher aqueductal flow than other study participants.

To test the hypothesis that aqueductal CSF flow may reveal shunt responders among LP/LD nonresponders, we evaluated the aqueductal flow rate and stroke volume of LP/LD responders and nonresponders depending on their shunt responses (On-line Fig 2). As expected, the LP/LD responders had significantly higher likelihood of having a favorable shunt surgery outcome than LP/LD nonresponders (90% versus 50%; Fisher exact test, P value = .03). Patients with a high flow rate or stroke volume, regardless of their LP/LD results, showed improvement after shunt surgery. A small number of patients with a 25 mL/min or higher flow rate or all patients with 180 μ L or higher stroke volume had favorable shunt surgery outcomes.

We next evaluated the diagnostic and prognostic values of low aqueductal stroke volume or low flow rate alone in predicting a shunt outcome. Receiver operating characteristic

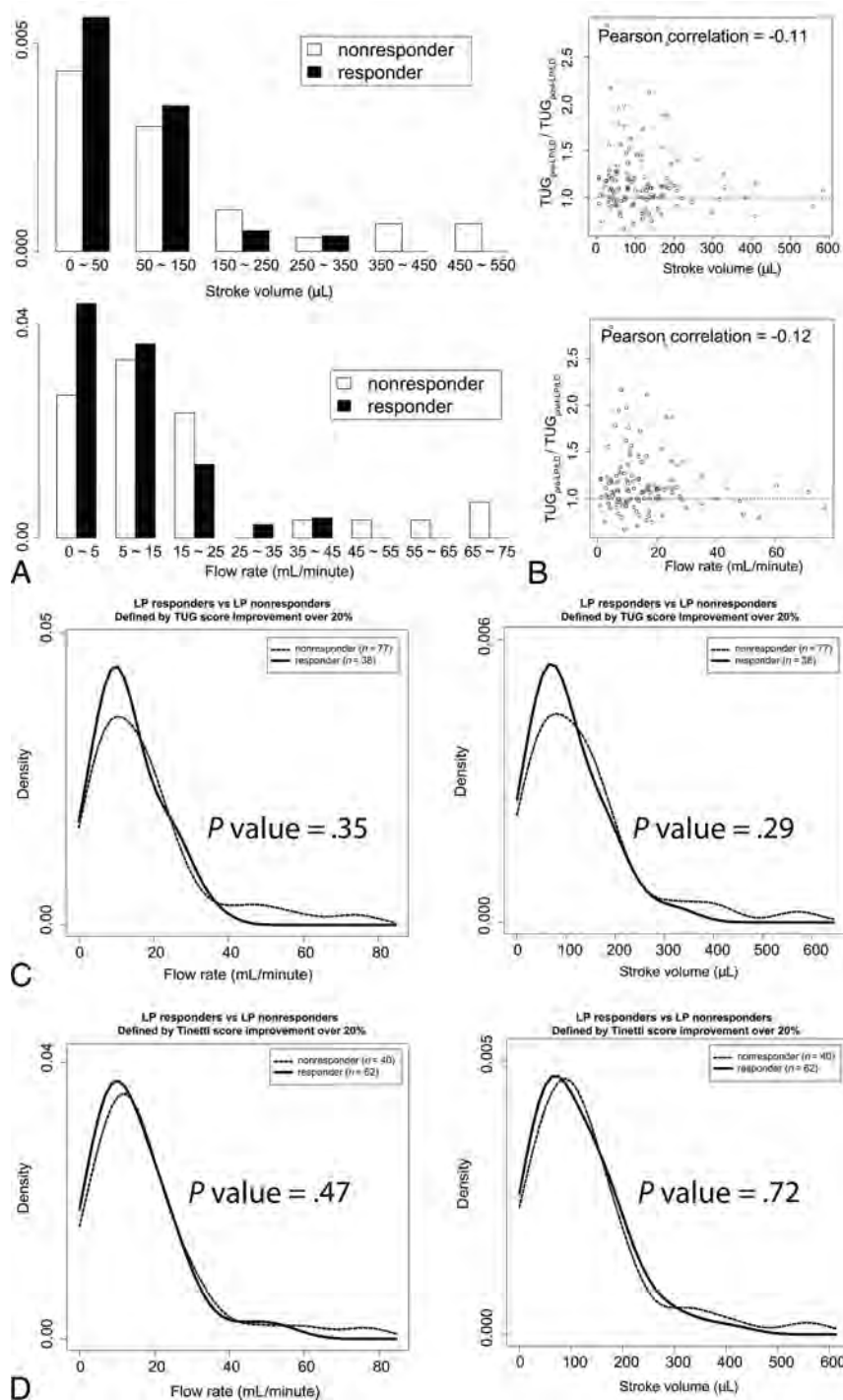


FIG 3. The aqueductal CSF flow and LP/LD response measured by subjective improvement and Tinetti and TUG score improvement. A, The distributions of aqueductal stroke volume (upper) and flow rate (lower) are compared between LP/LD responders and nonresponders. The aqueductal flow rate is significantly higher in LP/LD nonresponders than in responders (Wilcoxon rank sum test, $P = .03$ for stroke volume and $.028$ for flow rate). B, The aqueductal stroke volume (upper) and flow rate (lower) are plotted against the quantitative improvement of the TUG score (y-axis) after LP/LD. The Pearson correlation between the TUG score improvement and the stroke volume and flow rate are -0.113 and -0.116 , respectively. C, Twenty percent or greater improvement in the TUG score after LP/LD was used to define LP/LD responders, and $<20\%$ improvement in the TUG score after LP/LD was used to define LP/LD nonresponders. The number of patients in each group is shown as a number on the graph. The 2 groups exhibit an overlapping distribution of aqueductal flow rate and stroke volumes. D, "Tinetti score deficit" is defined as the difference between a perfect Tinetti score and the patient's Tinetti score. Twenty percent or greater improvement in the Tinetti score deficit after LP/LD was used to define LP/LD responders, and $<20\%$ improvement in the Tinetti score deficit after LP/LD was used to define LP/LD nonresponders. Again, the 2 groups exhibit overlapping distribution of aqueductal flow rate and stroke volumes.

analysis revealed that the diagnostic value of the AQ-PCMR-derived flow rate or stroke volume in predicting shunt outcome is minimal (On-line Fig 3).

DISCUSSION

In this study, we retrospectively evaluated the relationship between quantitative AQ-PCMR measures to LP/LD responsiveness and shunt responsiveness. We selected subjects with potentially treatable communicating CAH based on their responses to LP/LD. The patients' response to shunt surgery was determined by patients' subjective reports of gait, urinary, and cognitive symptom improvement. At our institution, surgical decisions are made on the basis of radiologic evaluation of the patency of the ventricular system on high-resolution MR imaging and AQ-PCMR and the patients' clinical symptom improvement after LP or LD.

The efficiency of shunt surgery in our study (87%) is comparable with that in previous studies.⁹ The positive and negative predictive values of LP/LD for shunt success (90% and 50%, respectively) are higher than those in most other studies.⁸ This result is potentially due to the stringent criteria we used to select patients with CAH. We used high-resolution imaging to exclude stenosis in the ventricular system by carefully examining any signs of obstruction at the foramen of Monro, cerebral aqueduct, and fourth ventricular outflow, findings that can be difficult to visualize using conventional 2D MR images or 3D acquisitions with larger voxel sizes. The patients with obstructive hydrocephalus who were excluded from our study are not expected to improve after LP/LD but would improve after shunt surgery. Including patients with obstructive hydrocephalus would cause underestimation of the specificity and negative predictive value of LP/LD.

Most prior research used either stroke volume or flow rate, leaving the possibility of the conclusion changing with other variables.^{5,10,11,21} Although related, these 2 variables are affected differentially by the heart rate. We used both stroke volume and flow rate to evaluate AQ-PCMR and found that the results were largely consistent between the 2 parameters.

We found that the CSF flow rate and stroke volume mostly overlapped between LP/LD nonresponders and responders. There are, however, a few patients with very high flow rates among LP/LD nonresponders, making the aqueductal flow parameters of LP/LD nonresponders significantly higher than those of LP/LD responders. Because the LP/LD responder group has a greater number of patients compared with LP/LD nonresponder group, the wider dispersion of LP/LD nonresponders is rather unexpected and implies underlying clinical significance. Most interesting, patients with the highest aqueductal flow do not to respond to LP/LD yet respond to shunt surgery. This result is indeed consistent with that of Dixon et al,¹¹ who showed that patients with high flow rates (>33 mL/min) were LP/LD nonresponders but shunt responders. Although there are not enough patients who did not respond to LP/LD but responded to shunt surgery in our study, our data suggest that LP/LD and shunt surgery results may be inconsistent for patients with high aqueductal flow.

Aqueductal stroke volume is a dynamic variable that increases at the early phase but decreases after a peak at the later disease course, potentially due to brain ischemia (On-line Fig 4).²²⁻²⁴ Because there are also significant heterogeneities in baseline aqueductal flow in the normal state, it is impossible to infer the extent of disease progression based on a single "snapshot" of aqueductal flow characteristics.^{5,18,19,23,25} LP and LD have high positive predictive values but low negative predictive values; thus, they may miss patients who would derive benefit from shunt surgery.⁹ If this model were true, patients with moderately progressed disease, who do not demonstrate response to LP/LD but still benefit from the shunt surgery (middle group in the On-line Fig 4) would have high aqueductal flow. In this setting, we can use AQ-PCMR as an adjunct tool in determining patients who can benefit from shunt surgery among LP/LD nonresponders. Additional studies targeting such patient populations should follow.

There are a few limitations to our study. First, it is a retrospective study. However, all surgery and assessments were performed in a standardized fashion under the guidance of a single surgeon (D.R.). When measuring aqueductal CSF flow, we minimized measurement variability using automated software to measure stroke volume and flow rate. Second, because we used LP/LD response to select patients to undergo an operation, the number of patients in the LP/LD non-responder group was smaller than LP/LD responder group. Most patients with high aqueductal flow among LP/LD nonresponders were excluded from shunt surgery. Third, the number of patients who failed to have improvement after shunt surgery was smaller than patients with improvement. Unlike patients with high aqueductal CSF flow in the smaller LP/LD negative group, patients with high aqueductal CSF flow in the larger shunt-positive group could simply be a result of random distribution. Finally, the relationship between aqueduct radius and stroke volume was not assessed in this study. Aqueductal radius plays an important role in the relationship between flow and pressure²⁶; thus, variation in the aqueductal radius may impact our findings. Additional studies will be required to determine the significance of the aqueductal radius as it relates to LP/LD response and shunt success.

In summary, although it has been previously suggested that the utility of phase-contrast imaging may lie in excluding those

patients with low aqueductal CSF flow from surgery, in fact, shunt responders can also be found among those patients with the lowest aqueductal CSF flow rates. The proportion of shunt responders to nonresponders was relatively high at each cerebral aqueductal flow value as a result of the prevalence of shunt responsiveness in the population studied. AQ-PCMR added little further benefit beyond clinical evaluation with suspicion of disease, though it may be useful as an adjunct tool to support low negative predictive values of LP/LD tests.

CONCLUSIONS

Shunt surgery can significantly improve symptoms and potentially stop the progression of CAH, but the response to the surgery is heterogeneous. The field is searching for less invasive and more accurate clinical assays to select surgical candidates. The evidence to support AQ-PCMR as a diagnostic and prognostic assay for CAH has been discordant. In this retrospective study, we show that AQ-PCMR alone has little diagnostic and prognostic value in determining shunt outcomes.

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REFERENCES

- Adams RD, Fisher CM, Hakim S, et al. **Symptomatic occult hydrocephalus with normal cerebrospinal-fluid pressure: a treatable syndrome.** *N Engl J Med* 1965;273:117–26 CrossRef Medline
- Edwards RJ, Dombrowski SM, Luciano MG, et al. **Chronic hydrocephalus in adults.** *Brain Pathol* 2004;14:325–36 CrossRef Medline
- Tarnaris A, Watkins LD, Kitchen ND. **Biomarkers in chronic adult hydrocephalus.** *Cerebrospinal Fluid Res* 2006;3:11 CrossRef Medline
- Marmarou A, Young HF, Aygok GA. **Estimated incidence of normal-pressure hydrocephalus and shunt outcome in patients residing in assisted-living and extended-care facilities.** *Neurosurg Focus* 2007;22:E1 Medline
- Kahlon B, Sjunnesson J, Rehnecrona S. **Long-term outcome in patients with suspected normal pressure hydrocephalus.** *Neurosurgery* 2007;60:327–32; discussion 332 CrossRef Medline
- Resnick SM, Pham DL, Kraut MA, et al. **Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain.** *J Neurosci* 2003;23:3295 Medline
- Vakili S, Moran D, Hung A, et al. **Timing of surgical treatment for idiopathic normal pressure hydrocephalus: association between treatment delay and reduced short-term benefit.** *Neurosurg Focus* 2016;41:E2 CrossRef Medline
- Halperin JJ, Kurlan R, Schwab JM, et al. **Practice guideline: idiopathic normal pressure hydrocephalus—response to shunting and predictors of response: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology.** *Neurology* 2015;85:2063–71 CrossRef Medline
- Wikkelsø C, Hellström P, Klinge PM, et al; European iNPH Multicentre Study Group. **The European iNPH Multicentre Study on the predictive values of resistance to CSF outflow and the CSF tap test in patients with idiopathic normal pressure hydrocephalus.** *J Neurol Neurosurg Psychiatry* 2013;84:562–68 CrossRef Medline
- Bradley WG, Scalzo D, Queral J, et al. **Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging.** *Radiology* 1996;198:523–29 CrossRef Medline
- Dixon GR, Friedman JA, Luetmer PH, et al. **Use of cerebrospinal fluid flow rates measured by phase-contrast MR to predict outcome**

- of ventriculoperitoneal shunting for idiopathic normal-pressure hydrocephalus. *Mayo Clin Proc* 2002;77:509–14 [CrossRef Medline](#)
12. Sankari SE, Fichten A, Gondry-Jouet C, et al. Correlation between tap test and CSF aqueductal stroke volume in idiopathic normal pressure hydrocephalus. *Acta Neurochir Suppl* 2012;113:43–46 [CrossRef Medline](#)
 13. Poca MA, Sahuquillo J, Busto M, et al. Agreement between CSF flow dynamics in MRI and ICP monitoring in the diagnosis of normal pressure hydrocephalus. Sensitivity and specificity of CSF dynamics to predict outcome. *Acta Neurochir Suppl* 2002;81:7–10
 14. Bradley WG. Intracranial pressure versus phase-contrast MR imaging for normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 2015;36:1631–32 [CrossRef Medline](#)
 15. Tisell M, Tullberg M, Hellström P, et al. Neurological symptoms and signs in adult aqueductal stenosis. *Acta Neurol Scand* 2003;107:311–17 [CrossRef Medline](#)
 16. Chiang WW, Takoudis CG, Lee SH, et al. Relationship between ventricular morphology and aqueductal cerebrospinal fluid flow in healthy and communicating hydrocephalus. *Invest Radiol* 2009;44:192–99 [CrossRef](#)
 17. Algin O, Hakyemez B, Parlak M. The efficiency of PC-MRI in diagnosis of normal pressure hydrocephalus and prediction of shunt response. *Acad Radiol* 2010;17:181–87 [CrossRef Medline](#)
 18. Kahlon B, Annertz M, Ståhlberg F, et al. Is aqueductal stroke volume, measured with cine phase-contrast magnetic resonance imaging scans useful in predicting outcome of shunt surgery in suspected normal pressure hydrocephalus? *Neurosurgery* 2007;60:124–29; discussion 129–30 [CrossRef Medline](#)
 19. Scollato A, Gallina P, Di Lorenzo N, et al. Is aqueductal stroke volume, measured with cine phase-contrast magnetic resonance imaging scans useful in predicting outcome of shunt surgery in suspected normal pressure hydrocephalus? *Neurosurgery* 2008;63:E1209; author reply E1209 [CrossRef Medline](#)
 20. Balédent O, Henry-Feugeas MC, Idy-Peretti I. Cerebrospinal fluid dynamics and relation with blood flow: a magnetic resonance study with semiautomated cerebrospinal fluid segmentation. *Invest Radiol* 2001;36:368–77 [CrossRef Medline](#)
 21. Al-Zain FT, Rademacher G, Meier U, et al. The role of cerebrospinal fluid flow study using phase contrast MR imaging in diagnosing idiopathic normal pressure hydrocephalus. *Acta Neurochir Suppl* 2008;102:119–23
 22. Bradley WG. CSF flow in the brain in the context of normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 2015;36:831–38 [CrossRef Medline](#)
 23. Scollato A, Tenenbaum R, Bahl G, et al. Changes in aqueductal CSF stroke volume and progression of symptoms in patients with unshunted idiopathic normal pressure hydrocephalus. *AJNR Am J Neuroradiol* 2008;29:192–97 [CrossRef Medline](#)
 24. Bradley WG. MR prediction of shunt response in NPH: CSF morphology versus physiology. *AJNR Am J Neuroradiol* 1998;19:1285 [Medline](#)
 25. Andréen K, Wikkelsø C, Tisell M, et al. Natural course of idiopathic normal pressure hydrocephalus. *J Neurol Neurosurg Psychiatry* 2014;85:806–10 [CrossRef Medline](#)
 26. Chaarani B, Capel C, Zmudka J, et al. Estimation of the lateral ventricles volumes from a 2D image and its relationship with cerebrospinal fluid flow. *Biomed Res Int* 2013;2013:215989 [CrossRef Medline](#)

Natural History of Endoscopic Third Ventriculostomy in Adults: Serial Evaluation with High-Resolution CISS

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ABSTRACT

BACKGROUND AND PURPOSE: Endoscopic third ventriculostomy is a well-accepted treatment choice for hydrocephalus and is used most frequently with a known impediment to CSF flow between the third ventricle and basal cisterns. However, there are scarce data on the imaging evolution of the defect in the floor of the third ventricle and how this affects patency rates and clinical outcomes. The purpose of this study was to assess whether, and how, the endoscopic third ventriculostomy defect changes in size with time.

MATERIALS AND METHODS: All high-resolution endoscopic third ventriculostomy protocol MRIs performed between 2009 through 2014 were retrospectively identified. Two fellowship-trained neuroradiologists, blinded to clinical information, independently reviewed all retrospective cases.

RESULTS: A total of 98 imaging studies were included from 34 patients. The average change in the area throughout the studied period was 0.02 mm²/day (7.5 mm²/year), with a higher increase in size noted in the first 3 postsurgical months, with a gradual decrease in the degree of defect-size change. Use of the NICO Myriad device was correlated with the area of the endoscopic third ventriculostomy defect on the last follow-up, demonstrating a larger final defect size in patients in whom the surgical technique included debridement of the endoscopic third ventriculostomy defect walls with the NICO Myriad device (28.21 versus 11.25 mm, $P < .05$).

CONCLUSIONS: High-resolution MR imaging with sagittal CISS images is useful in the postoperative evaluation of endoscopic third ventriculostomies. Such findings may prove useful in determining the optimal duration of follow-up with MR imaging of patients who have undergone endoscopic third ventriculostomy.

ABBREVIATION: ETV = endoscopic third ventriculostomy

Endoscopic third ventriculostomy (ETV) is a commonly performed procedure for the treatment of noncommunicating adult hydrocephalus when the obstruction is between the third ventricle and the basal cisterns. The procedure avoids insertion of a foreign body with its inherent shunt-related complications, such as obstruction, disconnection, catheter migration, infection, and over- or underdrainage.¹⁻³ ETV is a well-accepted treatment choice for hydrocephalus and is used most frequently in the presence of a known impediment to CSF flow between the third ventricle and the basal cisterns.⁴⁻⁸

Management of patients who have undergone ETV is not sim-

ple because symptoms may be attributable to failure of the ETV, recurrent symptoms from an intracranial process not treated or not fully treated by ETV, or another etiology entirely. Spontaneous closure of a once-patent ETV has also been reported, sometimes with fatal consequences.^{9,10} MR imaging may provide invaluable information in the assessment of patients with ETV because patency of the ETV defect can be assessed noninvasively. Postoperative imaging has mainly been directed at detecting a CSF flow void in the floor of the third ventricle. At our institution, due to the frequency of the request, a clinical “high-resolution endoscopic third ventriculostomy” protocol MR imaging (ETV protocol) has been established to aid in the evaluation of the patency of the ETV defect. The ETV protocol includes both high-spatial-resolution isotropic CISS imaging through the sagittal midline structures and cardiac-gated phase-contrast imaging through the floor of the third ventricle in the expected region of the ETV defect in addition to standard components of head MR imaging. High-resolution CISS permits identification of the anatomic patency of the surgical

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defect as well as its size, and phase-contrast imaging provides complementary data with respect to CSF movement through the ETV defect.

There are scarce data on the imaging evolution of the defect in the floor of the third ventricle and how this affects patency rates and clinical outcomes. The purpose of this study was to assess whether, and how, the ETV defect changes in size with time.

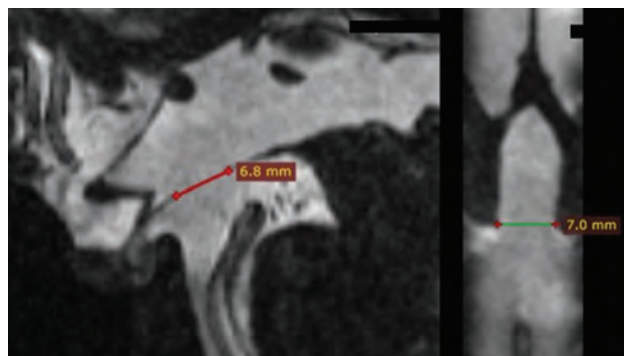


FIG 1. Representative sagittal CISS image and coronal MPR reconstruction of a third ventriculostomy defect with anteroposterior and third ventriculostomy defect size measurement.

Table 1: Demographic information

Demographics	%	No.
Sex		
Male	44%	15
Female	56%	19
Mean age (range) (yr)	54 (19–76)	

Table 2: Site of obstruction to the flow of CSF

Location of Obstruction	%	No.
Cerebral aqueduct	82%	28
Fourth ventricle outflow	3%	1
Prepontine cistern	9%	3
Unknown	3%	1
Other	3%	1
		34

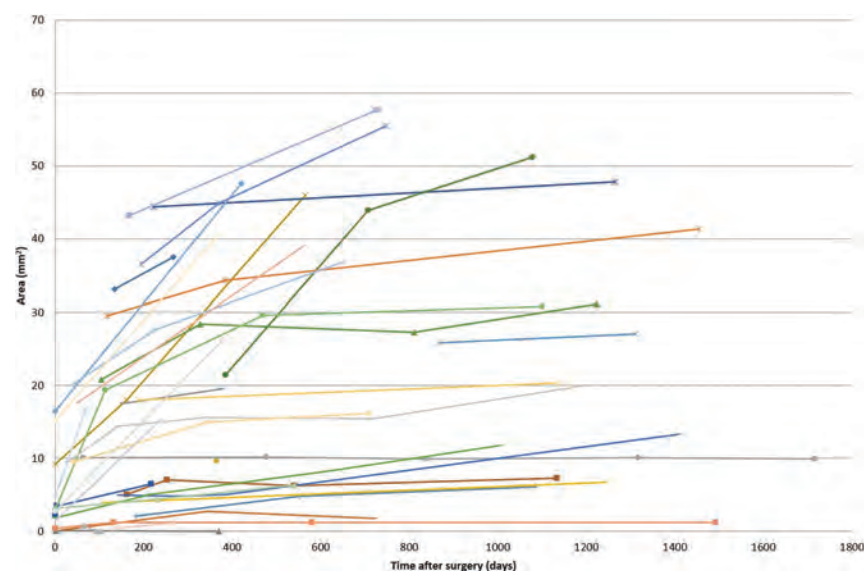


FIG 2. Defect size area across time after surgery.

MATERIALS AND METHODS

Patient Selection

All high-resolution endoscopic third ventriculostomy protocol MRIs performed between 2009 through 2014 at a single institution were identified following institutional review board approval. Two fellowship-trained neuroradiologists, blinded to clinical information, independently reviewed all retrospective cases. Patients with at least 2 postoperative ETV protocol studies were included. Patients who had previously undergone an intracranial operation before ETV, including ventriculostomy tube placement, were excluded. Cases with imaging performed on scanners other than 3T (ie, 1.5T) were excluded. Studies with significant motion (grade 3) were also excluded. The birth date, sex, and date of the operation were obtained from the patient's chart. The site of obstruction to the flow of CSF was obtained from presurgical imaging.

The clinical course defined by the treating physician as improved, stable, or worse was obtained from the chart including: headache, dizziness, nausea, vision deficit, gait problems, urinary incontinence, cognitive decline, other clinically relevant symptoms (ie, irritability, drowsiness, personality changes, seizures), and general clinical outcome. Symptom improvement, stability, or worsening was noted at the last follow-up; thus, patients with initial improvement who, during the follow-up course of the disease, had gradual symptom decline back to baseline status were defined as "stable." During the studied period, the neurosurgeons changed their surgical technique, adopting the NICO Myriad device (NICO Corporation, Indianapolis, Indiana) to debride the wall of the ventriculostomy site; the use of this device was also noted.¹¹

Imaging Analysis

High-resolution isotropic imaging in CISS was performed at 3T (MAGNETOM Trio, Siemens, Erlangen, Germany) field with 0.5- to 0.6-mm near-isotropic image resolution. Imaging parameters consisted of the following: TR/TE, 6.16/2.85 ms; 0.5-mm isotropic voxels; flip angle, 40°; FOV, 160 mm; matrix, 320 × 320. The presence of patient motion was graded from 1 to 3 (1 no motion; 2, mild motion; 3, severe motion). Using multiplanar

reformatting, we identified the presence of a patent ETV defect; if it was present, the greatest anteroposterior (AP) diameter was measured on sagittal images and the greatest transverse (AP) diameter was measured on coronal reformat images (Fig 1). Measurements were performed by an experienced neuroradiologist (M.T.). To assess the reproducibility of the measurements, a second radiologist (C.H.M.) repeated the measurements blinded to the prior results. The area of the defect was estimated using the ellipsoid formula:

$$\pi \times \frac{AP}{2} \times \frac{TV}{2}.$$

Statistical Analysis

Categorical variables are presented as percentages; continuous variables are presented as mean ± 95% confidence inter-



FIG 3. Representative case showing presurgical imaging, first follow-up at 1 day postsurgery, and final follow-up at 421 days postsurgery showing an increase in the ETV defect size.

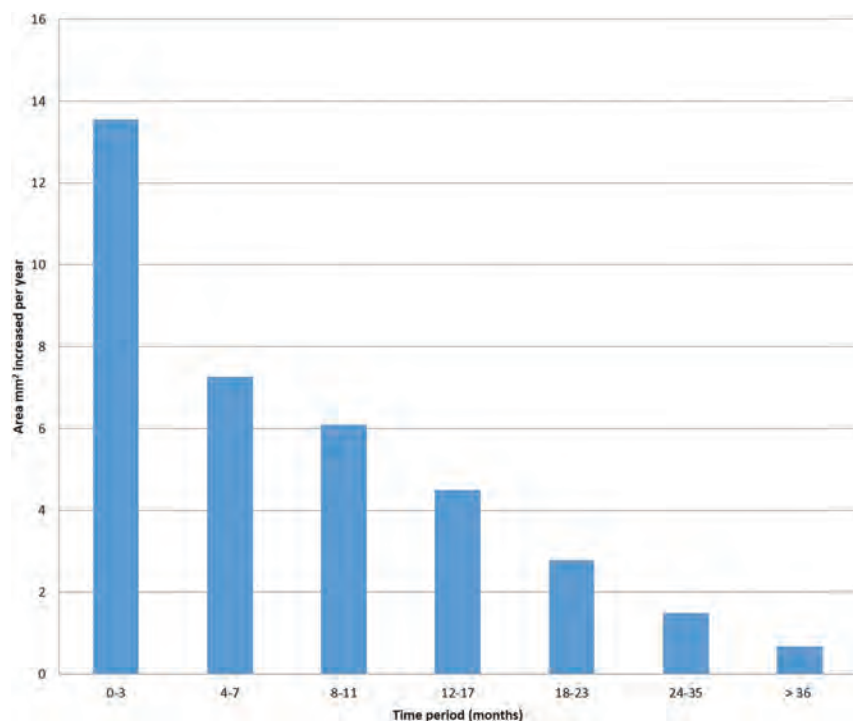


FIG 4. Average increase in the size of the defect across time.

val. The unpaired Student *t* test with 2 tails was used to test the statistical independence between groups. The Pearson correlation coefficient was used to measure the strength of the association between age and defect size. Interreader agreement was determined by the intraclass correlation coefficient for the area measurement. A value of $P < .05$ was considered statistically significant. Data analysis was performed with SPSS Statistics (Version 20; IBM, Armonk, New York). Graphs were constructed with Excel (Version 14; Microsoft, Redmond, Washington).

RESULTS

A total of 295 high-resolution ETV protocol MR imaging studies were identified in 84 patients. Fifty patients with 168 studies had prior intracranial operations or <2 postoperative studies, and 2 studies had severe motion and were excluded, leaving 125 studies in 34 patients (Table 1). Of these, 27 had been misclassified at the time of protocol code insertion and were preoperative studies. We

analyzed the remaining 98 postsurgical ETV protocol MRIs in 34 patients. The mean age was 54 years (range, 19–76 years) with a male/female ratio of 0.78 as shown in Table 1. The overall mean follow-up time, after ETV, was 25.3 ± 2.8 months. Follow-up did not significantly differ between those undergoing ETV with or without the NICO Myriad device ($P > .05$).

The location of obstruction to the flow of CSF is shown in Table 2. Obstruction was located at the cerebral aqueduct in 28 patients (82%), at the fourth ventricle outflow in 1 patient (3%), at the prepontine basal cistern in 3 patients (9%), at another site in 1 patient (3%), and was unknown in 1 patient (3%) who had the clinical diagnosis of normal pressure hydrocephalus. Prepontine obstruction occurred due to mechanical obstruction by thickened arachnoid membranes or arachnoid cysts.⁵

Two patients had their ETVs occlude during the first year of follow-up. All other patients showed an increase in the size of the ETV defect during the imaging time (Figs 2 and 3). The average change in the area throughout the studied period was $0.02 \text{ mm}^2/\text{day}$ ($7.5 \text{ mm}^2/\text{year}$) with a higher increase in size noted in the first 3 postsurgical months, with a gradual decrease in the degree of defect-size change as seen in Fig 4. Thirteen patients underwent a study in the 2 days following the operation, showing an average defect size of $2.2 \times 2.4 \text{ mm}$ (mean area, 4.6 mm^2 ; range, $0.3\text{--}13.0 \text{ mm}^2$). The intraclass correlation coefficient between both readers in the anteroposterior and third ventriculostomy measurements was 0.83 and 0.88, respectively.

The age at the operation was correlated to the area of the defect on the last follow-up examination showing a positive correlation, with older individuals having larger defects ($R = 0.625$, a moderate positive correlation; $P < .01$; Fig 5).

Use of the NICO Myriad device was correlated with the area of

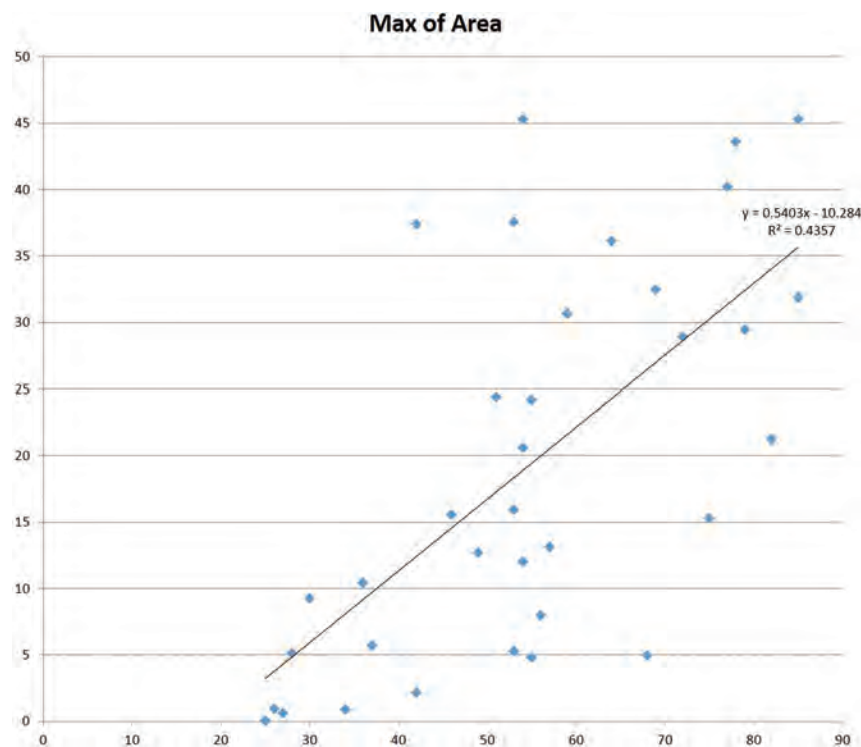


FIG 5. Maximum defect size and age at the operation.

Table 3: Average defect size $\pm$ 95% confidence interval and t test for the NICO Myriad device at last follow-up

	NICO Myriad Device Used		P Value
	Yes	No	
Average defect size at LFU (mean)	28.21 $\pm$ 7.48	11.25 $\pm$ 6.80	<.05

Note:—LFU indicates last follow-up.

Table 4: Presenting symptoms

	NICO Myriad Used	No NICO Myriad	P Value
Headache	60%	75%	>.05
Dizziness	26.7%	30%	>.05
Nausea	26.7%	35%	>.05
Vision deficit	40%	45%	>.05
Gait abnormality	53.3%	50%	>.05
Urinary incontinence	46.7%	35%	>.05
Cognitive dysfunction	53.3%	60%	>.05

the ETV defect on the last follow-up (Table 3), showing a larger final defect size in patients in whom the surgical technique included debridement of the ETV defect walls with the NICO Myriad device (28.21 versus 11.25 mm, $P < .05$).

The most common presenting symptoms were headache, cognitive dysfunction, and gait deficits (Table 4). There were no significant differences in presenting symptoms between patients undergoing ETV with and without the NICO Myriad device ($P > .05$ for all). For all symptoms assessed (ie, headache, dizziness, nausea, vision deficit, gait abnormality, urinary incontinence, cognitive dysfunction), most patients experienced symptom improvement at 6 months following ETV. Most interesting, there was a minor reduction in symptom improvement at last follow-up, which tended to favor the use of the NICO Myriad device (Table 5). However, due largely to sample size, there were no significant

differences in symptom improvement between the 2 follow-up time points or with respect to use of the NICO Myriad device ($P > .05$ for all).

DISCUSSION

This is the first article that, to our knowledge, follows a large group of patients with ETV who underwent repeat MR imaging. With the exception of 2 patients who had occluded ETVs, the remainder showed an increase in size of the ETV defect during the imaging period.

Why the ETV defects enlarged with time is unknown. On surgical videos from ETV procedures after the ETV defect has been created, one can sometimes see significant CSF pulsation causing inward and outward movement of the floor of the third ventricle.^{2,12-17} We postulate that such CSF pulsation and the resultant shear forces, when aggregated across days to months to years, could cause widening of the ETV defect. Our data showed a

tendency toward a greater increase in the ETV defect area in older individuals, perhaps reflecting a decreased ability of the ETV margin in older individuals to withstand such small shear stresses. Our data suggest that not all ETVs showed an increase in size. It is uncertain at this time whether the ETV defect size or the velocity of the ETV defect-size change influences disease progression, or if either size or velocity of change are related to clinical outcomes.

The occlusion rate observed in this study was low (2/34 patients or 6%), partly because some patients with occluded ETVs did not undergo >1 MR imaging and thus were not included in our studied population. This finding is similar to those in reports in the literature, however, which cite $\sim 9\%$ occlusion during a median follow-up of 8.5 months and older age as protective against shunt revision.¹⁸ Nonetheless, no patients had an occlusion 1 year after the operation, potentially reducing the need for imaging follow-up to evaluate obstruction after this time. Both patients with occluded ETVs were the youngest in the group at 19 and 22 years of age. The NICO Myriad device was not used in their operations. No other distinguishing feature was found. Similar to previous reports, use of the NICO Myriad device, an aspirating/resecting device to debride the walls of the ventriculostomy site, was associated with the area of the defect size on last follow-up.¹¹

Although not the main purpose of this study, symptom improvement increased at 6 months following ETV, but improvement diminished slightly at the last follow-up visit. There seemed to be greater sustained improvement with the use of the NICO Myriad device, but this was not statistically significant, due to the small sample size. The main limitations of this study arise from the retrospective nature of observation of examinations performed for clinical purposes. The ETV studies were not per-

Table 5: Clinical outcomes at 6 months and last follow-up after ETV^a

	Improved		Same as Baseline		Worse Compared with Baseline		P Value
	NICO Myriad Used	No NICO Myriad	NICO Myriad Used	No NICO Myriad	NICO Myriad Used	No NICO Myriad	
Headache							
6 Mo	88.9%	80%	11.1%	13.3%	0%	6.7%	>.05
LFU	77.8%	53.3%	22.2%	33.3%	0%	13.3%	>.05
Dizziness							
6 Mo	100%	83.3%	0%	16.7%	0%	0%	>.05
LFU	100%	83.3%	0%	16.7%	0%	0%	>.05
Nausea							
6 Mo	75%	75%	25%	25%	0%	0%	>.05
LFU	50%	75%	50%	25%	0%	0%	>.05
Vision deficit							
6 Mo	83.3%	77.8%	16.7%	22.2%	0%	0%	>.05
LFU	83.3%	77.8%	16.7%	22.2%	0%	0%	>.05
Gait abnormality							
6 Mo	100%	100%	0%	0%	0%	0%	>.05
LFU	100%	70%	0%	10%	0%	20%	>.05
Urinary incontinence							
6 Mo	100%	100%	0%	0%	0%	0%	>.05
LFU	85.7%	85.7%	0%	0%	14.3%	14.3%	>.05
Cognitive dysfunction							
6 Mo	87.5%	70%	12.5%	30%	0%	0%	>.05
LFU	87.5%	70%	12.5%	20%	0%	10%	>.05

Note:—LFU indicates last follow-up.

^a Outcomes are given among those with preoperative symptoms.

formed at regular intervals following the procedure, possibly due to follow-up studies being performed outside the institution or within the institution but not using the high-resolution ETV MR imaging protocol. We have accounted for this issue partly by recording the elapsed time from the ETV operation to each MR imaging study. The time to the first follow-up ranged from a few hours after the operation to almost 2 and a half years after the ETV operation.

Because examinations were performed for clinical purposes, symptomatic patients who eventually had failed ETV may be over-represented in our sample. Although phase-contrast imaging was part of the high-resolution ETV protocol, it was not used in this study. Follow-up MRIs were performed to clinically ensure the patency of the ETV defect and the success of the ventriculostomy, in addition to its research role as a high-resolution imaging technique. This follow-up imaging protocol has been established as a standard at the current institution to aid in the evaluation of ETV patency. To accomplish this study, we included all patients fitting the inclusion criteria and having undergone ETV. ETV has been successful in multiple disease processes, including a subsection of patients with refractory long-standing symptomatic normal pressure hydrocephalus with overt ventriculomegaly and other unknown causes of hydrocephalus.^{19–23} The inclusion of this case represents a rare indication for ETV and did not significantly impact the results of the study.

CONCLUSIONS

High-resolution MR imaging with sagittal CISS images is useful in the postoperative evaluation of ETVs. A small percentage closed in the first year of follow-up with an increase in size of the ETV defect in all remaining patients, without premature defect closure. Such findings may prove useful in determining the optimal dura-

tion of follow-up with MR imaging of patients who have undergone ETV.

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REFERENCES

- Di Rocco C, Massimi L, Tamburrini G. **Shunts vs endoscopic third ventriculostomy in infants: are there different types and/or rates of complications? A review.** *Childs Nerv Syst* 2006;22:1573–89 [Medline](#)
- Santamarta D, Martin-Vallejo J, Diaz-Alvarez A, et al. **Changes in ventricular size after endoscopic third ventriculostomy.** *Acta Neurochir (Wien)* 2008;150:119–27; discussion 127 [CrossRef Medline](#)
- van Beijnum J, Hanlo PW, Fischer K, et al. **Laser-assisted endoscopic third ventriculostomy: long-term results in a series of 202 patients.** *Neurosurgery* 2008;62:437–43; discussion 443–44 [CrossRef Medline](#)
- Yadav YR, Parihar V, Pande S, et al. **Endoscopic third ventriculostomy.** *J Neurosci Rural Pract* 2012;3:163–73 [CrossRef Medline](#)
- Anik I, Ceylan S, Koc K, et al. **Membranous structures affecting the success of endoscopic third ventriculostomy in adult aqueductus sylvii stenosis.** *Minim Invasive Neurosurg* 2011;54:68–74 [CrossRef Medline](#)
- Antes S, Tschann CA, Oertel JM. **An operative technique combining endoscopic third ventriculostomy and long-term ICP monitoring.** *Childs Nerv Syst* 2014;30:331–35 [CrossRef Medline](#)
- Dinçer A, Yildiz E, Kohan S, et al. **Analysis of endoscopic third ventriculostomy patency by MRI: value of different pulse sequences, the sequence parameters, and the imaging planes for investigation of flow void.** *Childs Nerv Syst* 2011;27:127–35 [CrossRef Medline](#)
- Feng HL, Huang GF, Liao XL, et al. **Endoscopic third ventriculostomy in the management of obstructive hydrocephalus: an outcome analysis.** *J Neurosurg* 2004;100:626–33 [CrossRef Medline](#)

9. Mobbs RJ, Vonau M, Davies MA. **Death after late failure of an endoscopic third ventriculostomy: a potential solution.** *Neurosurgery* 2003;53:384–85; discussion 385–86 [CrossRef Medline](#)
10. Fukuhara T, Luciano MG, Kowalski RJ. **Clinical features of third ventriculostomy failures classified by fenestration patency.** *Surg Neurol* 2002;58:102–10 [CrossRef Medline](#)
11. Goodwin CR, Sankey EW, Jusue-Torres I, et al. **The use of an aspirating/resecting device to reduce stoma closure following endoscopic third ventriculostomy for aqueductal stenosis.** *Oper Neurosurg (Hagerstown)* 2015;11:512–17 [CrossRef Medline](#)
12. Bargalló N, Olondo L, Garcia AI, et al. **Functional analysis of third ventriculostomy patency by quantification of CSF stroke volume by using cine phase-contrast MR imaging.** *AJNR Am J Neuroradiol* 2005;26:2514–21 [Medline](#)
13. Dlouhy BJ, Capuano AW, Madhavan K, et al. **Preoperative third ventricular bowing as a predictor of endoscopic third ventriculostomy success.** *J Neurosurg Pediatr* 2012;9:182–90 [CrossRef Medline](#)
14. Jallo GI, Kothbauer KF, Abbott IR. **Endoscopic third ventriculostomy.** *Neurosurg Focus* 2005;19:E11
15. Fischbein NJ, Ciricillo SF, Barr RM, et al. **Endoscopic third ventriculocisternostomy: MR assessment of patency with 2-D cine phase-contrast versus T2-weighted fast spin echo technique.** *Pediatr Neurosurg* 1998;28:70–78 [CrossRef Medline](#)
16. Hoffmann KT, Lehmann TN, Baumann C, et al. **CSF flow imaging in the management of third ventriculostomy with a reversed fast imaging with steady-state precession sequence.** *Eur Radiol* 2003;13:1432–37 [Medline](#)
17. Kulkarni AV, Drake JM, Armstrong DC, et al. **Imaging correlates of successful endoscopic third ventriculostomy.** *J Neurosurg* 2000;92:915–19 [CrossRef Medline](#)
18. Sankey EW, Elder BD, Liu A, et al. **Predictors of admission and shunt revision during emergency department visits for shunt-treated adult patients with idiopathic intracranial hypertension.** *J Neurosurg* 2017;127:233–39 [CrossRef Medline](#)
19. Balevi M. **Endoscopic third ventriculostomy in normal pressure hydrocephalus and symptomatic long-standing overt ventriculomegaly.** *Asian J Neurosurg* 2017;12:605–12 [CrossRef Medline](#)
20. Gangemi M, Maiuri F, Naddeo M, et al. **Endoscopic third ventriculostomy in idiopathic normal pressure hydrocephalus: an Italian multicenter study.** *Neurosurgery* 2008;63:62–67; discussion 67–69 [Medline](#)
21. Hailong F, Guangfu H, Haibin T, et al. **Endoscopic third ventriculostomy in the management of communicating hydrocephalus: a preliminary study.** *J Neurosurg* 2008;109:923–30 [CrossRef Medline](#)
22. Kiefer M, Eymann R, Steudel WI. **LOVA hydrocephalus: a new entity of chronic hydrocephalus** [in German]. *Nervenarzt* 2002;73:972–81 [CrossRef Medline](#)
23. Grand W, Leonardo J, Chamczuk AJ, et al. **Endoscopic third ventriculostomy in 250 adults with hydrocephalus: patient selection, outcomes, and complications.** *Neurosurgery* 2016;78:109–19

Brain Atrophy Is Associated with Disability Progression in Patients with MS followed in a Clinical Routine

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ABSTRACT

BACKGROUND AND PURPOSE: The assessment of brain atrophy in a clinical routine is not performed routinely in multiple sclerosis. Our aim was to determine the feasibility of brain atrophy measurement and its association with disability progression in patients with MS followed in a clinical routine for 5 years.

MATERIALS AND METHODS: A total of 1815 subjects, 1514 with MS and 137 with clinically isolated syndrome and 164 healthy individuals, were collected retrospectively. Of 11,794 MR imaging brain scans included in the analysis, 8423 MRIs were performed on a 3T, and 3371 MRIs, on a 1.5T scanner. All patients underwent 3D T1WI and T2-FLAIR examinations at all time points of the study. Whole-brain volume changes were measured by percentage brain volume change/normalized brain volume change using SIENA/SIENAX on 3D T1WI and percentage lateral ventricle volume change using NeuroSTREAM on T2-FLAIR.

RESULTS: Percentage brain volume change failed in 36.7% of the subjects; percentage normalized brain volume change, in 19.2%; and percentage lateral ventricle volume change, in 3.3% because of protocol changes, poor scan quality, artifacts, and anatomic variations. Annualized brain volume changes were significantly different between those with MS and healthy individuals for percentage brain volume change ($P < .001$), percentage normalized brain volume change ($P = .002$), and percentage lateral ventricle volume change ($P = .01$). In patients with MS, mixed-effects model analysis showed that disability progression was associated with a 21.9% annualized decrease in percentage brain volume change ($P < .001$) and normalized brain volume ($P = .002$) and a 33% increase in lateral ventricle volume ($P = .004$).

CONCLUSIONS: All brain volume measures differentiated MS and healthy individuals and were associated with disability progression, but the lateral ventricle volume assessment was the most feasible.

ABBREVIATIONS: CDMS = clinically definite MS; CIS = clinically isolated syndrome; DP = disability progression; EDSS = Expanded Disability Status Scale; HI = healthy individuals; LVV = lateral ventricle volume; MSSS = Multiple Sclerosis Severity Score; NBV = normalized brain volume; PBVC = percentage brain volume change; RR = relapsing-remitting

Brain atrophy assessment is an important biomarker in multiple sclerosis because of its relationship with neurodegeneration and disability progression (DP).^{1–3} Brain atrophy develops early in the disease,⁴ continues throughout its natural course, is

partially independent from lesion burden,⁵ is accelerated compared with normal aging,³ and predicts development of physical and cognitive disability.^{2,3,6,7} Thus, MR imaging–derived brain atrophy measurements were included in many recent phase III clinical trials as an important biomarker for determining the effect of disease-modifying treatment.^{3,8,9}

Evidence is mounting regarding the urgent need for incorporation of brain atrophy assessment into clinical routine and individual patient treatment monitoring.^{2,3,6,7} There is also an in-

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creasing interest and need for monitoring the effect of disease-modifying treatment on brain atrophy to make more personalized, patient-centric treatment choices.¹⁰ However, there are numerous challenges to the measurement of brain atrophy in a clinical routine.^{3,6,7} It is well-known that for reliable measurement of brain volume changes with time, patients should undergo imaging with the same scanner and without scanner/software/protocol changes.^{3,11} However, this is very difficult to achieve in a clinical routine.¹¹ At this time, there are no long-term, large-cohort studies that have investigated the feasibility of measuring brain atrophy in a real-world setting, and its association with clinical outcomes.

Against this background, the aim of this study was to investigate the feasibility of brain atrophy measurement and its association with DP in a large cohort of patients with MS and clinically isolated syndrome (CIS) followed in a clinical routine for 5 years.

MATERIALS AND METHODS

Subjects

This retrospective study, which included a collection of clinical and MR imaging data, enrolled 1815 subjects, of whom 1514 had MS, 137 had CIS, and 164 were healthy individuals (HI). The data were collected for 10 years. The inclusion criteria were the following: 1) consecutive subjects with MS and CIS and HI recruited and followed between 2006 and 2016 at an MS center; 2) age, sex, disease duration, and Expanded Disability Status Scale (EDSS) score (only for patients with MS and CIS) recorded at the first available MR imaging examination; 3) MR imaging examinations performed on 1.5T or 3T scanners; 4) two-dimensional T2-fluid attenuated inversion recovery and 3D T1-weighted imaging being part of standard clinical routine protocol; and 5) the presence of at least 2 longitudinal MR imaging pairs in the same individual subject ≥ 6 months apart. Exclusion criteria were the presence of a relapse and steroid treatment in the 30 days preceding the MR imaging examination for patients with CIS and MS, pre-existing medical conditions known to be associated with brain pathology (cerebrovascular disease, positive history of alcohol abuse), and pregnancy. On-line Fig 1 and the On-line Appendix provide details of the fulfilled inclusion and exclusion criteria and procedures in study subjects. The study was approved by the Human Subjects Institutional Review Board of the University at Buffalo.

MR Imaging Acquisition and Analysis

The MR imaging examinations used in the present study were performed on either 3T or 1.5T Signa Excite HD 12.0 Twin Speed 8-channel scanners (GE Healthcare, Milwaukee, Wisconsin). During the 10 years of the study, neither scanner underwent major hardware or software changes. Optimization of scanning protocols was allowed during the study, and details are provided in the On-line Appendix.

Whole-brain volume was determined on 3D T1WI that was modified using an inpainting technique to avoid tissue misclassification.¹² At baseline, normalized brain volume (NBV) was calculated using the FSL SIENAX method (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA>),¹³ whereas for longitudinal changes, the structural image evaluation, with normalization of atrophy

(SIENA) method (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA>) was used to calculate the percentage brain volume change (PBVC), and SIENAX was used to calculate the percentage NBV change.¹³ NeuroSTREAM software was used to assess baseline lateral ventricle volume (LVV) and change across time on 2D-FLAIR images.¹⁴ MR imaging analysis and quality control were performed in a fully blinded manner.

PBVC and percentage NBV and LVV changes were calculated between the first MR imaging and the most recent follow-up MR imaging and between all available MR imaging time points when >2 longitudinal MR imaging pairs were available (On-line Table 1). PBVC, and percentage NBV and LVV changes were annualized. Annualized PBVC and percentage NBV and LVV changes between serial imaging time points were also averaged on the basis of the number of all available serial MR imaging time points to obtain the annualized, cumulative yearly PBVC and percentage NBV and LVV change.

Statistical Analysis

Analyses were performed using Statistical Package for Social Science (SPSS), Version 24.0 (IBM, Armonk, New York). Differences among groups were analyzed using the χ^2 test, Student *t* test, Mann-Whitney rank sum test, and 1-way analysis of variance as appropriate. Brain volume differences among groups were calculated using analysis of covariance corrected for age, sex, and ratio of 1.5T and 3T MR imaging.

Additionally, to explore temporal associations between LVV, NBV, and PBVC and individual clinical measures (disease duration, EDSS, Multiple Sclerosis Severity Score [MSSS], and DP), univariate linear mixed-effects models with interaction terms across time were fitted and corrected for possible confounders (age, sex, field strength). LVV, NBV, and PBVC were used as dependent outcomes. Model fit was evaluated using the Akaike information criterion and included subject-level random intercept and/or time slopes. Analyses were performed in the entire study sample, as well as in the subpopulations of patients who had PBVC available between the first MR imaging and most recent follow-up. A nominal *P* value of $\leq .05$ was considered statistically significant using 2-tailed tests.

RESULTS

Study Sample

We enrolled 1815 subjects who met the inclusion and exclusion criteria (see Materials and Methods) (On-line Table 2). Demographic and clinical characteristics at baseline and during the follow-up are shown in On-line Table 2 and further described in the On-line Appendix.

MR Imaging Characteristics at Baseline and during Follow-Up

Of 11,794 MR imaging brain scans included in the analyses, 8423 MRIs were performed on a 3T, and 3371 MRIs, on a 1.5T scanner (On-line Table 2). The total number of MRIs from first MR imaging to most recent follow-up was 4.9 ± 3.1 for MS, 3.8 ± 1.9 for CIS, and 2.9 ± 1.1 for HI ($P < .001$). The cumulative number of subjects, MRIs, and time from first to most recent follow-up are shown in On-line Table 1.

Table 1: Brain volume measures in patients with MS and CIS and in HI^a

No. MS-CIS-HI	Measures	MS (Mean) (SD)	CIS (Mean) (SD)	HI (Mean) (SD)	P Value (MS/CIS/Hi)	P Value (MS/Hi)
1505-137-164	LVV at first MRI	22.9 (13.6)	15.7 (7.8)	16.8 (9.5)	.0001	.0001
1345-121-166	NBV at first MRI	1536.1 (102.6)	1590.3 (78.8)	1567.8 (93.1)	.0001	.001
1465-130-161	Percentage LVV change from first MRI to MRF	12.0 (18.3)	10.2 (16.5)	6.9 (10.9)	.001	.0001
1465-130-161	Annualized percentage LVV change from first to MRF MRI	3.0 (8.0)	3.7 (8.2)	1.6 (7.6)	.02	.01
1465-130-161	Annualized cumulative percentage LVV change from first to MRF MRI	2.9 (6.9)	4.1 (9.8)	1.9 (8.2)	.01	.03
1196-112-159	Percentage NBV change from first MRI to MRF	-3.4 (3.8)	-2.4 (2.7)	-1.2 (2.7)	.0001	.0001
1196-112-159	Annualized percentage NBV change from first to MRF MRI	-0.7 (1.5)	-0.6 (1.4)	-0.4 (1.8)	.007	.002
1196-112-159	Annualized cumulative percentage NBV change from first to MRF MRI	-0.8 (2.2)	-0.5 (1.8)	-0.5 (2.1)	.077	.045
902-93-154	PBVC from first MRI to MRF	-3.5 (2.8)	-2.1 (2.2)	-1.6 (1.9)	.0001	.0001
902-93-154	Annualized PBVC from first to MRF MRI	-0.9 (1.0)	-0.6 (0.9)	-0.4 (0.8)	.0001	.0001
902-93-154	Annualized cumulative PBVC from first to MRF MRI	-0.8 (1.2)	-0.6 (1.2)	-0.4 (1.0)	.001	.001

Note:—No. MS-CIS-HI indicates No. of patients with MS and CIS and HI included in each analysis.

^a The data are presented as mean (SD). The absolute values are expressed in milliliters. The differences among the MS, CIS, and HI groups were calculated using analysis of covariance adjusted for age at first MRI, sex, and field strength, as covariates.

Table 2: Univariate linear mixed-effect models describing the longitudinal relationship between yearly change in clinical measures and lateral ventricle volume change in patients with MS^a

Patients with MS	LVV (mL) (n = 1465)		NBV (mL) (n = 1196)		PBVC (%) (n = 902)	
	Est	P Value	Est	P Value	P Value	P Value
Intercept	22.618		1513.318		-.308	
DDY	0.022	.0001	-0.426	.0001	-.025	.0001
Intercept	22.43		1520.730		-.263	
EDSS	0.098	.0001	-2.187	.0001	-.134	.0001
Intercept	22.065		1511.644		-.214	
MSSS	0.078	.0001	-2.001	.0001	-.119	.0001
DP-intercept						
No	23.137		1523.405		-.125	
Yes	0.485	.0001	-10.214	.0001	-.766	.0001
Difference	0.591	.0001	-11.495	.0001	-.934	<.0001
	+0.105 (21.6%)	.001	-1.281 (-12.5%)	.03	-.169 (-21.9%)	.0001

Note:—Est indicates estimate; DDY, disease duration.

^a Intercept as depicted in milliliters is the predicted value of the dependent variable when all the independent variables are restrained to zero. Estimate is a representation of the LVV volume increase and NBV volume decrease in milliliters per 1-unit increase of the independent measure per year (the interaction term with time). Estimate of PBVC is the representation of change in percentage per 1-unit increase of the independent measure per year (the interaction term with time). Volumetric (milliliters) data were fitted to random intercept and slope models, while PBVC models were fitted with random slope models.

At baseline, LVV was available in 1806 (99.5%) subjects using NeuroSTREAM, and NBV was obtained in 1632 (89.9%) subjects using SIENAX. During the follow-up, calculation of NeuroSTREAM percentage LVV change failed in 59 (3.3%) subjects, while the figures were 348 (19.2%) for SIENAX percentage NBV change and 666 (36.7%) for SIENA PBVC.

Reasons for analysis failures are shown in On-line Table 3. In particular, there were no measurement failures due to scanner changes using LVV, whereas failures occurred in 175 (11.6%) patients using PBVC and in 73 (4.8%) patients using percentage NBV change.

Brain Volume Changes with Time

Table 1 and On-line Tables 4–6 describe brain volume measures at baseline and during the follow-up, according to the disease status (Table 1 and On-line Table 5) and MS subtype (On-line Tables 4 and 6).

At first MR imaging, the LVV was significantly higher in patients with MS compared with those with CIS and HI, while the NBV was significantly lower ($P < .001$ for both, Table 1). Brain volume changes from the first MR imaging to the most recent

follow-up among MS, CIS, and HI were significantly different for percentage LVV change ($P < .001$), percentage NBV change ($P < .0001$), and PBVC ($P < .001$). Annualized brain volume changes were significantly different among MS, CIS, and HI for percentage LVV change ($P = .02$), percentage NBV change ($P = .007$), and PBVC ($P < .001$).

At first MR imaging, LVV was significantly higher in patients with progressive MS, compared with those with relapsing-remitting MS (RRMS), while NBV was lower ($P < .001$ for both, On-line Table 4).

Longitudinal Relationship between Brain Volume Changes and Clinical Measures

Unadjusted univariate linear mixed-effect model analyses indicated that with time, longer disease duration (MS, $P < .001$; CIS, $P < .001$), higher MSSS (MS, $P < .001$; CIS, $P < .001$), and higher EDSS (MS, $P < .001$; CIS, $P < .001$) were associated with changes in LVV, NBV, and PBVC (Table 2). Patients with MS with DP had a decreased rate (-21.9%) of annualized PBVC ($P < .001$), an increased rate (+21.6%) of annualized LVV enlargement ($P < .001$), and a decreased rate (-12.5%) of annualized NBV change

($P = .03$) compared with patients without DP (Table 2 and On-line Fig 2, upper row). See On-line Tables 7 and 8 for additional information.

DISCUSSION

This study provides additional insight into brain atrophy progression in a large cohort of patients with CIS and MS followed in a clinical routine as well as the relationship between the development of brain atrophy and DP. The study used retrospectively collected data for 10 years from >1800 individuals who were followed for an average of almost 5 years, and brain volume data were derived from >11,500 MR imaging examinations.

Assessing brain atrophy in the clinical routine may become an important outcome for assessing the effectiveness of disease-modifying treatment. Several reports have shown it to be one of the most reliable biomarkers of neurodegeneration that correlates with physical and cognitive impairment in patients with MS.^{2-4,6,7,15-18} For more than a decade, randomized controlled trials have used brain atrophy measurement as a secondary or tertiary end point to determine the effectiveness of treatment.^{8,9,18} However, assessing brain atrophy in a clinical routine can be challenging due to several technical factors related to image acquisition and measurement methods.^{2,3,6,7} A recent multicenter, retrospective, real-world study (Multiple Sclerosis and Clinical Outcome and MR Imaging in the United States [MS-MRIUS]) investigated the feasibility of brain atrophy measurement in a clinical routine without MR imaging protocol standardization, using academic and nonacademic centers specialized in treatment and monitoring of MS.¹¹ The MS-MRIUS study showed that 72% of patients with MS had 2D T1WI and only 28% had 3D T1-weighted MR imaging sequences for longitudinal brain atrophy measurement. Scanner/protocol changes occurred in >50% of patients during the 16 months of follow-up.

Image contrast and image resolution are important for a reliable and optimal segmentation of brain volume, and 3D pulse sequences are preferred for measurement of brain atrophy as the criterion standard for brain volumetric imaging because of reduced partial voluming and more accurate coregistration, especially for serial imaging with time, compared with 2D imaging.^{2,3,6} In the present study, the main reasons for analysis failures were changes in imaging protocol, poor scan quality, and excessive motion artifacts. Although the scanner and software did not change during a 10-year period of data collection in the present study, subjects were examined on 2 different scanners (1.5T and 3T, On-line Table 1), and minor protocol optimization changes were allowed. Thus, measurement of whole-brain volume changes was not feasible in a substantial number of subjects. These findings are supported by the recent results of the multicenter MS-MRIUS study,¹¹ which found that the feasibility of brain atrophy measurement was substantially lower without the uniformity of scanners, resulting in even larger numbers of failures.

As per the inclusion criteria, all subjects underwent 3D T1WI at every time point of the study; however, longitudinal (PBVC) and cross-sectional-derived (percentage NBV change) whole-brain volume analysis of at least 2 pairs of MR imaging examinations failed in 36.7% and 19.2% of subjects, respectively. The

higher prevalence of examination failure with PBVC, compared with the percentage NBV change whole-brain volume analysis, is because SIENA PBVC is a longitudinal registration-based technique requiring concomitant evaluation of the 2 time points,¹³ whereas NBV is a cross-sectional measure performed on every scan separately; then, percentage changes are derived statistically between the 2 time points.¹³ Due to these inherent differences in the 2 methods, the decreased feasibility of PBVC-versus-NBV change measurement was also previously shown in a recent MS clinical trial,¹⁹ and our findings from clinical routine further confirm these findings. In the current study, scanner change was not defined a priori as a failed brain atrophy assessment. It is extremely difficult to ensure consistency of hardware and protocol use in the clinical routine over mid-to-long-term follow-up, even in the controlled setting of a specialized academic MS center. In addition, the results from the present study support previous multicenter findings¹¹ because we were able to obtain reliable LVV measurement in >96% of the study subjects longitudinally.

There is a strong need for developing and validating more simple brain volume measures that are resistant to MR imaging scanner and protocol changes and can be used in a clinical routine.¹¹ The assessment of LVV presents some advantages for calculation of brain atrophy on clinical routine practice scans compared with whole-brain volume measurements.^{11,14,20,21} These advantages are mainly because tissue borders of the lateral ventricles have high contrast with respect to the surrounding CSF, and the position of the ventricles centrally to the FOV makes them less likely to be affected by gradient distortions, coregistration, error of tissue segmentation, incomplete head coverage, and wrap-around artifacts.^{3,11,14,20,22} Therefore, LVV measurement has the potential to become a meaningful and reliable measure of brain atrophy assessment when scanning protocols cannot be standardized. Several algorithms were introduced for the assessment of LVV. Most of the approaches tend to rely on research quality scans, which are sometimes not obtained in the clinical practice.¹⁴ Contrary to those, NeuroSTREAM has the ability to operate with low-resolution scans, as confirmed in the present and previous studies.^{11,14,20}

We showed that patients with CIS and MS had higher annualized (first MR imaging to most recent follow-up MR imaging) and cumulative (using all available MR imaging examinations between different time points) brain volume changes compared with HI, using PBVC and percentage LVV change approaches. However, in a subsample of subjects who had PBVC, the percentage NBV change did not differentiate MS from HI; thus, cross-sectional-derived whole-brain volume measures are far from ideal.^{2,3,6,7} Patients with CIS showed the highest annualized cumulative percentage LVV change among all the 3 study groups (4.1% for CIS, 2.9% for MS, and 1.9% for HI). One study reported an annualized percentage LVV change of 3.4%,²³ while another study showed an annualized percentage LVV change of 5.5% in patients with RRMS.²⁴ A greater LVV change in patients with CIS who developed clinically definite MS (CDMS), compared with those who remained stable, was found within 1 year of follow-up.^{16,25} Recently, it was shown that annualized percentage LVV changes between 3.1% and 3.51% on T2-FLAIR²⁰ correspond to a

pathologic whole-brain atrophy rate of 0.4%²⁶ in patients with RRMS and that this LVV pathologic cutoff performs comparably with PBVC for predicting clinical outcomes.²⁰

The annualized LVV rates in patients with MS and CIS, as well as in HI observed in this study, are in line with the suggested LVV pathologic cutoff.²⁰ On the contrary, the annualized rate of whole-brain volume change (found with both longitudinal and cross-sectional–derived approaches) in this study was somewhat above the proposed pathologic cutoff of 0.4%.²⁶ This result can potentially be because most patients in the current study underwent first-generation disease-modifying treatments, which have a weak-to-modest impact on preventing brain atrophy^{8,9,27} or they were not treated at all. Moreover, the mean baseline age of patients with MS and HI was around 46 years, which could also have contributed to somewhat accelerated whole-brain atrophy due to an aging effect.^{2,3,6,7}

We also evaluated brain atrophy in different MS disease subtypes and did not find significant differences in rates among MS disease subtypes during the follow-up. Our results are in line with evidence indicating that brain atrophy rates are independent of MS phenotype.^{28,29}

Using linear mixed-effects analysis, we showed that all brain volume measures were associated with disease duration, EDSS, MSSS, and DP in patients with MS and CIS. In a subgroup of patients with MS who had PBVC available between the first MR imaging and most recent follow-up, we found that patients with MS with DP had a 33.1% higher LVV yearly increment and 21.9% higher PBVC and NBV change yearly decrease compared with those without DP. Similar findings were found in patients with CIS who converted to CDMS, though the results did not reach significance.

Potential limitations of this study are that it did not consider potential biologic confounders that may have an impact on atrophy assessments, including diurnal fluctuations of brain volume, hydration state, and menstrual cycle^{2,3,6,7} or the pseudoatrophy effect of disease-modifying treatments. However, due to the natural composition and size of the sample, we hypothesize that these confounding factors are largely driven when assessing group effects. Incorporating such confounds, though, will almost certainly be required when assessing individual patients, which would be the next step using the proposed MR imaging outcomes. A key strength of this study lies in the large number of subjects examined, with >11,500 MR imaging examinations and the follow-up of almost 5 years.

CONCLUSIONS

The present study is one of the first large cohort studies of brain atrophy measurement in patients with MS and CIS followed in a clinical routine. The study showed that T2-FLAIR–derived LVV measurement was the most feasible in a clinical routine. PBVC and percentage LVV change significantly differentiated patients with CIS and MS compared with HI, while all brain volume measures were independent of the disease subtype and predicted disability progression.

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REFERENCES

1. Bermel RA, Bakshi R. **The measurement and clinical relevance of brain atrophy in multiple sclerosis.** *Lancet Neurol* 2006;5:158–70 CrossRef Medline
2. De Stefano N, Airas L, Grigoriadis N, et al. **Clinical relevance of brain volume measures in multiple sclerosis.** *CNS Drugs* 2014;28:147–56 CrossRef Medline
3. Zivadinov R, Jakimovski D, Gandhi S, et al. **Clinical relevance of brain atrophy assessment in multiple sclerosis: implications for its use in a clinical routine.** *Expert Rev Neurother* 2016;16:777–93 CrossRef Medline
4. Uher T, Blahova-Dusankova J, Horakova D, et al. **Longitudinal MRI and neuropsychological assessment of patients with clinically isolated syndrome.** *J Neurol* 2014;261:1735–44 CrossRef Medline
5. Sormani MP, Arnold DL, De Stefano N. **Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis.** *Ann Neurol* 2014;75:43–49 CrossRef Medline
6. Rocca MA, Battaglini M, Benedict RH, et al. **Brain MRI atrophy quantification in MS: from methods to clinical application.** *Neurology* 2017;88:403–13 CrossRef Medline
7. Sastre-Garriga J, Pareto D, Rovira À. **Brain atrophy in multiple sclerosis: clinical relevance and technical aspects.** *Neuroimaging Clin N Am* 2017;27:289–300
8. Tsvigoulis G, Katsanos AH, Grigoriadis N, et al; HELANI (Hellenic Academy of Neuroimmunology). **The effect of disease-modifying therapies on brain atrophy in patients with clinically isolated syndrome: a systematic review and meta-analysis.** *Ther Adv Neurol Disord* 2015;8:193–202 CrossRef Medline
9. Tsvigoulis G, Katsanos AH, Grigoriadis N, et al. **The effect of disease-modifying therapies on brain atrophy in patients with relapsing-remitting multiple sclerosis: a systematic review and meta-analysis.** *PLoS One* 2015;10:e0116511 CrossRef Medline
10. Zivadinov R, Dwyer MG, Bergsland N. **Brain atrophy measurements should be used to guide therapy monitoring in MS: YES.** *Mult Scler* 2016;22:1522–24 CrossRef Medline
11. Zivadinov R, Bergsland N, Korn JR, et al. **Feasibility of brain atrophy measurement in clinical routine without prior standardization of the MRI protocol: results from MS-MRIUS, a longitudinal observational, multicenter real-world outcome study in patients with relapsing-remitting MS.** *AJNR Am J Neuroradiol* 2018;39:289–95 CrossRef Medline
12. Gelineau-Morel R, Tomassini V, Jenkinson M, et al. **The effect of hypointense white matter lesions on automated gray matter segmentation in multiple sclerosis.** *Hum Brain Mapp* 2012;33:2802–14 CrossRef Medline
13. Smith SM, Zhang Y, Jenkinson M, et al. **Accurate, robust, and automated longitudinal and cross-sectional brain change analysis.** *Neuroimage* 2002;17:479–89 CrossRef Medline
14. Dwyer MG, Silva D, Bergsland N, et al. **Neurological software tool for reliable atrophy measurement (NeuroSTREAM) of the lateral ventricles on clinical-quality T2-FLAIR MRI scans in multiple sclerosis.** *Neuroimage Clin* 2017;15:769–79 CrossRef Medline
15. Zivadinov R, Havrdová E, Bergsland N, et al. **Thalamic atrophy is associated with development of clinically definite multiple sclerosis.** *Radiology* 2013;268:831–41 CrossRef Medline

16. Dalton CM, Brex PA, Jenkins R, et al. **Progressive ventricular enlargement in patients with clinically isolated syndromes is associated with the early development of multiple sclerosis.** *J Neurol Neurosurg Psychiatry* 2002;73:141–47 [CrossRef Medline](#)
17. Vollmer T, Signorovitch J, Huynh L, et al. **The natural history of brain volume loss among patients with multiple sclerosis: a systematic literature review and meta-analysis.** *J Neurol Sci* 2015;357:8–18 [CrossRef Medline](#)
18. Zivadinov R, Reder AT, Filippi M, et al. **Mechanisms of action of disease-modifying agents and brain volume changes in multiple sclerosis.** *Neurology* 2008;71:136–44 [CrossRef Medline](#)
19. Radue EW, Sprenger T, Gaetano L, et al. **Teriflunomide slows BVL in relapsing MS: a reanalysis of the TEMSO MRI data set using SIENA.** *Neurol Neuroimmunol Neuroinflamm* 2017;4:e390 [CrossRef Medline](#)
20. Dwyer MG, Hagemer J, Bergsland N, et al. **Establishing pathological cut-offs for lateral ventricular volume expansion rates.** *Neuroimage Clin* 2018;18:494–501 [CrossRef Medline](#)
21. Weinstock-Guttman B, Medin J, Khan N, et al. **Assessing ‘no evidence of disease activity’ status in patients with relapsing-remitting multiple sclerosis receiving fingolimod in routine clinical practice: a retrospective analysis of the Multiple Sclerosis Clinical and Magnetic Resonance Imaging Outcomes in the USA (MS-MRIUS) study.** *CNS Drugs* 2018;32:75–84 [CrossRef Medline](#)
22. Caramanos Z, Fonov VS, Francis SJ, et al. **Gradient distortions in MRI: characterizing and correcting for their effects on SIENA-generated measures of brain volume change.** *Neuroimage* 2010;49:1601–11 [CrossRef Medline](#)
23. Zivadinov R, Uher T, Hagemer J, et al. **A serial 10-year follow-up study of brain atrophy and disability progression in RRMS patients.** *Mult Scler* 2016;22:1709–18 [CrossRef Medline](#)
24. Simon JH, Jacobs LD, Campion MK, et al. **A longitudinal study of brain atrophy in relapsing multiple sclerosis: the Multiple Sclerosis Collaborative Research Group (MSCRG).** *Neurology* 1999;53:139–48 [CrossRef Medline](#)
25. Brex PA, Jenkins R, Fox NC, et al. **Detection of ventricular enlargement in patients at the earliest clinical stage of MS.** *Neurology* 2000;54:1689–91 [CrossRef Medline](#)
26. De Stefano N, Stromillo ML, Giorgio A, et al. **Establishing pathological cut-offs of brain atrophy rates in multiple sclerosis.** *J Neurol Neurosurg Psychiatry* 2016;87:93–99 [CrossRef Medline](#)
27. Branger P, Parienti JJ, Sormani MP, et al. **The effect of disease-modifying drugs on brain atrophy in relapsing-remitting multiple sclerosis: a meta-analysis.** *PLoS One* 2016;11:e0149685 [CrossRef Medline](#)
28. De Stefano N, Giorgio A, Battaglini M, et al. **Assessing brain atrophy rates in a large population of untreated multiple sclerosis subtypes.** *Neurology* 2010;74:1868–76 [CrossRef Medline](#)
29. Kalkers NF, Ameziene N, Bot JC, et al. **Longitudinal brain volume measurement in multiple sclerosis: rate of brain atrophy is independent of the disease subtype.** *Arch Neurol* 2002;59:1572–76 [CrossRef Medline](#)

Hypertension Is Associated with White Matter Disruption in Apparently Healthy Middle-Aged Individuals

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ABSTRACT

BACKGROUND AND PURPOSE: Traditional cardiovascular risk factors have been associated with white matter disease. Because hypertension results in vascular stiffness and impaired cerebral perfusion, we hypothesized that it would be the most relevant risk factor for microstructural white matter disruption in apparently healthy middle-aged individuals with a family history of early-onset coronary artery disease.

MATERIALS AND METHODS: This was a cross-sectional analysis of participants in the Genetic Study of Atherosclerosis Risk with DTI. Regional fractional anisotropy of 181 segmented brain regions was measured using Eve WM Atlas. Risk factors were examined using univariate analysis for 48 regions representing deep WM structures. Minimal multivariable linear regression models adjusting for age, sex, and race and maximal linear regression models adjusting for cardiovascular risk factors were performed for regions meeting the Bonferroni threshold in the initial analysis.

RESULTS: Included were 116 subjects (mean age, 49 ± 11 years; 57% men) with a moderate load of cardiovascular risk factors. Subjects with hypertension had significantly lower regional fractional anisotropy in the right cingulum and left stria terminalis in the minimal and maximal regression models. Additionally, there was lower regional fractional anisotropy in the left fornix in the maximal model and right sagittal stratum in the minimal model. Systolic blood pressure values were significantly associated with regional fractional anisotropy in the left superior longitudinal fasciculus in the maximal model. There were no significant differences among regional fractional anisotropy values for other cardiovascular risk factors.

CONCLUSIONS: In middle-aged apparently healthy individuals with susceptibility to vascular disease, among all known cardiovascular risk factors, hypertension was associated with microstructural WM disruption.

ABBREVIATIONS: BMI = body mass index; BP = blood pressure; CSVD = cerebral small vessel disease; FA = fractional anisotropy; LDL = low-density lipoprotein; rFA = regional fractional anisotropy

White matter hyperintensities, frequently incidentally observed on brain MR imaging, have been attributed to cere-

bral small vessel disease (CSVD).¹ Histopathologically, WM hyperintensity areas show nonspecific changes of gliosis, myelin and axonal loss, tissue rarefaction, and lipohyalinosis.² The exact mechanisms leading to CSVD remain undefined.³ It has been hypothesized that interactions between genetics and environmental factors lead to small-vessel changes causing white matter damage secondary to vasculopathy and arteriosclerosis, resulting in hypoxia and hypoperfusion. These events are influenced by altered cerebrovascular autoregulation as well as endothelial and blood-brain barrier dysfunction.⁴ Among traditional cardiovascular risk factors, hypertension has been consistently found to be

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related to CSVD.⁵ Rat models of hypertension develop diffuse WM disease.⁶ Human studies have linked hypertension directly to arterial stiffness, leading to WM changes related to CSVD.^{7–9} Other traditional atherogenic risk factors such as diabetes, smoking, and hyperlipidemia have been less consistently linked to CSVD compared with hypertension.^{10,11} DTI has emerged as a valuable tool for assessment of WM in health and disease through measurement of signal attenuation in the fiber tracts.¹² DTI has an advantage over conventional T2 or FLAIR sequences due to improved mapping and 3D diffusion characterization incorporating spatial location. This property can be used to describe the magnitude, degree, and orientation of diffusion anisotropy.¹²

Fractional anisotropy (FA) is a sensitive biomarker for WM integrity, reflecting axonal loss or demyelination.¹² Decreased FA has been found in cases of demyelination, edema, or inflammation.¹² In patients with CSVD, impaired WM microstructure has been detected by DTI studies.¹³ In Nyquist et al,¹⁴ our group demonstrated that WM hyperintensity contributes to subclinical psychomotor impairment in apparently healthy subjects. In the current work, we aimed to investigate the relationship of various atherogenic vascular risk factors with the impairment of WM microstructure as measured by DTI. We hypothesized that early changes in regional WM can be detected by DTI in apparently healthy middle-aged individuals and that these changes are primarily associated most strongly with hypertension.

MATERIALS AND METHODS

Sample and Recruitment

We selected healthy participants who underwent DTI as part of the Genetic Study of Atherosclerosis Risk (GeneSTAR) silent stroke study. GeneSTAR is an ongoing prospective study of vascular disease risk factors, occult coronary artery disease and cerebrovascular disease, and incident coronary artery disease and strokes in 3533 initially healthy family members ascertained from probands hospitalized with documented coronary artery disease younger than 60 years of age.¹⁴ Of these initially healthy family members, 808 were screened with cranial MR imaging for WM hyperintensity; of those, 116 healthy subjects had DTI sequences.

The 116 participants included apparently healthy asymptomatic siblings, their offspring, and the offspring of the probands who were 30–72 years of age. None had a known history of coronary artery disease, stroke, or transient ischemic attacks and represented 97 families. Exclusion criteria included the following: chronic corticosteroids, life-threatening diseases, neurologic diseases impairing accurate MR imaging interpretation, implanted metals prohibiting MR imaging, atrial fibrillation, and symptomatic cardiovascular or cerebrovascular disease. The study was approved by the Johns Hopkins Medicine institutional review board (NA_00002856). All participants provided written informed consent before screening.

Participant Screening and Data Collection

Each participant was examined by a physician. All participants were screened for coronary artery disease and stroke risk factors, including hypertension, diabetes, total cholesterol, low-density

lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, body mass index (BMI), and cigarette smoking.¹⁵ Race was self-reported. Height and weight were measured and BMI was calculated.¹⁶ Current cigarette smoking was defined by self-report of any smoking within the past month and/or 2 expired carbon monoxide levels of ≥ 8 ppm. Blood pressure (BP) was measured 3 times during 1 day, and the average systolic and diastolic BP was used to characterize BP according to guidelines of the American Heart Association.¹⁷ Hypertension was defined as an average measured BP ≥ 140 mm Hg systolic or 90 mm Hg diastolic and/or use of antihypertensive drugs. Blood for measurements of cholesterol and glucose levels was collected following a 12-hour fast overnight. Type 2 diabetes was defined as a physician-diagnosed history, a fasting glucose level of ≥ 126 mg/dL, and/or use of hypoglycemic antidiabetic medications. Total cholesterol, high-density lipoprotein, and triglyceride levels were measured according to the United States Centers for Disease Control standardized methods.¹⁸ LDL cholesterol was estimated using the Friedewald formula.¹⁹

MR Imaging Acquisition

MR imaging was acquired on a 3T Achieva imaging unit (Philips Healthcare, Best, the Netherlands) according to standardized protocols. We acquired the following series: 1) axial T1-weighted MPRAGE—TR, 10 ms; TE, 6 ms; voxel size, $0.75 \times 0.75 \times 1$ mm³; contiguous slices; FOV, 240×240 mm; matrix, 320×320 mm; 2) axial spin-echo T2 images—TR, 4685 ms; TE, 78 ms; voxel size, $0.47 \times 0.47 \times 3$ mm³; contiguous slices; FOV, 240×240 mm; matrix, 512×512 ; 3) DTI—TR, 7043 ms; TE, 71 ms; voxel size, $0.83 \times 0.83 \times 2.2$ mm³; contiguous slices; FOV, 212×212 mm; matrix, 256×256 ; 32 directions; b-value = 700 s/mm².

DTI Processing and Analysis

DTI was preprocessed and analyzed using an MR imaging studio package (DTIstudio, DiffeoMap, ROIEditor) publicly available at www.mristudio.org through Johns Hopkins University. First, all images (T1, T2, DWI) were reviewed by a board-certified physician in neurology and neurocritical care (Y.H.) for the presence of any rotation, motion artifacts, or eddy current artifacts in the DTI studio image viewer application, which was followed by tensor calculation according to the standardized steps in DTIstudio.²⁰ 3D FA, mean diffusivity, and radial diffusivity maps were created following tensor calculation.

WM segmentation was performed in the subject's native space according to the Eve WM Atlas in the DifeoMap and ROIEditor package software.²¹ First, FA and mean B_0 maps were skull-stripped in ROIEditor. Following skull-stripping, a dual-channel large deformation diffeomorphic mapping algorithm was used in DifeoMap to perform linear and nonlinear registration to the Eve WM Atlas JHU-MNI-SS-SS template in the Montreal Neurological Institute space. This step allowed automated segmentation of the FA subject map in native space using the inverse registration matrix into 181 regions (On-line Figure A–C). The mean regional FA value (rFA) was calculated in each of the regions by choosing a voxel FA threshold of ≥ 0.2 to exclude voxels that included CSF and gray matter. Then, 48 regions of the Atlas representing the deep white matter regions primarily affected by CSVD were se-

lected for the subsequent statistical analysis (On-line Table 1 and On-line Figure D–F).

Statistical Analysis

Statistical analysis was performed using SAS software (Version 9.2; SAS Institute, Cary, North Carolina). Univariable analysis comparing the mean rFA between participants with and without current smoking, hypertension, and diabetes was completed using *t* tests. Spearman rank order correlations were used to test the associations among continuous variables, including: systolic BP,

diastolic BP; total cholesterol, triglyceride, high-density lipoprotein cholesterol, LDL cholesterol, and blood glucose levels; and BMI with a mean rFA. The significance threshold was defined using the Bonferroni method for adjustment for multiple comparisons as $P \leq .001$ (.05/48 rFA regions). A minimal linear regression model predicting rFA and adjusting for age, sex, and race was performed for the regions that met the Bonferroni significance threshold. Then, to understand the effect of the combination of atherogenic risk factors on rFA, we performed a maximal linear regression model predicting rFA and adjusting for age, sex, race, hypertension, diabetes, total cholesterol level, BMI, and smoking for these regions.

Table 1: Baseline characteristics of the study cohort (N = 116)

Characteristic	Mean or %
Age (yr)	49.6 ± 11.1
Education (yr)	14.4 ± 2.8
Male sex	49.1%
African American race	40.5%
Hypertension	36.2%
Diabetes	12.0%
LDL cholesterol (mg/dL)	110.4 ± 39.2
Current smoking status	23.3%
Systolic blood pressure (mm Hg)	122.7 ± 15.6
Diastolic blood pressure (mm Hg)	77.5 ± 8.9
Glucose level (mg/dL)	98.8 ± 29
Triglyceride level (mg/dL)	111.6 ± 68.3
BMI (kg/m ²)	28.7 ± 5.5

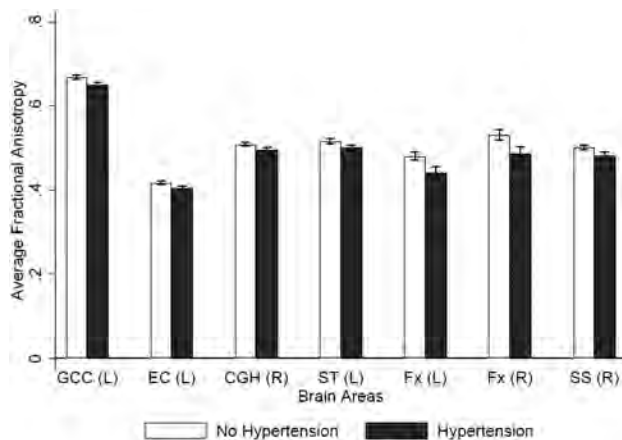


FIG 1. Bar chart of the regions that showed a significant difference in rFA between subjects with and without hypertension. CGH (R) indicates right cingulum; EC (L), left external capsule; Fx (L), left fornix; Fx (R), right fornix; GCC (L), left genu of the corpus callosum; SS (R), right sagittal stratum; ST (L), left stria terminalis.

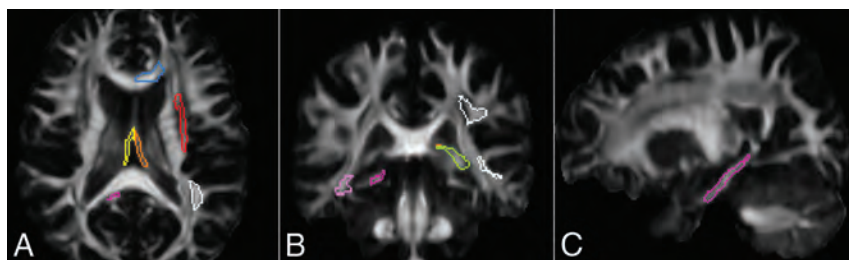


FIG 2. Axial, coronal, and sagittal sections of the FA map, showing areas, in distinct colors, that demonstrate a significant difference of rFA between patients with and without hypertension and areas that show correlation of rFA with systolic blood pressure. Magenta indicates right cingulum; red, left external capsule; orange, left fornix; yellow, right fornix; blue, left genu of the corpus callosum; pink, right sagittal stratum; green, left stria terminalis; white, left superior longitudinal fasciculus.

RESULTS

The study sample consisted of 116 middle-aged participants (mean age, 49.6 ± 11 years; 49.1% men; 40.5% African American), well-educated with moderate vascular risk factors (Table 1). Review of T2 sequences did not reveal any stroke or localized WM hyperintensity. WM hyperintensity involving the periventricular and deep WM areas was largely symmetric without predilection to any specific areas of the selected WM regions. Participants with hypertension showed widespread reduced rFA compared with participants with normal BP meeting the Bonferroni threshold (≤ 0.001) in the left genu of the corpus callosum, left external capsule, right cingulum, left stria terminalis, bilateral fornices, and right sagittal stratum (On-line Table 2 and Figs 1 and 2). This relationship remained significant in the minimal regression model, after adjusting for age, sex, and race, in the right cingulum; left stria terminalis; and right sagittal stratum (Table 2). Additionally, the relationship remained significantly independent of other atherogenic vascular risk factors in the maximal linear regression model in the right cingulum, left stria terminalis, and left fornix (Table 2). The mean rFA correlated with the average systolic BP in the left superior longitudinal fasciculus (On-line Table 3 and Figs 2 and 3). There was a trend toward significance of the relationship of the rFA of this region with hypertension in the minimal regression model ($P = .08$). However, this relationship was significant in the maximal regression model following adjustment for other vascular risk factors (Table 3).

Notably, rFA was not significantly associated with diabetes or current smoking status in any of the regions (On-line Tables 4 and 5). Additionally, rFA was not significantly correlated with blood glucose, LDL, high-density lipoprotein, total cholesterol, and triglyceride levels; diastolic BP; and BMI in any of the regions (On-line Tables 6–12).

DISCUSSION

In this cross-sectional study, we show that decreased rFA, reflecting microstructural WM disruption, is strongly associated with hypertension in middle-aged apparently healthy subjects at increased risk for vascular disease in the deep WM regions of the brain. We did not observe additional associations between rFA and other traditional athero-

Table 2: Minimal and maximal regression models predicting mean rFA of the WM regions that were significantly associated with hypertension in the univariate analysis

White Matter Structure	Normotensive		Hypertensive		T test P Value	Minimal Regression Model			Maximal Regression Model		
	Mean	SD	Mean	SD		β	SE	P Value	β	SE	P Value
Genu of corpus callosum (L)	0.668	0.02	0.651	0.02	.0003	−0.201	0.202	.32	−0.286	0.195	.14
External capsule (L)	0.417	0.02	0.403	0.02	.0002	−0.191	0.202	.34	−0.162	0.228	.48
Cingulum (R)	0.509	0.02	0.494	0.02	.0004	−0.586	0.193	.002 ^a	−0.635	0.202	.002 ^a
Stria terminalis (L)	0.516	0.02	0.5	0.02	.0008	−0.446	0.217	.04 ^a	−0.487	0.216	.03 ^a
Fornix (L)	0.48	0.04	0.441	0.05	<.0001	−0.267	0.172	.12	−0.51	0.191	.008 ^a
Fornix (R)	0.531	0.05	0.486	0.06	<.0001	0.026	0.171	.88	−0.068	0.186	.72
Sagittal stratum (R)	0.501	0.02	0.482	0.02	.0006	−0.527	0.201	.009 ^a	−0.256	0.292	.38

Note:—L indicates left, R, right; SE, standard error; SD, standard deviation.

^a Significant; $P < .05$.

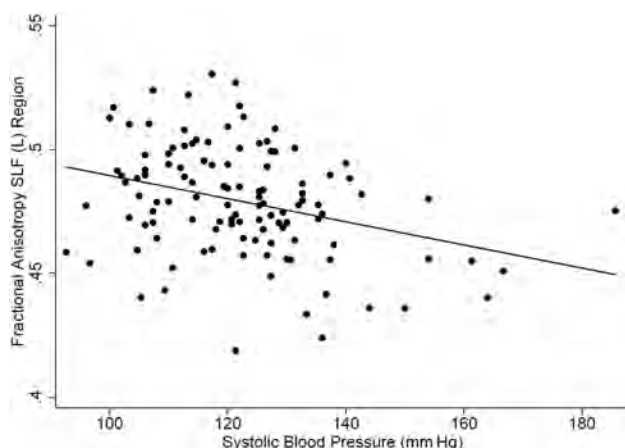


FIG 3. Scatterplot showing the relationship of rFA of the left superior longitudinal fasciculus and systolic blood pressure. SLF (L) indicates left superior longitudinal fasciculus.

genic vascular risk factors such as diabetes, total cholesterol level, LDL, BMI, or smoking. The role of DTI in detecting WM disruption in subjects with vascular risk factors has been addressed previously.^{22–39}

Hypertension has been consistently associated with decreased FA and elevated mean diffusivity in different WM regions, including normal-appearing WM.^{24,25,27–31} In addition, increased BP values linearly correlated with decreased FA in the right anterior corpus callosum, inferior fronto-occipital fasciculus, and the fibers that project from the thalamus to the superior frontal gyrus in 1 study.²² Most of these studies have assessed elderly subjects with an average age of 65.8–83 years^{25,27–29} or investigated the effect of hypertension in middle life on the development of WM disruption at a later age.³¹ Two previous studies investigated the relationship of systolic BP and WM microstructure at a younger age (39.2–48 years).^{22,24} One of them linked adiposity as measured by waist circumference with BP and WM microstructure.²⁴ The second article analyzed the systolic BP relationship with regional DTI metrics by measuring the number of voxels within each WM region that correlated with the systolic BP value.²² Our study used a different approach by analyzing the average rFA of a well-defined WM atlas in relation to vascular risk factors. Given the healthy nature of our relatively younger cohort compared with cohorts in the literature, we believe that we captured the disease at an early stage when it had not progressed yet to involve all the subcortical WM in a symmetric fashion. Indeed, our results reflect that by showing a lower rFA of selected WM regions.

Brain DTI of patients with diabetes showed reduced FA using Tract-Based Spatial Statistics (TBSS; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>) in patients with mild cognitive impairment compared with those without it.³⁹ A similar analytic method showed a significant decrease in the WM tract DTI metrics in closely related areas to the default mode network in patients with type 2 diabetes compared with healthy controls.³⁸ Finally, the Atherosclerosis Risk in Communities (ARIC) neurocognitive study found a relationship between midlife and late-life elevated blood glucose levels and worse WM microstructural integrity in late life.³¹ We did not observe a relationship between diabetes or glucose levels and rFA in our cohort. This is likely secondary to the healthy nature of our subjects, who are cognitively intact, younger in age, and with fewer atherogenic risk factors.

In contrast to diabetes and hypertension, the relationship between WM microstructures and other atherogenic vascular risk factors is modest and inconsistent. The ARIC study did not observe a relationship between lipid levels at midlife and late life with late-life DTI metrics.³¹ However, another study found an association between lipids, especially LDL levels, and WM microstructure integrity in 125 generally healthy older adults (mean age, 68 years).³² BMI was found to be associated with WM microstructure integrity in selected ROIs in a sample of older healthy community participants (mean age, 71.3 years).²³ The combination of atherogenic vascular risk factors (≥ 2) was associated with a longitudinal drop in FA in WM regions compared with no vascular risk factors in elderly subjects (mean age, 73.9 years).²⁵ Finally, smoking was associated with increased FA in WM regions in adolescent/young adult smokers in a recent systematic review.³⁵ Another study of chronic smokers showed decreased FA of the hippocampus in association with decreased memory performance compared with nonsmokers.³⁴

In summary, our study cohort is unique because it tests a relatively young and healthy group of subjects who are relatives of patients with coronary artery disease compared with most previous literature that evaluated elderly subjects, patients who have advanced vascular risk factors, or subjects with cognitive impairments. Our findings indicate hypertension as being the most important risk factor in otherwise healthy subjects at early stages of the disease. The identified WM regions in our study likely play important roles in cognition and memory. The stria terminalis and fornix are critical for normal cognitive functioning and memory.⁴⁰ Fornix pathology can be found in Alzheimer disease. The cingulum is known to play a role in exec-

Table 3: Minimal and maximal regression models predicting mean rFA of the WM region that were significantly associated with systolic blood pressure in the univariate analysis

White Matter Structure	Spearman Rank Test	P Value	Minimal Regression Model			Maximal Regression Model		
			β	SE	P Value	β	SE	P Value
Superior longitudinal fasciculus (L)	−0.309	.0007	−0.012	0.007	.08	−0.014	0.006	.03 ^a

Note:—L indicates left; SE, standard error.

^a Significant; $P < .05$.

utive control, emotion, and episodic memory, and it has been implicated in multiple psychiatric diseases and Alzheimer disease.⁴¹ The superior longitudinal fasciculus abnormalities on DTI have been attributed to age-related language decline.⁴² Finally, the sagittal stratum carries multiple functional fibers implicated in language and visual function.⁴³

Despite available animal and human data suggesting a mechanistic relationship of hypertension to CSVD, the underlying processes leading to these events are yet to be established.⁴ Arterial stiffness has been closely linked to hypertension and aging. Arterial stiffness results from remodeling of the arterial wall secondary to degradation of elastin and accumulation of collagen and calcium deposition.⁷ Measures of arterial stiffness such as the ankle-brachial pressure index have been associated with the development of CSVD findings.^{8,9} Additionally it is well-known that hypertension is associated with arteriosclerosis, which is the main pathologic feature of CSVD, characterized by fibrohyaline material, narrowing of the lumen, and thickening of the vessel wall.² Moreover, hypertension leads to impaired cerebral autoregulation, which results in cerebral hypoxia and WM injury.⁴⁴ It is plausible that hypertension plays an important role in early WM damage compared with other atherogenic risk factors in middle-aged apparently healthy subjects.⁴⁵ Recently, an alternative pathway involving disruption of the blood-brain barrier leading to CSVD has been heavily investigated.^{4,44} The exact relationship of hypertension to BBB dysfunction needs to be thoroughly investigated in the future.

Our study has certain limitations, and it should be interpreted within its context. First, given the cross-sectional nature of the study, a mechanistic relationship between the atherogenic vascular risk factors and WM microstructure disruption cannot be ascertained in our sample. Second, more regions of deep WM structures could have been involved in this disease; however, they were not detected given the relatively small sample size. We decided to choose a conservative method for adjustment for multiple comparisons (Bonferroni method) despite the distributed nature of the CSVD in the brain because we aimed to avoid any possibility of finding false-positive results. In addition, an interaction analysis among vascular risk factors and associated WM damage could not be performed due to the relatively small sample size. Finally, we did not examine the severity of hypertension and blood pressure control at baseline to assess its relationship to the severity of WM disease.

CONCLUSIONS

In apparently healthy middle-aged subjects at increased risk for vascular disease, among traditional risk factors, hypertension is most closely associated with microstructural WM impairment. These findings have implications for patient care by early selec-

tion of subjects who are at risk for future cognitive impairment through identification of these impaired tracts. This may even prove to be of further value because novel therapies are being developed for patients with CSVD.

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REFERENCES

- Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol* 2010;9:689–701 [CrossRef Medline](#)
- Craggs LJ, Yamamoto Y, Deramecourt V, et al. Microvascular pathology and morphometrics of sporadic and hereditary small vessel diseases of the brain. *Brain Pathol* 2014;24:495–509 [CrossRef Medline](#)
- Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol* 2013;12:483–97 [CrossRef Medline](#)
- Ihara M, Yamamoto Y. Emerging evidence for pathogenesis of sporadic cerebral small vessel disease. *Stroke* 2016;47:554–60 [CrossRef Medline](#)
- Gottesman RF, Coresh J, Catellier DJ, et al. Blood pressure and white-matter disease progression in a biethnic cohort: Atherosclerosis Risk in Communities (ARIC) study. *Stroke* 2010;41:3–8 [CrossRef Medline](#)
- Bailey EL, Smith C, Sudlow CL, et al. Is the spontaneously hypertensive stroke prone rat a pertinent model of sub cortical ischemic stroke? A systematic review. *Int J Stroke* 2011;6:434–44 [CrossRef Medline](#)
- Payne RA, Wilkinson IB, Webb DJ. Arterial stiffness and hypertension: emerging concepts. *Hypertension* 2010;55:9–14 [CrossRef Medline](#)
- Saji N, Shimizu H, Kawai T, et al. Increased brachial-ankle pulse wave velocity is independently associated with white matter hyperintensities. *Neuroepidemiology* 2011;36:252–57 [CrossRef Medline](#)
- Saji N, Kimura K, Shimizu H, et al. Silent brain infarct is independently associated with arterial stiffness indicated by cardio-ankle vascular index (CAVI). *Hypertens Res* 2012;35:756–60 [CrossRef Medline](#)
- Tamura Y, Araki A. Diabetes mellitus and white matter hyperintensity. *Geriatr Gerontol Int* 2015;15(Suppl 1):34–42 [CrossRef Medline](#)
- Khan U, Porteous L, Hassan A, et al. Risk factor profile of cerebral small vessel disease and its subtypes. *J Neurol Neurosurg Psychiatry* 2007;78:702–06 [Medline](#)
- Alexander AL, Lee JE, Lazar M, et al. Diffusion tensor imaging of the brain. *Neurotherapeutics* 2007;4:316–29 [CrossRef Medline](#)
- Maniega SM, Valdés Hernández MC, Clayden JD, et al. White matter hyperintensities and normal-appearing white matter integrity in the aging brain. *Neurobiol Aging* 2015;36:909–18 [CrossRef Medline](#)
- Nyquist PA, Yanek LR, Bilgel M, et al. Effect of white matter lesions on manual dexterity in healthy middle-aged persons. *Neurology* 2015;84:1920–26 [CrossRef Medline](#)
- Wang TJ, Massaro JM, Levy D, et al. A risk score for predicting stroke

- or death in individuals with new-onset atrial fibrillation in the community: the Framingham Heart Study. *JAMA* 2003;290:1049–56 [CrossRef Medline](#)
16. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary—Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults. *Am J Clin Nutr* 1998;68:899–917 [CrossRef Medline](#)
 17. Brook RD, Appel LJ, Rubenfire M, et al; American Heart Association Professional Education Committee of the Council for High Blood Pressure Research, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, and Council on Nutrition, Physical Activity. Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association. *Hypertension* 2013;61:1360–83 [CrossRef Medline](#)
 18. Myers GL, Kimberly MM, Waymack PP, et al. A reference method laboratory network for cholesterol: a model for standardization and improvement of clinical laboratory measurements. *Clin Chem* 2000;46:1762–72 [Medline](#)
 19. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502 [Medline](#)
 20. Jiang H, van Zijl PC, Kim J, et al. DtiStudio: resource program for diffusion tensor computation and fiber bundle tracking. *Comput Methods Programs Biomed* 2006;81:106–16 [CrossRef Medline](#)
 21. Oishi K, Faria A, Jiang H, et al. Atlas-based whole brain white matter analysis using large deformation diffeomorphic metric mapping: application to normal elderly and Alzheimer's disease participants. *Neuroimage* 2009;46:486–99 [CrossRef Medline](#)
 22. Maillard P, Seshadri S, Beiser A, et al. Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. *Lancet Neurol* 2012;11:1039–47 [CrossRef Medline](#)
 23. Bettcher BM, Walsh CM, Watson C, et al. Body mass and white matter integrity: the influence of vascular and inflammatory markers. *PLoS One* 2013;8:e77741 [CrossRef Medline](#)
 24. Allen B, Muldoon MF, Gianaros PJ, et al. Higher blood pressure partially links greater adiposity to reduced brain white matter integrity. *Am J Hypertens* 2016;29:1029–37 [CrossRef Medline](#)
 25. Maillard P, Carmichael OT, Reed B, et al. Cooccurrence of vascular risk factors and late-life white-matter integrity changes. *Neurobiol Aging* 2015;36:1670–77 [CrossRef Medline](#)
 26. Heye AK, Thrippleton MJ, Chappell FM, et al. Blood pressure and sodium: association with MRI markers in cerebral small vessel disease. *J Cereb Blood Flow Metab* 2016;36:264–74 [CrossRef Medline](#)
 27. Rosano C, Abebe KZ, Aizenstein HJ, et al; Health ABC Study. Longitudinal systolic blood pressure characteristics and integrity of white matter tracts in a cohort of very old black and white adults. *Am J Hypertens* 2015;28:326–34 [CrossRef Medline](#)
 28. Nitkunan A, Charlton RA, McIntyre DJ, et al. Diffusion tensor imaging and MR spectroscopy in hypertension and presumed cerebral small vessel disease. *Magn Reson Med* 2008;59:528–34 [CrossRef Medline](#)
 29. Gons RA, de Laat KF, van Norden AG, et al. Hypertension and cerebral diffusion tensor imaging in small vessel disease. *Stroke* 2010;41:2801–06 [CrossRef Medline](#)
 30. Yau PL, Hempel R, Tirsi A, et al. Cerebral white matter and retinal arterial health in hypertension and type 2 diabetes mellitus. *Int J Hypertens* 2013;2013:329602 [CrossRef Medline](#)
 31. Power MC, Tingle JV, Reid RI, et al. Midlife and late-life vascular risk factors and white matter microstructural integrity: the Atherosclerosis Risk in Communities Neurocognitive Study. *J Am Heart Assoc* 2017;6 [CrossRef Medline](#)
 32. Williams VJ, Leritz EC, Shepel J, et al. Interindividual variation in serum cholesterol is associated with regional white matter tissue integrity in older adults. *Hum Brain Mapp* 2013;34:1826–41 [CrossRef Medline](#)
 33. Alfaro FJ, Lioutas VA, Pimentel DA, et al. Cognitive decline in metabolic syndrome is linked to microstructural white matter abnormalities. *J Neurol* 2016;263:2505–14 [CrossRef Medline](#)
 34. Yuce I, Kantarci M, Keles P, et al. Diffusion tensor imaging of the hippocampus in chronic cigarette smokers. *Eur J Radiol* 2016;85:1538–44 [CrossRef Medline](#)
 35. Gogliettino AR, Potenza MN, Yip SW. White matter development and tobacco smoking in young adults: a systematic review with recommendations for future research. *Drug Alcohol Depend* 2016;162:26–33 [CrossRef Medline](#)
 36. van Bloemendaal L, Ijzerman RG, Ten Kulve JS, et al. Alterations in white matter volume and integrity in obesity and type 2 diabetes. *Metab Brain Dis* 2016;31:621–29 [CrossRef Medline](#)
 37. Reijmer YD, Brundel M, de Bresser J, et al; Utrecht Vascular Cognitive Impairment Study Group. Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes: a diffusion tensor imaging study. *Diabetes Care* 2013;36:137–44 [CrossRef Medline](#)
 38. Tan X, Fang P, An J, et al. Micro-structural white matter abnormalities in type 2 diabetic patients: a DTI study using TBSS analysis. *Neuroradiology* 2016;58:1209–16 [CrossRef Medline](#)
 39. Xiong Y, Sui Y, Xu Z, et al. A diffusion tensor imaging study on white matter abnormalities in patients with type 2 diabetes using tract-based spatial statistics. *AJNR Am J Neuroradiol* 2016;37:1462–69 [CrossRef Medline](#)
 40. Thomas AG, Koumellis P, Dineen RA. The fornix in health and disease: an imaging review. *Radiographics* 2011;31:1107–21 [CrossRef Medline](#)
 41. Bubb EJ, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: anatomy, function, and dysfunction. *Neurosci Biobehav Rev* 2018;92:104–27 [CrossRef Medline](#)
 42. Madhavan KM, McQueeney T, Howe SR, et al. Superior longitudinal fasciculus and language functioning in healthy aging. *Brain Res* 2014;1562:11–22 [CrossRef Medline](#)
 43. Chan-Seng E, Moritz-Gasser S, Duffau H. Awake mapping for low-grade gliomas involving the left sagittal stratum: anatomofunctional and surgical considerations. *J Neurosurg* 2014;120:1069–77 [CrossRef Medline](#)
 44. Iadecola C, Davisson RL. Hypertension and cerebrovascular dysfunction. *Cell Metab* 2008;7:476–84 [CrossRef Medline](#)
 45. Walker KA, Power MC, Gottesman RF. Defining the relationship between hypertension, cognitive decline, and dementia: a review. *Current Hypertens Rep* 2017;19:24 [CrossRef Medline](#)

Depiction of the Superior Petrosal Vein Complex by 3D Contrast-Enhanced MR Angiography

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ABSTRACT

BACKGROUND AND PURPOSE: Intraoperative obliteration of the superior petrosal vein complex has a relevant risk of postoperative complications. A large venous diameter and the absence of anastomoses have been previously suggested as possible risk factors. 3D contrast-enhanced MRA was evaluated for the identification of superior petrosal vein anatomy.

MATERIALS AND METHODS: Twenty-five patients (10 men; age, 20–77 years) with a 3D-MRA (voxel size, $0.4 \times 0.4 \times 0.5 \text{ mm}^3$) at 3T, including the posterior fossa, were retrospectively identified. Image evaluation was performed independently by 2 neuroradiologists with respect to overall image quality and the presence, location, size, tributaries, and anastomotic veins of the superior petrosal vein complex. Additionally, 8 neurosurgical cases with intraoperative validation of the venous anatomy were examined.

RESULTS: All studies were of diagnostic image quality. Interobserver agreement was excellent for image-quality measurements ($r = 0.751\text{--}0.982$) and good for measured vessel size ($r = 0.563\text{--}0.828$). A total of 83 superior petrosal veins were identified. The distribution of drainage locations and identification of tributaries and anastomotic veins were consistent with previous anatomic studies. The results showed that 4.8% of superior petrosal veins had a diameter of $>2 \text{ mm}$ and lacked a visible anastomosis. All surgical cases showed excellent agreement between the MRA and the intraoperative observations.

CONCLUSIONS: 3D-MRA with high resolution is appropriate for analyzing the size, course, tributaries, and anastomoses of the superior petrosal vein. A total of 4.8% of the identified superior petrosal veins had to be classified as potential high-risk veins. The measurements correlated with the intraoperative findings.

ABBREVIATIONS: SPS = superior petrosal sinus; SPV = superior petrosal vein

In the 1960s, radiologists first described the detailed anatomy of the venous drainage of the posterior fossa using conventional angiography^{1–3} and identified the diagnostic significance of the superior petrosal vein (SPV) in the evaluation of cerebellopontine angle tumors.² Several neurosurgical reports have described com-

plications arising from the sacrifice of the SPV due to compromise of the cerebellar deep venous outflow, leading to extensive venous infarction and hemorrhage.^{4–8} The exact anatomic location of the SPV plays a crucial role in evaluating the risks of a middle fossa approach with anterior petrosectomy and the retrosigmoid-suprameatal approach because the intraoperative location of at-risk veins differs greatly between the 2 approaches.⁹ Precise knowledge of the course, size, variations, and outflow system of associated anastomotic veins of the SPV is of great interest to neurosurgeons to plan the approach and thus reduce the risk of venous complications.

The SPV enters the superior petrosal sinus (SPS) and may be formed by the terminal segment of a single vein or by the common stem formed by the union of up to 5 veins.⁶ The most common tributaries of the SPV are the transverse pontine and pontotrigeminal veins (depending on the literature, also considered to be part of the lateral mesencephalic vein or referred to as the brachial tributary of the superior petrosal vein), the common stem of the superior cerebellar hemispheric veins, and the veins of the cer-

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Other patient samples with slightly different MR imaging protocols or small subgroups of the present article have been presented at the following meetings: Annual Meeting of the German Society of Skull Base Surgery, October 11–12, 2013; Tübingen, Germany; Plenary Annual Meeting of the European Skull Base Society, June 26–28, 2014; Paris, France; and Plenary Annual Meeting of the German Society of Neuroradiology, October 23–25, 2014; Cologne, Germany.

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ebellopontine fissure and the middle cerebellar peduncle.¹⁰⁻¹² The SPV can be classified as a lateral, intermediate, or medial type based on the anatomic relationships between the site of entry into the superior petrosal sinus and the internal acoustic meatus¹² and based on the relationship of the site of entry into the superior petrosal sinus to the internal acoustic meatus and the Meckel cave.⁹ The anterior pontomesencephalic and the lateral mesencephalic veins link the SPV complex and the basal vein of Rosenthal and thus represent the 2 main anastomoses between the supra- and infratentorial venous systems.^{13,14} In the case of several SPVs, there is also the possibility of an anastomosis between them.

Many MR imaging studies have shown that venous structures can be depicted with high diagnostic accuracy.¹⁵⁻²⁰ However, due to the variable diameter, the close relationship to nearby air-filled bone structures and the superior cerebellar artery, and the course along brain parenchyma, CSF, and bone, the depiction of the SPV and its tributaries is challenging. Knowledge about the size, tributaries, and anastomoses of the SPV mostly exists from microsurgical and anatomic studies^{9-12,14,21} or digital subtraction angiography.¹¹ A detailed preoperative MR imaging evaluation of the individual venous anatomy would meaningfully inform the surgical strategy.

The purpose of our study was to evaluate whether a contrast-enhanced MRA with high spatial resolution that cannot be obtained with 2D noncontrast venography can depict the variations, tributaries, and anastomoses of the SPV.

MATERIALS AND METHODS

Patients

All patients who underwent a high-resolution 3D-MRA at the 3T MR imaging scanner of the Department of Radiology, University Hospital Tübingen in 2013 were retrospectively identified by a radiologic information system search; patients younger than 18 years of age were excluded. A total of 25 patients were identified (10 men, 15 women; mean age, 49.3 ± 19.5 years; age range, 20–77 years) and included in the analysis. After transferring the clinical data and the results of the image evaluation into a research data base, we removed all identifying information before further evaluation. There was a broad spectrum of clinical indications.

Additionally, 8 patients with cerebellopontine angle tumors underwent preoperative 3D-MRA. For these cases, a comparison with the intraoperative findings from the surgical report and video documentation was conducted. Our study was approved by the local institutional review board, and the need for informed consent was waived due to the anonymous evaluation.

Imaging Technique

All studies were performed on a 3T MR imaging system (Magnetom Skyra; Siemens, Erlangen, Germany) with a 24-channel head-neck coil.

The 3D-MRA was performed 20 seconds after an intravenous injection of Gd-DTPA (0.1 mmol/kg body weight) at 1.5 mL/s, followed by a saline flush (40 mL) at 1.5 mL/s using an electronic power injector (Spectris MR injector; MedRad, Indianola, Pennsylvania). A fast 3D gradient recalled-echo sequence in the axial orientation was used (FOV, 240×210 mm²; matrix, 576×504 ; 1

slab; 176 slices; slice thickness, 0.5 mm; TR/TE, 8.44/2.8 ms; flip angle, 30°; bandwidth, 130 Hz/pixel), with elliptic centric *k*-space encoding, asymmetric *k*-space sampling (partial Fourier 6/8), and zero interpolation in all 3 planes.

Subsequent image-quality analysis was performed independently by 2 neuroradiologists, each with 6 years of experience. For cases in which the reported number of SPVs differed, a third senior neuroradiologist with 16 years of experience evaluated the case in a consensus reading with the first 2 raters. The original image data and thin-slab MIPs (3-mm-thick, reconstructed in steps of 1 mm) aligned to the superior petrosal sinus in all 3 axes were evaluated on the local PACS and a 3D volume viewer (syngo.via Siemens Healthineers, Erlangen, Germany). Separate image-reading sessions were organized for both readers. The MIP reconstructions were used to obtain a first overview of the relationship among the different tributaries of the SPVs. In all cases, an overlap between adjacent vessels was seen and the original image data were needed to separate branch communications from artificial overlap.

The readers were asked to assess the overall quality of MR angiograms with regard to venous enhancement and the presence of artifacts and/or noise using a 1–3 scoring scale (1, poor image quality: inadequate venous enhancement and/or the presence of relevant artifacts/noise impairing the diagnosis; 2, good image quality, sufficient for diagnosis: adequate venous enhancement and/or mild-to-moderate artifacts/noise, not interfering with diagnosis; and 3, excellent image quality for a highly confident diagnosis: good venous enhancement, no or minimal artifacts/noise).

Both raters were asked to draw an oval ROI in the basilar artery, brain stem, outside the brain within the noise, in the left and right transversal sinuses, and in the left and right petrosal sinuses. Within this ROI, mean signal intensity and SD were recorded.

Anatomic Analysis

According to the anatomic definition, every vein draining into the SPS was classified as an SPV. For the evaluation of the tributaries, the rater used a previously reported scheme that divides the tributaries into 4 groups: the anterior pontomesencephalic group, the tentorial group, the petrosal group, and the posterior mesencephalic group (Fig 1).¹¹ Each rater evaluated the presence and sizes of anastomoses between the supra- and infratentorial venous systems via the anterior pontomesencephalic and the posterior mesencephalic groups. If there was no direct anastomosis of an SPV, the raters were asked to judge whether an anastomosis to another SPV with infra- to supratentorial anastomosis was present. If 2 anastomoses (with diameter d_1 and d_2) were present for an SPV, the combined diameter d_c was calculated as follows:

$$d_c = 2 \times \sqrt{\left(\frac{d_1}{2}\right)^2 \pi + \left(\frac{d_2}{2}\right)^2 \pi}.$$

The SPV drainages were subdivided into lateral, intermediate, and medial groups based on the relationship between the site of entry into the superior petrosal sinus and the internal acoustic meatus on sagittal MPR reconstructions: Type I was defined as an

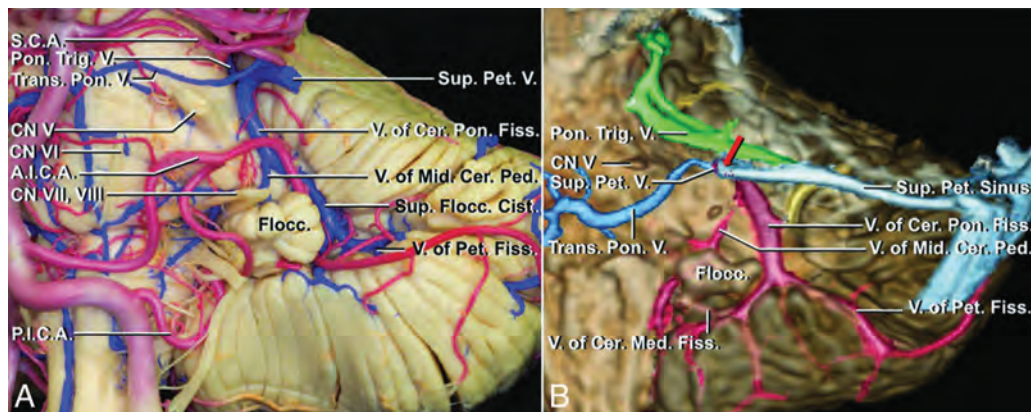


FIG 1. Anatomic overview of the tributaries of the superior petrosal veins (reproduced with permission of Oxford University Press from Matsushima K, Matsushima T, Kuga Y, et al. Classification of the superior petrosal veins and sinus based on drainage pattern. *Neurosurgery* 2014;10 Suppl 2:357–67).¹¹ **A**, Anterior view of the left petrosal cerebellar surface and anterolateral brain stem of an anatomic preparation with veins perfused with blue and arteries with red silicone. **B**, Colored multifusion image (T1 MPRAGE and conventional 3D digital subtraction angiography) with a similar view compared with **A**. The 4 drainage groups are red (petrosal group), blue (anterior pontomesencephalic group), green (posterior mesencephalic group), and yellow (tentorial group).

SPV that drains into the SPS lateral to the internal acoustic meatus, SPV type II drains into the SPS above the internal acoustic meatus, and type III drains into the SPS medial to the internal acoustic meatus.¹²

The sizes of the basal vein, SPV, anterior pontomesencephalic vein, and lateral mesencephalic vein were measured in millimeters. If the size was <0.5 mm (and therefore smaller than the acquired resolution), a value of 0.2 mm was used for statistical evaluation.

Statistical Evaluation

All statistical analyses were performed with SPSS (Version 22; IBM, Armonk, New York). Image-quality scores were plotted as median and range. A Wilcoxon rank sum test was used to evaluate the significance of the image-quality grading differences between the 2 readers. A Kruskal-Wallis test was used for between-group differences; post hoc analysis with correction for multiple comparisons was performed using the Dunn-Bonferroni test. To evaluate the effect size of the between-group differences, we calculated Pearson correlation coefficients (r) for significant results (0.1 = small, 0.3 = medium, 0.5 = large effect²²).

Interobserver agreement for subjective image-quality grading was determined by calculating the linear weighted κ coefficient (poor agreement, κ = 0; slight agreement, κ = 0.01–0.2; fair agreement, κ = 0.21–0.4; moderate agreement, κ = 0.41–0.6; good agreement, κ = 0.61–0.8; and excellent agreement, κ = 0.81–1²³). Interobserver agreement for objective image-quality measurements was evaluated by correlation coefficient analysis.

A 2-sided value of P < .05 was considered significant.

RESULTS

We examined 50 SPSs in 25 patients. Image quality was assessed as excellent in 13/25 cases by the first reader (B.B.) and in 17/25 cases by the second reader (A.K.); all other cases were considered good quality. The interobserver reliability was good (κ = 0.675). Figure 2 shows a typical MIP reconstruction at the level of the inflow of the SPV into the SPS.

Between raters, there was excellent correlation in the mea-

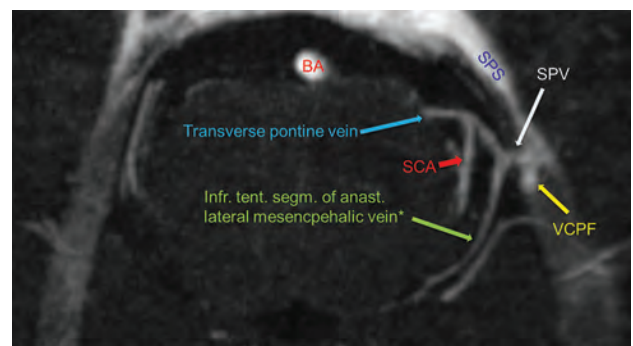


FIG 2. Transversal MIP at the level of the drainage of the SPV into the SPS (type II, internal acoustic meatus not shown). The tributary veins are clearly identifiable: lateral mesencephalic vein (asterisk, posterior mesencephalic group, anastomosis to the basal vein), transverse pontine vein (anterior pontomesencephalic group), and vein of cerebellopontine fissure (petrosal group). The artificial union of the SCA and the transverse pontine vein is clearly distinguishable on the original imaging data (asterisk, depending on the literature, also named pontotrigeminal vein and brachial tributary of the superior petrosal vein). BA indicates basilar artery; SCA, superior cerebellar artery; VCPF, vein of cerebellopontine fissure; infr. tent. segm. of anast., infratentorial segment of anastomosing.

sured signal intensities for the anatomic ROIs (Table 1) and good agreement for the measured diameters (Table 2). Objective image criteria of the area of interest were excellent; the mean SNR of the left SPS was 141.6 (range, 72.2–300.4), and the mean SNR of the right SPS was 143.2 (range, 76.5–273.6).

The first and second raters identified 42 and 48 SPVs, respectively, on the left side and 37 and 44 SPVs on the right side. The interrater reliability was moderate for both the right (κ = 0.496) and left (κ = 0.502) hemispheres.

Ten and 7 cases with a divergent judgment by the 2 reviewers on the left and right sides, respectively, were evaluated a second time in a consensus reading. After the consensus readings, 43 SPVs on the left side and 40 SPVs on the right side were identified. In all except 2 cases with a divergent judgment, the point of drainage of a transverse pontine vein (type III) was considered to be the SPS by one rater and the cavernous sinus by the other rater. In these cases, a line was drawn through the unambigu-

Table 1: Results of the ROI analysis for objective image quality and the calculated correlation coefficients for interobserver agreement^a

Anatomic Structure	Mean Rater 1 (A.U.)	Mean Rater 2 (A.U.)	No.	Pearson Correlation	
				Coefficient R	Significance
Noise ^a	4 ± 1	4 ± 1	25	0.818	<.001
Basilar artery	1110 ± 294	1170 ± 381	25	0.852	<.001
Brain stem	176 ± 24	179 ± 24	25	0.895	<.001
Vein of Galen	1040 ± 344	1020 ± 303	23	0.910	<.001
Transverse sinus (R)	905 ± 280	896 ± 276	25	0.982	<.001
Transverse sinus (L)	878 ± 232	902 ± 244	25	0.982	<.001
Basal vein (R)	812 ± 283	783 ± 243	19	0.910	<.001
Basal vein (L)	847 ± 233	839 ± 234	24	0.936	<.001
SPS (R)	561 ± 186	601 ± 183	25	0.852	<.001
SPS (L)	537 ± 233	612 ± 169	25	0.741	<.001

Note:—R indicates right; L, left; A.U., arbitrary units; No., number of cases.

^a For noise, the SD of the signal in the ROI is given; for all other ROIs, the mean signal is presented.

Table 2: Results of the evaluation of the diameters of the main vessels^a

Anatomic Structure	Mean Rater 1 (A.U.)	Mean Rater 2 (A.U.)	No.	Pearson Correlation	
				Coefficient R	Significance
Basal vein (R)	1.7 ± 0.4	1.6 ± 0.8	24	0.563	.003
Basal vein (L)	1.8 ± 0.4	1.7 ± 0.4	25	0.659	<.001
Lateral mesencephalic vein (R)	0.9 ± 0.5	0.9 ± 0.5	19	0.753	<.001
Lateral mesencephalic vein (L)	0.7 ± 0.7	0.8 ± 0.6	20	0.828	<.001
Anterior pontomesencephalic vein	0.6 ± 0.6	0.6 ± 0.5	25	0.726	<.001
SPS (R)	2.6 ± 0.5	2.5 ± 0.7	25	0.663	<.001
SPS (L)	2.6 ± 0.6	2.5 ± 0.6	25	0.595	.002

Note:—No. indicates the number of veins present; R, right; L, left; A.U., arbitrary units.

^a Missing veins were omitted for the calculation of the mean and rated as 0 mm for the correlation coefficient. Visible veins <0.5 mm were rated as 0.2 mm.

Table 3: Position and size of 83 petrosal veins in 25 patients without intraoperative validation and in 8 patients with intraoperative validation

Type of SPV	No. of SPVs in Patients		Mean Diameter (Range) (mm) in Patients	
	Without Surgery	With Surgery	Without Surgery	With Surgery
I, lateral	13 (15.7%)	1 (4.8%)	2.0 (0.5–2.9)	2.5 (2.5–2.5)
II, intermediate	41 (49.4%)	10 (47.6%)	2.4 (<0.5–5.6)	2.1 (1.5–3.6)
III, medial	29 (34.9%)	10 (47.6%)	1.3 (<0.5–2.7)	1.0 (<0.5–2.1)
I–III	83	21	2.0 (<0.5–5.6)	1.6 (<0.5–3.6)

Table 4: Frequencies of superior petrosal vein drainage groups for each cerebellopontine angle (n = 50) and each superior petrosal vein (n = 83)

Drainage Group	Frequency of Group/Side			Frequency of Group/SPV		
	Left	Right	Total	Left	Right	Total
Petrosal	25	24	49/50 sides (98%)	31	31	62/83 (74.7%)
Posterior mesencephalic	22	22	44/50 sides (88%)	22	23	45/83 (54.2%)
Anterior pontomesencephalic	23	21	44/50 sides (88%)	27	27	54/83 (65.1%)
Tentorial	14	15	29/50 sides (58%)	14	15	29/83 (34.9%)

ous course of the SPS; if a medial vein drained at the level of this line, it was considered an SPV during the consensus reading. If the drainage was medial to or below this line, it was not considered an SPV.

After the consensus readings, 22/50 SPSs (44%) had 1 SPV, 23/50 SPSs (46%) had 2 SPVs, and 5/50 (10%) had 3 SPVs. Table 3 summarizes the types and diameters of the SPVs. There was a significant difference in vein size for the 3 types ($H(2) = 28.871$, $P < .001$). Post hoc comparison indicated that type III veins were significantly smaller than type I ($z = 2.861$, $P = .01$, $r = 0.44$) and type II ($z = 5.333$, $P < .001$, $r = 0.64$) veins. Table 4 shows the distribution of the drainage groups. The most common tributary vein was the vein of the cerebellopontine fissure (petrosal group), which drained into an SPV in all except 1 case. Eighteen of the 83 SPVs (21.7%) had no visible infra-to-supratentorial anastomosis and were considered potentially dangerous SPVs in case of oblit-

eration. Of these 18 SPVs, 2 were type I (2.4% of all SPVs; 15.4% of type I), 6 were type II (7.2% of all SPVs; 14.6% of type II), and 10 were type III (12% of all SPVs; 34.5% of type III). The mean diameter of the potentially dangerous SPVs was 1.5 mm (<0.5–3 mm). Figure 3 illustrates the diameter of the SPVs in comparison with the diameter of the anastomosis.

Data for the intraoperative validation group are shown in Table 3 and On-line Table 1. In general, the distribution and size were comparable with those in the patient group without intraoperative validation. Many SPVs on the affected side were compressed at the entry into the SPS, with enlarged anastomoses. In all cases, there was excellent agreement with the intraoperative anatomy. In 2 cases, an SPV was sacrificed during an operation without adverse effects (patient 3, Fig 4 and patient 6, second type II SPV). In patient 1, the left SPV was preserved, though altered arachnoid mater and tumor covering parts of the SPV

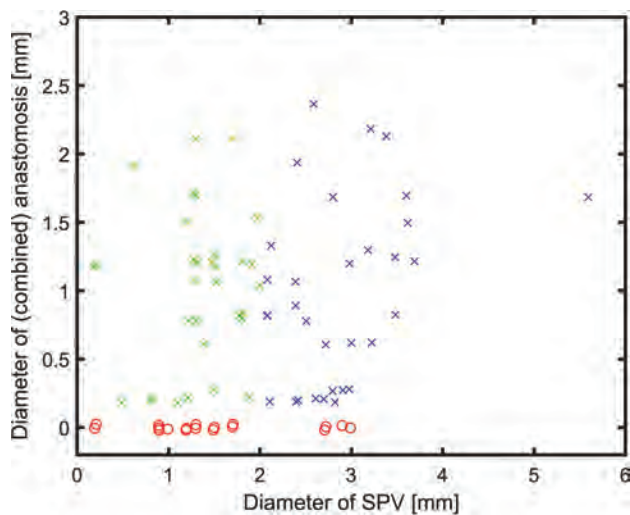


FIG 3. Scatterplot of the diameter of the SPV versus the combined diameters of its anastomoses. To better visualize overlaying data points, we added a random offset between -0.025 and 0.025 to each diameter. SPVs with no visible anastomosis are shown as red circles, while x represents SPVs with at least 1 anastomosis (green indicates the diameter of the SPV ≤ 2 mm; blue, diameter of the SPV > 2 mm). SPVs with a diameter of >2 mm are considered dangerous by Zhong et al.⁶

were seen (Fig 5). Because the fresh-frozen section was not conclusive, a radical approach with a sacrifice of the SPV was considered too dangerous, given the information from the preoperative MR imaging.

DISCUSSION

In this study, 3D-MRAs were retrospectively evaluated for image quality and anatomic depiction of the SPV. Objective imaging criteria and interrater reliability regarding subjective image quality were good to excellent. Anatomic depiction of the SPV and identification of its tributaries and anastomoses were possible in all cases, and the results are in good agreement with previous results.⁹⁻¹² There is a large variation in the reported frequency of drainage types.^{9,11,12} This variation can be explained, in part, by the difficulty in defining the exact border of the internal auditory meatus, as well as a slightly different classification scheme in 1 of the studies.⁹

In contrast to previous studies,^{9,11} SPSs with 2 or 3 draining SPVs were more common, with 42% and 10%, respectively, in comparison with 20% and 3%¹¹ and 23% and 0%.⁹ However, these frequencies are consistent with an earlier microsurgical study that found frequencies of 50% and 10%.¹² Only Huang et

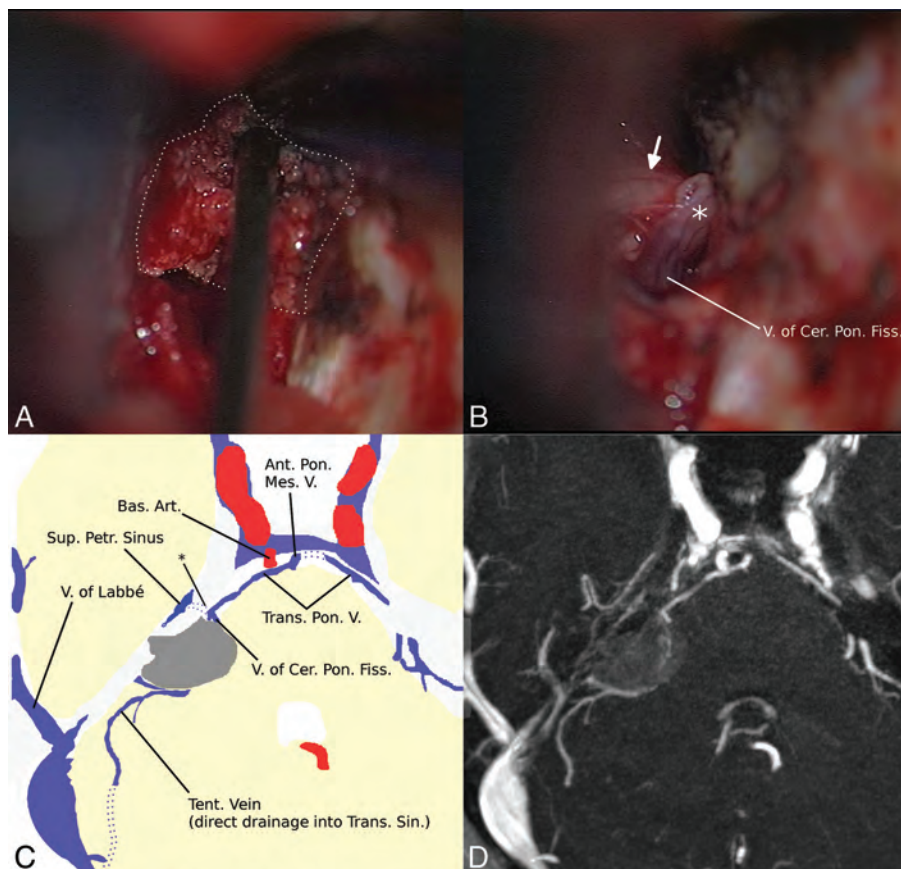


FIG 4. A, Intraoperative view shows that the venous anatomy is hidden for the neurosurgeon by the meningioma (white dots). B, After removal of the tumor, the neurosurgeon can see the medial superior petrosal vein (type III) and the trigeminal nerve (arrow). Two tributaries are encountered in concordance with the MR imaging. A schematic drawing (C) based on axial MIP reconstruction (D) of the preoperative 3D-MRA shows a compressed single SPV (asterisk in C) just ventral to the meningioma, with 2 tributaries and a main drainage via a pontine transverse vein and the anterior pontomesencephalic vein. Although the location was known, partial thermocoagulation (note the different color of the SPV marked with an asterisk in B) of the previously compressed SPV could not be prevented. The dorsal region of the cerebellum had direct drainage into the basal vein via a large lateral mesencephalic vein (not shown). V indicates vein; V. of Cer. Pon. Fiss., vein of the cerebellopontine fissure; Bas. Art., basal artery; Ant. Pon. Mes. V., anterior pontomesencephalic vein; Sup. Petr. Sinus, superior petrosal sinus; Trans. Pon. V., transverse pontine vein; Tent. Vein, tentorial vein; Trans. Sin., transverse sinus.

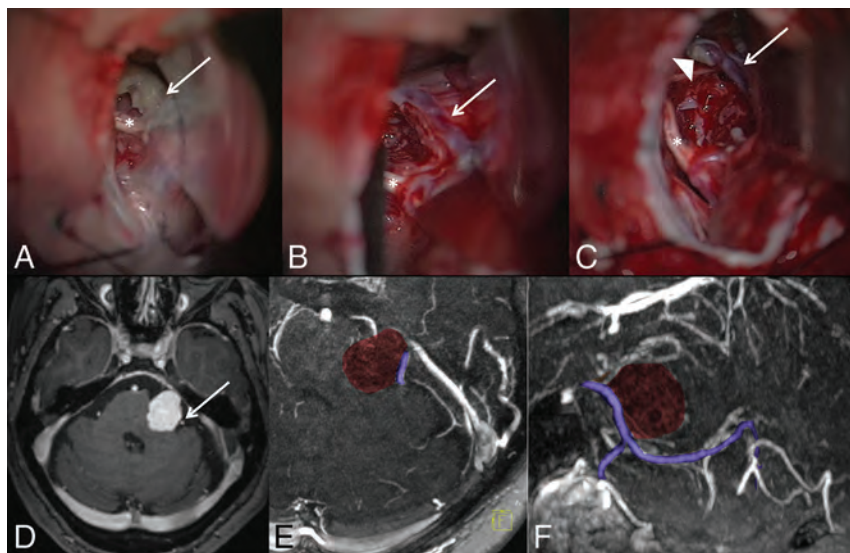


FIG 5. Intraoperative views of the tumor (A, white arrow) and after removal of the tumor (B and C): T1-weighted postcontrast scan (D) and axial (E) and sagittal (F) MIP reconstructions of the MR imaging. Nerves VII and VIII (asterisk) are seen directly below the tumor. A single large SPV (white arrow in B–D; purple colored in E,F) drains a large portion of the cerebellum and enters the SPS just in front of the tumor (type II). With a diameter of >2 mm and no visible collaterals in the MRA and intraoperatively, fibrous arachnoidea and tumor (arrowhead) sticking to the SPV were not removed due to the high risk of obliteration.

al³ noted that “not infrequently there are several venous stems which drain into the superior petrosal sinus at different points.”

Consistent with a previous study,¹¹ we found that the petrosal group was the largest and most common drainage group of the SPV and was present in all except 1 SPS. The posterior mesencephalic and the anterior pontomesencephalic groups were equally common and were present in 88% of SPSs, in agreement with a previous study,¹¹ considering the number of subjects evaluated in both studies. A noticeable difference was found for the tentorial group, which was found in only 58% of our patients but in 70% in the study by Matsushima et al.¹¹ The largest tributary of the tentorial group, the anterior lateral marginal vein,¹¹ is a very small vein and is the only vein for which the terminal size has been described as “very small” without a corresponding measurement (millimeters) in a microsurgical anatomic study.¹² With a resolution of $0.42 \times 0.42 \times 0.5$ mm, our MR image, therefore, might have missed some of the very small anterior lateral marginal veins with drainage into the SPS, and this group might be underestimated in our sample. Very small veins are usually not considered a problem during an operation⁶; therefore, the insufficient resolution for these veins is of no clinical relevance. In comparison with a recent study based on CT-venography,²⁴ 3D-MRA depicted more tributaries, probably due to the better resolution. Both methods can be easily incorporated into the standard work-up of planned surgical cases.

In the neurosurgical literature, the rate of complications after sacrificing an SPV varies. In a study of 30 patients with dissection of an SPV during resection of a petrous apex meningioma, minor complications were described in 23.3%, and major complications, in 6.6% of patients.⁴ Zhong et al⁶ identified 5/205 potential high-risk SPVs (2.4%) in patients undergoing microvascular decompression for trigeminal neuralgia. In 3/5 cases, the SPV was

occluded to achieve a decompression of the root entry zone, despite deterioration of the electrophysiologic recordings. All patients developed a major complication with cerebellar edema, brain shift, and the need for posterior fossa decompression. It is unclear from the publication whether minor complications occurred or whether they were evaluated. Anastomoses do not exist between the right and left SPV complex but only between the ipsilateral infratentorial and supratentorial compartments.¹⁴ In our study, we were able to evaluate the presence and size of the 2 major anastomotic pathways (the lateral mesencephalic vein and anterior pontomesencephalic vein) of the SPV to the deep supratentorial venous system, which are considered crucial for risk stratification.¹⁴ A third pathway formed by tiny branches, the anterolateral anastomosis, was not visible in our study, probably due to its size. Due to the small diameter, the role of the anterolateral

anastomosis as a sufficient alternative drainage after occlusion of a large SPV has to be discussed.

A total of 43.4% of the SPVs in our study were >2 mm and must be considered dangerous following the definition of Zhong et al.⁶ A total of 22% of SPVs had no visible anastomoses. In total, 4/18 SPVs without visible anastomoses were >2 mm. The frequencies of SPVs of >2 mm lacking anastomoses (4.8%) and SPVs of ≤2 mm without visible anastomoses (16.9%) nicely correlate with the rate of major (2.4%–6.6%) and minor (23.3%) complications in the literature.^{4,6}

Usually, veins are elastic and can increase in size if needed. For the pulmonary vein, a variability in the diameter of approximately 15%, as the heart cycles, can be found in the literature.²⁵ Additionally, very small anastomoses (not visible in our study) can probably further increase the flow through alternative pathways. It remains unclear how large the diameters of the visible anastomoses have to be in comparison with the SPV if it is sacrificed. In all surgical cases, the intraoperative anatomy correlated well with the findings of the preoperative MR imaging. In 1 case, a large SPV of 2.1 mm had to be sacrificed, and the visible anastomosis increased in size at follow-up examinations.

CONCLUSIONS

This study shows that with dedicated high-resolution MR angiography of the posterior fossa, one can identify the size, location, and presence of anastomoses of the SPV. This procedure permits the preoperative identification of patients at risk for postoperative complications if the SPV is sacrificed. Our data support the hypothesis that the combination of a large-diameter SPV and the absence of sufficient anastomoses might be a risk factor for complications after intraoperative sacrifice of the SPV.

REFERENCES

- Huang YP, Wolf BS. The veins of the posterior fossa—superior or galenic draining group. *Am J Roentgenol Radium Ther Nucl Med* 1965;95:808–21 [CrossRef Medline](#)
- Takahashi M, Wilson G, Hanafee W. The significance of the petrosal vein in the diagnosis of cerebellopontine angle tumors. *Radiology* 1967;89:834–40 [CrossRef Medline](#)
- Huang YP, Wolf BS, Antin SP, et al. The veins of the posterior fossa— anterior or petrosal draining group. *Am J Roentgenol Radium Ther Nucl Med* 1968;104:36–56 [CrossRef Medline](#)
- Koerbel A, Gharabaghi A, Safavi-Abbasi S, et al. Venous complications following petrosal vein sectioning in surgery of petrous apex meningiomas. *Eur J Surg Oncol* 2009;35:773–79 [CrossRef Medline](#)
- Koerbel A, Wolf SA, Kiss A. Peduncular hallucinosis after sacrifice of veins of the petrosal venous complex for trigeminal neuralgia. *Acta Neurochir (Wien)* 2007;149:831–32; discussion 832–33 [CrossRef Medline](#)
- Zhong J, Li ST, Xu SQ, et al. Management of petrosal veins during microvascular decompression for trigeminal neuralgia. *Neurol Res* 2008;30:697–700 [CrossRef Medline](#)
- Masuoka J, Matsushima T, Hikita T, et al. Cerebellar swelling after sacrifice of the superior petrosal vein during microvascular decompression for trigeminal neuralgia. *J Clin Neurosci* 2009;16:1342–44 [CrossRef Medline](#)
- Inamasu J, Shiobara R, Kawase T, et al. Haemorrhagic venous infarction following the posterior petrosal approach for acoustic neuroma surgery: a report of two cases. *Eur Arch Otorhinolaryngol* 2002; 259:162–65 [CrossRef Medline](#)
- Tanriover N, Abe H, Rhoton AL Jr, et al. Microsurgical anatomy of the superior petrosal venous complex: new classifications and implications for subtemporal transtentorial and retrosigmoid suprameatal approaches. *J Neurosurg* 2007;106:1041–50 [CrossRef Medline](#)
- Rhoton AL Jr. The posterior fossa veins. *Neurosurgery* 2000;47: S69–92 [Medline](#)
- Matsushima K, Matsushima T, Kuga Y, et al. Classification of the superior petrosal veins and sinus based on drainage pattern. *Neurosurgery* 2014;10(Suppl 2):357–67; discussion 367 [CrossRef Medline](#)
- Matsushima T, Rhoton AL Jr, de Oliveira E, et al. Microsurgical anatomy of the veins of the posterior fossa. *J Neurosurg* 1983;59:63–105 [CrossRef Medline](#)
- Ardeshiri A, Ardeshiri A, Tonn JC, et al. Microsurgical anatomy of the lateral mesencephalic vein and its meaning for the deep venous outflow of the brain. *Neurosurg Rev* 2006;29:154–58; discussion 158 [Medline](#)
- Ebner FH, Roser F, Shiozawa T, et al. Petrosal vein occlusion in cerebello-pontine angle tumour surgery: an anatomical study of alternative draining pathways. *Eur J Surg Oncol* 2009;35:552–56 [CrossRef Medline](#)
- Deda H, Erden I, Yagmurlu B. Evaluation of petrosal sinus patency with 3-dimensional contrast-enhanced magnetic resonance venography in petroclival meningiomas for surgical strategy. *Surg Neurol* 2005;64(Suppl 2):S67–71 [CrossRef Medline](#)
- Hu HH, Campeau NG, Huston J 3rd, et al. High-spatial-resolution contrast-enhanced MR angiography of the intracranial venous system with fourfold accelerated two-dimensional sensitivity encoding. *Radiology* 2007;243:853–61 [CrossRef Medline](#)
- Lee JM, Jung S, Moon KS, et al. Preoperative evaluation of venous systems with 3-dimensional contrast-enhanced magnetic resonance venography in brain tumors: comparison with time-of-flight magnetic resonance venography and digital subtraction angiography. *Surg Neurol* 2005;64:128–33; discussion 133–34 [CrossRef Medline](#)
- Lettau M, Sartor K, Heiland S, et al. 3T high-spatial-resolution contrast-enhanced MR angiography of the intracranial venous system with parallel imaging. *AJNR Am J Neuroradiol* 2009;30:185–87 [CrossRef Medline](#)
- Nael K, Fenchel M, Salamon N, et al. Three-dimensional cerebral contrast-enhanced magnetic resonance venography at 3.0 Tesla: initial results using highly accelerated parallel acquisition. *Invest Radiol* 2006;41:763–68 [CrossRef Medline](#)
- Ikushima I, Korogi Y, Kitajima M, et al. Evaluation of drainage patterns of the major anastomotic veins on the lateral surface of the cerebrum using three-dimensional contrast-enhanced MP-RAGE sequence. *Eur J Radiol* 2006;58:96–101 [CrossRef Medline](#)
- Ardeshiri A, Ardeshiri A, Linn J, et al. Microsurgical anatomy of the mesencephalic veins. *J Neurosurg* 2007;106:894–99 [CrossRef Medline](#)
- Cohen J. A power primer. *Psychol Bull* 1992;112:155–59 [CrossRef Medline](#)
- Altman DG. *Practical Statistics for Medical Research*. Boca Raton: Chapman & Hall; 1990:624
- Mizutani K, Toda M, Yoshida K. The analysis of the petrosal vein to prevent venous complications during the anterior transpetrosal approach in the resection of petroclival meningioma. *World Neurosurg* 2016;93:175–82 [CrossRef Medline](#)
- Hauser TH, Yeon SB, Kissinger KV, et al. Variation in pulmonary vein size during the cardiac cycle: implications for non-electrocardiogram-gated imaging. *Am Heart J* 2006;152:974.e1–6 [Medline](#)

Brain MR Imaging Findings in Woodhouse-Sakati Syndrome

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ABSTRACT

BACKGROUND AND PURPOSE: Woodhouse-Sakati syndrome is a rare autosomal recessive disorder characterized by hypogonadism, alopecia, diabetes mellitus, and progressive extrapyramidal signs. The disease is caused by biallelic pathogenic variants in the *DCAF17* gene. The purpose of this study was to describe the spectrum of brain MR imaging abnormalities in Woodhouse-Sakati syndrome.

MATERIALS AND METHODS: We reviewed brain MR images of 26 patients with a clinical and genetic diagnosis of Woodhouse-Sakati syndrome (12 males, 14 females; age range, 16–45 years; mean age, 26.6 years). Follow-up studies were conducted for 6 patients.

RESULTS: All patients had abnormal MR imaging findings. The most common abnormalities were a small pituitary gland (76.9%), pronounced basal ganglia iron deposition (73%), and white matter lesions in 69.2%. White matter lesions showed frontoparietal and periventricular predominance. All white matter lesions spared subcortical U-fibers and were nonenhanced. Prominent perivascular spaces (15.3%) and restricted diffusion in the splenium of the corpus callosum (7.6%) were less frequent findings. Follow-up studies showed expansion of white matter lesions with iron deposition further involving the red nucleus and substantia nigra. Older age was associated with a more severe degree of white matter lesions ($P < .001$).

CONCLUSIONS: Small pituitary gland, accentuated iron deposition in the globus pallidus, and nonenhancing frontoparietal/periventricular white matter lesions were the most noted abnormalities seen in our cohort. The pattern and extent of these findings were observed to correlate with older age, reflecting a possible progressive myelin destruction and/or axonal loss. The presence of pituitary hypoplasia and white matter lesions can further distinguish Woodhouse-Sakati syndrome from other neurodegenerative diseases with brain iron accumulation subtypes.

ABBREVIATIONS: NBIA = neurodegenerative diseases with brain iron accumulation; WSS = Woodhouse-Sakati syndrome; SNHL = sensorineural hearing loss

In 1983, Woodhouse and Sakati¹ described an autosomal recessive syndrome of hypogonadism, alopecia, diabetes mellitus, deafness, and extrapyramidal signs in several consanguineous Saudi families.^{2–5} To date, a total of 76 affected individuals, belonging to 32 families, have been reported in the literature.² While most cases are from Saudi Arabia and the Middle East,^{2,3} affected individuals from other ethnicities have been reported.^{6–11} Homozygous pathogenic variants in the *DCAF17* gene (formerly known as *C2ORF37*), allocated to chromosome 2q31.1, were discovered as the underlying cause of Woodhouse-Sakati syndrome

(WSS).^{3,12} The pathogenesis of the syndrome and the underlying gene remain unclear.

The affected individuals have distinctive dysmorphic features characterized by a long triangular face, prominent nasal bridge, and hypertelorism.^{1,2} The disease has a progressive nature, with predominant neuroendocrine manifestations that become increasingly more frequent during adolescence and early adulthood.⁴ Virtually all individuals will have the endocrine finding of progressive childhood-onset hair thinning as the initial manifestation of the disease.² All patients have hypogonadism of a mixed nature.¹³ More than half of individuals will have variable neurologic manifestations, including progressive extrapyramidal movements (dystonic spasms with dystonic posturing, dysarthria, and dysphagia), bilateral postlingual sensorineural hearing loss, and mild intellectual disability.^{2–5} Less frequently recognized manifestations include seizures, keratoconus, and electrocardiographic abnormalities.^{2,4}

The disease is characterized by wide phenotypic variabilities in

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the setting of white matter changes on brain images.^{2,14} There is no descriptive analysis of these changes, apart from very limited descriptions in some of the reported cases.

MATERIALS AND METHODS

Patients

This was a single-institution analysis of all available brain studies for patients with a clinically and genetically confirmed diagnosis of WSS (26 patients; 12 males, 14 females; age range, 16–45 years; mean age, 26.6 years). Subjects were recruited from June 2009 to September 2017.

All studies were performed at King Faisal Specialist Hospital & Research Center, a tertiary care referral center in Riyadh, Saudi Arabia.

Proband molecular genetic testing confirmed homozygous pathogenic variants in *DCAF17* in all participants. The institutional review board approved the study, with all patients providing written informed consent.

Clinical Assessment

A focused clinical examination with emphasis on neurologic involvement was conducted in all participants in an outpatient setting at the time of MR imaging acquisition. Muscle tone was rated using the Burke Fahn-Marsden Dystonia Rating Scale–Movement.¹⁵ Dystonia was defined as involuntary sustained or intermittent muscle contractions causing abnormal postures and/or repetitive movements. The involvement of 1 body part (cervical, mouth and jaw, larynx, limb) was labeled “focal dystonia.” Dystonia was defined as “multifocal” if at least 2 noncontiguous regions were affected, and “segmental,” if ≥ 2 contiguous regions were involved. Sensorineural hearing loss was confirmed through standardized audiologic assessment.

Brain Imaging Protocol

All MR imaging studies in our series, including those shown in the figures, are representative cases that were obtained using a 1.5T MR imaging scanner (Genesis Signa; GE Healthcare, Milwaukee, Wisconsin) with parameters that are widely accepted. Sequence acquisitions included sagittal T1-weighted images (TR/TE = 300–600/30 ms); axial T1- and T2-weighted images (TR/TE = 3000–7000/90 ms); T2*-weighted gradient recalled-echo images (TE = 750/50 ms); fluid-attenuated inversion recovery sequences (TR/TE = 8000–10,000/140 ms; TI = 2200 ms); and axial and coronal T1-weighted images with intravenous gadolinium. DWI was acquired with a single-shot EPI spin-echo sequence with TR/TE = 8000/87.6 ms; FOV = 26×26 cm²; matrix = 128×128 ; NEX 2, 24 sections; a 5-mm section thickness; and a 0.3-mm section gap. Eight patients underwent a special pituitary MR imaging protocol [T1- and T2-weighted spin-echo coronal and sagittal sections using a small FOV (20×25 cm) and thin slices (3 mm)] covering the sellar and parasellar regions.

In patients with craniocervical dystonia, head motion was minimized by firm sponge wedges around the head and restraining straps during and between the acquisition of images.

MR Imaging Analysis

MR images were reviewed by an expert, board-certified neuroradiologist (K.A.-A.) who was blinded to patients' clinical findings.

This was followed by a consensus agreement from the investigating group. The studies were systematically evaluated for any abnormalities of both cortical and subcortical anatomic white and gray matter structures.

White matter lesions were described according to their site, shape, confluency, and multifocality.¹⁶ The extent of these changes was subjectively graded and described as follows: absent (–); mild (predominantly scattered lesions or confluent periventricular) (+); moderate (patchy scattered) (++); or severe (predominantly diffuse, vanishing lesions) (+++). All 26 patients were studied with intravenous contrast material to analyze abnormal enhancement.

The pituitary gland was assessed with focus on the dimensions and size of the gland. The volume of the pituitary gland was determined by applying the cubic formula (length $\times$ width $\times$ height).^{17,18} Pituitary length was estimated from the maximum anteroposterior diameter parallel to the floor of the sella on the sagittal plane. The height was measured in sagittal and coronal sections, with midline measurement of the distance between the superior and inferior borders of the pituitary gland. The width of the gland was estimated with the 2 highest points on the lateral edges of the plateau of the fossa floor in the midcoronal plane. Measurements were compared with values of matched groups for both age and sex. In addition, the sellar and parasellar structures were observed for any abnormal pathology.

Areas rich in iron were defined on the basis of a standard protocol,¹⁴ and their appearance was described as hypointense on T2-weighted/FLAIR sequences, isointense on T1 sequences, and “blooming” hypointense on T2*-weighted acquisitions (gradient-echo sequences). Areas of focus included the caudate nucleus, putamen, globus pallidus, thalamus, red nucleus, and substantia nigra. Abnormal signals were addressed as present (+) or absent (–). MR spectroscopy was performed in 4 patients.

Diffusion restriction was defined as hyperintense on DWI, with low apparent diffusion coefficient map values.

Prominent perivascular spaces were described base on three characteristic anatomic locations,¹⁹ as type I: along the lenticulostriate arteries entering the basal ganglia through the anterior perforated substance; type II: along the path of the perforating medullary arteries as they enter the cortical gray matter over the high convexities and extend into the white matter; and type III: along the midbrain.

An additional area of focus was the internal auditory canal and its contents for any abnormal structural or signal abnormalities.

Follow-Up Studies

Six of 26 patients had repeat MR imaging, performed 2–5 years (mean duration, 3.2 years) from the initial study to assess radiologic progression.

Statistical Analysis

Data collection and analysis were performed using Research Electronic Data Capture (REDCap) tools and JMP statistical software, Version 14 (SAS Institute, Cary, North Carolina). REDCap is a secure web application for building and managing on-line surveys and data bases. Descriptive statistics for categorical variables are reported using frequencies and percentages. The Spearman test

Table 1: Clinical and imaging characteristics of WSS

Family	Sex	Age (Yr)	Neurologic			Radiologic		
			Dystonia	SNHL	Seizure	WM Changes	ID	Pituitary
1	F	18	Focal	—	—	Mild	—	Small
	M	19	—	—	+	Absent	+	Small
2	F	29	Generalized	—	—	Severe	+	Normal
	F	38	Focal	+	—	Moderate	+	Small
3	F	35	Focal	+	—	Mild	+	Small
	F	37	Focal	—	—	Severe	+	Small
4	M	45	Generalized	+	—	Severe	+	Small
	M	22	Focal	—	—	Mild	+	Normal
5	M	24	Generalized	—	—	Mild	+	Normal
	M	23	—	—	—	Mild	—	Small
6	F	21	—	—	—	Mild	+	Small
	M	16	—	—	—	Mild	—	Small
7	M	26	Generalized	+	—	Mild	+	Normal
	M	21	—	+	+	Absent	+	Normal
8	M	20	Generalized	—	—	Mild	—	Small
	F	21	—	—	—	Absent	+	Small
9	F	32	Multisegmental	—	—	Mild	+	Small
	F	22	Focal	—	—	Absent	—	Small
10	F	35	Focal	—	+	Severe	+	Small
	M	21	Multisegmental	+	—	Absent	+	Small
11	F	27	Focal	+	—	Absent	+	Small
	M	16	—	—	—	Absent	—	Small
12	F	41	Generalized	—	—	Moderate	+	Small
	M	37	Multisegmental	+	—	Moderate	+	Small
13	F	17	Multisegmental	—	—	Absent	+	Small
	F	29	—	—	—	Mild	—	Normal

Note:—SNHL indicates sensorineural hearing loss; ID, iron deposition; +, present; —, absent.

was used to assess the correlation between quantitative MR imaging severity (at the initial test) and age. $P \leq .05$ was considered statistically significant.

RESULTS

Patients

The clinical characteristics of patients are summarized in Table 1. Dystonia was the most common neurologic manifestation (18 patients, 69.2%), followed by sensorineural hearing loss and seizures seen in 30.7% and 11.5%, respectively. Focal dystonia (44%) was more common than generalized (23%) and multisegmental (15.3%) dystonia.

Description of MR Imaging Findings

Table 2 summarizes the detailed neuroimaging characteristics in our series.

A partially empty sella and a small pituitary gland were seen in 20 patients (76.9%); they were the most common MR imaging abnormalities in our cohort (Fig 1). Patients with WSS had a significantly smaller mean pituitary gland volume of $173 \pm 91 \text{ mm}^3$ compared with healthy control subjects with a mean of $480 \pm 85 \text{ mm}^3$ ($P < .005$). Six patients (23%) had normal pituitary gland volume. The pituitary stalk varied in size, but most of the affected individuals had a relatively small stalk. No abnormal suprasellar and parasellar structures were noted.

Evidence of iron deposition in the globus pallidus was observed in 19 patients (73%) (Fig 2A–C). Involvement of the substantia nigra and red nucleus was noted in 6 patients (23%) (Fig 2D). MR spectroscopy in 4 patients demonstrated normal major metabolite peaks. Despite the clinical finding of generalized or

focal dystonia, 3 patients showed no evidence of iron deposition on MR imaging.

White matter abnormalities on T2-weighted and FLAIR images were seen in 18 patients (69.2%). These changes varied in terms of distribution and extension (Fig 3). Extension of WM changes was characterized by a periventricular and frontoparietal predominance (Fig 4A, -B). Involvement of other subcortical (basal ganglia, thalamus) and infratentorial structures was seen in 3 patients (11.5%) (Fig 4C, -D). Older age was associated with more severe white matter lesions ($r = 0.71$, $P < .001$). All white matter lesions were nonenhancing and spared the U-fibers.

Prominent perivascular spaces were noted in 4 patients (15.3%), ranging from type 1 to type 3 (Fig 5). Diffusion restriction involving the splenium of the corpus callosum was noted in 2 patients (Fig 6). One patient had multiple subcortical diffusion restrictions.

Follow-up images were available for 6 patients, with a mean follow-up of 3.2 years from the initial studies (range, 2–5 years). Progression of WM extension and iron deposition were noted in all 6 patients.

DISCUSSION

Our study revealed variable abnormalities in all 26 patients, including some features described in prior reports (On-line Table). The observations of a small hypophysis, prominent perivascular spaces, transient signal changes of the splenium of the corpus callosum, and the progressive radiologic involvement are previously undescribed characteristics of the disease.

Endocrine involvement in WSS is invariable, and virtually all cases are associated with childhood-onset hair thinning with

Table 2: Characteristic brain MR imaging findings in WSS

Patient	Sex/Age (yr)	White Matter						Descriptive Features on MRI				Comments
		Frontal	Parietal	Temporal	Occipital	Infratentorial	Caudate	Putamen	RN/SN	Pituitary Atrophy	Diffusion Restriction	
1	F/18	+	+	—	+	—	—	—	—	+	+	—
2	M/19	—	—	—	—	—	—	+	—	+	—	Initial study showed no iron deposition
3	F/29	+++	+++	—	—	—	+	+	+	—	—	Extension of iron deposition on follow-up study
4	F/38	++	++	+	+	—	+	+	—	+	+	Prominent perivascular spaces
5	F/35	+	+	+	—	—	—	+	—	—	—	Prominent perivascular spaces
6	F/37	+++	+++	+	+	—	—	+	—	+	—	Calcification of the dentate nucleus
7	M/45	+++	+++	+	+	—	+	+	—	+	+	Loss of corpus callosum volume
8	M/22	+	+	—	—	—	—	+	—	+	—	—
9	M/24	+	+	—	—	—	—	+	—	—	—	Prominent perivascular spaces
10	M/23	+	+	—	—	—	—	—	—	+	—	—
11	F/21	+	+	—	—	—	—	+	—	+	—	—
12	M/16	+	+	—	—	—	—	—	—	+	—	Prominent perivascular spaces
13	M/26	+	+	+	+	—	—	+	+	+	—	—
14	M/21	—	—	—	—	—	—	+	+	—	—	—
15	M/20	+	—	—	—	—	—	—	—	+	—	—
16	F/21	—	—	—	—	—	—	+	+	+	—	—
17	F/32	+	+	+	+	—	—	+	—	+	—	—
18	F/22	—	—	—	—	—	—	—	—	+	—	—
19	F/35	+++	+++	+	+	+	—	+	—	+	—	Pontine WM signal
20	M/21	—	—	—	—	—	—	+	+	+	—	—
21	F/27	—	—	—	—	—	—	+	—	+	—	—
22	M/16	—	—	—	—	—	—	—	—	+	—	—
23	F/41	++	++	+	+	—	+	+	+	+	—	—
24	M/37	++	++	+	+	—	+	+	—	+	—	Dentate nucleus calcification
25	F/17	—	—	—	—	—	—	+	—	—	—	—
26	F/29	+	+	+	+	+	—	—	—	—	—	Cerebellar WM signal

Note:—RN indicates red nucleus; SN, substantia nigra; —, absent; +, mild (predominantly scattered lesions or confluent periventricular); ++, moderate (patchy scattered); + + +, severe (predominantly diffuse, vanishing lesions).

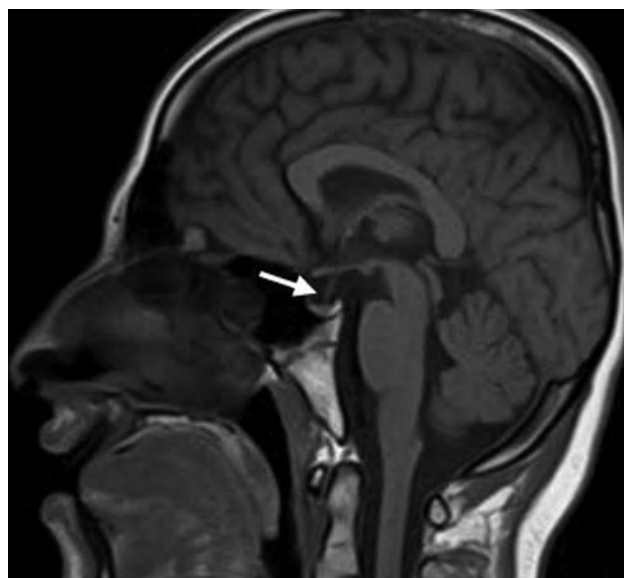


FIG1. Sagittal T1-weighted MR imaging for patient 22 shows a partially empty sella and a small pituitary gland (arrow).

frontotemporal alopecia, hypogonadism, and decreased insulin-like growth factor-1.^{2,4,13} Hypogonadism manifests as delayed puberty with a lack of secondary sexual characteristics. Hypogonadism is distinctive by mixed origin. Women tend to develop hypergonadotropic hypogonadism, while men have hypogonadotropic hypogonadism.¹³ Both sexes share an insufficient hypothalamic-pituitary response.^{2,4} Low insulin-like growth factor-1 and hypogonadism might be manifestations of a small hypophysis. Other endocrine manifestations, however, cannot be explained by pituitary hypoplasia. Hypothyroidism, reported in 30% of patients and usually observed after the age of 25,² is of a

peripheral origin. Type 2 diabetes mellitus was seen in up to 66% of patients and has no clear underlying pathology. In addition, diabetes is inconsistent with the observed low insulin-like growth factor-1 values. The hypothesized mechanism for the onset of diabetes, similar to that of hypothyroidism, in the absence of an underlying autoimmunity, is likely related to gonadal dysgeneses.^{1,10}

Pituitary hypoplasia in the setting of a genetically based syndrome has rarely been described.²⁰ Reproductive defects, hypogonadism along with confluent white matter abnormalities, and a partially empty sella on MR imaging are features similar to those seen in Gordon Holmes syndrome and Boucher-Neuhäuser syndrome. Both disorders are autosomal recessive as well.^{21,22} Cerebellar involvement in both conditions and chorioretinal dystrophy in Neuhäuser syndrome are features distinct from those in WSS.^{22,23}

Diffuse cerebral white matter signal abnormalities are a feature of many inherited degenerative disorders. White matter changes might be the result of cerebral white matter degeneration, demyelination, or hypomyelination. Vascular leukoencephalopathies might cause multifocal white matter abnormalities in the early stages, which eventually progress into more confluent lesions in advanced stages. Vasculopathies are characterized by the almost invariable presence of additional multifocal lesions in the basal ganglia, thalami, and the brain stem. This cohort showed rare involvement of these structures. Hypomyelination disorders are characterized by less marked and more widespread T2 hyperintensity compared with that seen in our series.¹⁶ The finding of transient signal changes of the splenium of the corpus callosum is a feature that might be seen in demyelinating or vascular conditions.^{24,25}

Preservation of U-fibers in diffuse white matter disease has

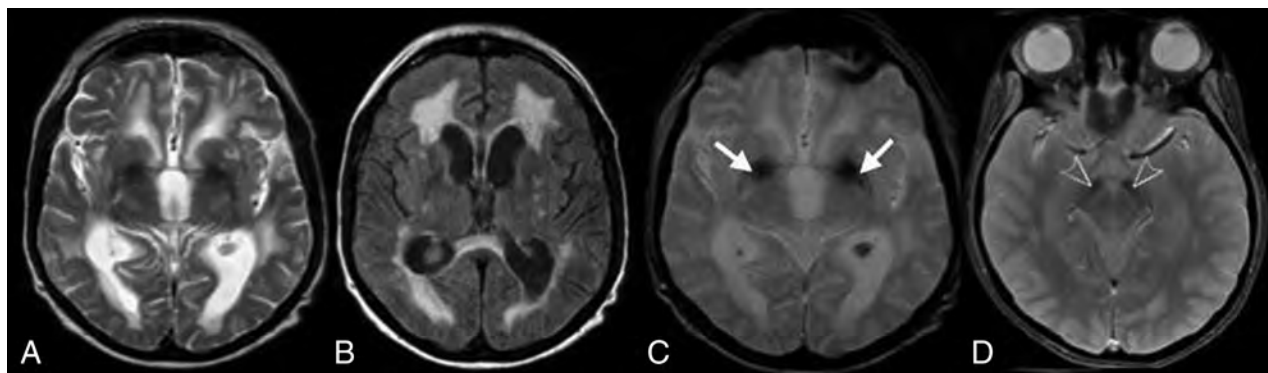


FIG 2. Axial T2-weighted (A), FLAIR (B), and T2* (C) MR images in case 11 show putaminal blooming artifacts (arrows) reflecting iron accumulation. An axial T2* MR image (D) in case 3 shows iron deposition in the substantia nigra (arrowheads).

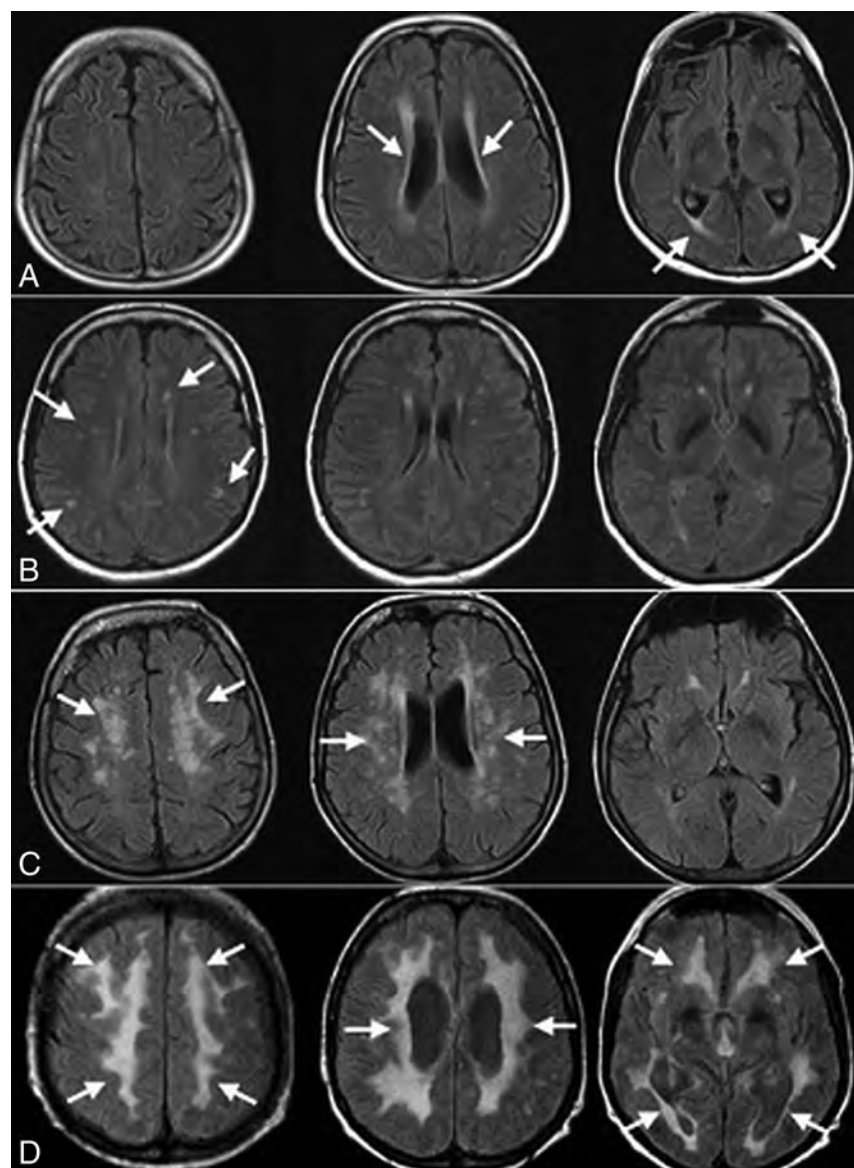


FIG 3. Axial FLAIR MR images show varying degrees of white matter lesions. Patients 1 and 26 (A and B) show a mild degree of white matter lesions, with faint periventricular (A; arrows) and small scattered signal intensities (B; arrows). In patient 4 (C), images show patchy signal intensities (arrows), representing a moderate degree of white matter lesions. A more diffuse, vanishing high signal intensity (arrows) is seen in images (D) for patient 7.

diagnostic utility.¹⁶ Alexander disease, metachromatic leukodystrophy, and X-linked adrenoleukodystrophy are the most notable disorders with this distinctive feature.²⁶⁻²⁹ Our cohort revealed a variable degree of subcortical periventricular and frontoparietal prominence WM changes of a progressive nature. These findings are opposed to frontal and parieto-occipital prominence in Alexander disease and X-linked adrenoleukodystrophy, respectively.^{16,26} In addition, contrast enhancement may be seen in both disorders and was not seen in any of our patients. Brain stem lesions, rarely seen in WSS, are a frequent feature of Alexander disease.³⁰

Although considered atypical, WSS shares some characteristics with neurodegenerative diseases with brain iron accumulation (NBIA). NBIA are a group of inherited neurologic disorders with hallmark clinical manifestations of progressive dystonia and spasticity in the setting of brain iron deposition^{31,32} and are characterized by symmetric accelerated iron deposition involving the gray matter nuclei (globus pallidus, substantia nigra, red nucleus, dentate nucleus, putamen, and thalamus).¹⁴ Iron deposition in the globus pallidus and, later in the disease, in the substantia nigra was observed in some of our patients. This feature has been described in neuroaxonal dystrophy, a rare progressive form of NBIA.¹⁴ Evidence of iron deposition may precede or follow the development of clinical symptoms in some NBIA, a characteristic also seen in our cohort.³² In comparison with other NBIA, extrapyramidal features in WSS consist of focal or multisegmental and, in some

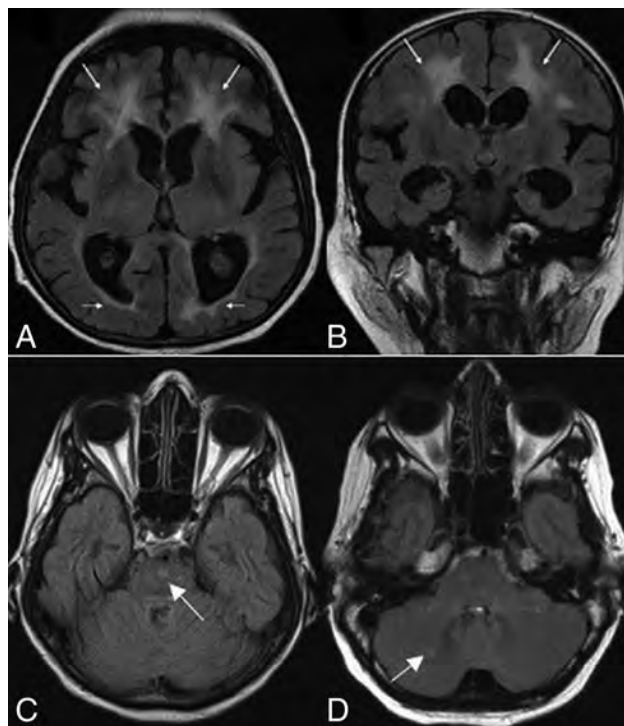


FIG 4. Axial (A) and coronal (B) FLAIR MR images for case 24 show white matter changes with frontal predominance (arrows). Axial FLAIR images show signal intensities (arrows) involving the pons (C) in patient 19 and the cerebellum (D) in patient 26.

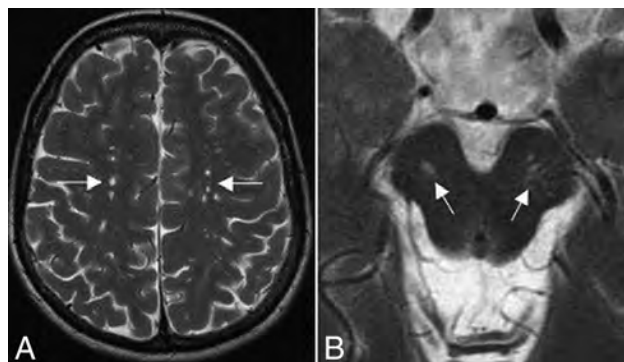


FIG 5. Axial T2 images show type I (A) and type III (B) prominent perivascular spaces.

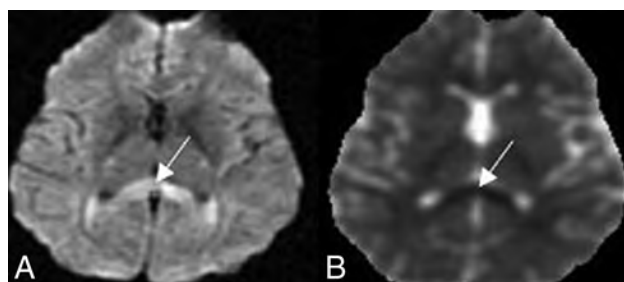


FIG 6. Axial DWI (A) and ADC map (B) sequences show diffusion restriction involving the splenium of corpus callosum.

patients, generalized dystonia.⁵ The presence of white matter changes and a small hypophysis in the setting of brain iron accumulation is a major distinction between WSS and other NBIA subtypes.

Interfamilial and intrafamilial phenotypic variability is a well-recognized feature of WSS.^{3,33} The spectrum of *DCAF17* gene mutations has expanded, with 9 mutations reported in the literature to date. When one considered all known variants, *DCAF17* was found to poorly correlate with the severity of the associated phenotypes.³ Our series revealed a similar discrepancy when correlating clinical features with neuroimaging findings. We found no correlation between iron deposition and neurologic involvement. Despite the clinical findings of generalized or focal dystonia, 3 patients showed no evidence of abnormal iron deposition on MR imaging.

Our study has several limitations. First, all participants were recruited at variable clinical stages of the disease. In addition, all follow-up studies were not systematically performed, with no specific time interval from the initial study. This feature would poorly characterize the rate of progression of the disease.

CONCLUSIONS

Small pituitary gland, accentuated iron deposition in the globus pallidus, and nonenhancing frontoparietal/periventricular WM changes are the most noted brain MR abnormalities in WSS. The presence of WM changes and pituitary involvement can further distinguish WSS from other NBIA subtypes. The progressive nature and variability of brain MR imaging findings that poorly correlate with the clinical characteristics, along with the lack of the underlying pathology, should be addressed in future studies.

ACKNOWLEDGMENTS

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REFERENCES

1. Woodhouse NJ, Sakati NA. A syndrome of hypogonadism, alopecia, diabetes mellitus, mental retardation, deafness, and ECG abnormalities. *J Med Genet* 1983;20:216–19 [CrossRef Medline](#)
2. Bohlega SA, Alkuraya FS. Woodhouse-Sakati syndrome. 2016 Aug 4. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*. <https://www.ncbi.nlm.nih.gov/books/NBK378974/>. Accessed May 16, 2018
3. Alazami AM, Schneider SA, Bonneau D, et al. C2orf37 mutational spectrum in Woodhouse-Sakati syndrome patients. *Clin Genet* 2010;78:585–90 [CrossRef Medline](#)
4. Al-Semari A, Bohlega S. Autosomal-recessive syndrome with alopecia, hypogonadism, progressive extra-pyramidal disorder, white matter disease, sensory neural deafness, diabetes mellitus, and low IGF1. *Am J Med Genet Part A* 2007;143A:149–160
5. Schneider SA, Bhatia KP. Dystonia in the Woodhouse Sakati syndrome: a new family and literature review. *Mov Disord* 2008;23:592–96 [CrossRef Medline](#)
6. Abdulla MC, Alazami AM, Alungal J, et al. Novel compound heterozygous frameshift mutations of C2orf37 in a familial Indian case of Woodhouse-Sakati syndrome. *J Genet* 2015;94:489–92 [CrossRef Medline](#)
7. Koshy G, Danda S, Thomas N, et al. Three siblings with Woodhouse-Sakati syndrome in an Indian family. *Clin Dysmorphol* 2008;17:57–60 [CrossRef Medline](#)
8. Habib R, Basit S, Khan S, et al. A novel splice site mutation in gene C2orf37 underlying Woodhouse-Sakati syndrome (WSS) in a consanguineous family of Pakistani origin. *Gene* 2011;490:26–31 [CrossRef Medline](#)
9. Hdiji O, Turki E, Bouzidi N, et al. Woodhouse-Sakati syndrome:

- report of the first Tunisian family with the C2orf37 gene mutation. *J Mov Disord* 2016;9:120–23 CrossRef Medline
10. Rachmiel M, Bistrizter T, Hershkoviz E, et al. **Woodhouse-Sakati syndrome in an Israeli-Arab family presenting with youth-onset diabetes mellitus and delayed puberty.** *Horm Res Paediatr* 2011;75:362–66 CrossRef Medline
 11. Steindl KL, Alazami AM, Bhatia KP, et al. **A novel C2orf37 mutation causes the first Italian cases of Woodhouse Sakati syndrome.** *Clin Genet* 2010;78:594–97 CrossRef Medline
 12. Alazami AM, Al-Saif A, Al-Semari A, et al. **Mutations in C2orf37, encoding a nucleolar protein, cause hypogonadism, alopecia, diabetes mellitus, mental retardation, and extrapyramidal syndrome.** *Am J Hum Genet* 2008;83:684–91 CrossRef Medline
 13. Agopiantz M, Corbonnois P, Sorlin A, et al. **Endocrine disorders in Woodhouse-Sakati syndrome: a systematic review of the literature.** *J Endocrinol Invest* 2014;37:1–7 CrossRef Medline
 14. Kruer MC, Boddart N, Schneider A, et al. **Neuroimaging features of neurodegeneration with brain iron accumulation.** *AJNR Am J Neuroradiol* 2012;33:407–14 CrossRef Medline
 15. Comella CL, Leurgans S, Wu J, et al; Dystonia Study Group. **Rating scales for dystonia: a multicenter assessment.** *Mov Disord* 2003;18:303–12 CrossRef Medline
 16. Schiffmann R, van der Knaap MS. **Invited article: an MRI-based approach to the diagnosis of white matter disorders.** *Neurology* 2009;72:750–59 CrossRef Medline
 17. McLachlan MS, Williams ED, Fortt RW, et al. **Estimation of pituitary gland dimensions from radiographs of the sella turcica: a post-mortem study.** *Br J Radiol* 1968;41:323–30 CrossRef Medline
 18. Doraiswamy PM, Potts JM, Axelson DA, et al. **MR assessment of pituitary gland morphology in healthy volunteers: age- and gender-related differences.** *AJNR Am J Neuroradiol* 1992;13:1295–99 Medline
 19. Kwee RM, Kwee TC. **Virchow-Robin spaces at MR imaging.** *Radiographics* 2007;27:1071–86 CrossRef Medline
 20. Murray RA, Maheshwari HG, Russell EJ, et al. **Pituitary hypoplasia in patients with a mutation in the growth hormone-releasing hormone receptor gene.** *AJNR Am J Neuroradiol* 2000;21:685–89 Medline
 21. Mehmood S, Hoggard N, Hadjivassiliou M. **Gordon Holmes syndrome: finally genotype meets phenotype.** *Pract Neurol* 2017;17:476–78 CrossRef Medline
 22. Synofzik M, Gonzalez MA, Lourenco CM, et al. **PNPLA6 mutations cause Boucher-Neuhauser and Gordon Holmes syndromes as part of a broad neurodegenerative spectrum.** *Brain* 2014;137:69–77 CrossRef Medline
 23. Salvador F, Garcia-Arúmi J, Corcóstequi B, et al. **Ophthalmologic findings in a patient with cerebellar ataxia, hypogonadotropic hypogonadism, and chorioretinal dystrophy.** *Am J Ophthalmol* 1995;120:241–44 CrossRef Medline
 24. Malhotra HS, Garg RK, Vidhate MR, et al. **Boomerang sign: clinical significance of transient lesion in splenium of corpus callosum.** *Ann Indian Acad Neurol* 2012;15:151–57 CrossRef Medline
 25. Bulakbasi N, Kocaoglu M, Tayfun C, et al. **Transient splenial lesion of the corpus callosum in clinically mild influenza-associated encephalitis/encephalopathy.** *AJNR Am J Neuroradiol* 2006;27:1983–86 Medline
 26. van der Knaap MS, Valk J, de Neeling N, et al. **Pattern recognition in magnetic resonance imaging of white matter disorders in children and young adults.** *Neuroradiology* 1991;33:478–93 CrossRef Medline
 27. Bobele GB, Garnica A, Schaefer GB, et al. **Neuroimaging findings in Alexander's disease.** *J Child Neurol* 1990;5:253–58 CrossRef Medline
 28. van der Knaap MS, Smit LM, Barth PG, et al. **Magnetic resonance imaging in classification of congenital muscular dystrophies with brain abnormalities.** *Ann Neurol* 1997;42:50–59 CrossRef Medline
 29. Schmähmann JD, Smith EE, Eichler FS, et al. **Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates.** *Ann N Y Acad Sci* 2008;1142:266–309 CrossRef Medline
 30. van der Knaap MS, Naidu S, Breiter SN, et al. **Alexander disease: diagnosis with MR imaging.** *AJNR Am J Neuroradiol* 2001;22:541–52 Medline
 31. Arber CE, Li A, Houlden H, et al. **Review: insights into molecular mechanisms of disease in neurodegeneration with brain iron accumulation—unifying theories.** *Neuropathol Appl Neurobiol* 2016;42:220–41 CrossRef Medline
 32. Hogarth P. **Neurodegeneration with brain iron accumulation: diagnosis and management.** *J Mov Disord* 2015;8:1–13 CrossRef Medline
 33. Almqdadi M, Kemppainen JL, Pichurin PN, et al. **Phenotypic variability of c.436delC DCAF17 gene mutation in Woodhouse-Sakati syndrome.** *Am J Case Rep* 2018;19:347–53 CrossRef Medline

Neuropsychiatric Lupus with Antibody-Mediated Striatal Encephalitis

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ABSTRACT

SUMMARY: Systemic lupus erythematosus is a chronic autoimmune disease characterized by the production of autoantibodies resulting in tissue injury across multiple organs; up to 50% of patients develop neurologic involvement, collectively referred to as neuropsychiatric systemic lupus erythematosus. The cases in this clinical report will highlight a subtype of neuropsychiatric systemic lupus erythematosus demonstrating imaging findings of striatal inflammation responsive to plasmapheresis similar to those in the subset of *N*-methyl-D-aspartate receptor autoimmune encephalitis that involves the striatum. Although the cause for this striking imaging appearance is not definitely known, literature will be presented supporting the hypothesis that it is due to peripheral anti-double-stranded DNA antibodies entering the central nervous system to cross-react with *N*-methyl-D-aspartate receptor antigens.

ABBREVIATIONS: ANA = antinuclear antibody; dsDNA = double-stranded DNA; NMDAr = *N*-methyl-D-aspartate receptor; NPSLE = neuropsychiatric systemic lupus erythematosus; SLE = systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disorder with an overall prevalence of 50 in 100,000 that most often affects women of child-bearing age and has an unpredictable clinical course characterized by periods of remission and acute flares.¹ Lupus can affect almost any organ system in the body but often has neuropsychiatric symptoms that still remain poorly understood despite being one of the most common manifestations of the disease.² The general term “neuropsychiatric systemic lupus erythematosus” (NPSLE) refers to any form of lupus with neuropsychiatric symptoms that are thought to be related to this systemic autoimmune condition.² NPSLE may be the first manifestation of SLE and can be seen in up to 50% of patients with lupus, but there is wide variation in the reported prevalence of NPSLE in lupus among adults (14%–80%) and children (22%–95%).^{2,3}

NPSLE has been associated with a number of specific autoantibodies, and while vascular complications of SLE resulting in acute ischemic stroke or dural venous sinus thrombosis are gen-

erally considered to have the closest association with antibodies related to antiphospholipid antibody syndrome,⁴ it remains unclear whether other antibody subtypes such as those targeting double-stranded DNA (dsDNA) or ribosomal P antigens are more closely associated with the development of NPSLE.^{1,2} Anti-dsDNA antibodies are an antinuclear antibody (ANA) subtype that targets antigens within the dsDNA and represent one of the most specific serum autoantibodies in SLE.^{3,5,6} Although not widely considered clinically, there is growing support in the literature for a form of autoimmune encephalitis in patients with lupus who present with neuropsychiatric symptoms caused by peripheral anti-dsDNA antibodies entering the central nervous system to cross-react with *N*-methyl-D-aspartate receptor (NMDAr) antigens.^{2,4-7} While certain aspects of this process remain unclear, such as whether peripheral dsDNA antibodies enter the CNS via the choroid plexus⁸ or by crossing a compromised blood-brain barrier,⁵ there is a consensus that on entering the CNS, cross-reactivity of anti-dsDNA antibodies with NMDAr antigens mediates a non-thrombotic and nonvasculitic pathology in NPSLE with features of neuronal excitotoxicity.⁴⁻⁸

Many of the functions of the striatum are facilitated by glutaminergic and dopaminergic input,⁹ and this may partially explain why anti-NMDAr and anti-dopamine D2 receptor antibodies are associated with this form of autoimmune encephalitis via targeting these antigens in the striatum.^{4,6,10} Anti-NMDAr encephalitis was the first form of autoimmune encephalitis described by Dalmau et al in 2007¹¹ and is now an established clinical diagnosis,

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Indicates article with supplemental on-line tables.



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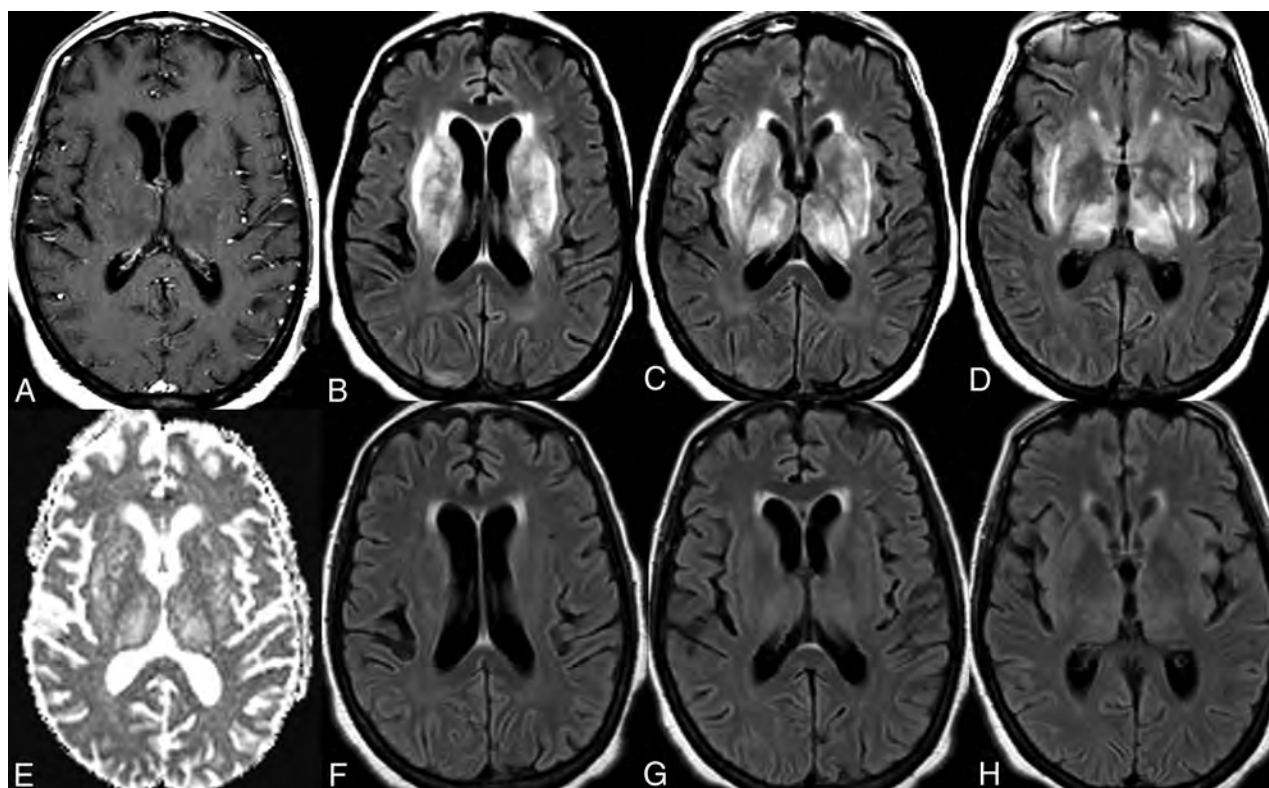


FIG 1. Neuropsychiatric lupus with antibody-mediated striatal encephalitis. A 68-year-old woman with a medical history of rheumatoid arthritis, systemic lupus erythematosus, type 2 diabetes mellitus, and hypertension presents with cognitive decline and generalized weakness. MR imaging of the brain demonstrates bilateral symmetric T2/FLAIR hyperintensity of the basal ganglia, thalami, and surrounding white matter (B–D) without restricted diffusion (E) or postcontrast enhancement (A). An IV steroid regimen was initiated but stopped due to gastrointestinal bleeding, and the patient received 5 rounds of plasmapheresis with a positive clinical response. Follow-up MR imaging of the brain demonstrates near-complete resolution of previous T2/FLAIR signal abnormality (F–H).

with subsequent discovery of many other antibodies responsible for various other forms of autoimmune encephalitis.^{10,12} Autoimmune encephalitis of the striatum is less common than other subtypes, only reported in 8% of anti-NMDAR cases in one of the largest studies conducted to date.¹³ Similarly, antibody-mediated inflammation of the striatum in SLE is also relatively uncommon, with basal ganglia involvement only reported in 7% of patients with lupus with neuropsychiatric symptoms.¹⁴

Antibody-mediated neuroinflammation often presents with nonspecific clinical features, which can lead to a delay in the diagnosis and treatment, but fortunately, these patients may respond favorably, in the absence of an underlying malignancy, to early intervention consisting of immunosuppression with pulse dose corticosteroids, plasmapheresis to remove the circulating antibodies, and long-term management with steroid-sparing monoclonal therapies capable of B-cell depletion such as rituximab.^{15–17} Antibody-mediated striatal inflammation in NPSLE is no exception and demonstrates similar clinical presentations, MRI findings, and early response to treatment as traditional autoimmune striatal encephalitis caused by anti-NMDAR antibodies.^{16,18,19}

This clinical report emphasizes the MR imaging brain findings and response to plasmapheresis in patients with SLE with antibody-mediated striatal encephalitis in the setting of anti-dsDNA antibodies. This retrospective study was approved by the institutional review board.

Case Series

Unless otherwise specified, all patients were afebrile and hemodynamically stable on presentation with a negative toxometabolic/infectious work-up, positive serum anti-dsDNA antibodies, and CSF analysis consistent with mild-to-moderate lymphocytic pleocytosis (defined as 10–100 white blood cells/ μ L and protein, 50–150 mg/dL).

Case 1

A 68-year-old woman with a medical history of rheumatoid arthritis, SLE, and type 2 diabetes mellitus presented with cognitive decline and generalized weakness. MR imaging of the brain demonstrated bilateral symmetric T2/FLAIR hyperintensity of the basal ganglia, thalami, and surrounding white matter without restricted diffusion or postcontrast enhancement (Fig 1A–E). An IV steroid regimen was attempted twice (methylprednisolone on both occasions) but was discontinued due to the complication of gastrointestinal bleeding. She was ultimately given the clinical diagnosis of autoimmune encephalitis and received 5 sessions of plasmapheresis with prompt clinical and radiologic improvement. Follow-up MR imaging of the brain demonstrated near-complete resolution of the previous T2/FLAIR signal abnormality (Fig 1F–H).

Case 2

A 20-year-old woman with a medical history of SLE presented with worsening headaches, anxiety, and cognitive impairment.

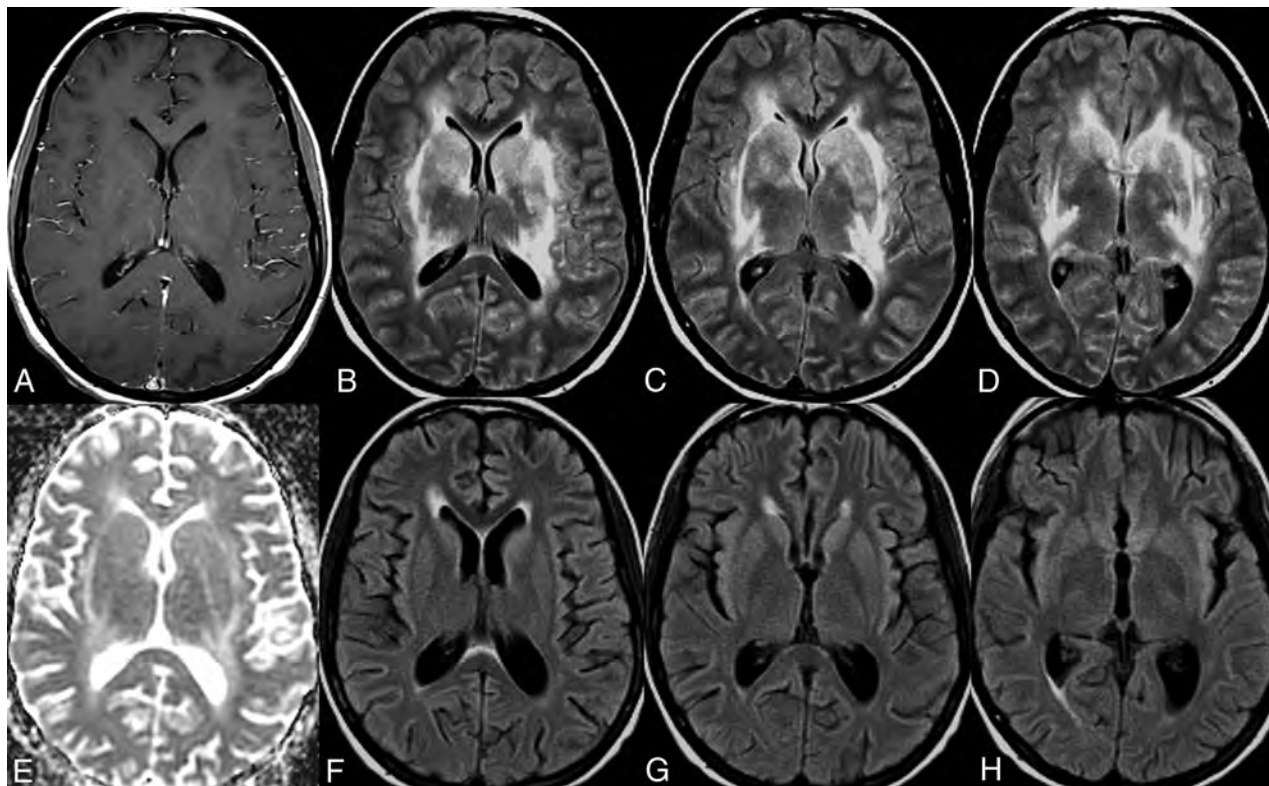


FIG 2. Neuropsychiatric lupus with antibody-mediated striatal encephalitis. A 20-year-old woman with a medical history of systemic lupus erythematosus, depression, and anxiety disorder presents with progressively worsening headaches, agitation, cognitive dysfunction, arthralgia, fever, and nausea. MR imaging of the brain demonstrates bilateral symmetric T2/FLAIR hyperintensity of the basal ganglia and surrounding white matter (B–D) without restricted diffusion (E) or postcontrast enhancement (A). The patient did not experience much improvement on oral or IV steroids but had a good clinical response to 6 sessions of plasmapheresis. Follow-up MR imaging of the brain demonstrates near-complete resolution of previous T2/FLAIR signal abnormality with interval development of generalized mild brain atrophy (F–H).

She was on levetiracetam and phenytoin after 1 episode of seizure that was thought to be secondary to lupus cerebritis. MR imaging brain examination demonstrated bilateral symmetric T2/FLAIR hyperintensity of the basal ganglia and surrounding white matter without restricted diffusion or postcontrast enhancement (Fig 2A–E). She did not experience much improvement on an oral/IV steroid regimen or cyclophosphamide infusion and experienced a breakthrough seizure during her inpatient work-up. She was ultimately given the clinical diagnosis of autoimmune encephalitis and received 6 rounds of plasmapheresis with clinical and radiologic improvement. Follow-up MR brain imaging demonstrated near-complete resolution of the previous T2/FLAIR signal abnormality with interval development of generalized mild brain atrophy (Fig 2F–H).

Case 3

A 24-year-old woman with a recent diagnosis of SLE presented with expressive aphasia and headaches. The MR imaging brain examination demonstrated bilateral symmetric T2/FLAIR hyperintensity of the caudate and, to a lesser degree, the lentiform nuclei, with patchy T2/FLAIR hyperintensity of the left greater-than-right thalami without restricted diffusion or postcontrast enhancement (Fig 3A–E). The patient experienced mild gradual improvement on IV steroid therapy with mild improvement in

T2/FLAIR signal abnormality on the 10-day follow-up MR imaging of the brain (Fig 3F–H).

Case 4

A 20-year-old man with a medical history of SLE and dilated cardiomyopathy presented with altered mental status. An MR imaging brain examination demonstrated diffuse cortical atrophy, bilateral symmetric T1 and T2/FLAIR hyperintensity of the basal ganglia, and scattered small foci of T2/FLAIR hyperintensity in the bilateral supratentorial white matter without restricted diffusion or suspicious postcontrast enhancement (Fig 4). The patient ultimately died of cardiac arrest. The postmortem examination revealed lupus-associated vasculitis in the small-caliber arteries of the brain with transmural infiltrates of polymorphonuclear inflammatory cells with areas of destruction of the elastic lamina and fibrosis of the intima and media. It was noted that the basal ganglia only demonstrated a few blood vessels with transmural inflammation but showed geographic areas of parenchymal necrosis with dystrophic calcification, infiltrates of foamy macrophages, gliosis, and rarefaction. Cortical neurons of the cerebrum, brain stem, and spinal cord were well-preserved and within normal limits.

Case 5

A 37-year-old man with a medical history of SLE presented to an outside hospital after a flulike episode with altered mental

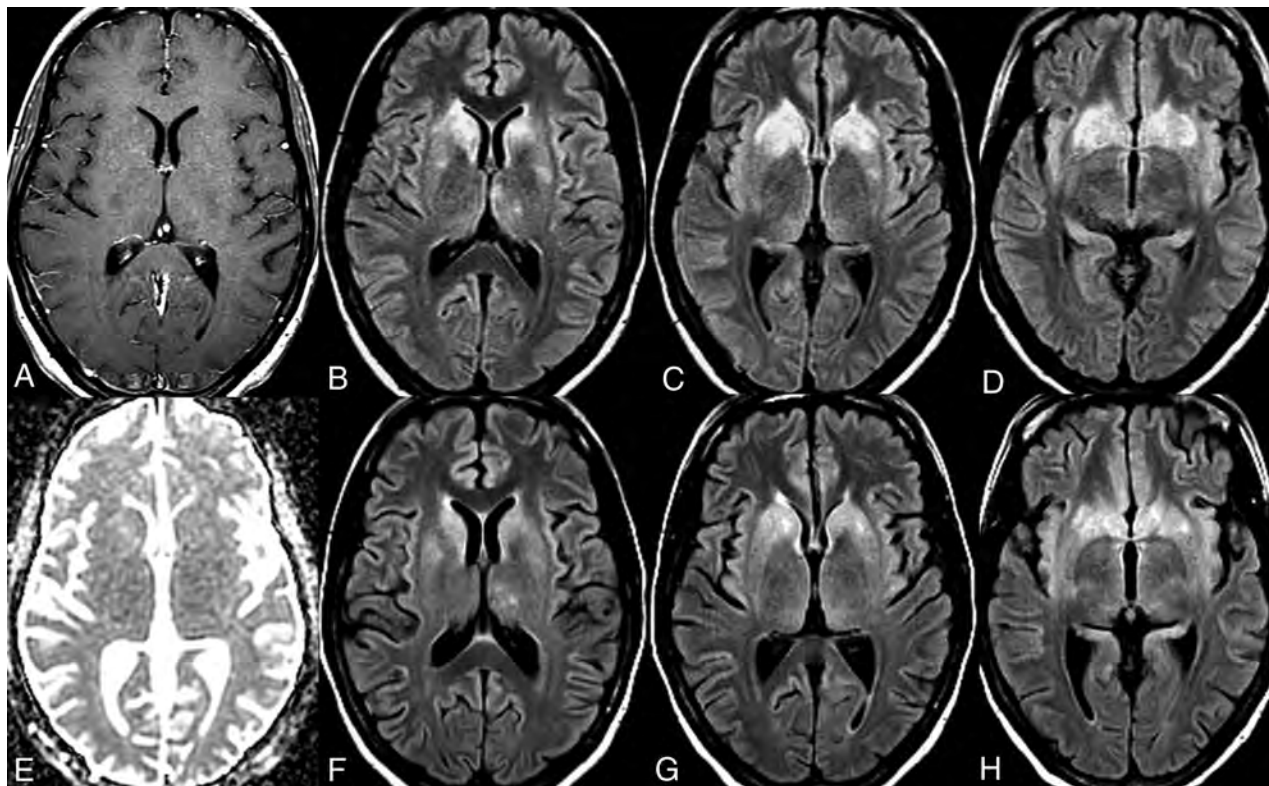


FIG 3. Neuropsychiatric lupus with antibody-mediated striatal encephalitis. A 24-year-old woman with a recent diagnosis of systemic lupus erythematosus on daily oral prednisone presents with discoid rash, aphthous oral ulcers, dysarthria, expressive aphasia, headaches, and vomiting. MR imaging of the brain demonstrates bilateral symmetric T2/FLAIR hyperintensity of the caudate and, to a lesser degree, the lentiform nuclei, with patchy T2/FLAIR hyperintensity of the left-greater-than-right thalami (*B–D*) without restricted diffusion (*E*) or postcontrast enhancement (*A*). The patient was treated with a 7-day course of IV steroid therapy without plasmapheresis and experienced mild gradual clinical improvement. Follow-up MR imaging of the brain demonstrates mild reduction in T2/FLAIR hyperintensity (*F–H*).

status, emesis, headaches, and dystonia, but he was transferred to our institution after development of refractory seizure and multisystem organ failure. An initial noncontrast MR imaging brain examination at the outside institution demonstrated extensive bilateral areas of restricted diffusion and T2/FLAIR hyperintensity throughout the supratentorial and infratentorial white matter with bilateral deep gray T2/FLAIR hyperintensity without restricted diffusion in the bilateral caudate, putamen, and thalamus (Fig 5*A–F*). Right frontal brain biopsy was also performed and revealed diffuse reactive astrocytosis with mild microglial activation, minimal perivascular lymphocytic infiltrates, and an unremarkable appearance of the parenchymal blood vessels of the cerebral cortex and white matter without features of spongiform encephalopathy or an infectious process. He was given the diagnosis of autoimmune lupus cerebritis with seizures and received 3 days of pulse dose IV steroids with prednisone taper. Serial MR imaging brain examinations during the 6-week inpatient admission demonstrated a progressive decrease in the T2/FLAIR signal abnormality. Outpatient 3-month follow-up MR imaging of the brain demonstrated decreased T2/FLAIR hyperintensity but interval development of prominent atrophy and intrinsic T1 hyperintensity in regions of previous signal abnormality (Fig 5*G*). His clinical follow-up was consistent with improved inflammation but severe chronic morbidity after this monophasic episode.

Companion Case (Anti-NMDAR Encephalitis)

A 38-year-old man presented with progressively worsening cognitive impairment, orofacial dyskinesia, and bilateral upper extremity chorea. MR imaging of the brain demonstrated bilateral symmetric T2/FLAIR hyperintensity of the dorsal striatum (caudate and lentiform nucleus) without restricted diffusion or postcontrast enhancement (Fig 6*A–C* and *E*). The autoimmune work-up was extensive but was initially negative for serum autoantibodies, including anti-dsDNA antibodies. He underwent a 3-day pulse IV steroid regimen with prednisone taper that resulted in gradual symptom improvement during 2–3 weeks but with persistent striatal T2/FLAIR abnormalities on the follow-up MR imaging of the brain, which also demonstrated interval development of some intrinsic T1 hyperintensity in the left striatum (Fig 6*D*). He was initially transferred to subacute rehabilitation but was readmitted for plasmapheresis when serum antibody testing was positive for anti-NMDAR antibodies. He completed 5 rounds of plasmapheresis with a good response. Follow-up MR imaging of the brain demonstrated reduced T2/FLAIR signal abnormality with atrophy of the caudate heads and persistent left striatal T1 hyperintensity (Fig 6*H*). Note that this patient did not have SLE or anti-dsDNA antibodies but instead had positive NMDAR antibodies with a similar therapeutic response to a treatment regimen tailored for autoimmune encephalitis.

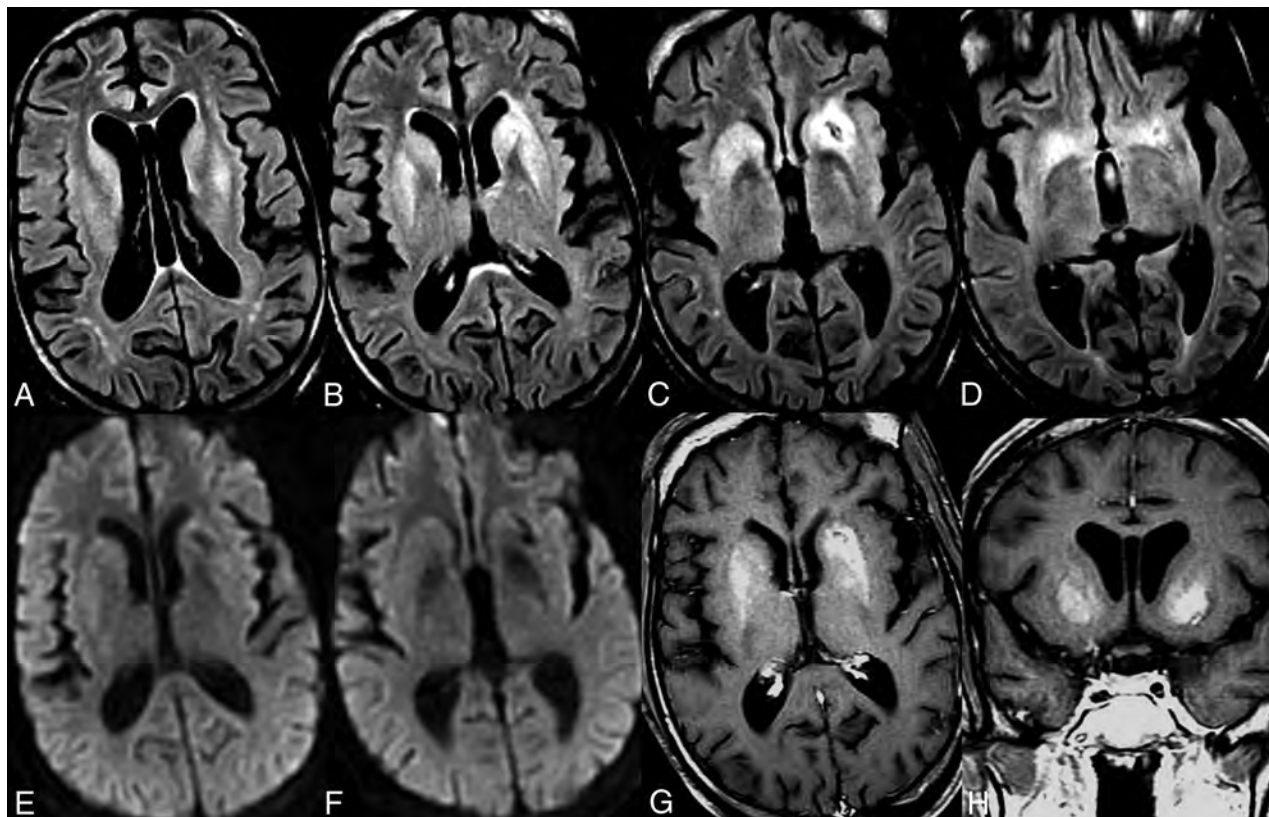


FIG 4. Neuropsychiatric lupus with antibody-mediated striatal encephalitis. A 20-year-old man with a medical history of systemic lupus erythematosus, paroxysmal atrial fibrillation, and dilated cardiomyopathy presents with altered mental status. MR imaging of the brain demonstrates advanced generalized brain atrophy with scattered bilateral frontoparietal T2/FLAIR white matter hyperintensities (A and B) and bilateral symmetric striatal abnormalities characterized by T2/FLAIR hyperintensity (A–D) and T1 hyperintensity (G and H) without postcontrast enhancement or restricted diffusion but blooming artifacts in the left striatum from hemosiderin deposition (E and F). The patient developed refractory heart failure and ultimately died of cardiac arrest. Note the intrinsic basal ganglionic T1 hyperintensity correlated with coagulative necrosis on brain postmortem examination.

DISCUSSION

All forms of antibody-mediated disease can be defined at the most basic level by a loss of tolerance to self that results in immune-mediated inflammation of target tissues.^{6,10,20} In patients with SLE, the loss of immune tolerance to autoantigens within the body stimulates the clonal expansion of selective B-cell populations that produce specific autoantibodies that are released into the circulation to eventually bind to their target and initiate an inflammatory immune response, which often has features of immune complex deposition, complement activation, inflammatory cytokine production, or local recruitment of macrophages.^{2,4} Despite the diversity of brain pathology that can occur in lupus, which is reflected in the wide range of MR imaging findings,¹⁴ the presence of bilateral symmetric T2/FLAIR hyperintense signal changes within the caudate and putamen without evidence of restricted diffusion or postcontrast enhancement represents a unique neuroimaging pattern that, in the appropriate clinical setting, is highly suggestive of autoimmune encephalitis of the striatum. Note also that in some of the presented cases, particularly those with the worst outcomes, intrinsic T1 hyperintensity was also seen within the basal ganglia, perhaps reflecting the development of coagulative necrosis in the setting of prolonged antibody-mediated inflammation and excitatory glutamate neurotoxicity, suggesting that this finding may represent a poor prognostic feature (Figs 4–6).

While it is clear that prompt diagnosis and treatment of autoimmune encephalitis is associated with improved clinical outcomes, establishing the diagnosis first requires exclusion of many more common causes of altered mental status, such as stroke, intracranial hemorrhage, trauma, infection, or toxometabolic encephalopathy.^{15,20} Neuroimaging plays an important role in this diagnostic work-up, and characteristic MR imaging brain findings of bilateral symmetric T2/FLAIR hyperintense signal changes within the caudate and putamen without restricted diffusion or postcontrast enhancement may be the first indication that autoimmune striatal encephalitis should be considered.^{10,19,21} Please see On-line Table 1 and On-line Figs 1–6 for a comprehensive list of diagnostic considerations in the setting of bilateral symmetric T2/FLAIR hyperintense signal changes within the caudate and putamen,^{22,23} as well as On-line Table 2 for suggested clinical and laboratory tests in patients with suspected autoimmune striatal encephalitis.^{15,20}

Maximizing clinical outcomes in these patients requires a multidisciplinary approach that relies on a combination of clinical, laboratory, and imaging data. The neuroimaging findings in these patients are quite striking, and though they are nonspecific, many of the other etiologies on the differential diagnosis can be excluded during the diagnostic work-up. Similar to autoimmune encephalitis, it is important to emphasize that positive antibody testing within serum or cerebrospinal

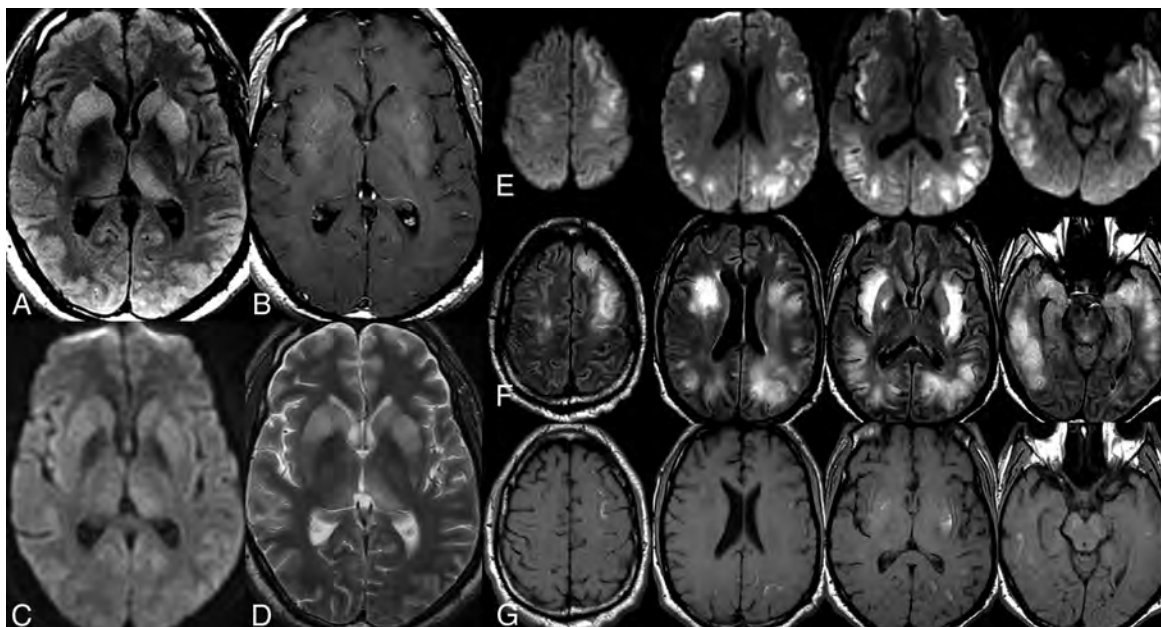


FIG 5. Neuropsychiatric lupus with antibody-mediated striatal encephalitis. A 37-year-old man develops encephalopathy and refractory seizures following flulike symptoms with subsequent development of multisystem organ failure. MR imaging of the brain demonstrates a diffuse extensive burden of restricted diffusion (E) and T2/FLAIR hyperintensity (F) in the supratentorial white matter with deep gray T2/FLAIR hyperintensity (A and D) without restricted diffusion (C) in the bilateral caudate, putamen, and thalami. The patient received supportive care in the intensive care unit with a 3-day course of IV steroids and prednisone taper without seizure recurrence. Serial MR imaging brain examinations demonstrated gradual resolution of restricted diffusion with a mild progressive decrease in both gray and white matter T2/FLAIR hyperintensity (not shown) but with progressive development of intrinsic T1 hyperintensity within the subcortical white matter (G) and basal ganglia (B), consistent with coagulative necrosis.

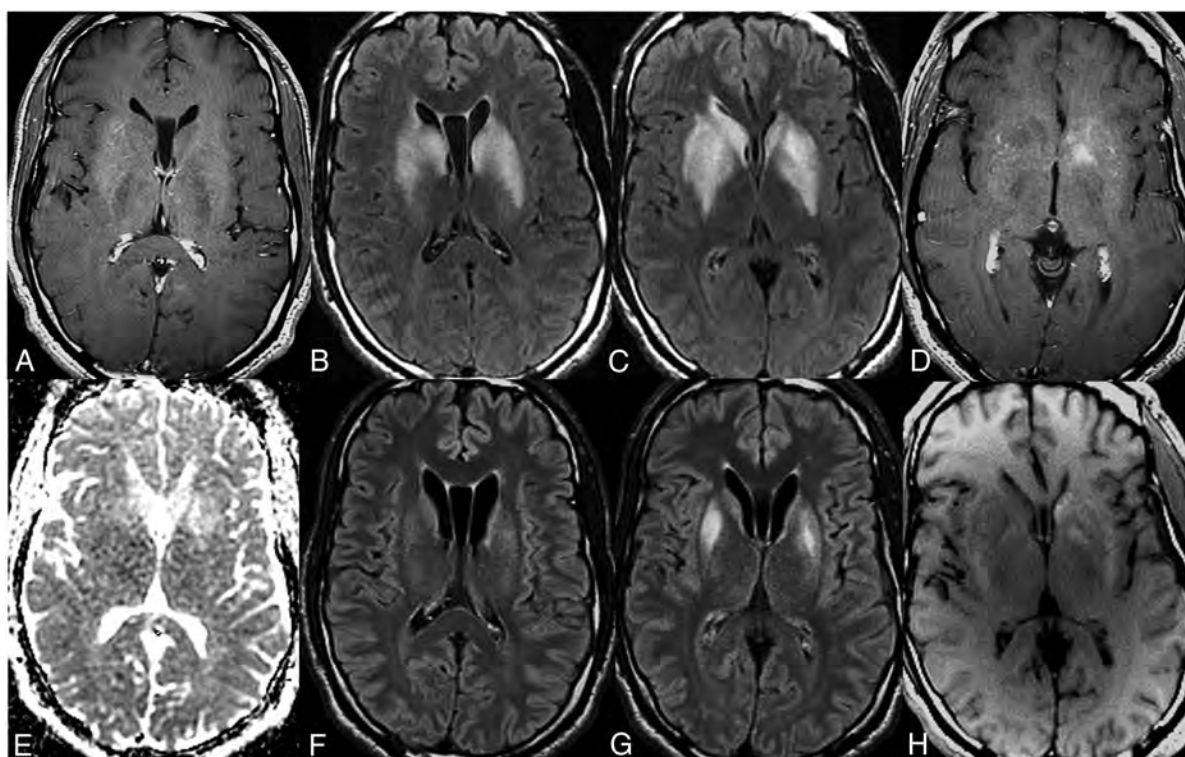


FIG 6. Anti-N-methyl-D-aspartate receptor striatal encephalitis. A 38-year-old man presents with progressively worsening cognitive decline, orofacial dyskinesia, and bilateral upper extremity chorea. MR imaging of the brain demonstrates bilateral symmetric T2/FLAIR hyperintensity of the dorsal striatum (caudate and lentiform nucleus) (B and C) without restricted diffusion (E) or postcontrast enhancement (A). The patient was treated with 3-day IV pulse steroids and 5 rounds of plasmapheresis with a positive clinical response. Follow-up MR imaging of the brain demonstrates reduced T2/FLAIR signal abnormality with atrophy of the caudate heads (F and G). Note the development of intrinsic T1 hyperintensity consistent with coagulative necrosis in the left striatum (D), which persists on follow-up (H).

fluid is not sufficient alone to establish a particular diagnosis.^{10,20} Antinuclear antibodies such as anti-dsDNA are seen in most patients with SLE and may exist in the absence of neuropsychiatric symptoms.^{1,24} The nonspecific nature of these circulating antibodies is further emphasized by studies demonstrating that various autoantibodies associated with lupus and autoimmune encephalitis have even been reported in asymptomatic, healthy volunteers.^{17,24} The significance of these antibodies in the absence of disease remains unclear, but the identification of specific circulating antibodies in the appropriate clinical context can support the diagnosis and subsequent treatment of an antibody-mediated disorder in patients with unexplained neurologic dysfunction.^{17,20}

CONCLUSIONS

Antibody-mediated diseases are complex and can occur anywhere in the body where the immune system is able to gain access to a target antigen. We believe that striatal-predominant CNS involvement of lupus may represent an under-recognized entity in the general category of NPSLE with features of autoimmune encephalitis, which include similar MR imaging findings and a similar therapeutic response to early plasmapheresis. The characteristic MRI findings of bilateral symmetric basal ganglionic T2/FLAIR hyperintensity without restricted diffusion or postcontrast enhancement are quite striking, and although these imaging findings are non-specific, many of the other possible etiologies can be excluded during the diagnostic workup. Neuroimaging has 4 important roles in this setting: excluding more common etiologies, demonstrating findings consistent with an underlying autoimmune process, monitoring the response to therapy (ie, reduction in T2/FLAIR hyperintensity), and identifying complications of the disease (ie, brain atrophy or intrinsic basal ganglionic T1 hyperintensity, possibly reflecting coagulative necrosis) that will impact the long-term prognosis after an episode of antibody-mediated neuroinflammation. Radiologists can have a tremendous impact if they are familiar with and recognize these kinds of antibody-mediated diseases in their practice.

REFERENCES

- Borchers AT, Naguwa SM, Shoenfeld Y, et al. **The geoepidemiology of systemic lupus erythematosus.** *Autoimmun Rev* 2010;9:A277–87 CrossRef Medline
- Popescu A, Kao AH. **Neuropsychiatric systemic lupus erythematosus.** *Curr Neuroparmacol* 2011;9:449–57 CrossRef Medline
- Kivity S, Agmon-Levin N, Zandman-Goddard G, et al. **Neuropsychiatric lupus: a mosaic of clinical presentations.** *BMC Med* 2015;13:43 CrossRef Medline
- Gerosa M, Poletti B, Pregnotato F, et al. **Antiglutamate receptor antibodies and cognitive impairment in primary antiphospholipid syndrome and systemic lupus erythematosus.** *Front Immunol* 2016;7:5 CrossRef Medline
- Kowal C, Degiorgio LA, Lee JY, et al. **Human lupus autoantibodies against NMDA receptors mediate cognitive impairment.** *Proc Natl Acad Sci U S A* 2006;103:19854–59 CrossRef Medline
- Brimberg L, Mader S, Fujieda Y, et al. **Antibodies as mediators of brain pathology.** *Trends Immunol* 2015;36:709–24 CrossRef Medline
- DeGiorgio LA, Konstantinov KN, Lee SC, et al. **A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus.** *Nat Med* 2001;7:1189–93 CrossRef Medline
- Gelb S, Stock AD, Anzi S, et al. **Mechanisms of neuropsychiatric lupus: the relative roles of the blood-cerebrospinal fluid barrier versus blood-brain barrier.** *J Autoimmun* 2018;91:34–44 CrossRef Medline
- Küppenbender KD, Standaert DG, Feuerstein TJ, et al. **Expression of NMDA receptor subunit mRNAs in neurochemically identified projection and interneurons in the human striatum.** *J Comp Neurol* 2000;419:407–21 CrossRef Medline
- Dalmau J, Graus F. **Antibody-mediated encephalitis.** *N Engl J Med* 2018;378:840–51 CrossRef Medline
- Dalmau J, Tüzün E, Wu HY, et al. **Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma.** *Ann Neurol* 2007;61:25–36 CrossRef Medline
- Kelley BP, Patel SC, Marin HL, et al. **Autoimmune encephalitis: pathophysiology and imaging review of an overlooked diagnosis.** *AJNR Am J Neuroradiol* 2017;38:1070–78 CrossRef Medline
- Dalmau J, Gleichman AJ, Hughes EG, et al. **Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies.** *Lancet Neurol* 2008;7:1091–98 CrossRef Medline
- Luyendijk J, Steens SC, Ouwendijk WJ, et al. **Neuropsychiatric systemic lupus erythematosus: lessons learned from magnetic resonance imaging.** *Arthritis Rheum* 2011;63:722–32 CrossRef Medline
- Rubin DB, Batra A, Vaitkevicius H, et al. **Autoimmune neurologic disorders.** *Am J Med* 2018;131:226–36 CrossRef Medline
- Lee WJ, Lee ST, Byun JI, et al. **Rituximab treatment for autoimmune limbic encephalitis in an institutional cohort.** *Neurology* 2016;86:1683–91 CrossRef Medline
- Lancaster E. **The diagnosis and treatment of autoimmune encephalitis.** *J Clin Neurol* 2016;12:1–13 CrossRef Medline
- Ramos-Casals M, Soto MJ, Cuadrado MJ, et al. **Rituximab in systemic lupus erythematosus: a systematic review of off-label use in 188 cases.** *Lupus* 2009;18:767–76 CrossRef Medline
- Tobin WO, Strand EA, Clark HM, et al. **NMDA receptor encephalitis causing reversible caudate changes on MRI and PET imaging.** *Neurol Clin Pract* 2014;4:470–73 CrossRef Medline
- Graus F, Titulaer MJ, Balu R, et al. **A clinical approach to diagnosis of autoimmune encephalitis.** *Lancet Neurol* 2016;15:391–404 CrossRef Medline
- Dale RC, Church AJ, Surtees RA, et al. **Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity.** *Brain* 2004;127:21–33 CrossRef Medline
- Brami-Zylberberg F, Méary E, Oppenheim C, et al. **Abnormalities of the basal ganglia and thalami in adults [in French].** *J Radiol* 2005;86:281–93 CrossRef Medline
- Anderson JC, Costantino MM, Stratford T. **Basal ganglia: anatomy, pathology, and imaging characteristics.** *Curr Probl Diagn Radiol* 2004;33:28–41 CrossRef Medline
- Menon S, Jameson-Shortall E, Newman SP, et al. **A longitudinal study of anticardiolipin antibody levels and cognitive functioning in systemic lupus erythematosus.** *Arthritis Rheum* 1999;42:735–41 CrossRef Medline

Pipeline Diameter Significantly Impacts the Long-Term Fate of Jailed Side Branches during Treatment of Intracranial Aneurysms

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ABSTRACT

BACKGROUND AND PURPOSE: Although covered side branches typically remain patent acutely following Pipeline Embolization Device embolization of intracranial aneurysms, the long-term fate of these vessels remains uncertain. We therefore elected to investigate factors that may influence the long-term patency of these covered side branches.

MATERIALS AND METHODS: We retrospectively evaluated the long-term patency of side branches covered by the Pipeline Embolization Device at our institution during treatment of intracranial aneurysms with at least 6 months of conventional angiography follow-up. Procedural and anatomic factors that might influence the fate of covered side branches were explored.

RESULTS: One hundred forty-eight Pipeline Embolization Device treatments in 137 patients met the inclusion criteria. In 217 covered side branches, 29 (13.4%) were occluded on follow-up, and 40 (18.4%) were stenotic. All stenoses and occlusions were asymptomatic. In the entire cohort and in the largest subset of ophthalmic arteries, a smaller Pipeline Embolization Device diameter was associated with branch vessel occlusion ($P = .001$, $P = .013$). When we considered stenotic and occluded side branches together, smaller Pipeline Embolization Device size ($P = .029$) and administration of intraprocedural abciximab ($P = .03$) predicted side branch stenosis/occlusion, while anterior choroidal branch type ($P = .003$) was a predictor of gross side branch patency.

CONCLUSIONS: A smaller Pipeline Embolization Device diameter is associated with delayed side branch stenosis/occlusion following Pipeline Embolization Device treatment, likely due to the higher metal density of smaller caliber devices. Although hemodynamic factors, including the potential for collateral flow, are still paramount in determining the fate of covered side branches, the amount of metal coverage at the side branch orifice also plays an important role.

ABBREVIATION: PED = Pipeline Embolization Device

Flow diversion using the Pipeline Embolization Device (PED; Covidien, Irvine, California) is an effective treatment for intracranial aneurysms.¹⁻⁵ Although originally indicated for large/giant wide-neck aneurysms arising from the internal carotid artery proximal to the posterior communicating artery origin, flow diversion is increasingly used for the treatment of smaller aneurysms and those arising from more distal vessels and the posterior circulation.⁶⁻⁹ The PED was designed to allow progressive thrombosis and remodeling of cerebral aneurysms while preserving flow in arterial side branches covered by the device. Although most covered side branches have been shown to remain patent acutely

following PED deployment, the long-term fate of these vessels remains uncertain. Prior reports have noted varying rates of delayed branch vessel occlusion following treatment with the PED, and the factors that determine long-term patency are unclear.¹⁰⁻¹⁴

We therefore elected to retrospectively evaluate the long-term patency of arterial side branches covered by the PED at our institution during the treatment of intracranial aneurysms. Procedural and anatomic factors that may influence the fate of covered side branches were explored.

MATERIALS AND METHODS

The protocol of this retrospective study was approved by the University of Maryland, Baltimore, institutional review board (HP-00077364). From a prospectively maintained clinical data base, we retrospectively identified all intracranial aneurysm treatments using the PED at our institution in which there was device coverage of ≥ 1 arterial side branch and the patient had undergone at least 1 follow-up catheter angiogram ≥ 6 months follow-

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ing flow-diverter placement. Information in the clinical data base was obtained from multiple sources. Patient demographics, clinical outcomes, and procedural details were acquired from procedure reports and the electronic medical record. Aneurysm and parent vessel characteristics and imaging follow-up of lesions, covered side branches, and parent vessels were obtained by review of the relevant catheter angiograms as detailed below.

Factors specifically evaluated for impact on branch vessel patency rates included the following: patient age, sex, rupture status, prior aneurysm treatment, procedure time, fluoroscopy time, number of PEDs deployed, use of a J-tip microwire or balloon angioplasty to achieve adequate device apposition, the use of the first-versus-second generation PED, maximum aneurysm sac size, aneurysm neck size, minimum and maximum parent vessel diameter, differences in the size of PEDs deployed, the minimum and maximum parent vessel diameters, branch vessel incorporation into the aneurysm sac, degree of periprocedural platelet inhibition as measured by the VerifyNow P2Y12 assay (Accumetrics, San Diego, California), intraprocedural administration of abciximab for intraprocedural platelet aggregation, the development of endothelial hyperplasia resulting in the PED construct on follow-up, length of DSA follow-up, and type of covered branch vessel. Patient-specific variables, such as smoking status or history of hypertension, were not included in the analysis because these data points were not collected in the prospective data base. Variables obtained by review of follow-up imaging, such as branch vessel stenosis/occlusion or the presence of endothelial hyperplasia, were evaluated only on the most recent catheter angiograms.

All relevant catheter angiograms were reviewed by at least 2 team members (T.R.M., M.J.K., E.J.L., S.J., G.C., G.J., D.G.), with any discrepancies in measurements obtained adjudicated by 2 attending neurointerventionalists (T.R.M., D.G.) with 6 and 13 years of experience. Aneurysm sac and neck sizes were measured on relevant 2D and 3D rotational catheter angiograms. In most instances, minimal and maximal parent vessel diameters were obtained from measurements made during PED treatment on magnified 2D angiography "working angle" views of the PED landing site and sent to the PACS. Multiple measurements were typically acquired by the treating interventionalist to ensure appropriate device sizing, including at the proximal and distal device landing sites. These measurements were often verified by inspection of the source imaging of 3D rotational angiography, which provides a cross-sectional view of the parent vessel. In instances in which intraprocedural measurements were not stored on the PACS, they were acquired by at least 2 members independently using all relevant imaging sources (at a minimum, the magnified 2D working angle angiography views and 3D rotational angiography source images). Then, the adequacy of device apposition was determined intraprocedurally by the treating neurointerventionalist by review of 2D rotational angiography imaging performed after device deployment. Occasionally, flat panel CT was performed to confirm the adequacy of device apposition. Finally, the degree of intimal hyperplasia on follow-up imaging was determined by measuring the gap between the PED and the patent vessel lumen on magnified 2D conventional angiography (best appreciated on nonsubtracted, native views).

Treatment Protocol

Treatment was performed by 1 of 3 neurointerventional radiologists (D.G., G.J., T.R.M.) at a single medical center using general endotracheal anesthesia. A dual antiplatelet regimen of aspirin and clopidogrel was initiated 2–4 weeks before treatment, with subsequent titration of clopidogrel dosing based on platelet inhibition testing using the P2Y12 assay (target range, 60–200 P2Y12 reaction units). Access was obtained using a triaxial system, beginning with placement of a 6F–7F shuttle sheath into the target cervical vessel. This was followed by navigation of an intermediate guide catheter, such as a 058 Navien distal intracranial support catheter (Covidien), through the shuttle to the skull base. Finally, through the intermediate catheter, PED deployment was performed using an 0.027 microcatheter such as the Marksman or Phenom (Covidien).

Placement of 1 PED was generally considered sufficient for aneurysm treatment in most cases, with deployment of multiple devices reserved primarily for instances of incomplete lesion coverage with the first device. Adjunctive coiling was used in cases in which the target lesion demonstrated high-risk features (eg, recent growth, irregular morphology) or if the risk of delayed rupture was thought to be significant (lesion size, ≥ 13 mm). Inadequate apposition of the PED with the parent vessel wall was treated with either a J-tip microwire and/or balloon angioplasty using a compliant balloon. Delayed angiography of the parent vessel was performed 10–15 minutes following PED placement to evaluate platelet aggregation, which, if present, was treated with abciximab. Postprocedure, patients were closely monitored overnight in an intensive care level unit and discharged after 1–2 days of postoperative observation.

Follow-Up Protocol

All patients were evaluated in our neurointerventional clinic 1–3 weeks following treatment. Dual antiplatelet therapy was continued for at least 6 months following the procedure, with continued adjustment of clopidogrel dosing based on the results of platelet inhibition testing (again, with a goal of 60–200 P2Y12 reaction units). Initial imaging follow-up of the treatment site was typically performed at 3 months using either MR imaging or CT angiography. If there were no clinical or imaging concerns, follow-up conventional angiography was then performed 6–12 months post-PED deployment. More long-term follow-up of the treatment site varied on the basis of the status of the target aneurysm and parent vessel, as well as the presence of additional intracranial aneurysms. However, most patients underwent additional follow-up imaging at 18–36 months.

Statistical Analysis

Data are presented as mean and range for continuous variables and frequency for categorical variables. Univariate analysis was performed using unpaired *t* tests and χ^2 tests as appropriate. Factors predictive in univariate analysis ($P \leq .1$) were then evaluated by multivariate regression analysis. To account for repeat measurements, we used a generalized estimating equation, centered on patients, with a logistic regression model and an exchangeable correlation matrix. *P* values $< .05$ were considered statistically

Table 1: Cohort demographics

Demographics	
No. of patients	137
No. of PED treatments	148
Average patient age (yr)	54.7
% Male per treatment	6.6%
No. of aneurysms treated	178
Average aneurysm size (mm)	5.2
% Aneurysms treated acutely/subacutely after rupture	3.3%
% Aneurysms with branch vessel incorporation	35%
Mean No. of PEDs per treatment	1.07
% Aneurysms adjunctively coiled	9.2%
% Treatments using J-tip microcatheter	17%
% Treatments using balloon angioplasty	6.1%
% Treatments requiring abciximab	4.8%
Mean length of DSA follow-up (mo)	18.4

significant. Statistical analysis was performed using STATA, Version 12.0 (StataCorp, College Station, Texas).

Receiver operating characteristic analysis was performed for continuous variables significantly associated with branch vessel occlusion in multivariate analysis. The receiver operating characteristic curves were plotted, and area under the curve values for relevant parameters were calculated and compared. Thresholds for optimal sensitivity and specificity were also calculated for relevant parameters.

RESULTS

Two hundred forty-two intracranial aneurysm treatments in 196 patients were performed at our institution using the PED from November 2011 to the time of data acquisition in October 2017. Of these, 148 PED treatments in 137 patients met the inclusion criteria. Twenty-nine cases were excluded due to a lack of covered side branches, while 65 were excluded due to insufficient follow-up (Table 1). Ten patients underwent 2 PED treatments of aneurysms located at different sites, while 3 patients underwent placement of a second PED 2–3 years after their initial treatment due to persistence of the target aneurysm. In these instances, follow-up of the first PED was considered to end at the time of placement of the second device.

A total of 178 intracranial aneurysms were treated in the cohort, with an average maximum sac diameter of 5.2 mm (range, 1–21 mm) and average neck width of 3.3 mm (range, 1–11 mm). Thirty-nine aneurysms had been previously treated by coil embolization (22%), while 3 had undergone prior microsurgical clipping. Five aneurysms in the cohort were treated in the acute-to-subacute period range: few days to one week following rupture because they were not amenable to more traditional treatment methods such as coil embolization or microsurgical repair. Finally, a branch artery was incorporated into the neck or body of 61 treated aneurysms (34%).

Most patients were treated with a single PED (average, 1.07 PEDs per treatment), with only 8 cases using 2 devices and a single case using 3 PEDs. Aneurysm neck coverage was complete in all cases except 1 in which a PED migrated into the distal M1 segment of the middle cerebral artery ipsilateral to the target paraclinoid internal carotid artery aneurysms. The patient subsequently underwent successful placement of a second PED for the paraclinoid lesions at a later date. Sixteen aneurysms were adjunctively coiled

Table 2: Branch vessel outcomes by type

Type	No.	Patent	Stenotic	Occluded
Ophthalmic artery	125	72%	22%	5.8%
PcomA	39	56.7%	10%	33.3%
Anterior choroidal artery	31	96.8%	0%	3.2%
A1 arterial segment	11	28%	36%	36%
PICA	3	33.4%	66.6%	0%
AcomA	3	33.4%	0%	66.6%
Other ^a	5	80%	0%	20%

Note:—PcomA indicates posterior communicating artery; AcomA, anterior communicating artery.

^a Detailed in Results section.

at the time of PED placement (9% of treated lesions in the cohort). In 25 instances, a J-tip microwire was used to improve apposition of the device with the parent vessel wall (17% of PED treatments), while a balloon catheter was necessary in 9 cases (6.1%). Finally, abciximab was administered in 7 cases (4.7% of treatments) due to signs of early platelet aggregation.

The mean length of conventional angiography follow-up in the cohort was 18.4 months (range, 6–61 months). However, the total length of imaging and clinical follow-up for most patients was significantly longer when including MR imaging and CT angiography of the treatment site. One hundred thirty-two aneurysms (74.2%) were completely occluded at the last imaging follow-up (DSA, CTA, or MRA), while 36 lesions were incompletely occluded.

Complications in the cohort included 4 instances of periprocedural ischemic events with resulting changes in contralateral strength and/or sensory findings that subsequently resolved, 1 small occipital intraparenchymal hematoma following treatment of a paraophthalmic aneurysm that resulted in a permanent quadrantsia, 2 retroperitoneal hematomas, and 1 instance of catheter-induced dissection of a cervical internal carotid artery during treatment of a paraclinoid aneurysm that healed without consequence. Delayed complications included 1 patient who developed a transient small area of edema and petechial hemorrhage without associated symptoms in the ipsilateral parieto-occipital lobes 2 months following PED treatment of a right paraophthalmic aneurysm. The abnormality resolved on follow-up without treatment. Finally, 1 patient treated for a giant posterior communicating artery aneurysm that recurred after coiling developed worsening contralateral arm and leg weakness due to mass effect after the lesion failed to close with the PED. The patient eventually died from the associated mass effect and edema 21 months after PED treatment. The overall rate of permanent neurologic morbidity and mortality in the cohort was 1.5% and 0.7%.

In total, there were 217 covered side branches in the cohort (Table 2), most of which were in the anterior circulation (98.2%). Covered side branches included 125 ophthalmic arteries, 39 posterior communicating arteries, 31 anterior choroidal arteries, 11 A1 anterior cerebral artery segments, 3 posterior inferior cerebellar arteries, 3 anterior communicating arteries, 1 M2 middle cerebral artery branch, 1 P3 posterior cerebral artery branch, 1 lenticulostriate perforator, and 2 anterior temporal arteries arising from the M1 middle cerebral artery segment (Table 2). Of the covered 39 posterior communicating arteries, 8 were of a fetal configuration.

Of 217 covered side branches, 29 (13.4%) were occluded on

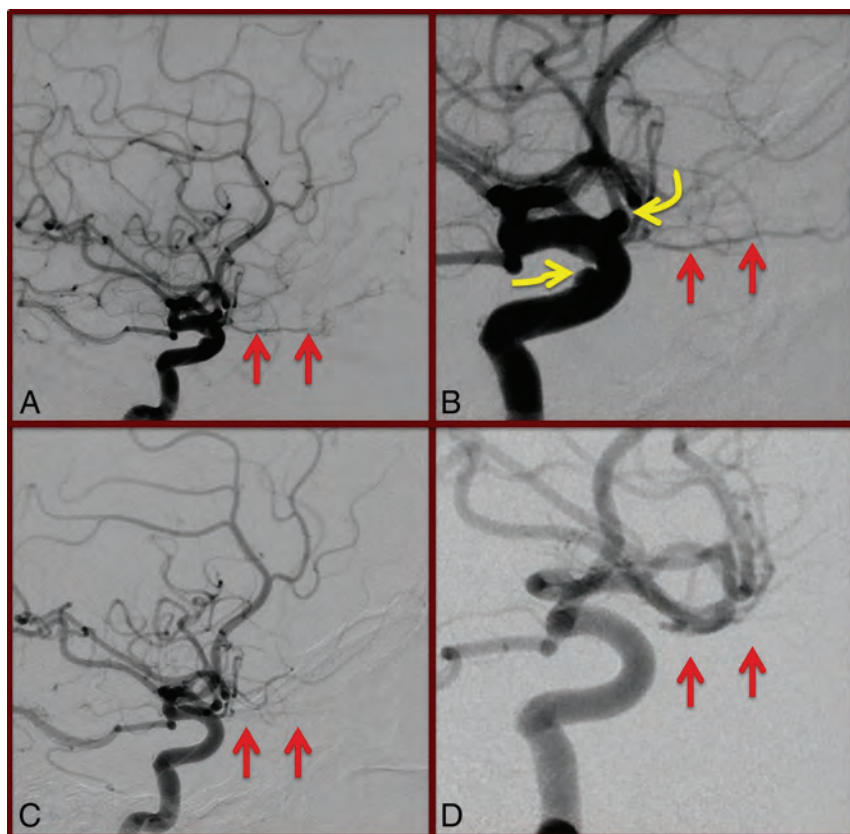


FIG 1. Global and magnified lateral views (A and B) of pre-PED right internal carotid artery angiography demonstrating gross patency of the right ophthalmic artery (straight arrows). The target paraophthalmic and cavernous aneurysms (curved arrows, B) are also visualized. Conventional angiography performed 6 months following PED deployment (C and D) demonstrates occlusion of the target aneurysms; however, the ophthalmic artery is also occluded (straight arrows). The patient was asymptomatic, and the ophthalmic artery was found to fill retrogradely on external carotid artery injections (not shown).

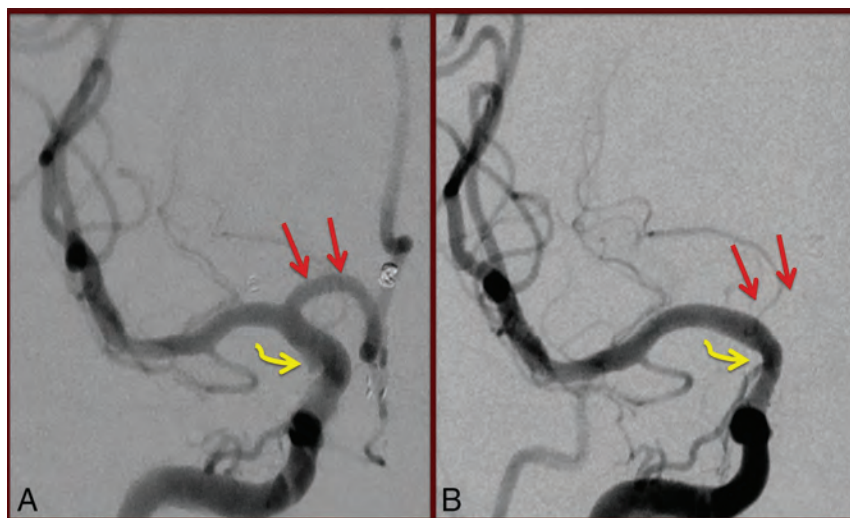


FIG 2. Anteroposterior magnified view (A) of pre-PED right internal carotid artery angiography demonstrating gross patency of the A1 segment of the right anterior cerebral artery (straight arrows). The target, irregular right anterior choroidal artery aneurysm is only partially visualized (curved arrow). On conventional angiography performed 6 months following PED deployment (B), the A1 segment of the right anterior cerebral artery no longer fills on right internal carotid artery injection. The target aneurysm is closed (curved arrow). The patient was asymptomatic, and the bilateral anterior cerebral arteries are noted to be filling via the left A1 segment on left internal carotid artery injections (not shown).

follow-up. Occluded branch vessels included 7 ophthalmic arteries (5.8%) (Fig 1), 13 posterior communicating arteries (33.3%), 4 A1 anterior cerebral artery segments (36%) (Fig 2), 2 anterior communicating arteries (66.6%), 1 anterior choroidal artery (3.2%), and 1 M2 MCA arterial segment (100%). Another 40 branch vessels (18.4%) were significantly stenotic, demonstrating a reduction in both caliber and flow on conventional angiography. These vessels were frequently noted to demonstrate a severe focal stenosis at their origin and included an additional 28 ophthalmic arteries (22%), 4 posterior communicating arteries (10%), 4 A1 anterior cerebral arteries (36%), and 2 posterior inferior cerebellar arteries (67%). All branch vessel occlusions and stenoses in the cohort were asymptomatic.

Univariate analysis was performed to assess significant factors associated with branch vessel occlusion (Table 3). On initial review of the data, minimum, maximum, and average parent vessel size and PED diameter were all found to be significant predictors of branch occlusion in the entire cohort, as well as in the largest subset of ophthalmic arteries. We therefore elected to evaluate PED size to simplify the subsequent analysis and remove any covarying factors. By univariate analysis, variables associated with a higher rate of branch vessel occlusion include older age (59.3 ± 10.2 versus 54.4 ± 12.2 years, $P = .04$), smaller PED diameter (4.0 ± 0.5 versus 3.5 ± 0.5 mm, $P < 0.001$), and branch vessel types of the A1 anterior cerebral artery segment ($P = .021$) and posterior communicating artery ($P < .001$). Ophthalmic artery branch vessel type was associated with a significantly lower rate of occlusion than average ($P < .001$). By multivariate modeling, only a smaller PED diameter ($P = .001$) remained an independent predictor of branch vessel occlusion.

Receiver operating characteristic analysis was performed to demonstrate the diagnostic accuracy for parent vessel diameter to predict branch vessel occlusion in the entire cohort. Sensitivity and specificity values were calculated for a range of thresholds, with the resulting curve shown in Fig 3. The area under the

Table 3: Factors impacting branch vessel patency—entire cohort^a

	Patent Branch Vessel	Occluded Branch Vessel	Univariate P Value	Multivariate P Value	OR (95% CI)
Mean patient age (yr)	54.4 ± 12.2	59.3 ± 10.2	.04	.179	1.03 (0.99–1.07)
Male	26 (13.8%)	4 (13.8%)	.996		
Acutely ruptured target lesion	7/188 (3.7%)	1/29 (3%)	.942		
Mean max aneurysm sac size	5.6 ± 3.8	4.2 ± 2.3	.067	.117	0.87 (0.73–1.04)
Mean aneurysm neck size	3.4 ± 1.7	3.0 ± 1.2	.139		
Mean procedural time (min)	206 ± 66	214 ± 60	.513		
Mean fluoroscopy time (min)	64 ± 36	62 ± 27	.764		
>1 PED deployed	17/188 (9.0%)	1/29 (3.4%)	.309		
% PED classic	107/125 (86%)	18/29 (62.1%)	.601		
Balloon angioplasty	13/188 (7%)	1/29 (7%)	.479		
Mean PED diameter (mm)	4.0 ± 0.5	3.5 ± 0.5	<0.001	.001	0.16 (0.06–0.45)
Mean Δmax size of parent vessel and PED	0.22 ± 0.19	0.26 ± 0.26	.405		
Mean Δmin size of parent vessel and PED	0.77 ± 0.41	0.67 ± 0.40	.230		
Branch vessel incorporation into aneurysm sac	52/188 (28%)	9/29 (31%)	.707		
Mean periprocedural P2Y12	127 ± 68	122 ± 80	.379		
Intraprocedural administration of abciximab	17/188 (9.0%)	3/29 (10.3%)	.821		
Presence of endothelial hyperplasia	43/185 (23%)	10/29 (34%)	.192		
Mean length of DSA follow-up (mo)	18.3 ± 9.9	20.1 ± 8.8	.351		
A1 ACA	7/11 (63.6%)	4/11 (36.3%)	.021	.813	1.29 (0.16–10.56)
Anterior choroidal artery	30/31 (96.8%)	1/31 (3.2%)	.073	.092	0.10 (0.01–1.46)
PcomA	26/39 (66.6%)	13/39 (33.3%)	<.001	.205	3.26 (0.52–20.28)
Ophthalmic artery	118/125 (94%)	8/125 (6%)	<.001	0.449	0.49 (0.08–3.07)

Note:—ACA indicates anterior cerebral artery; max, maximum; min, minimum; PcomA, posterior communicating artery.

^a Percentages reflect analysis per branch vessel.

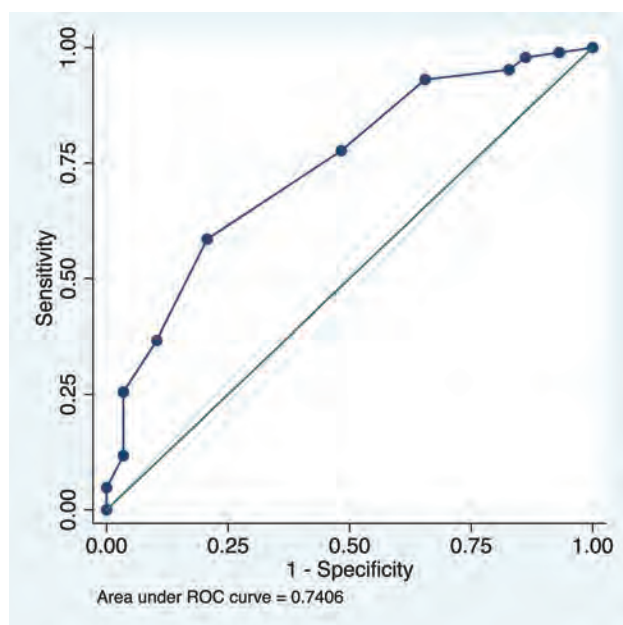


FIG 3. Receiver operating characteristic (ROC) curve demonstrating the diagnostic accuracy for parent vessel diameter to predict branch vessel occlusion in the entire cohort. The reference line is depicted as the solid line along the middle of the plot.

receiver operating characteristic curve was calculated (area under the curve = 0.741), and a PED diameter of 4.0 mm was found to have the most favorable cut-point by the Youden method.

Because the factors associated with branch vessel occlusion may vary on the basis of the type of branch vessel in question, particularly the potential for collateral supply to the branch vessel territory, we elected to repeat our analysis for the largest subgroup of covered side branches, ophthalmic arteries ($n = 125$) (Table 4). By univariate analysis, a smaller PED diameter (4.1 ± 0.5 versus

3.4 ± 0.6 mm, $P = .0006$) and the use of intraprocedural abciximab (25% versus 4.2%, $P = .013$) were associated with ophthalmic artery occlusion. By multivariate analysis, a smaller PED diameter ($P < .001$) again remained the only independent predictor of branch vessel occlusion.

Finally, because a significant minority of covered side branches demonstrated marked reductions in both caliber and flow on follow-up, we elected to repeat our analysis including these stenotic side branches with occluded vessels (Table 5). In univariate analysis, smaller PED diameter ($P = .013$), intraprocedural use of abciximab for platelet aggregation ($P = .019$), and A1 anterior cerebral artery segment branch vessel type ($P = .003$) were significant predictors of covered side branch stenosis or occlusion. Anterior choroidal branch vessel type was associated with gross side branch patency ($P < .001$). On multivariate analysis, PED diameter ($P = .029$) and the administration of intraprocedural abciximab ($P = .030$) remained independent predictors of side branch stenosis or occlusion. Finally, anterior choroidal artery branch type ($P = .003$) was an independent predictor of side branch patency.

DISCUSSION

To our knowledge, our study is the first to demonstrate that a smaller PED diameter is significantly associated with long-term covered side branch stenosis/occlusion following aneurysm treatment with a PED. Although prior authors have investigated the fate of covered side branches following PED deployment, none appear to have evaluated the impact of PED diameter. This correlation was present when we included only complete occlusion of covered side branches as well as when stenotic and occluded side branches were considered together. Furthermore, the association remained significant when analyzing the largest subgroup of side branches in our cohort, the ophthalmic arteries. The dependence

Table 4: Factors impacting branch vessel patency—ophthalmic artery^a

	Patent Branch Vessel	Occluded Branch Vessel	Univariate P Value	Multivariate P Value	OR (95% CI)
Mean patient age (yr)	53.8	60.1	.119		
Male	15 (12.7%)	0 (0%)	.283		
Mean max aneurysm sac	5.9 ± 3.8	5.8 ± 3.3	.977		
Mean aneurysm neck size	3.6 ± 1.6	3.6 ± 0.5	.998		
Acutely ruptured target lesion	4/118 (3.7%)	0/7 (0%)	.597		
Prior coiling	29/118 (24.6%)	1/7 (14.3%)	.438		
Mean procedural time (min)	200 ± 63	212 ± 60	.628		
Mean fluoroscopy time (min)	63 ± 37	53 ± 28	.429		
>1 PED deployed	10/118 (8.5%)	0/7 (0%)	.391		
% PED classic	70/75 (93.3%)	5/75 (6.7%)	.859		
Balloon angioplasty	9/118 (7.6%)	0/7 (0%)	.418		
Mean PED diameter (mm)	4.1 ± 0.5	3.4 ± 0.6	<0.001	<.001	0.10 (0.04–0.21)
Mean Δmax size of parent vessel and PED	0.23 ± 0.18	0.24 ± 0.21	.887		
Mean Δmin size of parent vessel and PED	0.79 ± 0.41	0.79 ± 0.48	.979		
Branch vessel incorporation into aneurysm sac	31/118 (26.3%)	2/7 (29%)	.937		
Mean periprocedural P2Y12	136 ± 68	150 ± 63	.597		
Intraprocedural administration of abciximab	5/118 (4.2%)	2/7 (29%)	.013	.194	4.09 (0.49–34.19)
Presence of endothelial hyperplasia	26/115 (22.6%)	3/7 (43%)	.337		
Mean length of DSA follow-up (mo)	17.9 ± 9.9	21.4 ± 13.8	.682		

^a Percentages reflect analysis per branch vessel.

Table 5: Factors impacting branch vessel patency vs occluded plus stenotic—entire cohort^a

	Patent Branch Vessel	Occluded/Stenotic Branch Vessel	Univariate P Value	Multivariate P Value	OR (95% CI)
Mean patient age (yr)	54.6 ± 12.6	56.0 ± 10.9	.426		
Male	19/148 (12.8%)	11/69 (15.9%)	.537		
Mean max aneurysm sac size	6.0 ± 4.0	5.6 ± 3.7	.096	.415	0.94 (0.82–1.09)
Mean aneurysm neck size	3.6 ± 1.7	3.4 ± 1.2	.054	.534	0.91 (0.67–1.22)
Acutely ruptured target lesion	4/148 (2.7%)	4/69 (5.8%)	.260		
Mean procedural time (min)	205 ± 65	210 ± 66	.658		
Mean fluoroscopy time (min)	65 ± 37	60 ± 30	.365		
>1 PED deployed	14/148 (9.5%)	4/69 (5.8%)	.362		
% PED classic	60/148 (40.5%)	32/69 (46.3%)	.418		
Balloon angioplasty	12/148 (8.1%)	2/69 (2.9%)	.146		
Mean PED diameter (mm)	4.0 ± 0.5	3.8 ± 0.5	.013	.029	0.46 (0.23–0.92)
Mean Δmax size of parent vessel and PED	0.21 ± 0.17	0.27 ± 0.25	.057	.142	3.60 (0.65–19.89)
Mean Δmin size of parent vessel and PED	0.78 ± 0.4	0.70 ± 0.42	.226		
Branch vessel incorporation into aneurysm sac	42/148 (28.3%)	16/69 (27.5%)	.898		
Mean periprocedural P2Y12	127 ± 68	125 ± 74	.855		
Intraprocedural administration of abciximab	9/148 (6.1%)	11/69 (15.9%)	.019	.030	4.26 (1.15–15.78)
Presence of endothelial hyperplasia	31/146 (21.2%)	22/68 (32.4%)	.079	.504	1.31 (0.59–2.94)
Mean length of DSA follow-up (mo)	18.8 ± 19.4	18.0 ± 8.2	.584		
A1 ACA	3/11 (27.2%)	8/11 (72.7%)	0.003	.114	3.12 (0.76–12.81)
Anterior choroidal artery	30/31 (96.8%)	1/31 (3.2%)	<.001	.003	0.04 (0.004–0.32)
PcomA	22/39 (56.4%)	17/39 (43.6%)	.081	.248	1.57 (0.73–3.40)
Ophthalmic artery	90/125 (71.2%)	36/125 (28.8%)	.23		

Note:—PcomA indicates posterior communicating artery; AcomA, anterior communicating.

^a Percentages reflect analysis per branch vessel.

of side branch patency on the PED diameter was not explained by a discrepancy in size between the PED and artery, the type of branch vessel covered, or the presence of endothelial hyperplasia in the flow-diverter construct on follow-up.

We believe that the association between PED diameter and delayed side branch occlusion or stenosis demonstrated in our cohort is best explained by the increased surface area metal coverage provided by smaller diameter devices. This increase in metal coverage is a natural consequence of all PEDs being constructed from the same number of metal strands of an approximately 30-μm diameter, which results in smaller devices having more metal density. Therefore, when appropriately sized, a smaller diameter PED will result in more metal coverage across the orifice of

a jailed side branch compared with a larger device.¹⁵ Our results suggest that these differences in metal density between PEDs of varying caliber have a significant influence on the long-term patency of covered side arteries. The importance of metal coverage in determining long-term side branch patency is supported by findings of Rangel-Castilla et al¹² of an association between the number of devices deployed and delayed side branch occlusion in a review of 127 anterior circulation branch vessels covered by PEDs. Although we did not find a similar association in our cohort, this likely reflects the small number of cases in our cohort using multiple PEDs.

However, the metal coverage provided by a deployed PED is dynamic, with the geometry of PED cells potentially influenced by

multiple factors. These include the degree of oversizing of the device relative to the parent vessel, the course of the artery at the landing site (eg, linear versus curved), and finally the method of PED deployment (eg, aggressive pushing of the PED out of the microcatheter during delivery with resulting device compaction).^{15,16} Although these factors undoubtedly affected the metal surface area coverage provided by PEDs in our cohort, we believe that differences between individual cases were minimized by the use of a standard PED deployment technique in our group. For example, we match the PED diameter to that of the parent vessel as closely as possible because device oversizing (mild to moderate in degree) may impact treatment efficacy by increasing cell size and decreasing metal coverage across the aneurysm neck.¹⁵ Furthermore, we avoid excessive compaction or stretching of the PED during deployment because the former is not necessarily required to achieve subsequent aneurysm closure, while the latter may result in inadequate device apposition.

We also noted that intraprocedural administration of abciximab for acute platelet aggregation during PED deployment was associated with occluded or stenotic side branches on follow-up. These findings suggest a possible role for the degree of platelet inhibition in determining covered branch patency, though the immediate preprocedural P2Y₁₂ value was not significantly associated with the status of branch vessels on follow-up.

Our results, when considered along with those of prior publications, suggest that the patency of covered side branches following PED treatment is determined by multiple factors, including hemodynamic factors, the amount of metal coverage at the jailed artery orifice, the degree of PED oversizing, and possibly the adequacy of platelet inhibition. A complex multifactorial process could explain, in part, why jailed side branch occlusion rates have varied so widely among prior publications (3.5%–53.3%).^{10–13} However, of all these variables potentially impacting the fate of covered side branches, hemodynamic factors involving the jailed side branch are likely paramount. For example, in instances in which there is less potential for collateral flow to the covered side branch territory (eg, the anterior choroidal artery), previously reported long-term patency rates have been extremely high (approaching 100%).¹³ Our own results corroborate these findings. However, in instances in which the availability of collateral flow to the side branch territory is more robust (eg, the ophthalmic artery or an A1 arterial segment), other factors, particularly the degree of metal coverage at the side branch orifice, also play an important role.

Consistent with the findings of prior authors, we noted that delayed side branch occlusion following PED deployment is most often clinically silent. This is presumably due to the rich collateral network available in many vascular territories in the brain, which is further served by the apparent slowly progressive nature of delayed side branch occlusions with the PED. However, symptomatic delayed side branch closures have been reported, and we have anecdotally noted a few cases in our practice (not included in the current study due to inadequate follow-up).¹¹ Furthermore, some ischemic events following side branch occlusion may be missed because patients do not routinely undergo cross-sectional imaging or a detailed ophthalmologic examination following treatment. This idea is supported by Rouchaud et al,¹⁷ who found that

ophthalmic complications were present in 39.3% of asymptomatic patients who underwent an extensive ophthalmologic examination in the first week following PED placement across the ophthalmic artery origin. Finally, the long-term consequences of branch vessel closures remain uncertain. For example, in patients with closure of an A1 segment of the anterior cerebral artery, there is the theoretic risk of inducing aneurysm growth in the region of the anterior communicating artery due to increased flow across the vessel from the contralateral A1 segment.

Due to the occasional symptomatic side branch occlusion, as well as the theoretic risks of silent ischemic events and longer-term sequelae, it is important for the neurointerventionalist to consider the potential for loss of covered side branches when evaluating a patient for possible aneurysm treatment with the PED. The risk of PED closure of covered side branches should be carefully weighed against the advantages of flow diversion, such as high aneurysm-occlusion rates, particularly when the lesion arises from a smaller caliber artery, which will necessitate the use of a smaller diameter, higher metal density device. In these instances, coil embolization or microsurgical repair, when feasible, may be preferable treatment options. Furthermore, in instances in which flow diversion is selected for aneurysm treatment, the potential for side branch occlusion should be discussed with the patient as part of the informed consent process.

The current study has several limitations, including its retrospective design and lack of data regarding patient-dependent variables such as smoking status and hypertension. However, prior reports have evaluated the impact of such variables on branch patency and did not find a significant association. The determination of branch artery stenosis was subjectively defined in our study and could include vessels moderately reduced in size to arteries that were nearly occluded. Furthermore, we did not evaluate the potential for collateral supply to a jailed side branch on a case-to-case basis (eg, evaluation of the contralateral A1 and anterior communicating artery caliber for all jailed A1 segments) because we are uncertain how to quantify the collateral potential in these instances. Instead, we believe that analysis by branch type is the best way to investigate the impact of collateral supply on long-term patency; therefore, we included branch type as a variable in our analysis. We also analyzed factors impacting branch patency in our largest subgroup of ophthalmic arteries and found results similar to those of the entire cohort. Finally, we did not evaluate other variables that may influence PED cell geometry/metal coverage, including purposeful device compaction by the interventionalist or deployment along a vessel curve. However, we believe that the use of a uniform PED deployment technique in our group helped to minimize these factors. Future studies, possibly using flat panel CT interrogation of the deployed flow diverter, may help to further clarify whether there is a quantitative association between the percentage of metal coverage and delayed side branch stenosis/occlusion.

CONCLUSIONS

Smaller PED diameter is significantly associated with delayed side branch stenosis/occlusion following intracranial aneurysm treatment with the PED. The higher metal density of smaller PEDs compared with larger diameter devices best explains this associa-

tion. Although hemodynamic factors, particularly the availability of collateral flow, are still paramount in determining the fate of covered side branches, the amount of metal coverage at the side branch orifice also plays an important role.

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REFERENCES

1. Becske T, Kallmes DF, Saatci I, et al. **Pipeline for uncoilable or failed aneurysms: results from a multicenter clinical trial.** *Radiology* 2013; 267:858–68 [CrossRef Medline](#)
2. Chiu AH, Cheung AK, Wenderoth JD, et al. **Long-term follow-up results following elective treatment of unruptured intracranial aneurysms with the Pipeline Embolization Device.** *AJNR Am J Neuroradiol* 2015;36:1728–34 [CrossRef Medline](#)
3. Fischer S, Vajda Z, Aguilar Perez M, et al. **Pipeline embolization device (PED) for neurovascular reconstruction: initial experience in the treatment of 101 intracranial aneurysms and dissections.** *Neuroradiology* 2012;54:369–82 [CrossRef Medline](#)
4. Kallmes DF, Hanel R, Lopes D, et al. **International retrospective study of the Pipeline embolization device: a multicenter aneurysm treatment study.** *AJNR Am J Neuroradiol* 2015;36:108–15 [CrossRef Medline](#)
5. Saatci I, Yavuz K, Ozer C, et al. **Treatment of intracranial aneurysms using the Pipeline flow-diverter embolization device: a single-center experience with long-term follow-up results.** *AJNR Am J Neuroradiol* 2012;33:1436–46 [CrossRef Medline](#)
6. Albuquerque FC, Park MS, Abila AA, et al. **A reappraisal of the Pipeline Embolization Device for the treatment of posterior circulation aneurysms.** *J Neurointervent Surg* 2015;7:641–45 [CrossRef Medline](#)
7. Chalouhi N, Zanaty M, Whiting A, et al. **Safety and efficacy of the Pipeline Embolization Device in 100 small intracranial aneurysms.** *J Neurosurg* 2015;122:1498–502 [CrossRef Medline](#)
8. Pistocchi S, Blanc R, Bartolini B, et al. **Flow diverters at and beyond the level of the circle of Willis for the treatment of intracranial aneurysms.** *Stroke* 2012;43:1032–38 [CrossRef Medline](#)
9. Colby GP, Bender MT, Lin LM, et al. **Endovascular flow diversion for treatment of anterior communicating artery region cerebral aneurysms: a single-center cohort of 50 cases.** *J Neurointervent Surg* 2017;9:679–85 [CrossRef Medline](#)
10. Daou B, Valle-Giler EP, Chalouhi N, et al. **Patency of the posterior communicating artery following treatment with the Pipeline Embolization Device.** *J Neurosurg* 2017;126:564–69 [CrossRef Medline](#)
11. Chalouhi N, Daou B, Kung D, et al. **Fate of the ophthalmic artery after treatment with the Pipeline Embolization Device.** *Neurosurgery* 2015;77:581–84; discussion 584 [CrossRef Medline](#)
12. Rangel-Castilla L, Munich SA, Jaleel N, et al. **Patency of anterior circulation branch vessels after Pipeline embolization: longer-term results from 82 aneurysm cases.** *J Neurosurg* 2017;126:1064–69 [CrossRef Medline](#)
13. Raz E, Shapiro M, Becske T, et al. **Anterior choroidal artery patency and clinical follow-up after coverage with the Pipeline Embolization Device.** *AJNR Am J Neuroradiol* 2015;36:937–42 [CrossRef Medline](#)
14. Bhogal P, Ganslandt O, Bätzner H, et al. **The fate of side branches covered by flow diverters: results from 140 patients.** *World Neurosurg* 2017;103:789–98 [CrossRef Medline](#)
15. Shapiro M, Raz E, Becske T, et al. **Variable porosity of the Pipeline embolization device in straight and curved vessels: a guide for optimal deployment strategy.** *AJNR Am J Neuroradiol* 2014;35:727–33 [CrossRef Medline](#)
16. Ma D, Xiang J, Choi H, et al. **Enhanced aneurysmal flow diversion using a dynamic push-pull technique: an experimental and modeling study.** *AJNR Am J Neuroradiol* 2014;35:1779–85 [CrossRef Medline](#)
17. Rouchaud A, Leclerc O, Benayoun Y, et al. **Visual outcomes with flow-diverter stents covering the ophthalmic artery for treatment of internal carotid artery aneurysms.** *AJNR Am J Neuroradiol* 2015; 36:330–36 [CrossRef Medline](#)

Toward Better Understanding of Flow Diversion in Bifurcation Aneurysms

 M. Shapiro,  A. Shapiro,  E. Raz,  T. Becske,  H. Riina, and  P.K. Nelson



ABSTRACT

BACKGROUND AND PURPOSE: Flow diversion is being increasingly used to treat bifurcation aneurysms. Empiric approaches have generally led to encouraging results, and a growing body of animal and ex vivo literature addresses the fate of target aneurysms and covered branches. Our prior investigations highlighted the dynamic nature of metal coverage provided by the Pipeline Embolization Device and suggested strategies for creating optimal single and multidevice constructs. We now address the geometric and hemodynamic aspects of jailing branch vessels and neighboring target aneurysms.

MATERIALS AND METHODS: Fundamental electric and fluid dynamics principles were applied to generate equations describing the relationships between changes in flow and the degree of vessel coverage in settings of variable collateral support to the jailed territory. Given the high complexity of baseline and posttreatment fluid dynamics, in vivo, we studied a simplified hypothetical system with minimum assumptions to generate the most conservative outcomes.

RESULTS: In the acute setting, Pipeline Embolization Devices modify flow in covered branches, principally dependent on the amount of coverage, the efficiency of collateral support, and intrinsic resistance of the covered parenchymal territory. Up to 30% metal coverage of any branch territory is very likely to be well-tolerated regardless of device or artery size or the availability of immediate collateral support, provided, however, that no acute thrombus forms to further reduce jailed territory perfusion.

CONCLUSIONS: Basic hemodynamic principles support the safety of branch coverage during aneurysm treatment with the Pipeline Embolization Device. Rational strategies to build bifurcation constructs are feasible.

ABBREVIATIONS: FD = flow diverter; PcomA = posterior communicating artery; PED = Pipeline Embolization Device

Flow-diversion therapy, exemplified by the Pipeline Embolization Device (PED; Medtronic, Dublin, Ireland) in the United States >7 years after its FDA approval based on results of the Pipeline for Uncoilable or Failed Aneurysms (PUFS) trial,¹ has revolutionized the treatment of brain aneurysms. Subsequently, PUFS results at 3² and 5³ years demonstrated both the durability and, uniquely, increasing efficacy of treatment over time. However, in a widely known trend and a matter of increasing concern, most aneurysms now treated with the PED fall outside the popu-

lation of adults with large or giant wide-neck intracranial aneurysms in the internal carotid artery from the petrous to the superior hypophyseal segments^{4–6} for which the device is indicated. Among these outside-of-indication targets, most appear to be <10-mm aneurysms located in the same petrous-to-posterior communicating artery range. However, both in the United States and, more commonly, abroad, the PED and other flow diverters (FDs) are being used to treat more distal aneurysms, including those affecting the MCA bifurcation,⁷ anterior communicating artery,⁸ posterior communicating artery (PcomA) segments (including in the setting of “fetal PcomA”⁹), distal anterior cerebral artery,¹⁰ and others.^{6,11,12} While reasons for these trends are complex and multifactorial, published results have been generally encouraging,^{7,8,11,12} with a few groups reporting a high burden of ischemic complications.^{13,14}

The mechanisms responsible for efficiency of flow diversion in aneurysm treatment have been well-described.¹⁵ Likewise, rational approaches to building both single- and multidevice¹⁶ constructs that maximize desired metal coverage of the aneurysm

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while minimizing coverage of adjacent perforator and other hazards have been outlined both by our group and others.^{17,18} The fates of some covered branches, such as the ophthalmic,¹⁹ anterior choroidal,²⁰ and posterior communicating⁹ arteries have been extensively examined, highlighting the critical role of collateral support in determining the long-term patency of covered branches. The unifying message is that good collaterals frequently lead to progressive occlusion of jailed branches, both in humans and in specifically designed animal models.¹⁷⁻²⁰ Unfortunately, quantifying the efficiency of collateral support at a given time point and estimating its subsequent change are extremely difficult. Likewise, the study of hemodynamic changes in aneurysms and adjacent covered branches is made difficult by the daunting complexity of in vivo fluid dynamics.²¹ Nevertheless, because flow diversion is being increasingly used, essentially on an empiric basis, in settings that require jailing branches of both substantial size and eloquence such as M2 segment divisions, some rational consideration of the immediate hemodynamic consequences of treatment is required.

To this end, we have considered a mathematic description of a simplified flow system based on an electric circuit analogy and fundamental fluid dynamics. The electric circuit analogy has a history of application in cerebrovascular pathology, including AVMs by Guglielmi²² and cervical carotid disease by Spencer and Reid.²³ The disadvantage is that electric currents do not behave in ways fully analogous to even idealized fluids and that, ultimately, to study fluid flow, we have to rely on fluid equations. However, even the simplest fluid systems are affected by many variables related to the nature and flow dynamics of fluid and flow channel morphology. When applied to fluids of blood complexity, in systems of complex pulsatile flow, and further modified by various feedback mechanisms that biologic systems bring to play once homeostasis is modified by changes such as FD implantation, it is easy, indeed, to recognize our limits of understanding. It is important to appreciate these humbling limits. While computational and other advances may someday allow solutions to systems of such complexity, we thought that an alternative approach of describing a basic system with minimal assumptions, designed to produce the most conservative outcomes, would be useful in defining conservative limits of flow changes in states of branch coverage.

MATERIALS AND METHODS

Electric circuits were modeled to illustrate the effects of jailing a branch vessel with variable metal coverage under conditions of variable collateral support to the compromised vascular territory. The efficiency of the collateral network or networks was defined relative to the primary supplying branch, as a ratio of collateral pathway to primary pathway flow resistance. Variable resistance of the parenchymal territory (classically defined according to the Ohm law as a ratio of territory perfusion pressure to its flow^{24,25}) supplied by the covered branch was also considered. The relative change in the amount of flow to the downstream brain territory as a function of the % metal coverage was calculated for systems over a complete range of collateral support. Flow relationships were based on the conservative assumption of flow change proportionality to the second power of the channel cross-sectional area, in

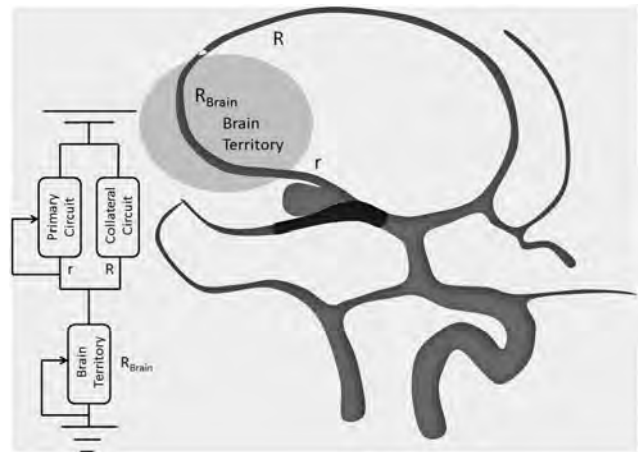


FIG 1. Schematic illustration of the electric circuit analogy for a bifurcation aneurysm. In this MCA example, implantation of a flow diverter from M1 to the inferior division of M2 results in jailing of the superior division, which is the main source of supply to its brain territory, with a flow resistance r (the effect of implanting a flow diverter is to increase r by reducing the M2 cross-sectional area in proportion to the amount of metal coverage). The collateral circuit to the same brain territory, in this example the anterior cerebral artery–MCA leptomeningeal collaterals, is associated with a combined resistance R . The brain parenchyma supplied by this circuit has its own resistance, R_{brain} . These constitute parallel circuits, with downstream resistance R_{total} at point P. FD treatment of any branch point aneurysm can be described by this model.

contrast to the linear relationship in electric circuits. Likewise, feedback effects of biologic systems, which act to minimize flow changes by mechanisms that include vasodilation and hypertension, were ignored to produce the simplest and most conservative outcomes.

The circuit analogy to the biologic system exemplified by a middle cerebral artery aneurysm is shown in Fig 1. The circuit consists of a primary pathway with resistance, r , and a secondary/collateral pathway or pathways with a sum total resistance, R , together supplying the brain parenchyma, which has its own resistance, R_{brain} . In this circuit the total resistance is

$$1) \quad R_{\text{total}} = 1/(1/r + 1/R) + R_{\text{brain}}.$$

The effect of FD placement (for example from M1 to the inferior division of M2 in Fig 1) is to increase r (resistance in the covered superior division branch). The degree to which r increases corresponds to the second power of change in the cross-sectional area A of covered branch, expressed as

$$2) \quad A_{\text{post-PED}} = A_{\text{pre-PED}} \times p,$$

where p is porosity, ranging from 0 to 1 (% Metal Coverage = $1/p \times 100\%$). Thus, the change in r following FD placement is proportional to r/p^2 . Therefore, total resistance post-flow diverter placement is

$$3) \quad R_{\text{post-PED}} = 1/(p^2/r + 1/R) + R_{\text{brain}}.$$

Because flow, I , is inversely related to resistance according to the Ohm law, $I = V/R$ (V is voltage in electric circuits and fluid pressure, such as blood pressure, in fluid systems), for a constant V (no change in perfusion pressure), the fractional change, ΔI , in blood flow through the brain subserved by the jailed branch may be stated as

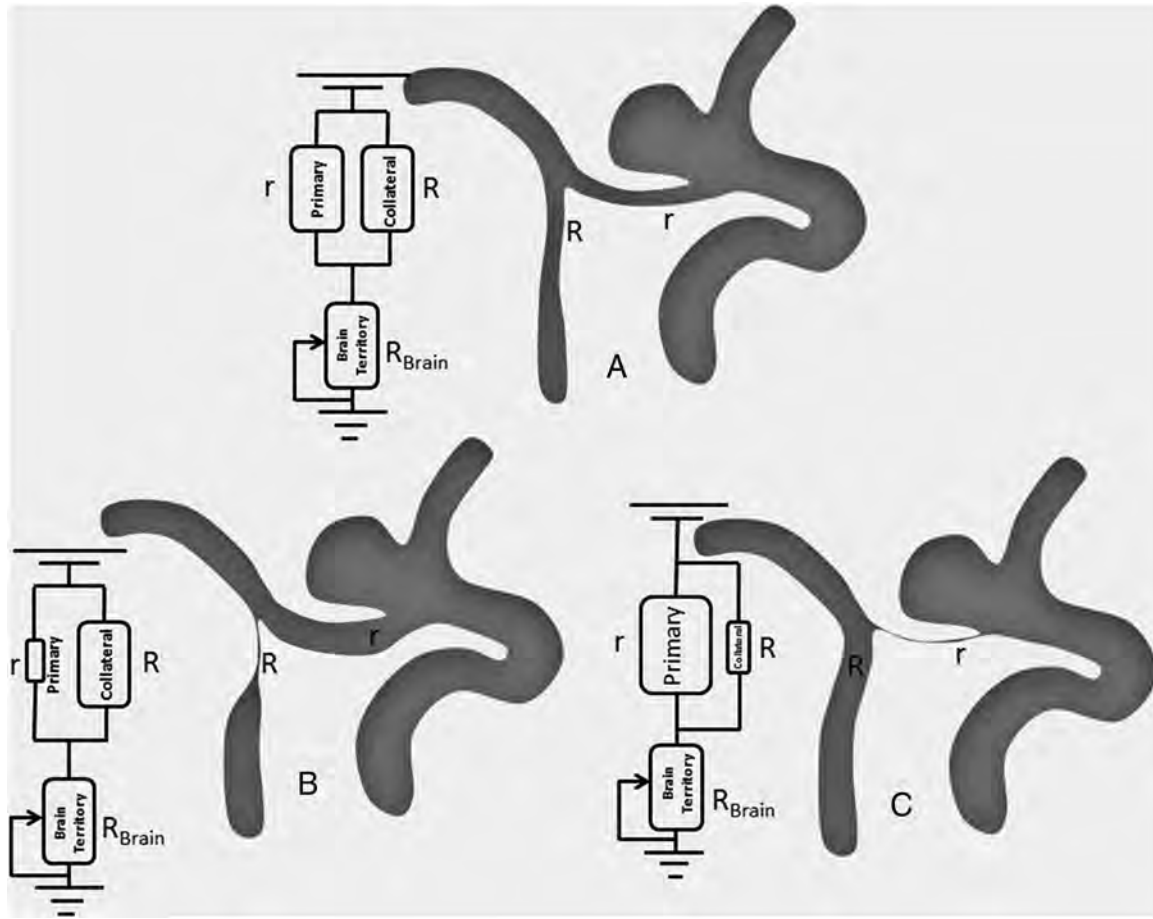


FIG 2. Schematic illustration of circuit model application to 3 types of PcomA aneurysms. A, Equally well-developed P1 and PcomA segments, where $R = r$. B, Fetal PcomA configuration where $R \gg r$ (negligible collateral support by a hypoplastic P1 segment). C, Dominant P1 segment with a hypoplastic PcomA segment, corresponding to $R \ll r$.

4)

$$\Delta I = [1/(1/r + 1/R) + R_{\text{brain}}]/[1/(p^2/r + 1/R) + R_{\text{brain}}].$$

This equation can be simplified if $R_{\text{brain}} = 0$ (the most unfor- giving and conservative assumption if we consider the effects of decreasing porosity on total blood flow)—the greater R_{brain} be- comes, the less change in total flow is affected by decreasing p . If $R_{\text{brain}} = 0$, then I at point P after flow-diverter implantation of porosity p is

$$5) \quad I \sim p^2 + r/R.$$

Thus, fractional flow change after device implantation com- pared with pre-FD deployment ($p = 1$) is

$$6) \quad \Delta I = (p^2 + r/R)/(1 + r/R).$$

Thus, ΔI is dependent on a ratio of r/R rather than absolute values of r and R .

In the extreme example of no collateral ($R = \infty$),

$$\Delta I = p^2.$$

Therefore, when $P = 1$ (no FD), there is no change in I . When $P = .5$ (50% coverage), there is $0.5^2 = 1/4$ of baseline flow present.

At the other extreme of perfect collateral with $R \rightarrow 0$, $\Delta I = 1$ (no flow change) regardless of p .

Most important, in this model, flow in the covered branch is independent of collateral status (as in any parallel circuit, flow in each parallel circuit component is independent and is only dictated by voltage and the individual resistance of the circuits).

RESULTS

Figure 2 shows application of this model to 3 types of PcomA aneurysms that correspond to the above extremes of $R = \infty$ (fetal PcomA), $R = 0$ (no PcomA), and $r = R$ (balanced PcomA and P1).

Figure 3 shows various aneurysms and corresponding $R:r$ relationships. In the hypothetical MCA aneurysm with more effective MCA–anterior cerebral artery leptomeningeal collaterals compared with MCA–posterior cerebral artery collaterals, the flow diverter is implanted in the inferior division to take advantage of more effective anterior cerebral artery–MCA collaterals. This approach is not rigid; in a nondominant hemisphere, it might be preferable to jail the inferior division regardless of its collateral status.

Figure 4 shows the relationship of fractional flow, ΔI , to % metal coverage for a variety of more-or-less effective collaterals. An extensive literature review of studies establishing human cerebral ischemia thresholds by Baron²⁴ suggests that a 60% flow reduction (0.4 fractional flow) represents a reasonable ischemic threshold; a more conservative fraction can be adopted on the

basis of the individual comfort level. On the x-axis, based on our prior work,²⁶ implantation of a single PED, depending on the relative size of the device to the parent artery, results in a range of % metal coverage between ~18% and 35%. Thus, according to Fig 4, placement of a single PED will not result in >50% reduction in branch flow and is, thus, unlikely to produce ischem-

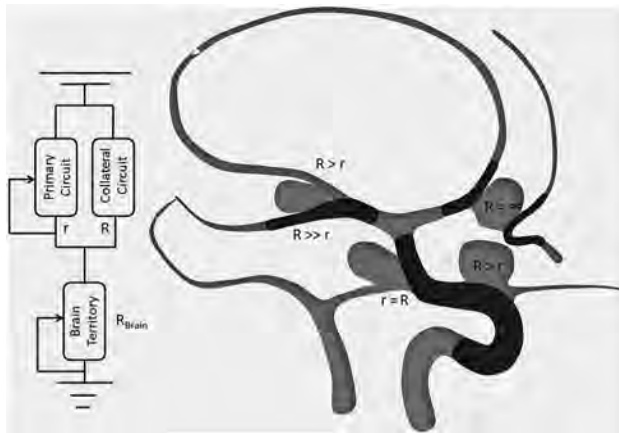


FIG 3. Schematic illustration of various branch aneurysms and associated primary and collateral pathway efficiencies, demonstrating the applicability of the parallel circuit model to different branch aneurysm configurations. In this figure, for example, MCA–posterior cerebral artery leptomeningeal collaterals are less efficient than MCA–anterior cerebral artery collaterals, prompting implantation of an FD into the inferior division, which has less collateral support. For an anterior communicating artery aneurysm with well-developed A1 and A2 segments bilaterally, an H-type FD treatment would correspond to a high value of R .

emia. For multiple overlapping PEDs, the resultant % metal coverage can also be acceptable; however, this approach requires attention to individual porosities. Tables of these relationships are available.¹⁶

The above model is highly conservative because it forbids a number of realistic and often highly effective in vivo adoptive changes,²⁷ all of which are directed at minimizing ΔI following FD implantation. These include adaptive hypertension, vasodilation in both primary and collateral circuits (decrease in R , R_{brain} , and r), and, most important, long-term increases in collateral efficiency (further drop in R). As explained above, it also assumes that in the jailed territory $R_{\text{brain}} = 0$, which is the most unfavorable situation. For example, Fig 5 shows the effects of increasing R_{brain} in a disposition with unfavorable collaterals ($R:r = 10:1$); here, increasing R_{brain} results in progressively less change in flow, ΔI , for all values of % metal coverage. When collaterals are “good” ($R:r = 2:1$), increasing R_{brain} allows the brain to tolerate significantly higher degrees of metal coverage. For all the above reasons, the practical limit of safe % metal coverage is likely to be >30%. Furthermore, on the basis of known PED size/coverage relationships,²⁶ as well as of in vivo experience,²⁸ single PED coverage is likely to remain below 30%.

DISCUSSION

The above model is consistent with most published bifurcation aneurysm FD treatment experience.²⁹ In the largest to date MCA experience by Iosif et al,⁷ the low incidence of ischemic complications was attributed by the authors to careful antiplatelet management and preferential use of a single, slightly oversized flow

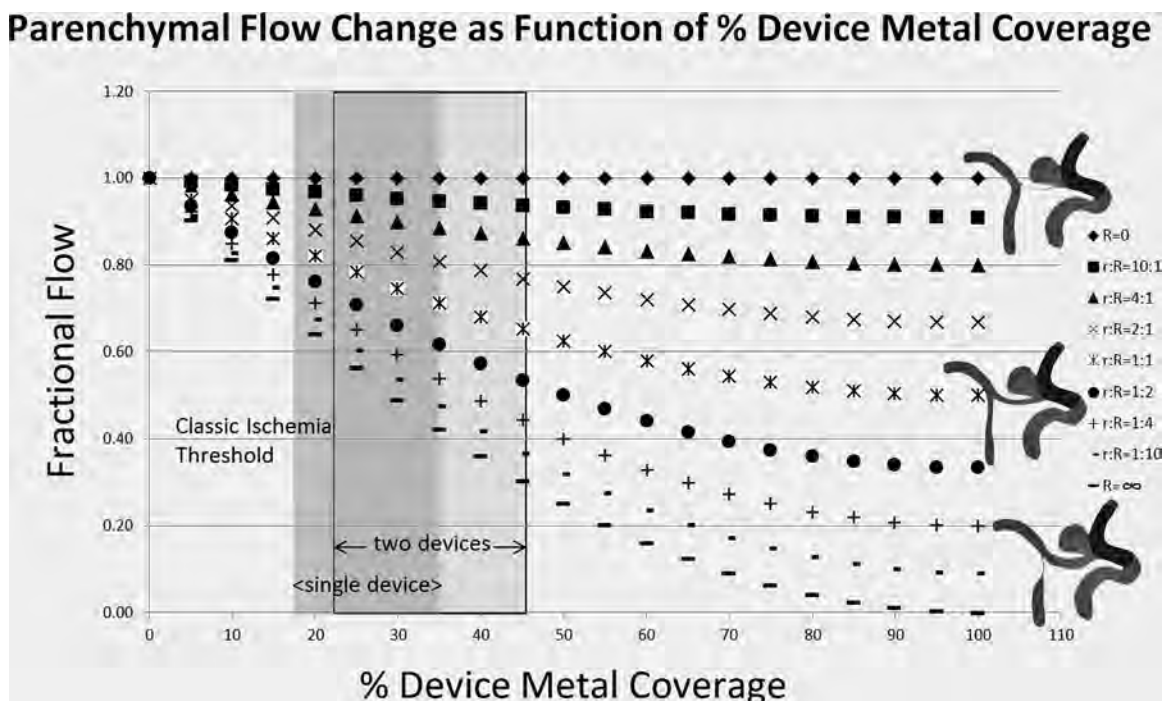


FIG 4. Fractional flow change as function of % metal coverage following FD implantation for a range of collateral circuit efficiencies. The ratio of $r:R$ represents a primary-to-collateral circuit relative resistance, with higher $r:R$ values corresponding to increasingly efficient support. In the extreme example of $R = 0$, flow into the parenchymal territory remains unchanged regardless of metal coverage. At the other extreme of $R = \infty$ (no collaterals), flow falls to zero at 100% metal coverage. The classic ischemia threshold is set at 0.4 (60% flow reduction). A range of % device metal coverage for the single- and double-coverage PED is provided. According to this model, single-device coverage is extremely unlikely to precipitate ischemia unless followed by acute thrombosis.

Flow Change in Tissue with Poor Collaterals ($R:r=10:1$) as Function of Metal Coverage, for Tissues of Various Resistances

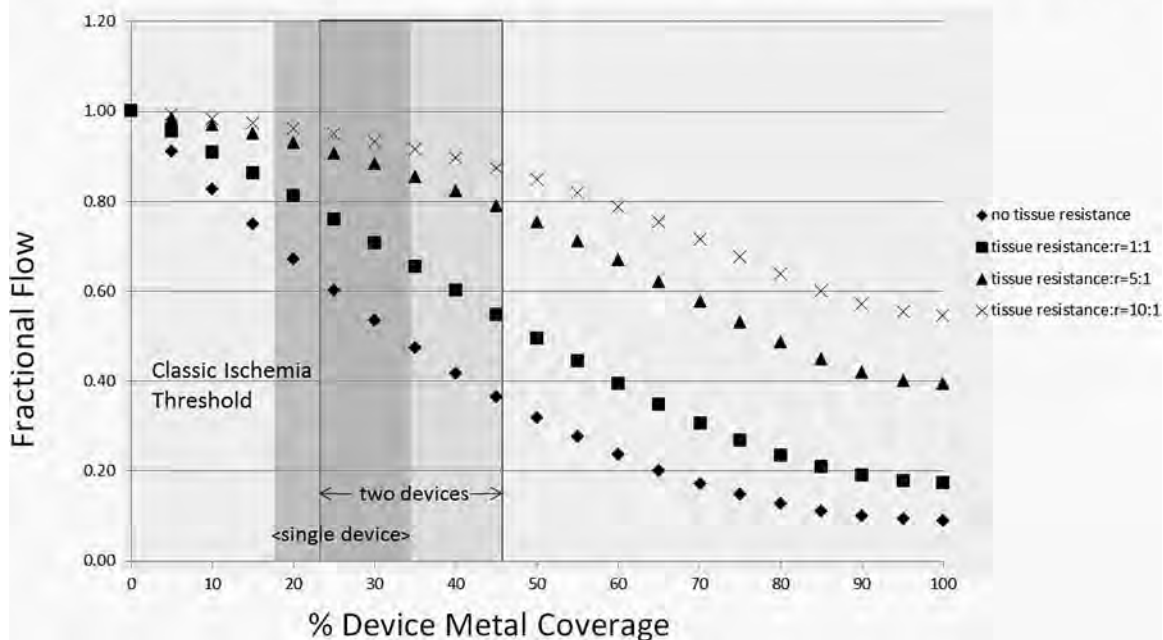


FIG 5. Fractional change in flow under conditions of varied brain parenchymal resistance for tissue with poor collaterals ($R:r = 10:1$). The actual value of brain resistance is both difficult to determine and variable but, under all circumstances, is greater than zero. It is probably comparable with large-artery flow resistance (tissue resistance: $r = 1:1$) according to Faraci and Heistad.²⁵ These functions illustrate that jailing territories of higher parenchymal resistance leads to less change in perfusion than jailing territories of lower resistance.

diverter to minimize metal coverage. Both conditions are consistent with our calculations. Beyond our rigid model, long-term biologic adaptations tend to promote growth of collaterals when available, leading to eventual occlusion of covered branches, which likely proceeds after the reduction in demand for flow through the branch is followed by gradual endothelial overgrowth; this progressive occlusion has been consistently found by multiple groups in various settings to be overwhelmingly asymptomatic.^{5,7,9,11,12,29,30} Furthermore, predictable enlargement of collaterals can be part of a staged treatment strategy. When collaterals are not readily available, as may be expected in a number of MCA bifurcation situations for example, covered branches tend to remain patent.²⁷ What remains unpredictable, at least in our experience, is why, under conditions of continued branch patency, the associated aneurysm sometimes disappears and sometimes does not. There is evidence to suggest that collateral circulation continues to evolve well beyond the typical 12-month posttreatment efficacy benchmark, contributing to progressive occlusion of branch-associated aneurysms.³⁰ Recent advances in the development of less thrombogenic implants such as the Pipeline Shield (Medtronic) may further improve the safety profile of bifurcation aneurysm treatment by establishing a less thrombogenic environment,³¹ though this hypothesis remains unproven.

The one critical condition on which patency of any covered branch depends is that flow-diverter implantation not precipitate acute thrombosis (further increase in r beyond r/p^2 resulting from FD placement). This is an intuitive and inflexible condition that, in practice, demands strict antiplatelet monitoring. Indeed, re-

ports of high ischemic complications in bifurcation aneurysm treatment with flow diverters illustrate proved instances of acute thrombosis-related occlusions.¹³

Study Limitations

Already acknowledged above are many limitations of our model, which favors simplicity and conservative assumptions. We have relied on well-established equations rather than creating a physical flow model to test our conclusions. The realities of in vivo fluid systems are infinitely more complex; however, we believe that these are also likely to be more forgiving. Indeed, animal model data support both continued patency and essentially unchanged flow rates in covered branches without adequate collateral support, a situation that requires significant adaptive changes.²⁷ Quantifying efficiency of collateral support remains difficult. Parenchymal resistance, R_{brain} , is both variable and difficult to estimate; however, to the extent that it is always greater than zero, increasing parenchymal resistance permits increasing metal coverage. One of the consequences of assuming $R_{\text{brain}} = 0$ is likely unphysiologically high blood pressure drops across jailed branches. However, to the extent that this is an unforgiving consequence of our model, lesser pressure drops are likely to be better tolerated. We did not discuss the effects of global hypotension; the mathematics of this change in our model is straightforward, and global hypotension is an undesirable event anytime. The model ignores all aspects of implant and jailed branch geometry and nonzero thickness of the implant (braid diameter $\sim 30 \mu\text{m}$). Both R and r are treated in a relative manner. Finally, our model only

deals with branch coverage safety and does not address treatment efficacy. It is not directly related to a growing body of increasingly sophisticated computational flow dynamics knowledge. Finally, returning to our early point, treatment of bifurcation aneurysms currently remains outside PED indications, at least in the United States. We believe that its safety and efficacy in this setting should be subjected to a prospective controlled trial, guided by principles established in this and related articles, animal models, and already existing encouraging human experience.

CONCLUSIONS

Basic principles of fluid mechanics support the safety of Pipeline Embolization Device use in bifurcation aneurysms. Lack of acute thrombus formation is a key precondition. Therefore, careful attention to antiplatelet coverage is essential.

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REFERENCES

1. Becske T, Kallmes DF, Saatci I, et al. **Pipeline for Uncoiled or Failed Aneurysms: results from a multicenter clinical trial.** *Radiology* 2013; 267:858–68 [CrossRef Medline](#)
2. Becske T, Potts MB, Shapiro M, et al. **Pipeline for Uncoiled or Failed Aneurysms: 3-year follow-up results.** *J Neurosurg* 2017;127: 81–88 [CrossRef Medline](#)
3. Becske T, Brinjikji W, Potts MB, et al. **Long-term clinical and angiographic outcomes following Pipeline Embolization Device treatment of complex internal carotid artery aneurysms: five-year results of the Pipeline for Uncoiled or Failed Aneurysms Trial.** *Neurosurgery* 2017;80:40–48 [CrossRef Medline](#)
4. Kallmes DF, Hanel R, Lopes D, et al. **International retrospective study of the Pipeline embolization device: a multicenter aneurysm treatment study.** *AJNR Am J Neuroradiol* 2015;36:108–15 [CrossRef Medline](#)
5. Saatci I, Yavuz K, Ozer C, et al. **Treatment of intracranial aneurysms using the Pipeline flow-diverter embolization device: a single-center experience with long-term follow-up results.** *AJNR Am J Neuroradiol* 2012;33:1436–46 [CrossRef Medline](#)
6. Patel PD, Chalouhi N, Atallah E, et al. **Off-label uses of the Pipeline Embolization Device: a review of the literature.** *Neurosurg Focus* 2017;42:E4 [CrossRef Medline](#)
7. Iosif C, Mounayer C, Yavuz K, et al. **Middle cerebral artery bifurcation aneurysms treated by extrasaccular flow diverters: midterm angiographic evolution and clinical outcome.** *AJNR Am J Neuroradiol* 2017;38:310–16 [CrossRef Medline](#)
8. Colby GP, Bender MT, Lin LM, et al. **Endovascular flow diversion for treatment of anterior communicating artery region cerebral aneurysms: a single-center cohort of 50 cases.** *J Neurointerv Surg* 2017;9:679–85 [CrossRef Medline](#)
9. Daou B, Valle-Giler EP, Chalouhi N, et al. **Patency of the posterior communicating artery following treatment with the Pipeline Embolization Device.** *J Neurosurg* 2017;126:564–69 [CrossRef Medline](#)
10. Nossek E, Zumofen DW, Setton A, et al. **Treatment of distal anterior cerebral artery aneurysms with the Pipeline Embolization Device.** *J Clin Neurosci* 2017;35:133–38 [CrossRef Medline](#)
11. Saleme S, Iosif C, Ponomarjova S, et al. **Flow-diverting stents for intracranial bifurcation aneurysm treatment.** *Neurosurgery* 2014; 75:623–31; quiz 631 [CrossRef Medline](#)
12. Gawlitza M, Januel AC, Tall P, et al. **Flow diversion treatment of complex bifurcation aneurysms beyond the circle of Willis: a single-center series with special emphasis on covered cortical branches and perforating arteries.** *J Neurointerv Surg* 2016;8:481–87 [CrossRef Medline](#)
13. Caroff J, Neki H, Mihalea C, et al. **Flow-diverter stents for the treatment of saccular middle cerebral artery bifurcation aneurysms.** *AJNR Am J Neuroradiol* 2016;37:279–84 [CrossRef Medline](#)
14. Cagnazzo F, Cappucci M, Dargazanli C, et al. **Treatment of distal anterior cerebral artery aneurysms with flow-diverter stents: a single-center experience.** *AJNR Am J Neuroradiol* 2018;39:1100–06 [CrossRef Medline](#)
15. Fiorella D, Lylyk P, Szikora I, et al. **Curative cerebrovascular reconstruction with the Pipeline Embolization Device: the emergence of definitive endovascular therapy for intracranial aneurysms.** *J Neurointerv Surg* 2009;1:56–65 [CrossRef Medline](#)
16. Shapiro M, Raz E, Becske T, et al. **Building multidevice Pipeline constructs of favorable metal coverage: a practical guide.** *AJNR Am J Neuroradiol* 2014;35:1556–61 [CrossRef Medline](#)
17. Makoyeva A, Bing F, Darsaut TE, et al. **The varying porosity of braided self-expanding stents and flow diverters: an experimental study.** *AJNR Am J Neuroradiol* 2013;34:596–602 [CrossRef Medline](#)
18. Bing F, Darsaut TE, Salazkin I, et al. **Stents and flow diverters in the treatment of aneurysms: device deformation in vivo may alter porosity and impact efficacy.** *Neuroradiology* 2013;55:85–92 [CrossRef Medline](#)
19. Chalouhi N, Daou B, Kung D, et al. **Fate of the ophthalmic artery after treatment with the Pipeline Embolization Device.** *Neurosurgery* 2015;77:581–84; discussion 584 [CrossRef Medline](#)
20. Raz E, Shapiro M, Becske T, et al. **Anterior choroidal artery patency and clinical follow-up after coverage with the Pipeline embolization device.** *AJNR Am J Neuroradiol* 2015;36:937–42 [CrossRef Medline](#)
21. Sforza DM, Putman CM, Cebal JR. **Computational fluid dynamics in brain aneurysms.** *Int J Numer Method Biomed Eng* 2012;28:801–08 [CrossRef Medline](#)
22. Guglielmi G. **Analysis of the hemodynamic characteristics of brain arteriovenous malformations using electrical models: baseline settings, surgical extirpation, endovascular embolization, and surgical bypass.** *Neurosurgery* 2008;63:1–10; discussion 11 [CrossRef Medline](#)
23. Spencer MP, Reid JM. **Quantitation of carotid stenosis with continuous-wave (C-W) Doppler ultrasound.** *Stroke* 1979;10:326–30 [CrossRef Medline](#)
24. Baron JC. **Perfusion thresholds in human cerebral ischemia: historical perspective and therapeutic implications.** *Cerebrovasc Dis* 2001; 11(Suppl 1):2–8 [Medline](#)
25. Faraci FM, Heistad DD. **Regulation of large cerebral arteries and cerebral microvascular pressure.** *Circ Res* 1990;66:8–17 [CrossRef Medline](#)
26. Shapiro M, Raz E, Becske T, et al. **Variable porosity of the Pipeline embolization device in straight and curved vessels: a guide for optimal deployment strategy.** *AJNR Am J Neuroradiol* 2014;35:727–33 [CrossRef Medline](#)
27. Iosif C, Berg P, Ponsonnard S, et al. **Role of terminal and anastomotic circulation in the patency of arteries jailed by flow-diverting stents: from hemodynamic changes to ostia surface modifications.** *J Neurosurg* 2017;126:1702–13 [CrossRef Medline](#)
28. Jou LD, Chintalapani G, Mawad ME. **Metal coverage ratio of Pipeline embolization device for treatment of unruptured aneurysms: reality check.** *Interv Neuroradiol* 2016;22:42–48 [CrossRef Medline](#)
29. Brinjikji W, Lanzino G, Cloft HJ, et al. **Patency of the posterior communicating artery after flow diversion treatment of internal carotid artery aneurysms.** *Clin Neurol Neurosurg* 2014;120:84–88 [CrossRef Medline](#)
30. Chiu AH, Cheung AK, Wenderoth JD, et al. **Long-term follow-up results following elective treatment of unruptured intracranial aneurysms with the Pipeline Embolization Device.** *AJNR Am J Neuroradiol* 2015;36:1728–34 [CrossRef Medline](#)
31. Hagen MW, Girdhar G, Wainwright J, et al. **Thrombogenicity of flow diverters in an ex vivo shunt model: effect of phosphorylcholine surface modification.** *J Neurointerv Surg* 2017;9:1006–11 [CrossRef Medline](#)

Initial and Long-Term Outcomes of Complex Bifurcation Aneurysms Treated by Y-Stent-Assisted Coiling with Low-Profile Braided Stents

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ABSTRACT

BACKGROUND AND PURPOSE: Coiling complex intracranial bifurcation aneurysms often necessitates the implantation of double stents in various configurations, such as Y-stent placement. Low-profile braided stents have been introduced recently to facilitate the endovascular treatment of wide-neck aneurysms. We aimed to investigate the feasibility, safety, efficacy, and durability of Y-stent-assisted coiling with double low-profile braided stents for the treatment of complex bifurcation aneurysms.

MATERIALS AND METHODS: A retrospective review was performed to identify patients who were treated using Y-stent-assisted coiling with low-profile braided stents. Technical success was assessed, as were initial and follow-up clinical and angiographic outcomes. Periprocedural and delayed complications were reviewed. Preprocedural and follow-up clinical statuses were assessed using the modified Rankin Scale.

RESULTS: Forty patients with 40 intracranial aneurysms were included in the study. Y-stent placement was successfully performed in all cases. Immediate postprocedural digital subtraction angiography images revealed total aneurysm occlusion in 72.5% of cases. The mean angiographic follow-up time was 24.8 months. The last follow-up angiograms showed complete occlusion in 85% of patients. During follow-up, only 1 patient showed an increase in the filling status of the aneurysm and that patient did not require retreatment. There was no mortality in this study. The overall procedure-related complication rate, including asymptomatic complications, was 17.5%. A permanent morbidity developed in 1 patient (2.5%).

CONCLUSIONS: The long-term angiographic and clinical outcomes of this retrospective study demonstrate that Y-stent-assisted coiling using low-profile braided stents is an effective, relatively safe, and durable endovascular treatment for wide-neck and complex bifurcation aneurysms.

Stent-assisted coiling is an endovascular technique that has been described as a method to treat wide-neck intracranial aneurysms. Implantation of a self-expandable stent creates a mechanical scaffold in the parent artery to prevent coil protrusion during the endovascular treatment of wide-neck aneurysms. Several studies have demonstrated the safety, efficacy, and durability of stent-assisted coiling procedures for the treatment of wide-neck aneurysms.¹⁻³ The availability of self-expandable intracranial stents enabled the endovascular treatment of wide-neck

aneurysms that could not be previously coiled. However, endovascular treatment of complex bifurcation aneurysms incorporating >1 daughter branch remains a challenge for neurointerventionalists. Implantation of a single stent may not be sufficient to protect both daughter branches that originate from the neck of a bifurcation aneurysm. Therefore, endovascular treatment of complex bifurcation aneurysms involving multiple daughter branches often necessitates implantation of double stents in various configurations, such as X-, T-, and Y-stent placement.⁴⁻⁸ Among these dual stent-placement techniques, Y-stent-assisted coiling was described by Chow et al⁹ in 2004 and has been widely used to treat complex bifurcation aneurysms.¹⁰ Several studies have shown the safety and efficacy of the Y-stent-assisted coiling procedure using various combinations of open-cell and closed-cell laser-cut stents. However, data regarding the angiographic and clinical outcomes of Y-stent-assisted coiling with 2 braided stents are very limited in the literature.¹¹⁻¹⁵

Low-profile braided stents have been introduced recently to assist in the endovascular treatment of wide-neck intracranial an-

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eurysms located in small arteries.¹⁶⁻¹⁸ These stents can be delivered through microcatheters with an internal diameter of 0.0165 inches; this small diameter facilitates navigation in small vessels and improves the safety of stent placement during the treatment of distal wide-neck aneurysms. Low-profile braided stents have several advantages over laser-cut stents. The former type has a sliding-strut design that allows improved wall apposition and scaffolding compared with what laser-cut stents can achieve. However, because the metal density of low-profile braided stents is higher and the pore sizes are smaller than those of laser-cut stents, there are concerns about the feasibility and safety of performing a Y-stent placement procedure with 2 low-profile braided stents.

In this retrospective study, we aimed to investigate the feasibility, safety, and efficacy of the Y-stent-assisted coiling procedure with double low-profile braided stents for the treatment of complex bifurcation aneurysms. In this study, we used only LEO Baby stents (Balt Extrusion, Montmorency, France), and we also assessed the long-term angiographic and clinical outcomes of patients with complex bifurcation aneurysms treated with Y-stent-assisted coiling using only low-profile braided stents.

MATERIALS AND METHODS

Patient Population

After approval was obtained from the institutional review board of Istanbul Faculty of Medicine, we performed a retrospective review of the interventional data base records. Patients with an intracranial bifurcation aneurysm who were treated with the Y-stent-assisted coiling technique using only low-profile braided stents between July 2012 and January 2018 were identified. In each case with a diagnosis of intracranial aneurysm, the decisions regarding the indication for treatment and the most appropriate method of treatment were made by multidisciplinary neurovascular teams of experienced interventional neuroradiologists and vascular neurosurgeons, who considered multiple factors such as the morphology of the aneurysm sac, the morphologic relationships between the aneurysm neck and daughter branches, the anatomy of the target and parent arteries, the medical condition of the patient, and any contraindications for antiplatelet therapy. A Y-stent-assisted coiling procedure was performed to treat patients with wide-neck and complex bifurcation aneurysms. Wide-neck aneurysms were defined as aneurysms with a dome-to-neck ratio of <2 or a neck diameter of >4 mm. Complex bifurcation aneurysms were defined as wide-neck aneurysms incorporating >1 daughter vessel of an intracranial bifurcation. The patients' medical records and radiologic images were collected. Three interventional neuroradiologists (K.A., S.M., S.A.) evaluated the patients' procedure reports, medical charts, and radiologic images. The patients' demographics, presenting symptoms, location and size of aneurysms, medical history related to intracranial aneurysms, stent deployment success, technical and clinical complications, and degree of aneurysm occlusion were recorded.

Endovascular Procedure

Antiplatelet therapy including 75 mg of clopidogrel and 300 mg of aspirin daily was started at least 5 days before the endovascular procedure in every patient. Platelet aggregation inhibition was

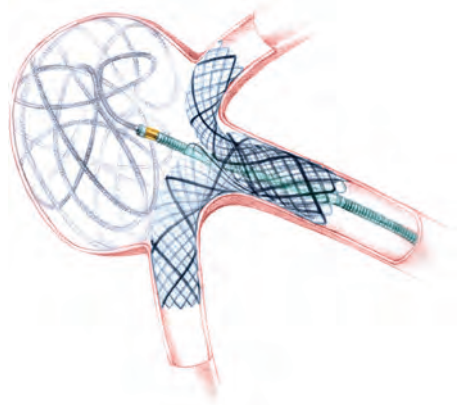


FIG 1. An illustration demonstrating the Y-stent-assisted coiling procedure using 2 braided stents.

tested before the procedure (Multiplate Analyzer, Roche Diagnostics, Mannheim, Germany; or VerifyNow P2Y12 assay, Accu-metrics, San Diego, California) to confirm a good response to clopidogrel. Patients who responded inadequately to clopidogrel were switched to prasugrel (10 mg/day) or ticagrelor (2×90 mg/day).

Every endovascular procedure was performed using a femoral approach with the patient under general anesthesia. Intraprocedural anticoagulation was initiated immediately after the insertion of a femoral introducer sheath with a bolus dose of 5000 IU, followed by a heparin infusion to maintain an activated clotting time between 250 and 300 seconds during the procedure. A 6F guiding sheath (Neuron Max 088; Penumbra, Alameda, California) or an 8F guiding catheter (Envoy; Codman & Shurtleff, Raynham, Massachusetts) was placed into the target artery. Two milligrams of nimodipine (Nimotop) diluted with 0.9% NaCl to a concentration of 0.05 mg/mL was infused through a guiding catheter for 15 minutes (10 mL/min) to prevent the development of vasospasm caused by guidewire or catheter maneuvers. A microcatheter with an internal diameter of 0.0165 inches (Echelon 10 microcatheter, Covidien, Irvine, California; or Vasco 10, Balt Extrusion) for the delivery of the first stent was placed into the daughter branch arising at a more acute angle from the aneurysm neck. Another microcatheter for coiling (Echelon 10; or Headway 17, MicroVention, Tustin, California) was jailed in the sac of the aneurysm before the stents were deployed. A LEO Baby stent was deployed into the first daughter branch, extending proximal to the main parent artery. Then, the second daughter branch was catheterized with a stent-delivery microcatheter by passing through the interstices of the initial stent. The second LEO Baby stent was deployed into the second daughter branch extending proximal to the main parent artery by passing through the interstices of the initial stent, creating a Y-stent configuration. The second stent was deployed by pushing the delivery catheter together with the deployment wire to ensure good expansion of the stent in the interstices of the initial stent. After the deployment of both stents, the coiling procedure was initiated with various bare platinum coils (Target Detachable Coils, Stryker Neurovascular, Kalamazoo, Michigan; MicroPlex/Cosmos/HyperSoft 3D, MicroVention; Axium, Covidien) (Fig 1).

The coiling procedure was considered complete when com-

plete occlusion of the aneurysm sac was achieved or no further coils could be safely deployed (Fig 1). At the end of the endovascular procedure, immediate control digital subtraction angiography images were obtained to check the filling status of the aneurysm and the patency of the stents and intracranial arteries in the territory of the target artery. Hemostasis at the femoral puncture site was achieved using an arterial closure device (ExoSeal, Cordis, Miami Lakes, Florida; or Angio-Seal, St. Jude Medical, St. Paul, Minnesota). A control cranial CT examination was performed before the patient was transferred to the neurointensive care unit. Platelet aggregation testing was repeated before hospital discharge to confirm an inhibition ratio between 60% and 90%. If needed, the antiplatelet drug dosage was adjusted according to the results of platelet aggregation testing. Dual antiplatelet therapy was continued for at least 6 months. Dual antiplatelet therapy was switched to aspirin thereafter.

Angiographic Follow-Up

Immediate postprocedural control DSA images were obtained at the end of the endovascular procedures to assess aneurysm occlusion according to the Raymond classification.¹⁹ The first angiographic follow-up was performed at 6–9 months after the endovascular procedure. The second angiographic follow-up was performed between 12 and 18 months. Considering the results of the second follow-up, the last follow-up DSA was performed at 24–48 months. Thereafter, patients were followed up with MR angiography. Follow-up angiograms were obtained to assess the aneurysm filling status and the development of in-stent stenosis or thrombosis. Progressive thrombosis on follow-up imaging was defined as an improvement in the Raymond class from sac or neck filling (Raymond class 3 or 2) to total occlusion (Raymond class 1). Recanalization was defined as a worsening of the Raymond class.

Clinical Follow-Up

A detailed neurologic examination was performed immediately after the endovascular procedure and at clinical follow-up to assess the development of any neurologic symptoms. Any clinical symptoms or signs that developed during the postoperative period were recorded. Patients' neurologic statuses were evaluated using the modified Rankin Scale during discharge and at clinical follow-up. Clinical follow-up was performed every 3 months in the first year, every 6 months in the second year, and annually thereafter.

Complications developing during the endovascular procedure or within 7 days following the procedure were defined as periprocedural. Clinical complications developing >7 days later were considered delayed complications.

RESULTS

Patients, Demographics, and Aneurysms

Forty patients (25 females and 15 males) with 46 intracranial aneurysms were identified. The mean age of the patients was 52.1 ± 11.4 years (range, 16–65 years). Forty bifurcation aneurysms treated with the Y-stent-assisted coiling technique using LEO Baby stents were included in this study. Six aneurysms treated with other endovascular techniques were excluded from the statistical analyses. Thirty-eight of 40 aneurysms reported in this

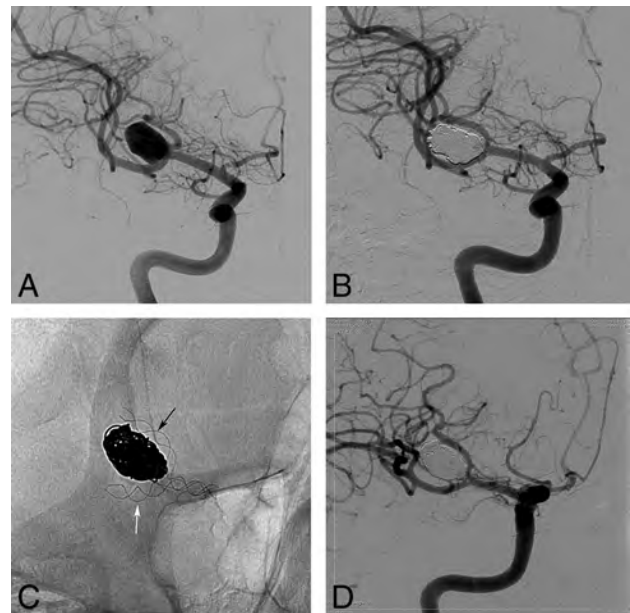


FIG 2. Procedural and follow-up angiographic images of a 58-year-old female patient with an unruptured MCA aneurysm. *A*, A preprocedural DSA image reveals a 12-mm, complex, wide-neck MCA bifurcation aneurysm. The neck of the aneurysm involves the origins of both daughter branches of the bifurcation. *B*, Immediate postprocedural DSA image shows that the aneurysm is completely occluded. *C*, Immediate postprocedural nonsubtracted angiogram obtained just before the contrast injection. The image shows the Y-configuration of the LEO Baby stents overlapping in the M1 segment of the MCA and extending into the upper (black arrow) and lower (white arrow) trunks of the MCA. *D*, A 12-month follow-up DSA image demonstrates complete occlusion of the aneurysm.

study were unruptured. One patient had a wide-neck internal carotid artery bifurcation aneurysm that had ruptured 2 weeks before the endovascular treatment. Another patient had a recurrent anterior communicating artery aneurysm that had been previously coiled following its rupture. Thirty-seven of 40 aneurysms had not been treated previously. Two patients had recanalized anterior communicating artery aneurysms that had been previously treated by balloon-assisted coiling. Another patient with a middle cerebral artery aneurysm was referred to our hospital after a failed open surgery (clipping).

Twenty-two of 40 aneurysms were located in the MCA (55%); 9, in the anterior communicating artery (22.5%); 7, in the basilar bifurcation (17.5%); and 2, in the ICA bifurcation (5%) (Fig 2). The mean size of the aneurysms was 8.4 ± 3.6 mm (range, 3–16 mm). In 3 patients (7.5%), Y-stent-assisted coiling was performed as a bailout technique following coil protrusions developed during the single stent-assisted coiling procedures (Fig 3). Preoperative mRS scores were zero in all patients except 1 who had an mRS score of 2 because of a recent subarachnoid hemorrhage.

Immediate Angiographic Results

The deployment of 2 LEO Baby stents in a Y-configuration was achieved in all cases. A minor technical complication developed during stent deployment in 2 patients (5%). In both patients, the first stents were not fully apposed to the vessel walls. An in-stent balloon angioplasty (Eclipse 2 L, GE Healthcare, Milwaukee, Wisconsin; Scepter XC, MicroVention) achieved full wall apposition

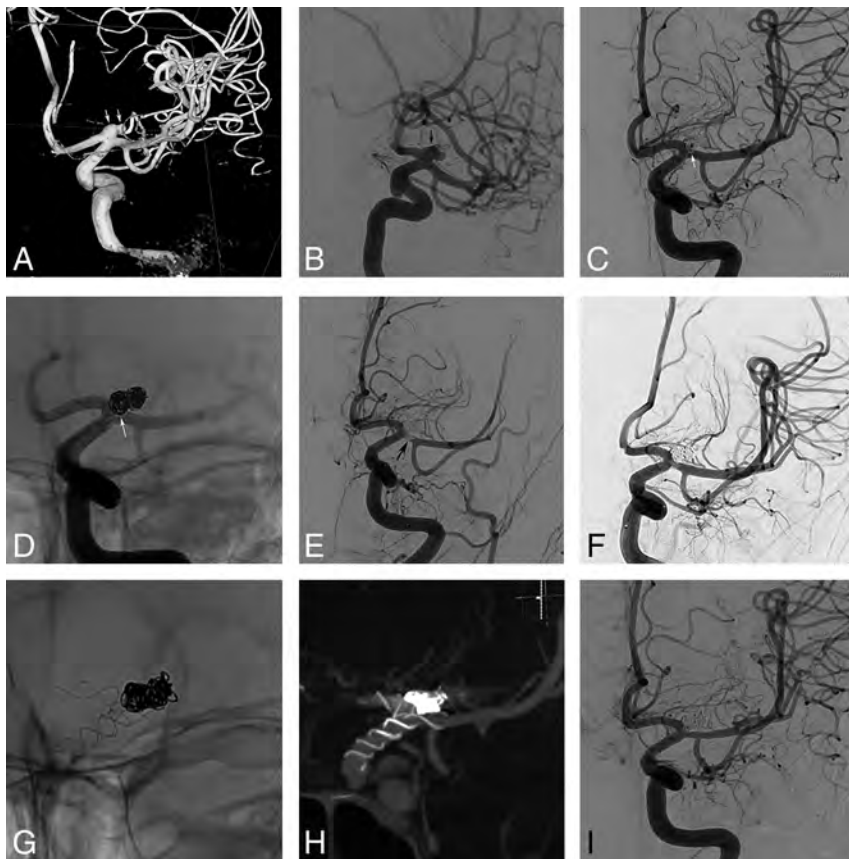


FIG 3. Procedural and follow-up angiograms of a 23-year-old male patient with unruptured bilateral ICA bifurcation aneurysms. Y-stent placement was performed as a bailout procedure after coil protrusion and consequent thrombus development following a single stent-assisted coiling treatment. *A* and *B*, Preprocedural DSA and 3D reconstructed angiograms show a wide-neck 6-mm aneurysm (arrows) located at the left ICA bifurcation. *C* and *D*, Procedural control DSA and nonsubtracted angiograms show that the aneurysm has been coiled with the assistance of a single LEO Baby stent extending from the ICA to the left anterior cerebral artery. The coil mesh (arrows) protrudes into the M1 segment of the MCA. *E*, A procedural DSA image reveals the development of a thrombus (arrow) in the M1 segment of the MCA. *F*, DSA image obtained after a bailout deployment of a second LEO Baby stent into the MCA, creating a Y-configuration with the first stent. As shown in the image, the deployment of the second stent successfully treated the coil protrusion and restored the patency of the MCA. *G* and *H*, Nonsubtracted angiography and an MIP reconstruction image of flat panel CT show the Y-stent configuration with 2 LEO Baby stents. The images clearly show that there is no constriction of the second stent (deployed into the MCA) at the intersection point of the stents. *I*, A 12-month follow-up DSA image shows complete occlusion of the aneurysm and the patency of the stents.

in both cases. The immediate control DSA images revealed total aneurysm occlusion (Raymond class 1) in 29 patients (72.5%), neck filling (Raymond class 2) in 10 aneurysms (25%), and sac filling (Raymond class 3) in 1 aneurysm (2.5%).

Complications

There was no mortality in this study. Periprocedural (6 patients, 15%) or delayed (2.5%) complications developed in 7 patients (17.5%). The complications resulted in neurologic symptoms in 5 patients (12.5%) and a permanent neurologic deficit in 1 patient (2.5%). In 2 patients, intraprocedural control DSA images revealed the development of in-stent thrombi. An intra-arterial bolus infusion of tirofiban (Aggrastat, 1.25 mg diluted in 20 mL of saline) just proximal to the thrombi through the stent-delivery microcatheter caused complete resolution of thrombi in both cases. However, one of these patients experienced mild weakness in the contralateral upper extremity that completely regressed

within 6 hours, and the mRS score of this patient was zero during discharge. One patient with a left MCA aneurysm developed right hemiplegia and dysphasia 4 hours after the completion of the endovascular procedure. Emergent DSA revealed total occlusion of the stent deployed into the upper MCA trunk. A bolus infusion of intra-arterial tirofiban through a microcatheter placed in the M1 segment of the MCA resulted in total recanalization. Although full recanalization was achieved, moderate hemiparesis and dysphasia persisted in this case. The patient's cranial MR imaging examination demonstrated cerebral infarction in the left parietal cortex, and his mRS score was 3 at the final clinical follow-up. In 1 patient with an ICA bifurcation aneurysm, Y-stent placement was performed as an emergent bailout technique to treat coil protrusion and consequent thrombus formation during a single stent-assisted coiling procedure. This patient developed dysphasia that completely resolved within 6 weeks. We observed minor hemorrhagic periprocedural complications in 2 patients (5%) with MCA aneurysms. The immediate postembolization CT images revealed a thin layer of contrast extravasation confined to the ipsilateral Sylvian fissures in both cases. Neither patient developed any neurologic symptoms other than headache that lasted for 1–2 weeks. The mRS score of each patient was zero at discharge.

We observed a delayed thromboembolic complication (2.5%) that remained asymptomatic. The first follow-up DSA of a patient with an ICA bifurcation aneurysm revealed the occlusion of the stent extending into the A1 segment of the anterior cerebral artery. The A2 segment and the cortical branches continued to fill from the anterior communicating artery, and the patient remained asymptomatic.

Preoperative platelet aggregation tests revealed an inadequate response to clopidogrel in 6 patients (15%). The antiplatelet therapy was switched to prasugrel or ticagrelor, and no thromboembolic complication developed in these cases.

Preoperative platelet aggregation tests revealed an inadequate response to clopidogrel in 6 patients (15%). The antiplatelet therapy was switched to prasugrel or ticagrelor, and no thromboembolic complication developed in these cases.

Follow-Up

Every patient had at least 1 follow-up angiographic examination. The mean duration of angiographic follow-up was 24.8 months (range, 6–48 months). The final follow-up angiographic examination revealed Raymond class 1 occlusion in 34 patients (85%), Raymond class 2 occlusion in 5 patients (12.5%), and Raymond class 3 in 1 patient (2.5%). The follow-up angiography of a basilar

tip aneurysm (2.5%) with an immediate Raymond class 1 occlusion showed recanalization (Raymond class 3), after which it remained stable and did not require retreatment. Six of 11 aneurysms (54.5%) with an immediate partial occlusion (Raymond class 2 or 3) showed progressive thrombosis resulting in an advancement in the Raymond class during follow-up.

The mean duration of clinical follow-up was 26.6 months (range, 6–48 months). The mRS score at the final clinical follow-up was zero in 38 of 40 patients. The mRS score of the patient with a preprocedural score of 2 did not change during the follow-up period. The patient who developed a periprocedural MCA infarction had an mRS score of 3 at the final clinical follow-up examination.

DISCUSSION

The Y-stent-assisted coiling technique involves the deployment of 2 proximally overlapping stents into the daughter branches of a bifurcation to reconstruct the wide neck of an aneurysm to prevent coil protrusion. The navigation of stent delivery catheters in the angulated daughter branches, the correct positing of stents, navigation of the second stent through the struts of the first deployed stent, and adequate expansion of the second stent at the intersection point are the relatively complicating technical parts of the Y-stent placement procedure.^{5,20} Laser-cut stents have been used in most previous studies on Y-stent placement.^{4–7,9} In the literature, the technical success rate of Y-stent-assisted coiling ranges between 86% and 100%.^{4–7,9,21} Recently, Bartolini et al⁵ reported the results of X- and Y-stent-assisted coiling treatment of bifurcation aneurysms in 97 patients. These authors preferred to use open/open-cell or open/closed-cell laser-cut stent combinations for Y-stent placement. In their study, they reported the technical complications of excessively distal stent placement and dislocation of the first stents into the aneurysm sacs, resulting in incomplete treatment in 6.2% of the cases.

In a multicenter study reporting the results of Y-stent-assisted coiling using various open- and closed-cell stent combinations, technical complications related to stent deployment occurred in 6.7% of cases.⁶ In the current study, the rate of technical success was comparable with those reported in previous Y-stent-assisted coiling studies. Minor technical complications occurred in 2 patients (5%). However, the complications did not cause treatment failure or permanent morbidity. In this study, we used LEO Baby stents, which could be delivered through low-profile microcatheters with luminal diameters of 0.0165 inches. Navigation in the acutely branched small-sized daughter vessels is easier and safer with low-profile microcatheters than with 0.21-inch microcatheters. Furthermore, because the LEO Baby stents have a braided construction, they are resheathable or repositionable up to approximately 95% of their length, which is a major advantage over nonretrievable open-cell stents for precise stent placement.⁸ Because low-profile braided stents have smaller cell sizes than laser-cut stents, there were unfounded concerns about the technical feasibility of Y-stent placement using low-profile braided stents. However, low-profile braided stents have a sliding-strut design that permits the movement of the struts over each other, causing the expansion of cells in the first stent to accommodate the second deployed stent in Y-stent placement.^{11,22}

In a benchtop study, Makoyeva et al²² reported that Y-stent placement using self-expandable braided stents did not lead to metallic stenosis at the site of stent crossing. The compliant cell size of braided stents facilitates the passage of the microcatheter through the stent and reduces the constriction of the second stent between the struts of the first stent.²³ In our cases, we applied a controlled axial force during the deployment of the second stent by pushing the delivery catheter together with the stent wire. This maneuver facilitates the expansion of the second stent during its deployment between the struts of the first stent. In this study, Y-stent construction was successfully achieved in every case with no major technical complications. The results of this study demonstrate that Y-stent placement using low-profile braided stents is technically feasible.

In this study, we observed the development of complications in 17.5% of cases. Most complications did not result in neurologic deficits, and permanent morbidity developed in only 2.5% of the patients. In a multicenter retrospective study, Fargen et al⁶ analyzed the clinical and angiographic outcomes of 45 aneurysms treated with a Y-stent-assisted coiling technique. Most included aneurysms were unruptured basilar tip aneurysms, and the investigators found a complication rate of 11.1%. Bartolini et al⁵ reported a periprocedural complication rate of 19.6% and a permanent morbidity rate of 10% following Y- or X-stent-assisted coiling procedures. In another study, Spiotta et al²¹ assessed the medium-term results of Y-stent-assisted coiling procedures performed using first- and second-generation Neuroform stents (open cell; Stryker Neurovascular). The investigators observed an exceptionally high periprocedural complication rate of 31.6%. Möhlenbruch et al¹³ reported the medium-term results in 8 patients who were treated with Y-stent-assisted coiling using a double LVIS Jr stent (MicroVention), which is a low-profile braided stent. The team observed a periprocedural ischemic complication in 1 of 8 patients (12.5%) without any permanent consequences. The complication and morbidity rates of the current study are comparable with those of previous Y-stent-placement studies. The favorable clinical outcomes of the patients in the current study suggest that Y-stent-assisted coiling using double low-profile braided stents is a relatively safe endovascular procedure for the treatment of complex bifurcation aneurysms.

In the literature, the immediate aneurysm occlusion rates following Y-stent-assisted coiling are variable.^{4–7,9,21} Spiotta et al reported that immediate complete occlusion was achieved in only 23.6% of the aneurysms treated with Y-stent-assisted coiling.²¹ In the study conducted by Fargen et al,⁶ the immediate total occlusion rate was 43%. Bartolini et al⁵ reported an immediate complete occlusion rate of 46.7%. In the literature, the immediate total occlusion rates following Y-stent-assisted coiling procedures are relatively low compared with the results of single-stent-assisted coiling studies.^{5,19,21} However, when interpreting these results, one should consider that aneurysms treated with the Y-stent-assisted coiling technique are usually large and challenging with highly complex morphology. Furthermore, some surgeons might not force the coiling procedures to achieve immediate complete occlusion, relying instead on the flow-diverting capacity of the Y-stent placement configuration.⁹

In the current study, the rate of immediate total aneurysm

occlusion was 72.5%. These data show that complex bifurcation aneurysms could be effectively treated by coiling with the assistance of double low-profile stents in a Y-configuration. We observed immediate total or near-total occlusion (Raymond classes 1 and 2) in 97.5% of our cases, which is a noticeably high rate compared with the results of previous Y-stent-assisted coiling studies.^{4–8,21} The high scaffolding and flow-diversion capacity of the low-profile braided stent used in this study may have contributed to this relatively high immediate aneurysm occlusion rate.^{23,24} Furthermore, we did not rely on the flow-diversion capacity of the stents, and we continued the coiling procedure until complete occlusion was achieved or no further coils could be safely deployed.

The recurrence risk of aneurysms treated with stent-assisted coiling is significantly lower than that of aneurysms treated with primary coiling or balloon-remodeling techniques.²⁵ Stents have some biologic and hemodynamic effects on the parent arteries that promote the progressive thrombosis of aneurysms and reduce the risk of recanalization. Implantation of stents causes a flow-diversion effect that decreases the hemodynamic stress on the aneurysm sac and facilitates thrombosis of aneurysms.²⁶ Moreover, stent implantation induces endothelialization that progresses over the stent struts and leads to healing of the aneurysm neck.²⁷ Kono and Tereda²⁸ used a computational fluid dynamics model to investigate the hemodynamic effects of different stent-placement configurations. Those investigators found that the Y-stent-placement configuration caused the strongest reduction of flow velocity in aneurysms. Chalouhi et al²⁹ reported that the recurrence and retreatment rates of basilar bifurcation aneurysms treated with Y-stent-assisted coiling were significantly lower than those of aneurysms coiled with the assistance of single stents. In support of these findings, we observed progressive thrombosis in 54.5% of the aneurysms with initial partial filling, and complete aneurysm occlusion was achieved in 85% of patients during the 24.8-month follow-up. Only 1 patient showed a recurrence, which did not require retreatment.

The current study has some limitations that should be acknowledged. This study was a nonrandomized retrospective study. Therefore, there was no control group of patients who underwent alternative endovascular treatments. Additionally, the effects of patient-selection bias cannot be excluded from the results.

CONCLUSIONS

Coiling with the assistance of double low-profile braided stents in a Y-configuration is a feasible endovascular technique. The long-term angiographic and clinical outcomes of this retrospective study demonstrate that Y-stent-assisted coiling using low-profile braided stents is an effective, relatively safe, and durable endovascular method for the treatment of wide-neck and complex bifurcation aneurysms.

REFERENCES

1. Akpek S, Arat A, Morsi H, et al. **Self-expandable stent-assisted coiling of wide-necked intracranial aneurysms: a single-center experience.** *AJNR Am J Neuroradiol* 2005;26:1223–31 Medline
2. Piotin M, Blanc R, Spelle L, et al. **Stent-assisted coiling of intracranial aneurysms: clinical and angiographic results in 216 consecutive aneurysms.** *Stroke* 2010;41:110–15 CrossRef Medline
3. Lopes DK, Johnson AK, Kellogg RG, et al. **Long-term radiographic results of stent-assisted embolization of cerebral aneurysms.** *Neurosurgery* 2014;74:286–91 CrossRef Medline
4. Thorell WE, Chow MM, Woo HH, et al. **Y-configured dual intracranial stent-assisted coil embolization for the treatment of wide-necked basilar tip aneurysms.** *Neurosurgery* 2005;56:1035–40; discussion 1035–40 Medline
5. Bartolini B, Blanc R, Pistocchi S, et al. **“Y” and “X” stent-assisted coiling of complex and wide-neck intracranial bifurcation aneurysms.** *AJNR Am J Neuroradiol* 2014;35:2153–58 CrossRef Medline
6. Fargen KM, Mocco J, Neal D, et al. **A multicenter study of stent-assisted coiling of cerebral aneurysms with a Y configuration.** *Neurosurgery* 2013;73:466–72 CrossRef Medline
7. Akgul E, Aksungur E, Balli T, et al. **Y-stent-assisted coil embolization of wide-neck intracranial aneurysms: a single center experience.** *Interv Neuroradiol* 2011;17:36–48 CrossRef Medline
8. Aydin K, Sencer S, Barbuoglu M, et al. **Midterm results of T-stent-assisted coiling of wide-necked and complex intracranial bifurcation aneurysms using low-profile stents.** *J Neurosurg* 2017;127:1288–96 CrossRef Medline
9. Chow MM, Woo HH, Masaryk TJ, et al. **A novel endovascular treatment of a wide-necked basilar apex aneurysm by using a Y-configuration, double-stent technique.** *AJNR Am J Neuroradiol* 2004;25:509–12 Medline
10. Limbucci N, Renieri L, Nappini S, et al. **Y-stent assisted coiling of bifurcation aneurysms with Enterprise stent: long-term follow-up.** *J Neurointerv Surg* 2016;8:158–62 CrossRef Medline
11. Akmangit I, Aydin K, Sencer S, et al. **Dual stenting using low-profile LEO baby stents for the endovascular management of challenging intracranial aneurysms.** *AJNR Am J Neuroradiol* 2015;36:323–29 CrossRef Medline
12. Behme D, Weber A, Kowoll A, et al. **Low-profile visualized intraluminal support device (LVIS Jr) as a novel tool in the treatment of wide-necked intracranial aneurysms: initial experience in 32 cases.** *J Neurointerv Surg* 2015;7:281–85 CrossRef Medline
13. Möhlenbruch M, Herweh C, Behrens L, et al. **The LVIS Jr. microstent to assist coil embolization of wide-neck intracranial aneurysms: clinical study to assess safety and efficacy.** *Neuroradiology* 2014;56:389–95 CrossRef Medline
14. Conrad MD, Brasiense LB, Richie AN, et al. **Y stenting assisted coiling using a new low profile visible intraluminal support device for wide necked basilar tip aneurysms: a technical report.** *J Neurointerv Surg* 2014;6:296–300 CrossRef Medline
15. Samaniego EA, Mendez AA, Nguyen TN, et al. **LVIS Jr device for Y-stent-assisted coil embolization of wide-neck intracranial aneurysms: a multicenter experience.** *Interv Neurol* 2018;7:271–83 CrossRef Medline
16. Shankar JJS, Quateen A, Weill A, et al. **Canadian registry of LVIS Jr for Treatment of Intracranial Aneurysms (CaRLA).** *J Neurointerv Surg* 2017;9:849–53 CrossRef Medline
17. Iosif C, Piotin M, Saleme S, et al. **Safety and effectiveness of the low profile visualized intraluminal support (LVIS and LVIS Jr) devices in the endovascular treatment of intracranial aneurysms: results of the TRAIL multicenter observational study.** *J Neurointerv Surg* 2018;10:675–81 CrossRef Medline
18. Aydin K, Arat A, Sencer S, et al. **Stent-assisted coiling of wide-neck intracranial aneurysms using low-profile LEO Baby stents: initial and midterm results.** *AJNR Am J Neuroradiol* 2015;36:1934–41 CrossRef Medline
19. Raymond J, Roy D. **Safety and efficacy of endovascular treatment of acutely ruptured aneurysms.** *Neurosurgery* 1997;41:1235–45; discussion 1245–46 CrossRef Medline
20. Spiotta AM, Lena J, Chaudry MI, et al. **Y-stenting for bifurcation aneurysm coil embolization: what is the risk?** *Stroke Res Treat* 2014;2014:762389 CrossRef Medline
21. Spiotta AM, Gupta R, Fiorella D, et al. **Mid-term results of endovascular coiling of wide-necked aneurysms using double stents**

- in a Y configuration. *Neurosurgery* 2011;69:421–29 [CrossRef Medline](#)
22. Makoyeva A, Darsaut TE, Salazkin I, et al. **Y-crossing of braided stents with stents and flow diverters does not cause significant stenosis in bench-top studies.** *Interv Neuroradiol* 2013;19:455–60 [CrossRef Medline](#)
 23. Aydin K, Barbuoglu M, Sencer S, et al. **Flow diversion with low-profile braided stents for the treatment of very small or uncoilable intracranial aneurysms at or distal to the circle of Willis.** *AJNR Am J Neuroradiol* 2017;38:2131–37 [CrossRef Medline](#)
 24. Cho SH, Jo WI, Jo YE, et al. **Bench-top comparison of physical properties of 4 commercially-available self-expanding intracranial stents.** *Neurointervention* 2017;12:31–39 [CrossRef Medline](#)
 25. Chalouhi N, Starke RM, Koltz MT, et al. **Stent-assisted coiling versus balloon remodeling of wide-neck aneurysms: comparison of angiographic outcomes.** *AJNR Am J Neuroradiol* 2013;34:1987–92 [CrossRef Medline](#)
 26. Cantón G, Levy DI, Lasheras JC. **Hemodynamic changes due to stent placement in bifurcating intracranial aneurysms.** *J Neurosurg* 2005;103:146–55 [CrossRef Medline](#)
 27. Kadirvel R, Ding YH, Dai D, et al. **Cellular mechanisms of aneurysm occlusion after treatment with a flow diverter.** *Radiology* 2014;270:394–99 [CrossRef Medline](#)
 28. Kono K, Terada T. **Hemodynamics of 8 different configurations of stenting for bifurcation aneurysms.** *AJNR Am J Neuroradiol* 2013;34:1980–86 [CrossRef Medline](#)
 29. Chalouhi N, Jabbour P, Gonzalez LF, et al. **Safety and efficacy of endovascular treatment of basilar tip aneurysms by coiling with and without stent assistance: a review of 235 cases.** *Neurosurgery* 2012;71:785–94 [CrossRef Medline](#)

How to Size Intracranial Aneurysms: A Phantom Study of Invasive and Noninvasive Methods

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ABSTRACT

BACKGROUND AND PURPOSE: Endovascular treatment of intracranial aneurysms has relevantly changed over the past decades. Multiple new devices such as intrasaccular flow diverters have broadened the treatment spectrum but require very exact aneurysm sizing. In this study, we investigated multidetector and flat panel angiographic CT and digital subtraction imaging as well as different postprocessing methods (multiplanar reconstruction, volume-rendering technique, 3D DSA, and conventional 2D angiography) for their ability to exactly size 2 aneurysm models.

MATERIALS AND METHODS: Two aneurysm models with known aneurysm sizes were placed inside a human skull. After injection of iodine contrast media, imaging was performed using a 128-slice CT scanner or an Artis Q biplane angiosuite, respectively. Aneurysms were measured for width, neck, and height, and the mean difference from the known sizes was calculated for each technique. The technique with the most exact measurement was defined as the criterion standard. We performed Bland-Altman plots comparing all techniques against the criterion standard.

RESULTS: Angiograms adjusted according a previous 3D run with a short object-to-detector distance resulted in the most exact aneurysm measurement: -0.07 ± 0.61 mm for aneurysm 1 and 0.17 ± 0.39 mm for aneurysm 2. Measurements of conventional DSA images were similar, and CT-based images were significantly inferior to the criterion standard.

CONCLUSIONS: 2D DSA with a short objective-to-detector distance adjusted according to a previous 3D run resulted in the most exact aneurysm measurement and should therefore be performed before all endovascular aneurysm treatments.

ABBREVIATIONS: FDCTA = flat panel detector CTA; MDCTA = multidetector row CTA; VRT = volume-rendering technique

Endovascular treatment of ruptured aneurysms has become the standard of care, and it is also a well-accepted alternative to microsurgical clipping for the treatment of unruptured aneurysms.^{1,2} However, in anatomically challenging aneurysms such as broad-based bifurcational aneurysms, coil embolization alone is of limited use. Therefore numerous adjunctive devices and intraluminal and intrasaccular flow diverters for intra-arterial aneurysm repair have been developed during the past decade and are currently used in clinical practice.³⁻⁵ Some of these new devices such as the Woven EndoBridge (WEB) aneurysm embolization system (Sequent Medical, Aliso Viejo, California) require a very

exact preinterventional aneurysm sizing for favorable angiographic results.⁴ Simultaneously, aneurysm imaging has emerged significantly with the introduction of 3D digital subtraction angiography and different reconstruction modalities (MPR) and the volume-rendering technique (VRT) for multidetector row CT angiography (MDCTA) and flat panel detector CT angiography (FDCTA). However, until recently, only a few studies have examined the capability of these different techniques regarding the accuracy of intracranial aneurysm sizing, yielding contradictory findings.⁶⁻⁹ The aim of this study was to evaluate different image-acquisition and reconstruction techniques in regard to their ability to optimize preinterventional device sizing in endovascular aneurysm repair.

MATERIALS AND METHODS

Phantom Preparation and Image Acquisition

Intracranial aneurysms were simulated using 2 different 3D aneurysm models printed according to a 3D angiographic dataset with a Form 2 printer (Formlabs, Somerville, Massachusetts). Known sizes of the aneurysms were the following—aneurysm 1:

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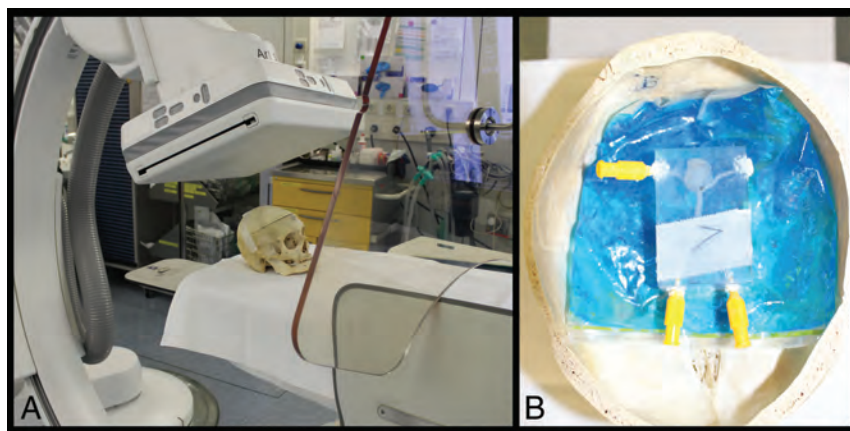


FIG 1. Experimental setup of an aneurysm model inside a human skull on the biplane Artis Q angiosuite.

Table 1: Examination parameters

	MDCTA	FDCTA	3D DSA	DSA
FOV (cm)	10 × 10	10 × 10	10 × 10	15 × 15
Matrix size	512 × 512	512 × 512	512 × 512	1024 × 1024
In-plane resolutions (mm)	0.2	0.2	0.29	0.15
Cumulative dose (mGy)	30	40	9	53

neck, 7.5 mm; height, 10.9 mm; width, 11.0 mm; aneurysm 2: neck, 3.2 mm; height, 3.7 mm; width, 3.4 mm.

For a better simulation of a clinical setting, the models were placed in a human skull (Fig 1). Both models were examined in the 3 different modalities (MDCTA, FDCTA, DSA) 5 times with different positions of the model. For MDCTA and FDCTA, the silicone models were filled with diluted iodinated contrast agent (Imeron 400, iopamidol; Bracco, Milan, Italy). For DSA runs, 50% diluted contrast agent and saline flush were injected during image acquisition. DSA runs were performed with 3 different detector distances from the model (as short as technically possible = near; as far away as possible = long; and in middle position = middle); 3D DSA and DSA runs that were adjusted to the optimal projection of the 3D run, again with 3 different positions of the detector. Each examination was performed with 5 different positions of the skull/aneurysm, resulting in 90 acquisitions and 120 datasets.

The nomenclature used in this study is as follows: MDCTA or FDCTA, MPR and VRT. DSA long, middle, or near represents 2D-DSA images with different detector differences; and DSA rotation near, middle, and long represents 2D-DSA images that were acquired according an optimal projection from the rotational images of a 3D-DSA. Additionally, 3D-DSA MPR and VRT represent reconstructed images from the 3D-DSA.

DSA and FDCTA images were acquired with biplane flat panel angiography (Artis Q; Siemens, Erlangen, Germany). For the FDCTA, we used a commercially available FDCTA sequence (DynaCT Clear; Siemens) with 10 seconds of rotation, 70 kV, 1.2 μ Gy/frame, 200° angle, 0.8°/frame angulation step, weighted CT dose index of approximately 40 mGy. For 3D DSA, we applied the syngo DynaCT (Siemens) 3D setup with 5-second rotational time, 70 kV, 0.36 μ Gy/frame, 200° angle, 0.8°/frame angulation step, weighted CT dose index of approximately 9mGy. MDCTA images were acquired on a 128-section CT scanner (Somatom

Definition AS+; Siemens) with the following parameters: 128-row collimation at 0.6 mm; pitch = 0.6; acquisition parameters at 120 kV/140 effective mA (Table 1). The raw data were transformed into a volume dataset using a sharp reconstruction kernel (only for MDCTA) and a slice thickness of 0.6 mm. Postprocessing of the rotational data and measurements of the MDCTA and FDCTA as well as VRT and MPR images was performed on a syngo workstation (syngo X Workplace; Siemens) using the 3D or/and 4D tool (Siemens). Reconstruction of the 3D-DSA VRT and FDCTA VRT images was performed with a smooth kernel and small VOI, whereas MPR images were acquired from a normal kernel and large VOI (Fig 2).

Image and Statistical Analysis

Each examination was analyzed and measured individually on the previously mentioned syngo workstation by 3 readers

with different experiences in aneurysm diagnostics and treatment (M.N.P. with > 7 years, D.B. with >5 years, N.A. with >3 years) who did not perform the examinations. The readers were blinded to the aneurysm model. They were asked to measure 3 dimensions of the aneurysm: neck and maximal width and height. Window levels and settings for MPR as well as VRT were not standardized, allowing all readers to choose their personal preferences. The mean of the 3 raters was compared with the known sizes of the aneurysms. The differences in the means for all techniques were calculated. The technique with the smallest deviation (in mean and smallest SD) from the known aneurysm sizes was defined as the criterion standard. To compare the different techniques, we generated Bland-Altman plots for all techniques comparing them to the criterion standard by plotting the differences between the 2 methods against the mean of the 2 techniques. Arithmetic mean, 95% CI of the arithmetic mean, lower and upper limits (± 1.96 SD), and 95% confidence intervals were calculated. We calculated interrater agreement using the interclass correlation coefficient, considering an interclass correlation coefficient of >0.8 as representing almost perfect agreement. Statistical analyses were performed using MedCalc for Windows (MedCalc Software, Mariakerke, Belgium).

RESULTS

Of all applied techniques and reconstructions, 2 DSA images acquired in an optimal projection according to a previous rotational angiogram and a short object-to-detector distance (DSA rotation near) resulted in the smallest mean difference and SD compared with the known aneurysm size. The measurements of all 3 raters resulted in a -0.07 ± 0.61 mm mean difference for aneurysm 1 and 0.12 ± 0.25 mm mean difference for aneurysm 2. 2D-DSA images with medium and long detector distances resulted in similar measurements, whereas MPR and VRT from either MDCTA, FDCTA, or even DSA resulted in larger mean differences. (For an overview of all techniques, see Tables 2 and 3 and Fig 3.) Accordingly, the analysis of the

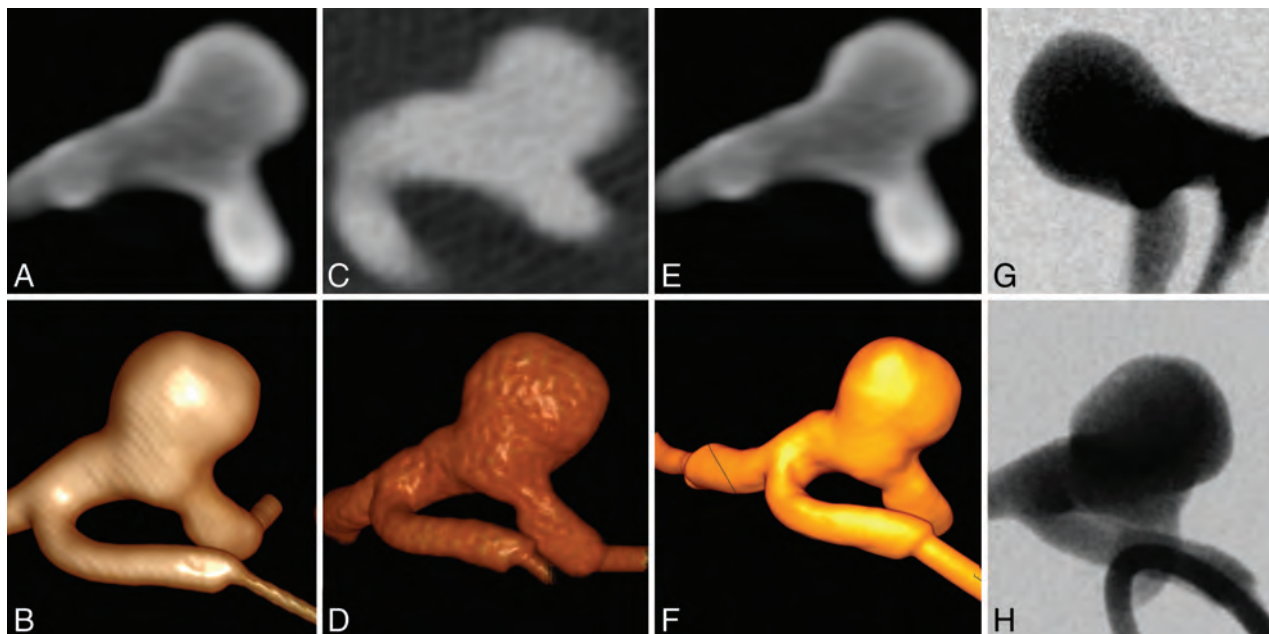


FIG 2. Examples of the different image techniques applied: MPR and VRT of MDCTA images (A and B), MPR and VRT images of FDCTA images (C and D), MPR and VRT images obtained from a 3D-DSA run (E and F), short object-to-detector distance DSA image no optimal projection (G), and optimized projection DSA image with short object-to-detector distance (H, DSA rotation near).

Table 2: Aneurysm model 1—mean of differences in known aneurysm sizes (all 3 dimensions combined)

Statistics/Technique	Mean (mm)	SD	SE of Mean	Lower 95% CI	Upper 95% CI
FDCTA MPR	0.75	1.64	0.24	0.26	1.24
FDCTA VRT	0.99	0.69	0.10	0.78	1.20
MDCTA MPR	1.15	1.26	0.19	0.77	1.52
MDCTA VRT	1.91	0.69	0.10	1.70	2.11
DSA long	0.50	0.84	0.13	0.25	0.75
DSA middle	0.65	0.52	0.08	0.49	0.80
DSA near	0.66	0.71	0.11	0.45	0.87
3D DSA MPR	1.10	1.55	0.23	0.63	1.56
3D DSA VRT	1.19	0.69	0.10	0.98	1.40
DSA rotation long	−0.05	1.71	0.25	−0.56	0.47
DSA rotation middle	−0.15	0.64	0.09	−0.34	0.04
DSA rotation near	−0.07	0.61	0.09	−0.25	0.18

Note:—SE indicates standard error.

Table 3: Aneurysm model 2—mean of differences in known aneurysm sizes (all 3 dimensions combined)

Statistics/Technique	Mean (mm)	SD	SE of Mean	Lower 95% CI	Upper 95% CI
FDCTA MPR	0.62	0.60	0.09	0.44	0.79
FDCTA VRT	0.40	0.48	0.07	0.25	0.54
MDCTA MPR	0.54	0.31	0.05	0.45	0.63
MDCTA VRT	0.83	0.37	0.06	0.72	0.94
DSA long	0.57	0.69	0.10	0.37	0.78
DSA middle	0.51	0.66	0.10	0.31	0.70
DSA near	0.63	0.73	0.11	0.41	0.85
3D DSA MPR	0.41	0.40	0.06	0.29	0.53
3D DSA VRT	0.68	0.49	0.07	0.53	0.82
DSA rotation long	−0.05	0.34	0.05	−0.15	0.05
DSA rotation middle	0.17	0.39	0.06	0.052	0.28
DSA rotation near	0.12	0.25	0.04	0.05	0.20

Note:—SE indicates standard error.

mean differences in DSA rotation near was defined as the criterion standard, and Bland-Altman plots were calculated for all other techniques compared with the criterion standard (Fig 3). When com-

pared with DSA images acquired in the same projection (optimized according the rotational images) but with other distances of the detector, the smallest differences in the mean were found. The arithmetic mean difference between DSA rotation near and DSA rotation middle was 0.01 (95% CI, −0.08–0.11; lower limit: −0.89; 95% CI, −1.05–0.7; upper limit: 0.91; 95% CI, 0.75–1.08) and 0.9 (95% CI, −0.04–0.21, lower limit: −1.13; 95% CI, −1.36 to −0.91; upper limit: 1.31; 95% CI, 1.09–1.54) for DSA rotation long, respectively. In comparison with normal DSA images (no optimized projection), the smallest difference in the mean was found for the DSA images obtained with a long detector-to-object distance, with a mean difference of −0.48 (95% CI, −0.63 to −0.33; lower limit: −1.90; 95% CI, −2.16 to −1.64; upper limit: 0.94; 95% CI, 0.68–1.20). The mean difference was −0.51 (95% CI, −0.67 to −0.36; lower limit: −1.98; 95% CI, −2.25 to −1.71; upper limit: 0.95; 95% CI, 0.68–1.22) for the middle distance and −0.58 (95% CI, −0.75 to −0.41; lower limit: −2.15; 95% CI, −2.44 to −1.86; upper limit: 0.99; 95% CI, 0.70–1.28) for the near detector position.

When comparing DSA rotation near measurements with MPR and VRT images derived from 3D-DSA, a smaller mean difference was found for rotational DSA MPR images: −0.72 (95% CI, −0.98 to −0.46; lower limit: −3.19, 95% CI, 3.64 to −2.74; upper limit: 1.75; 95% CI, 1.30–2.20 versus −0.86; 95% CI, −1.03 to −0.69; lower limit: −2.49, 95% CI, −2.9 to −2.19, upper limit: 0.77; 95% CI, 0.47–1.07) for rotational DSA VRT images. The comparison with angiographic images from MDCT resulted in a mean difference of −0.84 (95% CI, −1.05 to −0.62; lower limit: −2.89; 95% CI, −3.27 to −2.52; upper limit: 1.22; 95% CI, 0.85–1.60). Comparable measurements were obtained using VRT images derived from the MDCTA data, resulting in a mean difference from DSA rotational near of −1.34 (95% CI, −1.56 to −1.13; lower limit: −3.37; 95% CI, −3.74 to −2.99; upper limit: 0.68; 95% CI, 0.31–1.05).

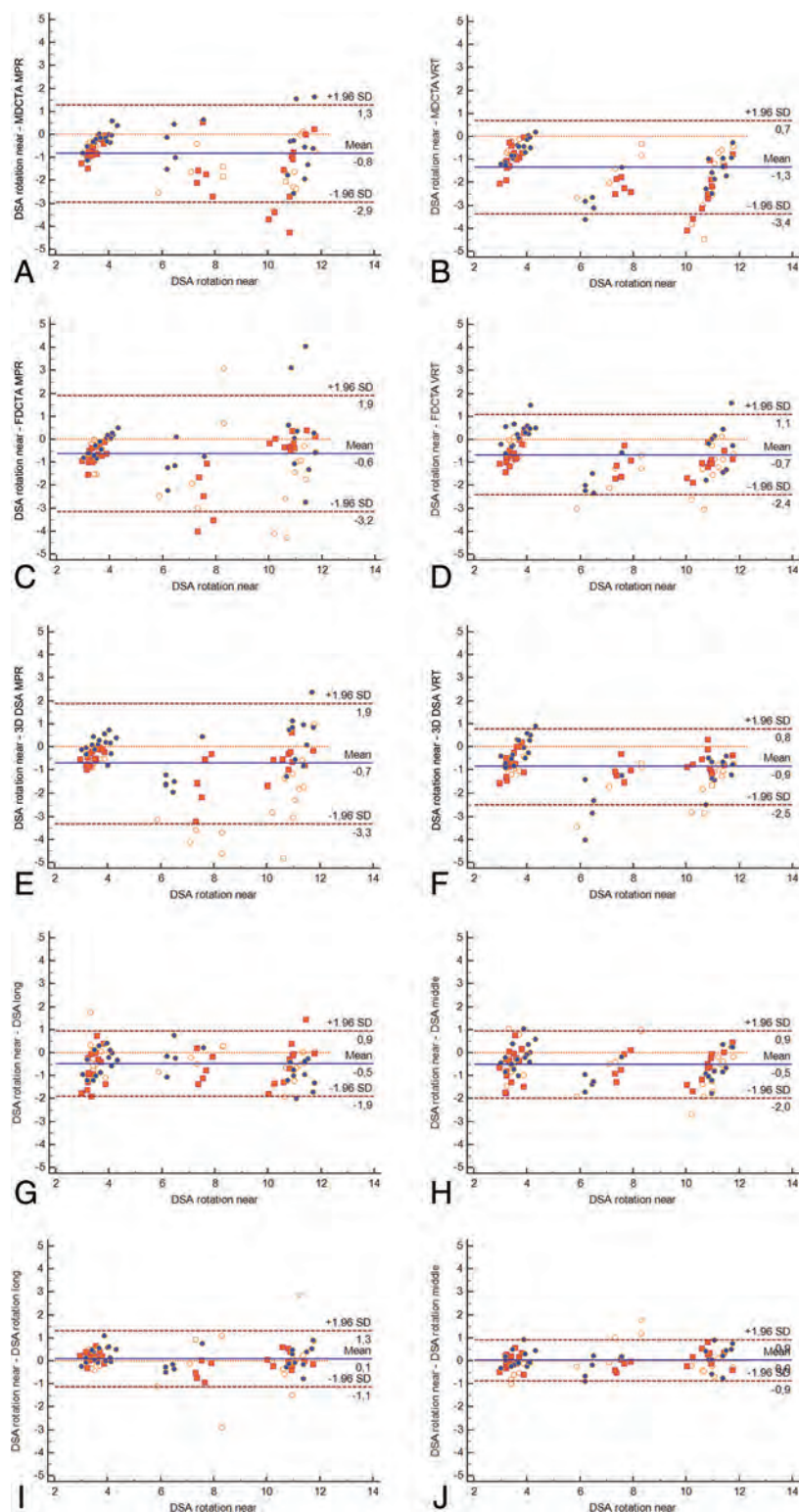


FIG 3. Bland-Altman plots comparing all techniques with DSA rotation near MDCTA MPR (A) versus DSA rotation near MDCTA VRT (B) versus DSA rotation near FDCTA MPR (C) versus DSA rotation near FDCTA VRT (D) versus DSA rotation near 3D DSA MPR (E) versus DSA rotation near 3D DSA VRT (F) versus DSA rotation near DSA long (G) versus DSA rotation near DSA middle (H) versus DSA rotation near DSA rotation long (I) versus DSA rotation near DSA rotation middle (J).

When image acquisition was performed using the flat panels of the angiography scanner, we measured the following mean differences: -0.67 (95% CI, -0.86 to -0.49 ; lower limit: -2.37 ; 95%

CI, -2.68 to -2.06 ; upper limit: 1.02 ; 95% CI, 0.71 – 1.33) for VRT images reconstructed from a FDCTA run and -0.64 (95% CI, -0.91 to -0.37 ; lower limit: -3.14 ; 95% CI, -3.60 to -2.68 ; upper limit: 1.86 ; 95% CI, 1.40 – 2.32). For an overview of all arithmetic means and lower and upper limits including CIs see Table 4; all Bland-Altman plots can be found in Fig 3.

DISCUSSION

Endovascular aneurysm repair has become the standard of care for ruptured intracranial aneurysms during the past decades.¹ Along with this clinical development, a broad range of adjunctive devices for the endovascular treatment of intracranial aneurysms has been developed, and several of them are currently used in clinical practice. For all of these devices, sizing is a critical issue and additionally too adjunctive devices and all types of flow diverters; even the sizing of standard coils has a relevant impact on occlusion rates after endovascular treatment.^{4,10,11} From a technical and clinical point of view, sizing should thereby have the accuracy of ± 1 mm because most devices are available in 1-mm steps. However, until recently, there were no guidelines or consensus on how intracranial aneurysm sizing should be performed, and only a few studies have focused on this issue though there is growing evidence for the importance of the chosen image technique and reconstruction method applied.^{12–14} Considering the above-mentioned dimension of 1-mm deviation to be clinically relevant, our study revealed 2D-DSA images adjusted to previous 3D DSA (optimal projection) performed the best in terms of accuracy when comparing the absolute mean difference and SD of the aneurysm dimensions with -0.07 ± 0.61 for aneurysm 1 and 0.12 ± 0.25 for the second aneurysm model. Therefore, all other techniques in this study were compared with this predefined criterion standard.

Considering the lower and upper limits of the Bland-Altman plots to represent our defined goal of 1-mm accuracy, only DSA images with optimized

projection (according to a previous 3D run) and middle detector position fulfilled the requirement of being equivalent to 2D-DSA images with optimal projection and short detector distance

Table 4: Statistical analyses of the Bland-Altman plots comparing all techniques against DSA rotation “near” images

Statistics/Technique	Arithmetic Mean Differences (95% CI)	Lower Limit (95% CI)	Upper Limit (95% CI)
FDCTA MPR	−0.64 (−0.91 to −0.37)	−3.14 (−3.60 to −2.68)	1.86 (1.40–2.32)
FDCTA VRT	−0.67 (−0.86 to −0.49)	−2.37 (−2.68 to −2.06)	1.02 (0.71–1.33)
MDCTA MPR	−0.84 (−1.05 to −0.62)	−2.89 (−3.27 to −2.52)	1.22 (0.85–1.60)
MDCTA VRT	−1.34 (−1.56 to −1.13)	−3.37 (−3.74 to −2.99)	0.68 (0.31–1.05)
DSA long	−0.48 (−0.63 to −0.33)	−1.90 (−2.16 to −1.64)	0.94 (0.68–1.20)
DSA middle	−0.51 (−0.67 to −0.36)	−1.98 (−2.25 to −1.71)	0.95 (0.68–1.22)
DSA near	−0.58 (−0.75 to −0.41)	−2.15 (−2.44 to −1.86)	0.99 (0.70–1.28)
3D DSA MPR	−0.72 (−0.98 to −0.46)	−3.19 (−3.64 to −2.74)	1.75 (1.30–2.20)
3D DSA VRT	−0.86 (−1.03 to −0.69)	−2.49 (−2.9 to −2.19)	0.77 (0.47–1.07)
DSA rotation long	0.89 (−0.04 to −0.21)	−1.13 (−1.36 to −0.91)	1.31 (1.09–1.54)
DSA rotation middle	0.01 (−0.08 to −11)	−0.89 (−1.05 to −0.71)	0.91 (0.75–1.08)

Table 5: Interclass correlation coefficient for all techniques

Technique	ICC	95% CI
FDCTA MPR	0.8801	0.7932–0.9366
FDCTA VRT	0.9518	0.9078–0.9759
MDCTA MPR	0.9532	0.9065–0.9772
MDCTA VRT	0.9849	0.9712–0.9925
DSA long	0.9652	0.9377–0.9820
DSA middle	0.9838	0.9705–0.9917
DSA near	0.9806	0.9648–0.9901
3D DSA MPR	0.9063	0.7781–0.9577
3D DSA VRT	0.8638	0.7676–0.9275
DSA rotation long	0.8638	0.7676–0.9275
DSA rotation middle	0.9834	0.9700–0.9915
DSA rotation near	0.9855	0.9737–0.9926

Note:—ICC indicates interclass correlation coefficient.

(Table 4) with an arithmetic mean difference of 0.01 and a lower limit of −0.89 and an upper limit of 0.91 (Table 4). Although all techniques besides MDCTA VRT had arithmetic mean differences of <1 mm (Table 4), their lower and upper limits were significantly different (Fig 3) and the 95% CI of the mean difference was outside our 1-mm goal. Accordingly, in general, small differences in the interclass correlation coefficient were very high in all techniques, favoring VRT over MPR reconstructions for MDCTA- and FDCTA and with slightly better results for DSA images (Table 5) compared with CT images.

If not only mean differences of the techniques but also 95% CI as well as upper and lower limits of the Bland-Altman plots are considered, 2D DSA images performed in a projection adjusted to a previous 3D run are the only images that fulfilled our predefined quality standards in virtually all investigations. When we looked more closely at the results of the CT-based CTA analysis, this study shows that MDCTA MPR and VRT measurements of both aneurysms resulted in significant overestimation of the aneurysm size. For MDCTA MPR, the mean difference was 1.15 ± 1.26 mm for aneurysm 1 and 0.54 ± 0.31 mm for aneurysm 2 compared with the known sizes of the aneurysms. The Bland-Altman plots depicted larger discrepancies between the MDCTA-derived MPR and VRT images for larger dimensions of the aneurysms (Fig 3). These results confirm what has been known of the capability of MDCTA-derived measurements of intracranial stenosis.¹⁵ Regarding MDCTA, a sharp reconstruction kernel is thought to lead to very exact aneurysm imaging compared with a smooth kernel, and if a 3D DSA was used as the criterion standard what could not been proved in our study because in our setting 3D DSA also overestimated aneurysm sizes.¹³ However, the use of different reconstruction kernels does play a critical role in not only

MDCTA but also 3D-DSA as has been described recently by Lauric et al.¹²

In this study, different kernels were used for different purposes, and we found 3D-DSA VRT and MPR images from smooth/normal kernel reconstructions to overestimate aneurysm sizes, in line with findings of Lauric et al¹² recently. Most interesting, Lauric et al and O’Meara et al¹³ compared different techniques and different reconstruction kernels with 3D-DSA images, which we found to significantly overestimate aneurysm sizes and therefore were not recommended for use as a criterion standard in aneurysm sizing. In another study, Ruedinger et al¹⁶ reported that edge-enhancement reconstructions with a smooth or normal kernel resulted in the most accurate measurements of aneurysms, which supports our experimental setup using these reconstruction algorithms. Additionally, Bland-Altman plot analysis showed that 3D-DSA MPR and VRT images overestimated larger aneurysm dimensions more than smaller dimensions. In terms of accuracy, FDCTA MPR and VRT images had smaller mean differences to the known aneurysm sizes compared with MDCTA or 3D-DSA (Tables 2 and 3). When we compared FDCTA VRT and MPR versus MDCTA VRT and MPR, it became evident that both had smaller mean differences in sizing with the chosen criterion standard (DSA rotation near). These findings are similar to those reported in the literature for intracranial vessels or stenosis measurement and for intracranial aneurysms.^{6,7,15,17}

From a clinical point of view, most techniques investigated in this study produced accurate measurements of the aneurysm models. However, when it comes to device sizing, one should be aware that only optimized DSA images (ie, optimal projection) resulted in almost perfect measurements with <1-mm deviation toward the lower and upper limits of the Bland-Altman plots. Regarding the radiation dose applied, a 3D-DSA run with a 5-second rotation time has a significantly lower dose compared with a biplane DSA run or MDCTA/FDCTA, which suggests that an initial 3D run for planning of optimized 2D images (optimized projection) leads to optimal 2D images for aneurysm measurement and treatment planning and lower doses.^{18,19}

There are several limitations to our study. The main limitation is the phantom design, though it allows a comparison with known aneurysm sizes. However, as we have described above, 3D printing may have influenced our study results. Additionally, there were only 2 aneurysm models, and both were saccular aneurysms; the investigation of very complex aneurysms, therefore, might have led to other results. Another limitation is the use of standardized contrast attenuation for most investigations (MDCTA and

FDCTA), which usually varies in patients for several reasons. Moreover, aneurysms in real patients may be located close to the skull base and therefore may be more challenging to investigate compared with our aneurysm models, though they were placed in a skull. Notably, all our findings are limited to Siemens scanners and may not be true for CT scanners or angiostates of other vendors.

CONCLUSIONS

2D-D-DSA with a short object-to-detector distance adjusted according to a previous 3D-D-DSA run resulted in the most exact aneurysm measurement and is therefore recommended for device sizing.

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REFERENCES

- Molyneux A, Kerr R, Stratton I, et al; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. **International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial.** *Lancet* 2002;360:1267–74 [CrossRef Medline](#)
- Wiebers DO, Whisnant JP, Huston J 3rd, et al; International Study of Unruptured Intracranial Aneurysms Investigators. **Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment.** *Lancet* 2003;362:103–10 [CrossRef Medline](#)
- Behme D, Weber A, Kowoll A, et al. **Low-profile Visualized Intraluminal Support device (LVIS Jr) as a novel tool in the treatment of wide-necked intracranial aneurysms: initial experience in 32 cases.** *J Neurointerv Surg* 2015;7:281–85 [CrossRef Medline](#)
- Behme D, Berlis A, Weber W. **Woven EndoBridge intrasaccular flow disrupter for the treatment of ruptured and unruptured wide-neck cerebral aneurysms: report of 55 cases.** *AJNR Am J Neuroradiol* 2015; 36:1501–06 [CrossRef Medline](#)
- Gory B, Aguilar-Pérez M, Pomero E, et al. **One-year angiographic results after pCONus stent-assisted coiling of 40 wide-neck middle cerebral artery aneurysms.** *Neurosurgery* 2017;80:925–33 [CrossRef Medline](#)
- Struffert T, Doelken M, Adamek E, et al. **Flat-detector computed tomography with intravenous contrast material application in experimental aneurysms: comparison with multislice CT and conventional angiography.** *Acta Radiol* 2010;51:431–37 [CrossRef Medline](#)
- Zwarzany L, Poncyłjusz W, Burke TH. **Flat detector CT and its applications in the endovascular treatment of wide-necked intracranial aneurysms—A literature review.** *Eur J Radiol* 2017;88:26–31 [CrossRef Medline](#)
- Wong GK, Yu SC, Poon WS. **Radiological measurements of dimensions of acutely ruptured internal carotid artery aneurysm: a comparative study between computed tomographic angiography and digital subtraction angiography.** *Clin Pract* 2012;2:e75 [CrossRef Medline](#)
- Wong SC, Nawawi O, Ramli N, et al. **Benefits of 3D rotational DSA compared with 2D DSA in the evaluation of intracranial aneurysm.** *Acad Radiol* 2012;19:701–07 [CrossRef Medline](#)
- Hodis S, Ding YH, Dai D, et al. **Relationship between aneurysm occlusion and flow diverting device oversizing in a rabbit model.** *J Neurointerv Surg* 2016;8:94–98 [CrossRef Medline](#)
- Griessenauer CJ, Adeeb N, Foreman PM, et al. **Impact of coil packing density and coiling technique on occlusion rates for aneurysms treated with stent-assisted coil embolization.** *World Neurosurg* 2016;94:157–66 [CrossRef Medline](#)
- Lauric A, Hippelheuser JE, Malek AM. **Critical role of angiographic acquisition modality and reconstruction on morphometric and haemodynamic analysis of intracranial aneurysms.** *J Neurointerv Surg* 2018;10:911–15 [CrossRef Medline](#)
- O'Meara B, Rahal JP, Lauric A, et al. **Benefit of a sharp computed tomography angiography reconstruction kernel for improved characterization of intracranial aneurysms.** *Neurosurgery* 2014; 10(Suppl 1):97–105; discussion 105 [CrossRef Medline](#)
- Lauric A, Heller RS, Schimansky S, et al. **Benefit of cone-beam CT angiography in visualizing aneurysm shape and identification of exact rupture site.** *J Neuroimaging* 2015;25:56–61 [CrossRef Medline](#)
- Psychogios MN, Schramm P, Amelung N, et al. **Evaluation of non-invasive follow-up methods for the detection of intracranial in-stent restenosis: a phantom study.** *Invest Radiol* 2013;48:98–103 [CrossRef Medline](#)
- Ruedinger KL, Rutkowski DR, Schafer S, et al. **Impact of image reconstruction parameters when using 3D DSA reconstructions to measure intracranial aneurysms.** *J Neurointerv Surg* 2018;10:285–89 [CrossRef Medline](#)
- Yang P, Schafer S, Royalty K, et al. **Measurement in the angiography suite: evaluation of vessel sizing techniques.** *J Neurointerv Surg* 2016; 8:965–68 [CrossRef Medline](#)
- Struffert T, Hauer M, Banckwitz R, et al. **Effective dose to patient measurements in flat-detector and multislice computed tomography: a comparison of applications in neuroradiology.** *Eur Radiol* 2014;24: 1257–65 [CrossRef Medline](#)
- Guberina N, Lechel U, Forsting M, et al. **Dose comparison of classical 2-plane DSA and 3D rotational angiography for the assessment of intracranial aneurysms.** *Neuroradiology* 2016;58:673–78 [CrossRef Medline](#)

Contralateral Approach to Coil Embolization of Proximal A1 Aneurysms Using the Anterior Communicating Artery

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ABSTRACT

BACKGROUND AND PURPOSE: Aneurysms arising from the proximal A1 segment of the anterior cerebral artery are rare, and their distinctive configurations often pose technical challenges during endovascular embolization. Herein, we present 11 patients with proximal A1 aneurysms requiring a contralateral approach (via the anterior communicating artery) to coil embolization.

MATERIALS AND METHODS: From a prospectively collected data repository, we retrieved records of 11 patients consecutively treated for proximal A1 aneurysms between January 2011 and March 2018. In each instance, coil embolization was performed by the contralateral route. Outcomes were analyzed in terms of morphologic features and clinical status.

RESULTS: Aneurysms in all 11 patients were directed posteriorly and were small (<5 mm). A contralateral approach (via the anterior communicating artery) was used after ipsilateral attempts at aneurysm selection failed in each instance, despite using a variety of microcatheters. Single punctures and single guiding catheters sufficed in 9 patients, but 2 patients required dual punctures and 2 guiding catheters. All endovascular treatments ultimately yielded excellent outcomes. Although 1 symptomatic infarct was manifested in the course of ipsilateral treatment, no morbidity or mortality resulted from the contralateral access.

CONCLUSIONS: Due to angio-anatomic constraints, a contralateral strategy for coil embolization of proximal A1 aneurysms is acceptable if ipsilateral access is technically prohibitive and the vessels (contralateral A1 and anterior communicating artery) are amenable to the passage of microdevices.

ABBREVIATION: AcomA = anterior communicating artery

Procommunicating (A1) segment aneurysms of the anterior cerebral artery are rare and pose technical challenges for both surgical clipping and endovascular coiling. According to relevant reports, on open surgical access, an important issue in treating proximal A1 aneurysms is branch or perforator injury during dissection or clipping.¹ Endovascular embolization of proximal A1 aneurysms is also technically problematic, given the distinctive features of such lesions (ie, diminutive size, proximity to the internal carotid artery bifurcation, and association with perforators).²⁻⁵ Aneurysm selection by microcatheter is perhaps most

difficult in this setting, particularly in proximal segment lesions directed posteriorly. If an ipsilateral approach failed in selecting proximal A1 aneurysms, despite the use of several microcatheters and exhaustive effort, we applied a contralateral approach (via the anterior communicating artery [AcomA]) to consecutively select these problematic lesions. The feasibility and safety of this approach were thus explored in a limited group of patients whose angiographic and clinical outcomes are detailed herein.

MATERIALS AND METHODS

Patient Population

A total of 4172 patients with 5391 aneurysms, including 1215 lesions impinging on the anterior cerebral artery, underwent coil embolization at 2 institutions between January 2011 and March 2018. Proximal A1 aneurysms accounted for 70 of these lesions, 59 of which were successfully treated by an ipsilateral approach. The remaining 11 aneurysms either could not be selected by microcatheters, or coil insertion failed due to unfavorable orientation or poor microcatheter support. Clinical and radiographic features of aneurysms in the patients under study (women, 8; men, 3; mean age, 53.2 ± 12.0 years), culminating in selection by

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Summary of patient data

No.	Age (yr)	Sex	An Status	Size of An (mm)	D/N Ratio	Double Guiding/Puncture	Degree of Occlusion	Complication	Follow-Up
1	61	M	UR	2.8	0.8	Single	Near-total	None	Complete occlusion at 18 mo
2	61	F	UR	3.4	1.4	Single	Subtotal	Symptomatic infarction	Minor recanalization at 18 mo
3	36	F	UR	2.4	1.4	Single	Near-total	None	Complete occlusion at 18 mo
4	41	M	UR	3.1	2.1	Single	Total	None	Complete occlusion at 72 mo
5	60	M	UR	2.6	2.0	Single	Total	None	Complete occlusion at 48 mo
6	62	F	UR	3.8	2.3	Single	Near-total	None	Complete occlusion at 6 mo
7	39	F	UR	3.0	1.9	Single	Near-total	None	No follow-up
8	52	F	UR	2.7	1.2	Double	Total	None	Complete occlusion at 18 mo
9	42	F	UR	2.6	1.5	Double	Total	None	Complete occlusion at 6 mo
10	58	F	UR	3.0	2.0	Single	Total	None	Complete occlusion at 6 mo
11	73	F	UR	3.5	1.8	Single	Near-total	None	No follow-up

Note:—An indicates aneurysm; D/N, depth to neck; UR, unruptured.

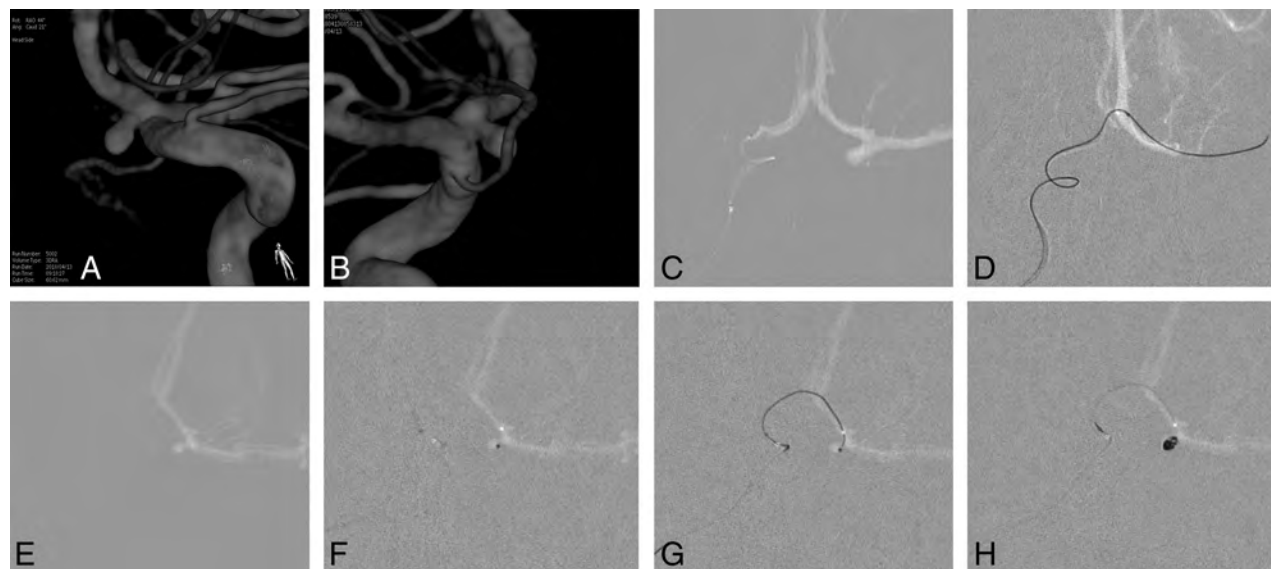


FIG 1. A and B, 3D image demonstrates a left proximal A1 aneurysm. C, Microcatheter navigated from the contralateral A1 into the anterior communicating artery. D, Retrograde introduction of a microcatheter into the ipsilateral A1 via the AcomA. E, Use of a microcatheter for selective angiography, delineating the configuration of the aneurysm. F, Saccular insertion of a microcatheter. G and H, Coil embolization undertaken using a single catheter.

a contralateral approach, are shown in the Table. All aneurysms were unruptured and small (largest diameter, <5 mm). After thorough evaluation, perceived risks, benefits, and treatment options (including aneurysm clipping) were discussed with each patient and family, who then granted informed consent. Therapeutic alternatives were formulated by neurosurgical and neuro-interventional teams in a multidisciplinary decision-making process. This study was conducted with approval of institutional review boards at both hospitals.

Therapeutic Strategy

As depicted in Fig 1, we took the following tactical steps: 1) microcatheter delivery into the contralateral ICA; 2) retrograde advancement of the microcatheter into the ipsilateral distal A1 segment through the patent AcomA; 3) selective angiography of the proximal A1, close to the aneurysm; 4) selection of the aneurysm by the microcatheter; 5) framing the aneurysm with the first coil, sufficiently lengthy for coil stability; and 6) filling the residual sac with coils.

This technique is not advocated as a first-line method and is unwarranted if ipsilateral coiling is achievable. Contralateral ac-

cess (via the AcomA) was our recourse for aneurysm selection if repeat attempts at ipsilateral microcatheter delivery failed and key vessels (contralateral A1 and AcomA) allowed passage of needed microdevices. Double guiding catheters generally may be used with the ipsilateral catheter serving for angiography and the contralateral catheter for coil delivery. In most of our series, however, use of a single guiding catheter and single femoral puncture readily sufficed in this setting because selective angiography performed before coiling, using the same microcatheter to then deliver the coil, furnished valuable angio-anatomic insight (Fig 1).

Endovascular Procedure

All the procedures were performed with the patient under general anesthesia. Configurations and arterial architectures of aneurysms were evaluated using Integris V and Allura Clarity (Philips Healthcare, Best, the Netherlands) or an Innova IGS 630 (GE Healthcare, Milwaukee, Wisconsin) biplane system, including 3D rotational angiography. In each patient, a 300-mg loading dose of clopidogrel was given 1 day in advance of the procedure, and it was supplemented by a morning dose (75 mg) on the day of the procedure. Poor responders to clopidogrel (ie, P2Y12 reactivity

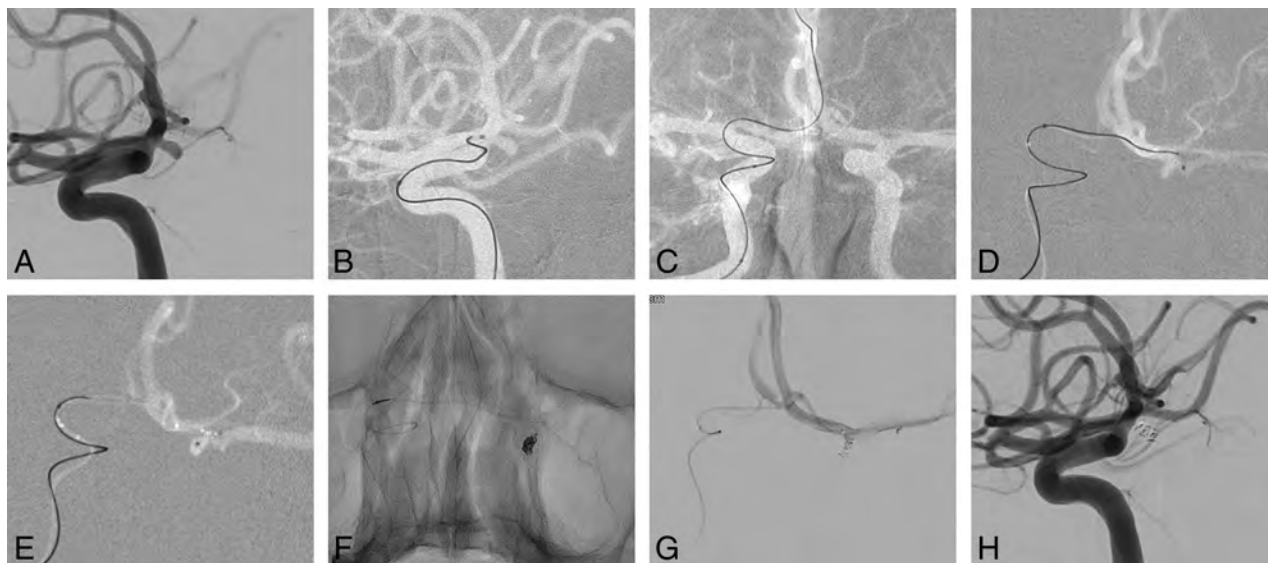


FIG 2. A, Conventional angiography shows a small proximal A1 aneurysm directed posteriorly. B, Failure of aneurysm selection through the ipsilateral ICA, despite repeat attempts using variably shaped microcatheters. C and D, Microcatheter for coil delivery navigated from the contralateral A1 to the ipsilateral A1 segment via the AcomA. E, The microcatheter is advanced into the sac after being used in selective angiography (near to the aneurysm). F, Coil insertion performed. G and H, Completion angiography confirms total occlusion of the aneurysm.

units of >285 , indicated by the VerifyNow P2Y12 assay [Accu-metrics, San Diego, California]) received aspirin as well (300-mg loading dose). A bolus of heparin (3000 IU) was administered after femoral artery sheath placement, intermittent bolus doses (1000 IU/h) were delivered thereafter, and activated clotting times were monitored. Following procedures, no maintenance anti-platelet medications were routinely prescribed.

Immediate and Final Outcome

Degrees of saccular occlusion were gauged during completion angiography using a 3-point scale of contrast retention: total occlusion (no residual filling), near-total occlusion (minimal residual filling at the base), and subtotal occlusion (any saccular filling). Clinical outcomes were assessed using the Glasgow Outcome Score, and follow-up anatomic results were categorized as complete occlusion, minor recanalization, or major recanalization.

RESULTS

In all 11 instances, the aneurysms were directed posteriorly and were devoid of branches. The maximum diameter of each was <5 mm. Angio-anatomic configurations related to the aneurysms, including the ipsilateral A1, contralateral A1, AcomA diameter, and so forth, are summarized in the On-line Table. The ipsilateral approach had regularly failed in microcatheter selection of proximal A1 aneurysms, despite multiple attempts using variably shaped catheters, so a contralateral approach via the AcomA was used. Single punctures and single guiding catheters sufficed for coil embolization in 9 patients, but 2 patients required dual punctures and 2 guiding catheters. A distal access catheter was used in 1 older patient. Immediately after coil embolization, 10 aneurysms appeared successfully occluded with a residual sac persisting in only 1 lesion. A procedure-related adverse event occurred in 1 patient who had symptomatic infarction. The ischemia was induced in the course of selecting the aneurysm by an ipsilateral (not a contralateral) approach. Nine patients (2 treated recently

being exempt) underwent follow-up evaluations, including MRA and/or conventional angiography. Eight patients showed complete occlusion, without recanalization. In 1 patient, minor recanalization was evident. There were no delayed complications such as thromboembolic infarction or hemorrhage.

Patient 6

A 62-year-old woman was admitted for treatment of an unruptured, posteriorly directed left proximal A1 aneurysm (3.8 mm; depth-to-neck ratio, 2.3). The A1 segment (diameter, 2.2 mm) of the anterior cerebral artery originated from the ICA at an acute angle (58°), but the contralateral A1 (1.5 mm) and AcomA (1.6 mm) were of sufficient caliber to allow microcatheter passage. Once a 6F guiding catheter was placed in the cervical portion of left ICA, aneurysm selection by microcatheter was attempted repeatedly but failed, despite various catheter shapes (including steam-shaped S and preshaped S) used. The guiding catheter was then moved into the right ICA, and a preshaped C microcatheter was navigated retrograde from the right A1 into the left A1 via the AcomA. The microcatheter was first used for selective angiography of the proximal A1 close to the aneurysm, delineating its configuration. Once introduced into the sac, a frame coil of adequate length for stability was inserted, and additional coiling was performed. The aneurysm was thereby successfully occluded, and the patient was discharged complication-free on the following day (Fig 2).

DISCUSSION

A retrograde or nonantegrade approach to coil embolization was first described by Moret et al, in 2000.⁶ In their series, aneurysms subjected to this innovative technique were situated as follows: basilar bifurcation, 5; ICA bifurcation, 2; posterior communicating artery, 2; superior cerebellar artery, 2; and posterior inferior cerebellar artery, 1. The balloon-remodeling technique was used in all lesions. With the same objective in mind, a number of au-

thors have described the use of a retrograde approach with stent assistance.⁷⁻¹² Although their original intent was delivery of protection devices for optimal neck coverage, we believe that retrograde access is also useful in proximal A1 aneurysms, helping in the selection of aneurysms after failed ipsilateral attempts. By comparison, a contralateral (versus ipsilateral) approach affords smoother routes to the aneurysm sacs. Although all aneurysms in this series were unruptured and devoid of branches, this retrograde approach may be applied even in their counterparts (when perforators arise from the aneurysm or the patient presents with hemorrhage) if the aneurysm configuration is suitable for coil embolization and key vessels (contralateral A1 and AcomA) are amenable to the passage of microdevices.

Selection of proximal A1 aneurysms is particularly difficult due to their small size, proximity to ICA bifurcation, and posterior orientation; and, the acutely angled origin of the A1 from the ICA bifurcation is problematic. As noted by Cho et al,¹³ a pre-shaped S-curve microcatheter may be preferential in the first attempts at ipsilateral selection. This microcatheter has a reported success rate of 63%. In addition to proximal angulation, it bears a tightly angled distal aspect that is almost impossible to replicate by steam-shaping. However, Lee et al¹⁴ have similarly claimed that a Z-shaped microcatheter, formed by steam-shaping, is an asset under these circumstances. Although contralateral access is also feasible, the AcomA must be patent and capable of accommodating a microcatheter.

Another important point is that a retrograde approach via the AcomA does not always require 2 guiding catheters and dual femoral punctures. In double-guiding scenarios, 1 catheter generally serves for coil delivery and the other allows angiographic delineation of lesions. The present series, however, confirms that the use of a single guiding catheter and single femoral puncture readily suffices in this setting. Protection devices or additional microcatheters were not otherwise required in the patients we treated. These aneurysms were devoid of branches and were small enough to characterize through selective angiography using the same microcatheter intended for subsequent coil insertion.

At present, we do not advocate contralateral access as a first-line approach for embolization of proximal A1 aneurysms. The efficacy and safety of this approach must be further established in a larger study population. Nevertheless, it may constitute a viable alternative in disadvantaged situations in which standard methods do not apply.

CONCLUSIONS

Given the inherent angio-anatomic hindrances to coil embolization of proximal A1 aneurysms, a contralateral approach may be reasonable if ipsilateral access proves prohibitive and key vessels

(the contralateral A1 and AcomA) are amenable to the passage of microdevices.

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REFERENCES

1. Lee JM, Joo SP, Kim TS, et al. **Surgical management of anterior cerebral artery aneurysms of the proximal (A1) segment.** *World Neurosurg* 2010;74:478–82 CrossRef Medline
2. Suzuki M, Onuma T, Sakurai Y, et al. **Aneurysms arising from the proximal (A1) segment of the anterior cerebral artery: a study of 38 cases.** *J Neurosurg* 1992;76:455–58 CrossRef Medline
3. Wanibuchi M, Kurokawa Y, Ishiguro M, et al. **Characteristics of aneurysms arising from the horizontal portion of the anterior cerebral artery.** *Surg Neurol* 2001;55:148–54; discussion 154–55 CrossRef Medline
4. Dashti R, Hernesniemi J, Lehto H, et al. **Microneurosurgical management of proximal anterior cerebral artery aneurysms.** *Surg Neurol* 2007;68:366–77 CrossRef Medline
5. Wakabayashi T, Tamaki N, Yamashita H, et al. **Angiographic classification of aneurysms of the horizontal segment of the anterior cerebral artery.** *Surg Neurol* 1985;24:31–34 CrossRef Medline
6. Moret J, Ross IB, Weill A, et al. **The retrograde approach: a consideration for the endovascular treatment of aneurysms.** *AJNR Am J Neuroradiol* 2000;21:262–68 Medline
7. Blackburn SL, Kadkhodayan Y, Shekhtman E, et al. **Treatment of basilar tip aneurysms with horizontal PCA to PCA stent-assisted coiling: case series.** *J Neurointerv Surg* 2013;5:212–16 CrossRef Medline
8. Pride GL Jr, Welch B, Novakovic R, et al. **Retrograde crossing stent placement strategies at the basilar apex for the treatment of wide necked aneurysms: reconstructive and deconstructive opportunities.** *J Neurointerv Surg* 2009;1:132–35 CrossRef Medline
9. Puri AS, Erdem E. **Unusual intracranial stent navigation through the circle of Willis in a patient with recurrent basilar tip aneurysm during stent-assisted coiling: a case report.** *Interv Neuroradiol* 2009;15:81–86 CrossRef Medline
10. Kelly ME, Turner R, Gonugunta V, et al. **Stent reconstruction of wide-necked aneurysms across the circle of Willis.** *Neurosurgery* 2007;61(5 Suppl 2):249–54 CrossRef Medline
11. Cho YD, Kim KM, Lee WJ, et al. **Retrograde stenting through the posterior cerebral artery in coil embolization of the posterior communicating artery aneurysm.** *Neuroradiology* 2013;55:733–39 CrossRef Medline
12. Cho YD, Kang HS, Lee WJ, et al. **Stent-assisted coil embolization of wide-necked posterior inferior cerebellar artery aneurysms.** *Neuroradiology* 2013;55:877–82 CrossRef Medline
13. Cho YD, Ahn JH, Jung SC, et al. **Coil embolization in precommunicating (A1) segment aneurysms of anterior cerebral artery.** *Neuroradiology* 2014;56:219–25 CrossRef Medline
14. Lee HY, Ahn JS, Suh DC, et al. **Z-shaped microcatheter tip shaping for embolization of aneurysms at the proximal A1 segment of the anterior cerebral artery: a technical note.** *Neurointervention* 2011;6:95–99 CrossRef Medline

Cannulation of Occluded Inferior Petrosal Sinuses for the Transvenous Embolization of Cavernous Sinus Dural Arteriovenous Fistulas: Usefulness of a Frontier-Wire Probing Technique

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ABSTRACT

BACKGROUND AND PURPOSE: Pursuing an alternative access route for transvenous embolization of cavernous sinus dural arteriovenous fistulas can be challenging in patients with an occluded inferior petrosal sinus. We found that cannulation of even a completely occluded inferior petrosal sinus is feasible, especially when using a standard hydrophilic-polymer-jacketed 0.035-inch guidewire as a frontier-wire for probing.

MATERIALS AND METHODS: From 2002 to 2017, the frontier-wire technique was tried in 52 patients with occluded inferior petrosal sinuses for transvenous embolization of cavernous sinus dural arteriovenous fistulas at our center. Technical success was defined as access into the affected cavernous sinus compartment with a microcatheter through the occluded inferior petrosal sinus and deployment of at least 1 coil. The complications and treatment outcomes were analyzed.

RESULTS: The frontier-wire technique was applied in 52 patients with 57 occluded inferior petrosal sinuses (52 ipsilateral and 5 contralateral inferior petrosal sinuses). Technical success rates were 80.8% (42/52) of patients and 73.7% (42/57) of inferior petrosal sinuses. Alternative transvenous routes were used in 3 patients, and transarterial access was used in 7 patients. Complete embolization of fistulas was achieved in 82.2% (37/45) of patients in the transvenous embolization group and in 14.3% (1/7) of patients in the transarterial group. No procedure-related morbidity or mortality was observed.

CONCLUSIONS: Transvenous embolization of cavernous sinus dural arteriovenous fistulas, even through a completely occluded inferior petrosal sinus, is feasible. The difficulty of passing the microcatheter can be minimized by prior probing of the occluded inferior petrosal sinus using a standard 0.035-inch guidewire; the trace of the guidewire on the roadmap image serves as a guide for microcatheter navigation through the inferior petrosal sinus on fluoroscopy.

ABBREVIATIONS: CS = cavernous sinus; CSDAVF = cavernous sinus dural arteriovenous fistula; IJV = internal jugular vein; IPS = inferior petrosal sinus; TVE = transvenous embolization

Cavernous sinus dural arteriovenous fistula (CSDAVF) is defined as an abnormal arteriovenous connection involving the dura mater within or near the walls of the cavernous sinus (CS).¹ Due to multiple small feeding arteries to CS fistulas and some of the feeders supplying the vasa nervorum of cranial nerves, transarterial embolization of CSDAVFs is viewed as a low-cure and

high-risk treatment approach.^{2,3} Typically, transvenous embolization (TVE) confers better outcomes and is still the standard treatment for CSDAVFs.^{3,4}

The inferior petrosal sinus (IPS) provides a relatively direct and shortest route from the internal jugular vein (IJV) to the CS and is the most commonly used transvenous approach to obliterate the compartments of the affected sinus or, optimally, the shunt hole itself.⁵ However, this route is occasionally thrombosed or collapsed and angiographically invisible at the time of treatment.² Although alternative venous approaches have been reported, including the superior petrosal sinus,⁶ the facial vein,^{1,2} and direct exposure of the superior ophthalmic vein,⁷ the ipsi- or contralateral IPS is still considered the first-line access route for approaching the CS, even in the case of occlusion.^{2,4}

Due to the large difference in the diameters of the IJV and the IPS and the angulated course of the IPS itself, it is not easy to find the ostium of the occluded IPS directly with a microguidewire and

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to advance the microguidewire to probe the occluded IPS into the CS. On the basis of our previous experience with cannulating the IPS for petrosal sinus blood sampling with regular diagnostic catheters (4F, Glidecath; Terumo, Tokyo, Japan) and 0.035-inch, polymer-jacketed guidewires (Radifocus; Terumo; or Crescendo; Sungwon Medical, Chungbuk, Korea), we thought that the regular 0.035-inch guidewire would show better performance because it had better controllability and could provide more support than a microguidewire. Once the tip of the guidewire is engaged in the orifice of the IPS, the guidewire can be advanced against the resistance from the collapsed IPS. However, the potential complications such as a venous injury in the posterior fossa may worry some operators in clinical practice.

The purpose of this study was to report our experience with the frontier-wire technique using a 0.035-inch hydrophilic guidewire for cannulating occluded IPSs in patients undergoing TVE of CSDAVFs. The efficacy and safety of the technique are described.

MATERIALS AND METHODS

Study Population

We retrospectively reviewed our institutional data base (Asan Medical Center) of patients who underwent endovascular treatment for CSDAVFs from January 2002 to September 2017 ($n = 126$). Feeding arteries, fistula locations, and their venous drainage patterns were evaluated by reviewing diagnostic cerebral angiography before endovascular treatment. Two biplane angiography systems (Artis zee; Siemens, Erlangen, Germany) were used for image acquisition and endovascular treatment.

Among those patients with CSDAVFs, the ones included in this study met the following criteria: 1) angiographic complete occlusion of the IPS either ipsilateral to the fistula side or bilateral IPS occlusions, and 2) primary treatment attempted with TVE via the occluded IPS, which had been probed with a 0.035-inch guidewire. Exclusion criteria for this study were the following: 1) angiographic patency of the ipsilateral IPS, or 2) catheterization of the occluded IPS with a microguidewire and microcatheter, without prior probing with a 0.035-inch guidewire.

A total of 52 patients met the inclusion criteria. General characteristics of the cohort are summarized in the Table. Therapeutic alternatives were discussed as a multidisciplinary decision-making process. Informed procedural consent had been obtained from patients before they underwent endovascular treatment. Institutional review board approval was obtained for this retrospective study.

Endovascular Treatment

The procedures were performed with the patient under general anesthesia. During the procedure, each patient received 50–80 IU/kg of intravenous heparin to attain an activated clotting time of approximately 250–300 seconds. An additional 1000 IU of heparin per hour was given to maintain the activated clotting time. Usually, a 4F angiography catheter was introduced into the external or internal carotid artery by way of main feeding arteries for the control angiographies during the TVE approach, and a 5F ($n = 8$) or 6F ($n = 44$) guiding catheter (Envoy, Codman Neurovascular, Raynham, Massachusetts) was navigated into the IJV for TVE. If cannulation of the occluded IPS failed, alternative trans-

Characteristics of the 52 patients in the study population

Characteristics	(No.) (%)
Age (mean) (yr)	59.1 ± 10.7
Sex	
Male	12 (23.1)
Female	40 (76.9)
Type	
Idiopathic	50 (96.2)
Traumatic	2 (3.8)
Surgical	0 (0.0)
Symptoms	
Ocular	47 (90.4)
Cranial nerve palsy	23 (44.2)
Headache	15 (28.8)
Tinnitus	11 (21.2)
Cognard classification	
IIa	25 (48.1)
IIa+IIb	13 (25.0)
III	2 (3.8)
IV	12 (23.1)
Side of shunts	
Right	28 (53.8)
Left	24 (46.2)
Contralateral-IPS occlusion	42 (80.8)

venous routes such as the contralateral IPS, ipsilateral superior petrosal sinus, or facial vein were considered. If transarterial embolization was needed, the 4F catheter was changed into a 6F guiding

catheter for the arterial feeder approach. The side arms of the angiographic catheter and the guiding catheter were flushed continuously with pressurized and heparinized normal saline. The percutaneous ophthalmic vein approach was only used if all other approaches were infeasible.

Probing Technique with a 0.035-Inch Hydrophilic Guidewire (Frontier-Wire Technique)

The technical steps of the procedure are as follows (Fig 1): 1) Advance the guiding catheter inferior to the jugular bulb under the guidance of the jugular venographic roadmap and turn the tip of the curved guiding catheter anteromedially to face the orifice of the occluded IPS. Sometimes a thronelike structure can be seen. 2) By means of the 0.035-inch guidewire, probe the orifice of the IPS on the anteromedial wall of the IJV, even without any visible structure at the orifice. 3) Once the orifice is selected, gently rotate and advance the guidewire through the occluded IPS along the imaginary anatomic course until there is any resistance or blocking. 4) Obtain a new jugular venographic roadmap through the guiding catheter while the guidewire is in situ. 5) Pull back and remove the guidewire to leave a bright guidewire track as part of the roadmap image. 6) Referring to that roadmap information, insert a microcatheter (Excelsior 1018, Stryker, Kalamazoo, Michigan; Headway 17, MicroVention, Tustin, California; Echelon 10, Covidien, Irvine, California; or Prowler Plus, Codman & Shurtleff, Raynham, Massachusetts) over a microguidewire (Traxcess 14, MicroVention; Transend 14, Stryker; or Synchro 14, Stryker) along the bright track and advance it further into the CS sac. 7) Inject a small amount of contrast media through the microcatheter to confirm that the microcatheter tip is in the target compartment right before the coil packing.

The following anatomic and technical points are helpful (Fig

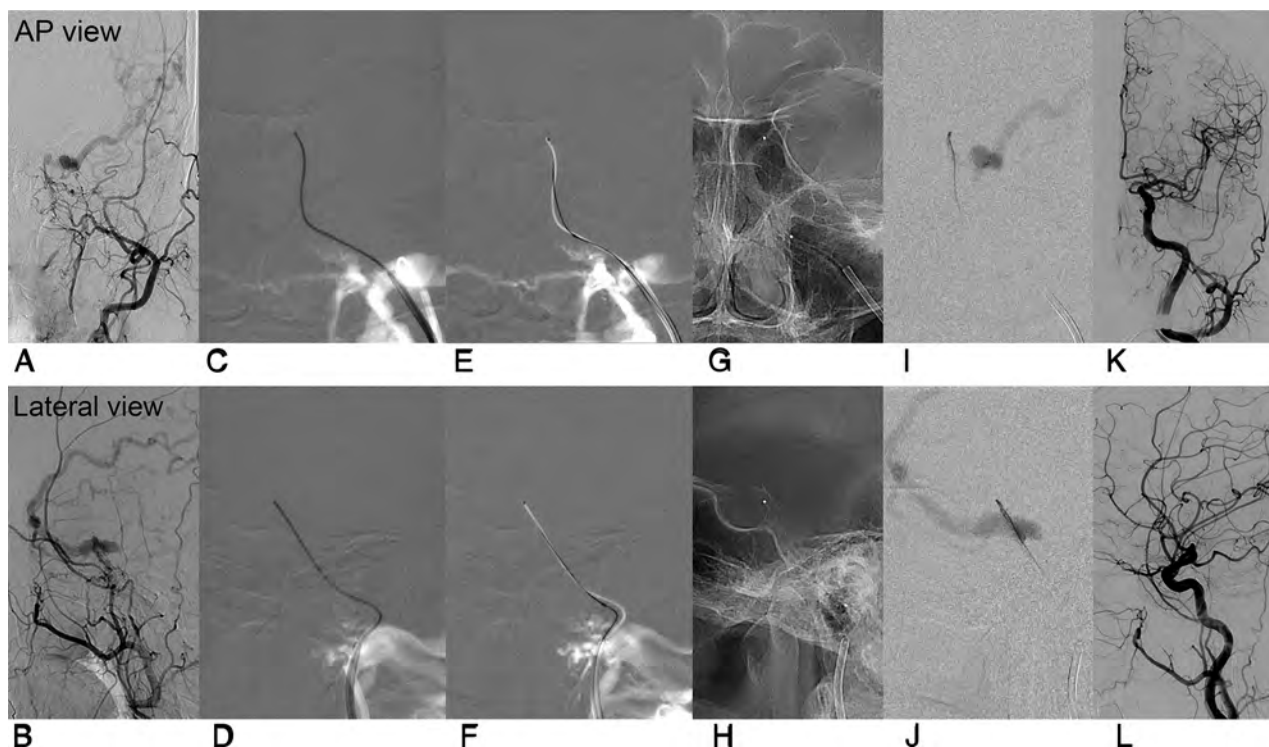


FIG 1. A representative case showing the probing technique (the patient presented with left proptosis, chemosis for 10 months, and development of headache and nausea in the preceding month). *A* and *B*, Left CSDAVFs shown by left external carotid artery angiography. Note ipsilateral-IPS occlusion and main venous drainage of the superficial middle cerebral vein. The fistula was supplied by multiple dural branches of both the ICA and external carotid artery. *C* and *D*, With a 5F guiding catheter positioned in the left IJV, the IPS was selected and probed with a 0.035-inch guidewire to the area of the CS. *E* and *F*, A new roadmap was obtained with retrograde injection of contrast through the guiding catheter. A white mark was left on the roadmap by pulling back the guidewire. A microguidewire and microcatheter were introduced into the IPS and advanced into the CS under the guidance of the roadmap. *G* and *H*, Note the microcatheter tip relative to bony structures. *I* and *J*, DSA images demonstrate gentle hand injection of the left CS, with subsequent filling of left middle cerebral vein. *K* and *L*, Transvenous coil embolization was performed, and no residual fistula was observed on completion angiography. AP indicates anteroposterior.

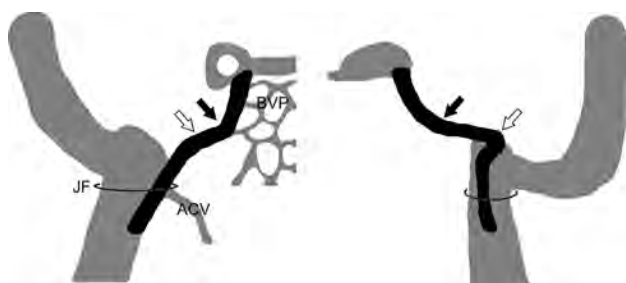


FIG 2. Illustration of the IPS in an anteroposterior (*left*) and lateral (*right*) view. The IPS mostly arises from the anteromedial wall of the IJV, lower than the level of the JF. In general, the IPS runs anterior, medial, and cephalad; however, the course is not simply straight, and usually, 2 curves can be identified. There is a lower curve where the IPS leaves the jugular foramen, appearing as a smooth course on the anteroposterior view, but as a sharp angle on the lateral view (*open arrows*). There is an upper curve where the IPS runs in the inferior petrosal sulcus (*closed arrows*). Around this curve, there are many anastomotic channels between the IPS and the basilar venous plexus (anteroposterior view, *closed arrow*). JF indicates jugular foramen; ACV, anterior condylar vein.

2) to facilitate safe and effective probing: 1) The IPS arises from the anteromedial wall of the IJV, usually lower than the level of the jugular foramen. 2) There are 2 obvious curves in the course of the IPS (Fig 2), and the guidewire tip should be turned to adapt to the course at these 2 curves. 3) As described previously,⁴ 2 methods can be used to reinforce the guidewire: Either insert the guid-

ing catheter as close as possible to the IPS orifice, or by means of the coaxial technique, introduce an intermediate 4F catheter into the orifice of the IPS following the guidewire. In contrast to the patent sinus situation, the diagnostic catheter most often cannot be advanced deep into the occluded IPS. 4) A 6F guiding catheter can accommodate a 0.035-inch guidewire and a microcatheter (Headway 17, Excelsior 1018, or Echelon 10) in parallel. Therefore, the 0.035-inch guidewire may be left in the IPS partially to direct the guiding catheter toward the orifice of the IPS, which can facilitate the introduction of the microcatheter into the IPS. 5) After successful passage of the 0.035-inch guidewire through the collapsed IPS, successive microguidewire navigation is usually accomplished without difficulty.

Technical, Imaging, and Clinical Outcomes

The anatomic level of advancement of the 0.035-inch guidewire along the imaginary course of the occluded IPS was classified as proximal or distal using the upper curve of the venous course (Fig 2). Technical success of the frontier-wire technique was defined as access into the involved CS compartment with the microcatheter through the occluded IPS and deployment of at least 1 coil into the target compartment.

At the end of the procedure, final angiographic results were classified as complete occlusion (no residual shunt), near-complete occlusion (small residual shunt with a marked reduction in

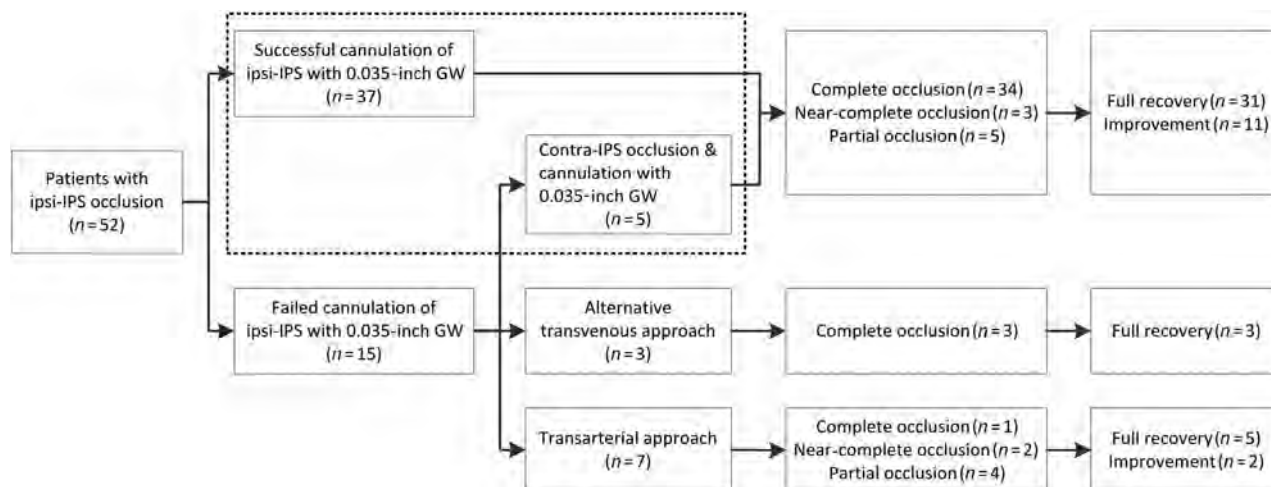


FIG 3. Flowchart for initial cannulation of the occluded ipsilateral-IPS. Patients within the *dashed line* had successful IPS cannulation. Ipsilateral indicates ipsilateral; Contra-, contralateral; GW, guidewire.

volume), and partial occlusion (large residual shunt with slight reduction).² To obviate additional cranial nerve palsy related to mass effect or the coil mass, we tried to minimize coil volume as much as possible. We defined procedural success when the final angiography showed complete or near-complete occlusion of the shunt.

Clinical follow-up occurred at 1 and 3 months for patients with completely occluded fistulas. MR angiography was performed in patients with residual symptoms or residual shunts. Follow-up with digital subtraction angiography was performed selectively in patients with substantial residual symptoms or signs or an aggravated clinical condition. Clinical outcomes were classified as full recovery, improvement, or no change/aggravation.

Statistical Analysis

Baseline characteristics were summarized for patient groups as a number (percentage) for categorical variables and as the mean $\pm$ SD for continuous variables. Differences were compared using the *t* test for continuous variables, and the χ^2 test or Fisher exact test for categorical variables. All reported probability values were 2-sided, and a probability value.

RESULTS

Cannulation of the occluded ipsilateral IPS using the frontier-wire technique was attempted in all 52 patients and was successful in 37 patients. Cannulation of the occluded contralateral IPS was attempted and was successful in 5 patients (Fig 3). Accordingly, the technical success rates of the frontier-wire technique were 73.7% (42/57) of occluded IPSs and 80.8% (42/52) of patients.

The 0.035-inch guidewire could be successfully advanced over the upper curve of the occluded vein in 45 of the 57 IPSs we attempted to cannulate, and technical success was achieved in 39 of the 45 (86.7%). However, the 0.035-inch guidewire could not be advanced over the upper curve in the other 12 occluded IPSs. Of those 12, we could advance the microcatheter system into the involved CS compartment in only 3 IPSs (25%). Therefore, advancement of the guidewire over the upper curve was associated with a higher technical success rate ($P < 0.001$).

Due to failure to access the lesion even through the contralat-

eral occluded IPS, alternative transvenous routes were used in 3 patients, including 1 patent contralateral IPS, 1 facial vein, and 1 superior ophthalmic vein with direct exposure. Thus, 45 patients underwent TVE. Complete occlusion was achieved in 37 patients; near-complete occlusion, in 3 patients; and partial occlusion, in 5 patients (88.9% procedural success rate). Four patients underwent additional transarterial embolization of external carotid artery feeders using polyvinyl alcohol particles ($n = 3$) and glue ($n = 1$). Postprocedural symptom improvement was observed in all 45 patients (Fig 3).

Transarterial access was performed in 7 patients, and only external carotid artery feeders were selected and embolized (Fig 3). Single embolic material polyvinyl alcohol particles were used in 5 patients, coils were used in 1, and glue embolization with coils was used in 1 patient. Complete occlusion was achieved in 1 patient; near-complete occlusion, in 2 patients; and partial occlusion, in 4 patients. One patient underwent a second transarterial embolization, and 1 patient underwent radiation surgery for a residual fistula. Postprocedural symptom improvement was observed in all 7 patients. No procedure-related complications were observed in any of the 52 patients.

DISCUSSION

Although most patients with CSDAVFs present with benign neuro-ophthalmic symptoms, patients with higher risk CSDAVFs (such as fistulas with cortical venous drainage or hemorrhage) and patients with intolerable symptoms (such as diplopia, severe headache, or severe cosmetic disfigurement) usually require endovascular treatment to occlude the abnormal shunting of blood.^{1,2} TVE is regarded as the first-line treatment, and the ipsilateral IPS is usually the favored access route, whether the IPS is occluded or patent.^{2-4,8} The rate of successful catheterization of an occluded IPS with conventional methods varies but is reported to be approximately 54.3%.³ Though Cho et al⁴ reported a microguidewire looping technique for breaching the ipsilateral IPS with a technical success rate of 80.0% (8/10), navigation through the invisible, obliterated IPS with a microcatheter and microguidewire still remains a challenging barrier.

In this study, we present the frontier-wire technique using a 0.035-inch guidewire as a reproducible and robust method for cannulating the occluded IPS. A similar method was described in 1 case report³; however, the efficacy and safety of this approach have not been established in a larger study population. The physical basis of better performance of a guidewire thicker than a microguidewire system could be the following: 1) better controllability, 2) better pushability, and 3) the nature of the venous sinus obliteration. Because the occluded IPS is invisible on fluoroscopy, a blind manipulation procedure is necessary.³ Therefore, detailed knowledge of the anatomy of the IPS is essential for the effective and safe cannulation of an occluded IPS.

The IPS begins in the posteroinferior part of the CS; courses along the medial-lateral, anteroposterior, and rostral-caudal planes; and ends in the IJV.⁹ It is situated in the inferior petrosal sulcus, which is formed by the junction of the petrous part of the temporal bone with the basilar part of the occipital bone.^{9,10}

To perform TVE through a thrombosed IPS, one must first identify the orifice of the IPS.^{3,8} According to a 3D rotational venography study, the drainage patterns of the IPS can be classified into the following 6 types based on the level of the IPS-IJV junction⁵: The IPS drains into the jugular bulb (type A, 1.2%); the IPS drains into the IJV at the level of the extracranial opening of the hypoglossal canal (type B, 34.9%); the IPS drains into the lower extracranial IJV (type C, 37.3%); the IPS forms a plexus and has multiple junctions to the IJV around the jugular foramen (type D, 6.0%); the IPS drains into the vertebral venous plexus with no connection to the IJV (type E, 3.6%); and the IPS is absent (type F, 16.9%). Thus, types B and C are most common and should be considered first.

In the current study, we relied on only the anatomic knowledge and tactile sense of the operator to identify the IPS with 2D images of a biplane imaging system. Despite the high technical success rate, we may have failed in some difficult cases due to anatomic variations (such as no connection between the IPS and the IJV or an extremely low IPS orifice).^{5,11} Some alternative methods may be useful in such situations. Srivatanakul et al³ used 3D venography of the IJV to identify the remnant of the IPS. The best working angle for entering the IPS was found, and catheterization of the occluded IPS was performed by analyzing the 3D volume-rendering image. Yamauchi et al⁸ reported the usefulness of intravascular ultrasonography for detecting the caudal end of occult IPSs in patients with CSDAVFs.

Over the course of the IPS, there are many anastomotic channels among the IPS, the basilar venous plexus, the vertebral venous plexus, and the epidural venous plexus.¹¹ The anastomotic channels connecting the IPS to the vertebral venous plexus (such as the anterior condylar vein) usually form an acute angle with the IPS, so the probing guidewire will usually not enter the anastomotic channels easily. However, in our experience, the probing guidewire tip could easily lodge in the anastomotic channels of the basilar venous plexus, which course in a direction similar to that of the IPS.¹² Therefore, the guidewire tip should be turned upward to adapt to the course of IPS at its upper curve (Fig 2) and to avoid entering the anastomotic channels. Accordingly, we found that the passage of the upper curve with the probing guidewire is

associated with a higher technical success rate of reaching the CS with the microcatheter.

There could be a psychological disinclination to perform blind manipulation with a regular 0.035-inch guidewire through the IPS. However, in our study, no IPS perforation was observed. Hemorrhagic complications are also rare according to the medical literature on TVE of CSDAVFs; only 2 IPS perforations and 1 clival dura dissection were reported.^{1,13,14} In our experience, gentle manipulation of the guidewire based on the knowledge of IPS anatomy can effectively avoid perforation. If the guidewire goes medially and encounters resistance, the operator should be aware of the potential for injury to the basilar venous plexus and pull back the guidewire to probe another potential route. If there is substantial resistance when advancing the wire, switching to a microguidewire and a microcatheter is also a sensible alternative. If IPS perforation occurs, coil embolization may control the bleeding without difficulty due to the low pressure in the venous sinus.¹ Furthermore, unlike bleeding from the artery, subarachnoid hemorrhage of venous origin secondary to sinus or dural injury may not require any further manipulation as long as the operator does not re-attempt cannulation through the injured IPS.

There are several limitations of this study. First, due to its retrospective nature, we could not distinguish the technical performance of the frontier-wire technique and the commonly used method with a microguidewire and a microcatheter. There could be a certain group enjoying successful cannulation with those microsystems. Second, 3D venography of the IJV was not performed to show the IPS-IJV junction anatomy; thus, we cannot correlate any anatomic variations to the causes of technical failure in this study. Third, as was seen in our report, successful cannulation of the IPS did not always guarantee a procedural success. Further morphologic analyses would help obviate unnecessary cannulation of the occluded IPS requiring an alternative treatment approach.

CONCLUSIONS

TVE of CSDAVFs, even through a completely occluded IPS, is feasible. The difficulty of passing a microcatheter can be minimized by prior probing of the occluded IPS using a standard 0.035-inch guidewire; the trace of the guidewire can serve as a guide for microcatheter navigation through the IPS on fluoroscopy. Further study of IPS-IJV junction anatomy in difficult cases is needed to enhance the success rate of the frontier-wire technique.

REFERENCES

1. Kim DJ, Kim DI, Suh SH, et al. **Results of transvenous embolization of cavernous dural arteriovenous fistula: a single-center experience with emphasis on complications and management.** *AJNR Am J Neuroradiol* 2006;27:2078–82 [Medline](#)
2. Rhim JK, Cho YD, Park JJ, et al. **Endovascular treatment of cavernous sinus dural arteriovenous fistula with ipsilateral inferior petrosal sinus occlusion: a single-center experience.** *Neurosurgery* 2015; 77:192–99; discussion 199 [CrossRef Medline](#)
3. Srivatanakul K, Osada T, Aoki R, et al. **Transvenous embolization of cavernous sinus dural arteriovenous fistula through a thrombosed inferior petrosal sinus utilizing 3D venography.** *Interv Neuroradiol* 2015;21:362–65 [CrossRef Medline](#)

4. Cho YD, Rhim JK, Yoo DH, et al. **Transvenous microguidewire looping technique for breach of ipsilateral inferior petrosal sinus occlusions en route to cavernous sinus dural arteriovenous fistulas.** *Interv Neuroradiol* 2016;22:590–95 CrossRef Medline
5. Mitsuhashi Y, Nishio A, Kawahara S, et al. **Morphologic evaluation of the caudal end of the inferior petrosal sinus using 3D rotational venography.** *AJNR Am J Neuroradiol* 2007;28:1179–84 CrossRef Medline
6. Mounayer C, Pötin M, Spelle L, et al. **Superior petrosal sinus catheterization for transvenous embolization of a dural carotid cavernous sinus fistula.** *AJNR Am J Neuroradiol* 2002;23:1153–55 Medline
7. Quiñones D, Duckwiler G, Gobin PY, et al. **Embolization of dural cavernous fistulas via superior ophthalmic vein approach.** *AJNR Am J Neuroradiol* 1997;18:921–28 Medline
8. Yamauchi S, Nishio A, Takahashi T, et al. **An innovative technique for detecting the caudal end of occluded inferior petrosal sinus in cavernous arteriovenous fistula using intravascular ultrasonography: technical note.** *Neuroradiology* 2015;57:799–804 CrossRef Medline
9. Ayeni SA, Ohata K, Tanaka K, et al. **The microsurgical anatomy of the jugular foramen.** *J Neurosurg* 1995;83:903–09 CrossRef Medline
10. Lo WW, Solti-Bohman LG. **High-resolution CT of the jugular foramen: anatomy and vascular variants and anomalies.** *Radiology* 1984;150:743–47 CrossRef Medline
11. Miller DL, Doppman JL, Chang R. **Anatomy of the junction of the inferior petrosal sinus and the internal jugular vein.** *AJNR Am J Neuroradiol* 1993;14:1075–83 Medline
12. Mortazavi MM, Griessenauer CJ, Krishnamurthy S, et al. **The inferior petrosal sinus: a comprehensive review with emphasis on clinical implications.** *Childs Nerv Syst* 2014;30:831–34 CrossRef Medline
13. Oishi H, Arai H, Sato K, et al. **Complications associated with transvenous embolisation of cavernous dural arteriovenous fistula.** *Acta Neurochir (Wien)* 1999;141:1265–71 CrossRef Medline
14. Luo CB, Chang FC, Teng MM, et al. **Transvenous embolization of cavernous sinus dural arteriovenous fistula via angiographic occlusive inferior petrous sinus.** *J Chin Med Assoc* 2015;78:526–32 CrossRef Medline

Transdural Blood Supply in Cerebral Arteriovenous Malformations: A Systematic Evaluation of Angioarchitecture

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ABSTRACT

BACKGROUND AND PURPOSE: Arterial transdural blood supply is a rare angiographic phenomenon in cerebral AVMs. This study aimed to evaluate angiographic transdural blood supply characteristics and to describe the clinical peculiarities of these lesions.

MATERIALS AND METHODS: A prospective AVM data base of 535 patients, enrolled from 1990 to 2016, was analyzed retrospectively. Clinical information was reviewed through patients' medical charts and radiologic studies. Patients with previous AVM treatment were excluded ($n = 28$).

RESULTS: Patients with ($n = 32$, male/female ratio = 10:22; mean age, 46 ± 15 years; range, 13–75 years) and without transdural blood supply ($n = 475$, male/female ratio = 260:215; mean age, 40 ± 18 years; range, 2–87 years) did not show significant differences in clinical presentation (age, hemorrhage, seizures, chronic headache). The predominant nidus size in patients with transdural blood supply was ≥ 30 mm, with significantly more patients with large AVMs (>60 mm, $P = .001$). To describe the transdural blood supply, we used 3 grades based on the angiographic transdural blood supply proportion and intensity of AVM nidus perfusion (I–III). Fifty-seven percent of patients with chronic headache had a strong and substantial transdural nidus perfusion (III) and a high-flow transdural blood supply.

CONCLUSIONS: Cerebral AVMs with transdural blood supply represent a rare and heterogeneous subgroup. Lesions can be graded by quantifying the transdural blood supply of the nidus and by capturing hemodynamic characteristics. The broad spread of angiographic features and comparable clinical patterns of patients with or without transdural blood supply raises questions about the relevance of the transdural blood supply to the natural history risk of an AVM and the intention for treatment.

ABBREVIATIONS: ECA = external carotid artery; TDBS = transdural blood supply

Arterial transdural blood supply (TDBS) by branches of the external carotid artery (ECA) is an uncommon angiographic characteristic in cerebral AVMs. The rate of TDBS in AVMs is reported inconsistently. Previous reports described a prevalence of up to 50%, mainly due to preselection of patients or inclusion of distinct pathologies such as dural arteriovenous fistulas.^{1–3} In contrast, recent publications emphasized a prevalence of 7% and 6.6%, confirming the assumption of a rare phenomenon.^{4,5} Little is known about the impact of the TDBS on clinical presentation and biologic behavior, with only a few publications trying to capture the clinical and pathophysiologic aspects of these particular

AVMs.^{3,5,6} A systematic angiographic evaluation of TDBS characteristics so far has not been attempted, though transdural feeding patterns might influence surgical and endovascular treatment strategies.⁷ This study aims to systematically evaluate angiographic TDBS characteristics and to describe the clinical peculiarities of this rare subgroup among cerebral AVMs.

MATERIALS AND METHODS

A prospective data base of AVMs was examined, and a consecutive series of 535 patients, enrolled between 1990 and 2016, was analyzed retrospectively. Clinical information (basic demographic data, clinical presentation, vascular architecture) was reviewed through patients' medical charts and radiologic studies.

Because prior and partial AVM treatments potentially influence the natural course and formation of TDBS, patients with previous AVM treatment were not analyzed.⁶

Hemorrhage was defined as the acute onset of clinical and neurologic symptoms, combined with detection of blood on CT or MR imaging. Seizures and chronic headache were only as-

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Table 1: Suggested grading of TDBS, depending on the proportion and intensity of nidus perfusion

	TDBS Grade		
	I	II	III
Proportion of nidus perfusion	Marginal (<5%)	Partial (5%–50%)	Substantial (>50%)
Intensity of nidus perfusion	Weak	Distinct	Strong

sumed to be predominant symptoms when unrelated to hemorrhage. Chronic headache was defined as ≥ 15 days/month for at least 3 months, following the International Classification of Headache Disorders.⁸ Thus, patients with sporadic headache or migraine were not incorporated in this subgroup. Patients with incidental lesions as well as patients with intermittent neurologic deficits or nonspecific symptoms leading to the diagnosis of the AVM were summarized in 1 group (Other).

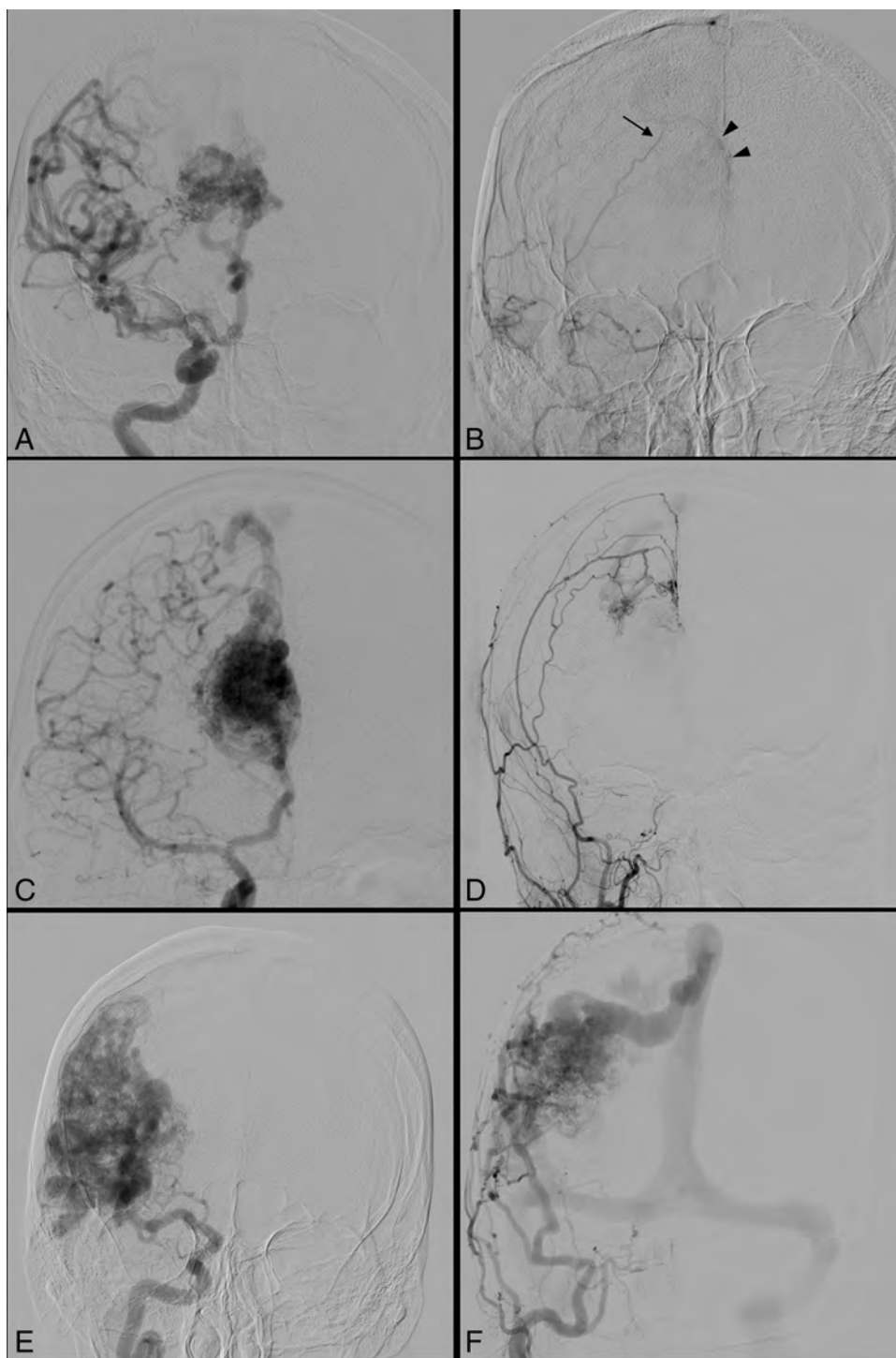


FIG 1. Representative angiograms of the 3 applied TDBS grades (left side ICA, right side ECA). A and B, TDBS I with weak and marginal contrast of the nidus (arrowheads) by a single meningeal feeder (arrow). C and D, TDBS II with distinct and partial ECA supply. E and F, TDBS III with a strong and substantial nidal filling from the ECA branches.

Table 2: Clinical presentation of 507 patients with cerebral AVMs

	TDBS (No.) (%)	No TDBS (No.) (%)	Multinomial Logistic Regression	
			P Value	Odds Ratio
All patients (<i>n</i> = 535)	39	496		
Previous AVM treatment	7 (18)	21 (4)		
Enrolled patients (<i>n</i> = 507)	32	475		
Male	10 (31)	260 (55)	.004	3.433
Hemorrhage	9 (28)	225 (47)	.3	0.968
Seizures	8 (25)	79 (17)	.4	1.672
Headache	7 (22)	44 (9)	.06	3.024
Other	8 (25)	127 (27)		
Age (<i>U</i> test) (yr)				
Mean	46 ± 14	40 ± 18	.07	
Range	13–75	2–87		

Table 3: Angiographic characteristics in 507 patients with cerebral AVMs

	TDBS (No.) (%)	No TDBS (No.) (%)	Multinomial Logistic Regression	
			P Value	Odds Ratio
All patients	32	475		
Location				
Supratentorial	27 (84)	399 (84)		
Infratentorial	5 (16)	76 (16)		
Size				
<30 mm	7 (22)	253 (53)	<.0001	117.703
>30–60 mm	17 (53)	199 (42)		
>60 mm	8 (25)	23 (5)	.001	16.852
Eloquence	24 (75)	252 (53)	.08	4.001
Venous drainage				
Deep	12 (38)	175 (37)	.2	2.268
Spetzler-Ponce class				
A	9 (28)	250 (53)	.04	0.042
B	13 (41)	137 (29)		
C	10 (31)	88 (18)	.03	0.099

Radiologic Evaluation

Depending on the clinical presentation and condition, patients were examined with CT and/or MR imaging followed by DSA. Following a standardized protocol, a complete angiography was performed (frame rate, 6 frames/s) with bilateral and selective injection into the vertebral artery, the internal carotid artery, and ECA on admission or before treatment. Radiologic findings were categorized following the guidelines from the Joint Writing Group for the Reporting Terminology for Brain Arteriovenous Malformation and Clinical and Radiographic Features for Use in Clinical Trials.⁹ AVMs were classified according to Spetzler and Ponce.¹⁰

To capture the heterogeneity of TDBS characteristics, we graded the proportion and intensity of AVM nidus perfusion, maintained by feeders of the ECA. Patients were divided into 3 groups following the distribution of angiographic peculiarities and adapting recently suggested thresholds to quantify interventional AVM embolization volumes (Table 1 and Fig 1).¹¹ In case of an overlap of different perfusion patterns or distinct feeding varieties in 1 individual, the following grade was applied. Furthermore, flow rates for both the ICA and ECA supply were classified as suggested by Koo et al.⁵ The flow rate was classified as high if the draining vein was seen at the same time or 1 frame after visualization of the nidus. A low flow was assumed if the draining vein was seen on/after frame 2. Special attention was directed to the predominant ECA feeders.

Statistical Analyses

All statistical analyses were performed using SPSS software (Version 22; IBM, Armonk, New York). Categorical data (clinical presentation, angiographic characteristics) were studied using a multinomial logistic regression analysis. Continuous data were analyzed using unpaired *U* tests (2-tailed) after examining the homogeneity of variances by means of the Levene test. A *P* value < .05 indicated statistical significance.

RESULTS

Patient Demographics and Clinical Presentation

The clinical characteristics of patients with and without TDBS are summarized in Table 2. Overall, 28 patients were excluded from further analysis due to prior AVM treatment. Treatment modalities in these cases included either radiation therapy (*n* = 13) or endovascular embolization (*n* = 5) or a combination of modalities, including partial surgical resection (*n* = 10). Among these patients, 12 individuals (TDBS, *n* = 3; no TDBS, *n* = 9) previously underwent proton beam therapy in the 1980s and early 1990s.

Angiographic Characteristics

Angiographic AVM characteristics are shown in Table 3. The predominant nidus size in patients with TDBS was ≥30 mm, with significantly more patients having large AVMs (>60 mm). Together with a high (though not statistically significant) number of eloquent locations, these large AVMs in this subgroup were classified Spetzler-Ponce class C in a substantial number of patients.

TDBS Grading

When we applied the suggested TDBS grading, 11 patients had a weak and marginal (I, 34%), 10 patients had a distinct and partial (II, 32%), and 11 patients had a strong and substantial (III, 34%) perfusion of the AVM nidus through feeders of the ECA. Due to the small number of cases, a statistical analysis was not performed. The distribution of clinical symptoms is shown in Fig 2.

The clinical presentation in relation to the nidus flow patterns is shown in Fig 3. Forty-seven percent (*n* = 15) of all patients had high-flow nidus perfusion, either by the ICA and/or ECA branches. Among those, 8 patients (25%) had a high-flow TDBS. Flow patterns in correlation to the suggested TDBS grading are shown in Fig 4.

Typing of ECA Supply

When we defined the predominant arterial ECA feeders, 3 phenotypes of TDBS could be identified (Fig 5):

Temple type (*n* = 21, 65%): mainly distinct feeders, including

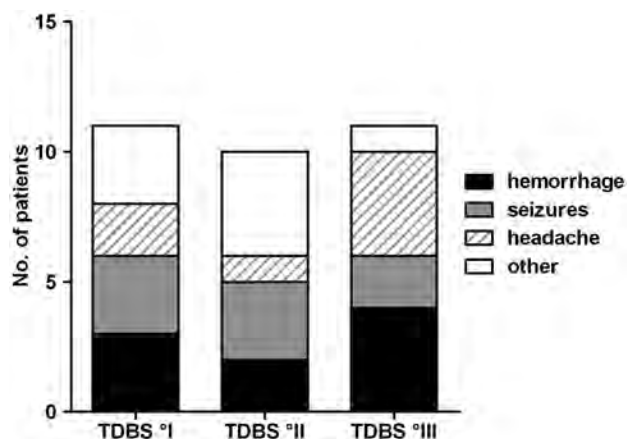


FIG 2. Clinical symptoms in 32 patients with TDBS according to the suggested grading.

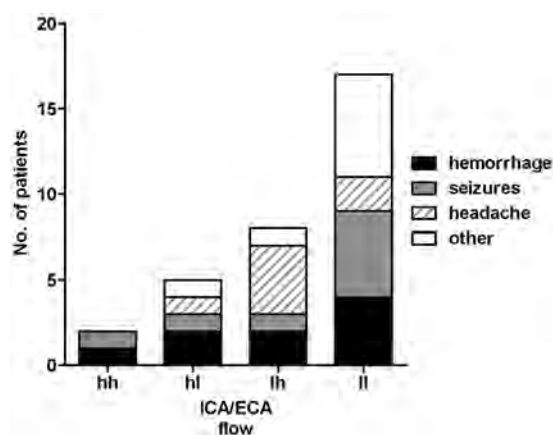


FIG 3. Clinical symptoms of 32 patients in relation to ICA/ECA flow patterns (low [l] versus high [h]).

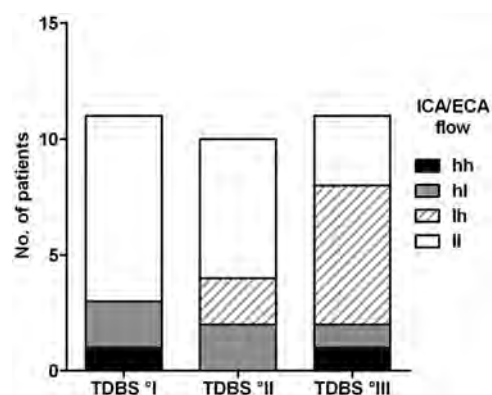


FIG 4. Flow patterns in 32 patients in correlation with the applied TDBS grading.

all branches of the middle meningeal artery (anterior and posterior branch) and the superficial temporal artery.

Occipital type ($n = 5$, 16%): including all branches of the occipital artery and the posterior auricular artery.

Transbasal type ($n = 6$, 19%): often diffuse, involving the terminal branches of the ECA and the facial artery, the maxillary artery, and the ascending pharyngeal artery, including the posterior meningeal artery.

The side of dural transition was always directly adjacent to the AVM nidus. In those cases of temple type TDBS, all AVMs had a nidus partially or in total involving the surface of the cerebral ($n = 20$) or cerebellar ($n = 1$) convexity. AVM nidi of the transbasal type were either located infratentorially ($n = 3$; brain stem, $n = 2$) or included those brain areas facing the temporal or frontal skull base ($n = 3$). Lesions with an occipital-type TDBS could be found superficially in the cerebellum ($n = 1$) or in the occipital and parietal lobes ($n = 4$). Most interesting, no primary TDBS from the anterior meningeal artery could be found in our cohort. The distribution of clinical symptoms within the 3 subtypes is shown in Fig 6.

DISCUSSION

TDBS Grading and Clinical Presentation

Our suggested grading represents a systematic analysis of angiographic characteristics in the subgroup of patients with brain AVMs with TDBS. Due to the immense heterogeneity of angiographic features and small numbers, we chose a descriptive semi-quantitative approach. The applied grading system, apart from quantitative capture, also considered hemodynamic aspects, which is illustrated in a high rate of high-flow ECA supply in patients with TDBS III (55%). Thus, certain aspects of the clinical presentation within these groups are remarkable:

1) We did not recognize a difference among these groups in terms of hemorrhagic presentation. In general, patients with or without TDBS had (statistically) comparable clinical patterns (age at first diagnosis, hemorrhage, seizures, chronic headache). These findings are different from those in previous reports, emphasizing higher rates of nonhemorrhagic symptoms and patients with TDBS being older.^{4,5} In contrast and as described in the literature, we likewise saw a significantly larger number of Spetzler-Ponce class B and C AVMs with TDBS as a logical consequence of predominantly large AVMs.^{4,5}

2) Fifty-seven percent of patients with chronic headache were graded TDBS III. Although well-recognized, the association of AVMs and nonhemorrhagic headache is poorly understood. Explanations for potential mechanisms include cerebral ischemia, increased intracranial pressure, cortical spreading depressions, and activation of trigeminovascular nerve afferents.¹² In case of AVMs with TDBS, meningeal irritation or cerebral hyperemia, due to additional ECA blood shunt volume, is likewise conceivable.

3) Fifty-seven percent of patients with chronic headache as chief symptom had a high-flow TDBS. These findings could underline the role of hemodynamics and shear stress across the meningeal transition zone.

Limitations of TDBS Grading

Mainly due to the immense number of angiographic varieties, the implementation of the applied TDBS grading was limited in several aspects: 1) Small and heterogeneous samples only allowed a descriptive approach. 2) The retrospective analysis of patients' radiologic studies prevented a volumetric determination of proportional nidus perfusion. 3) Dividing the groups descriptively into marginal/weak, partial/distinct, and substantial/strong certainly constituted an approximation of thresholds. 4) Our classi-

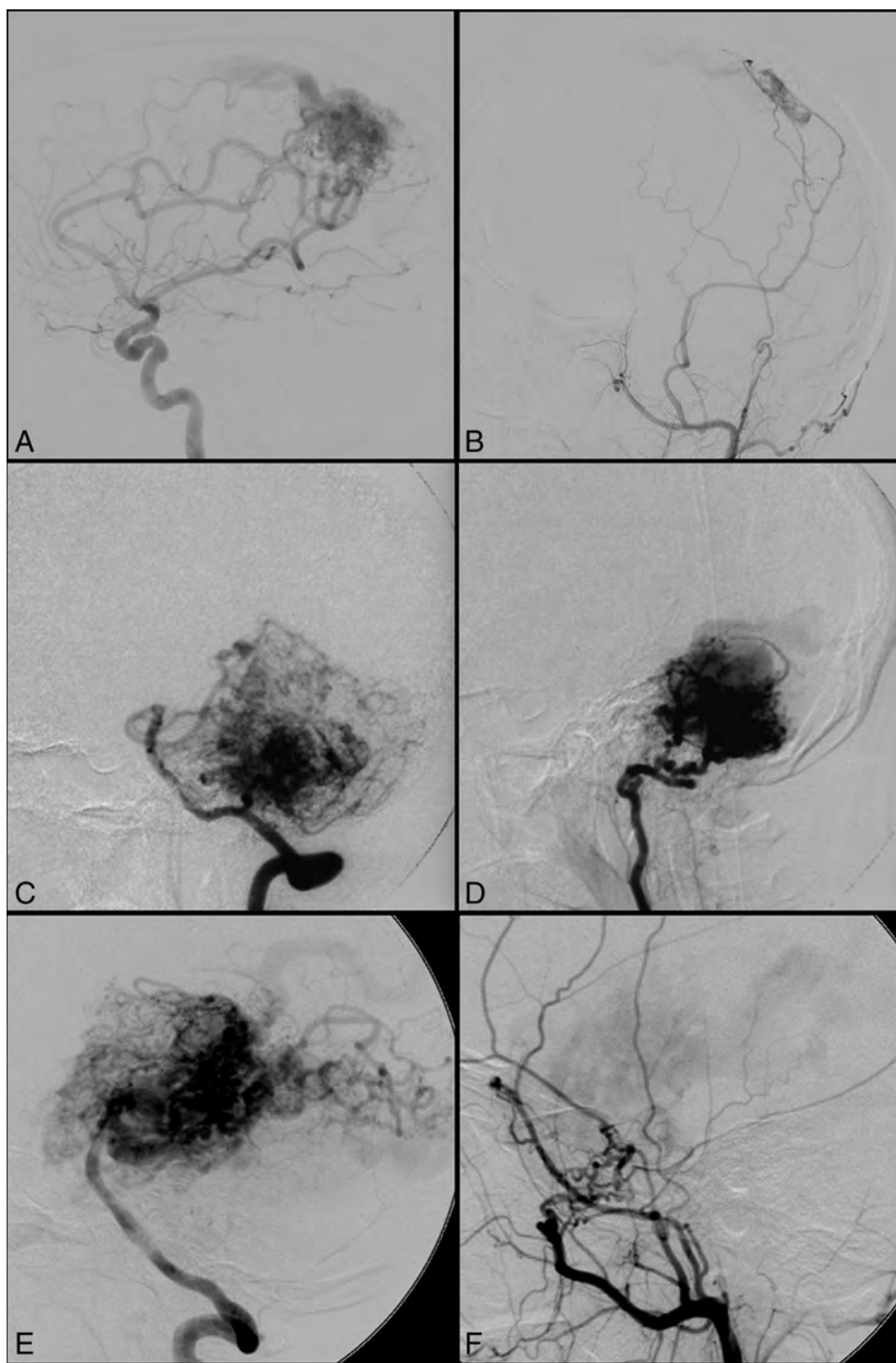


FIG 5. Representative angiograms of the 3 identified vascular phenotypes of TDBS (left side ICA, right side ECA). A and B, Temple type. C and D, Occipital type. E and F, Transbasal type.

fication did not capture every aspect of TDBS, such as the number of ECA feeders or an overlap of diverse vascular patterns within 1 individual, especially when multiple nidus compartments could be found.

Typing of ECA Supply

In all patients with TDBS, the dural transition zone directly adjoined the nidus of the AVM. Bervini et al⁴ previously described

this phenomenon. The same authors extensively discussed potential pathophysiologic mechanisms of TDBS formation, including increased angiogenesis, due to local hypoxia or wall shear stress, as well as ECA feeders developing from pre-existing small bridging arteries. We agree with the assumption of a multifactorial angiogenic genesis, which can be triggered by additional stimuli such as transarterial embolization or radiation therapy.^{6,13,14} The high rate of pretreated, though excluded, patients with TDBS in our

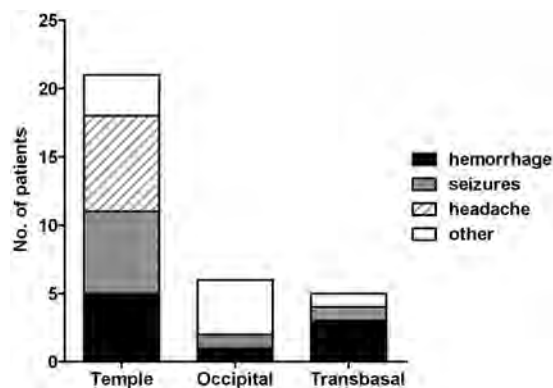


FIG 6. Clinical symptoms in 32 patients with TDBS, according to the 3 ECA phenotypes.

cohort underlines this assumption. Therefore, TDBS reflects a secondary vascular recruitment rather than a congenital vascular supply of the AVM.^{1,4}

In the same context, the described vascular phenotypes in our cohort more likely represent a property of anatomic location and neighborhood. Most patients (74%) with seizures were associated with the temple type because frontal, temporal, and parietal locations are known predictors of initial presentation of epilepsy.¹⁵ In contrast, chronic headache, often accompanying AVMs in the occipital lobe, was exclusively found within the temple type group (100%) and not within the occipital type group.^{15,16}

CONCLUSIONS

Cerebral AVMs with TDBS represent a rare and heterogeneous subgroup. Despite their immense variety of angiographic characteristics, these lesions can be graded by quantifying the ECA blood supply of the AVM nidus and by capturing hemodynamic properties. The broad spread of angiographic features and comparable clinical patterns of patients with or without TDBS raises questions about the relevance of TDBS to AVM natural history risk and the intention for treatment.

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REFERENCES

- Miyachi S, Negoro M, Handa T, et al. Contribution of meningeal arteries to cerebral arteriovenous malformations. *Neuroradiology* 1993;35:205–09 CrossRef Medline
- Newton TH, Cronqvist S. Involvement of dural arteries in intracranial arteriovenous malformations. *Radiology* 1969;93:1071–78 CrossRef Medline
- Willinsky R, Lasjaunias P, Terbrugge K, et al. Brain arteriovenous malformations: analysis of the angio-architecture in relationship to hemorrhage (based on 152 patients explored and/or treated at the hopital de Bicêtre between 1981 and 1986). *J Neurosurg* 1988; 15:225–37 Medline
- Bervini D, Morgan MK, Stoodley MA, et al. Transdural arterial recruitment to brain arteriovenous malformation: clinical and management implications in a prospective cohort series. *J Neurosurg* 2017;127:51–58 CrossRef Medline
- Koo HW, Jo KI, Yeon JY, et al. Clinical features of superficially located brain arteriovenous malformations with transdural arterial communication. *Cerebrovasc Dis* 2016;41:204–10 CrossRef Medline
- Söderman M, Rodesch G, Lasjaunias P. Transdural blood supply to cerebral arteriovenous malformations adjacent to the dura mater. *AJNR Am J Neuroradiol* 2002;23:1295–300 Medline
- Faria MA Jr, Fleischer AS. Dual cerebral and meningeal supply to giant arteriovenous malformations of the posterior cerebral hemisphere. *J Neurosurg* 1980;52:153–61 CrossRef Medline
- Headache Classification Committee of the International Headache Society (IHS). *The International Classification of Headache Disorders, 3rd edition (beta version)*. *Cephalalgia* 2013;33:629–808 CrossRef Medline
- Atkinson RP, Awad IA, Batjer HH, et al; Joint Writing Group of the Technology Assessment Committee American Society of Interventional and Therapeutic Neuroradiology; Joint Section on Cerebrovascular Neurosurgery a Section of the American Association of Neurological Surgeons and Congress of Neurological Surgeons; Section of Stroke and the Section of Interventional Neurology of the American Academy of Neurology. Reporting terminology for brain arteriovenous malformation clinical and radiographic features for use in clinical trials. *Stroke* 2001;32:1430–42 CrossRef Medline
- Spetzler RF, Ponce FA. A 3-tier classification of cerebral arteriovenous malformations: clinical article. *J Neurosurg* 2011;114: 842–49 CrossRef Medline
- Rivera R, Sordo JG, Echeverria D, et al. Quantitative evaluation of arteriovenous malformation hemodynamic changes after endovascular treatment using parametric color coding: a case series study. *Interv Neuroradiol* 2017;23:650–55 CrossRef Medline
- Ellis JA, Mejia Munne JC, Lavine SD, et al. Arteriovenous malformations and headache. *J Clin Neurosci* 2016;23:38–43 CrossRef Medline
- Sandalcioglu IE, Asgari S, Wende D, et al. Proliferation activity is significantly elevated in partially embolized cerebral arteriovenous malformations. *Cerebrovasc Dis* 2010;30:396–401 CrossRef Medline
- Asgari S, Bassiouni H, Gizewski E, et al. AVM resection after radiation therapy: clinico-morphological features and microsurgical results. *Neurosurg Rev* 2010;33:53–61 CrossRef Medline
- Tong X, Wu J, Lin F, et al. The effect of age, sex, and lesion location on initial presentation in patients with brain arteriovenous malformations. *World Neurosurg* 2016;87:598–606 CrossRef Medline
- Rohn B, Hänggi D, Etminan N, et al. Relief of epilepsy and headache and quality of life after microsurgical treatment of unruptured brain AVM-audit of a single-center series and comprehensive review of the literature. *Neurosurg Rev* 2017;40:59–65 CrossRef Medline

MR Imaging for Differentiating Contrast Staining from Hemorrhagic Transformation after Endovascular Thrombectomy in Acute Ischemic Stroke: Phantom and Patient Study

S.-H. You, B. Kim, B.K. Kim, and S.-i. Suh



ABSTRACT

BACKGROUND AND PURPOSE: Early differentiation of contrast staining from hemorrhagic transformation in patients with acute ischemic stroke who have undergone endovascular treatment is critical in preventing the delayed administration of antiplatelet agents. We aimed to demonstrate the usefulness of an immediate postinterventional DWI protocol including B_0 and gradient recalled-echo sequences to discriminate those 2 conditions through phantom and preliminary retrospective patient studies.

MATERIALS AND METHODS: On 3T MR imaging, the signal intensities of the phantom models consisting of iodinated contrast agents diluted with normal saline and arterial blood were compared using T1WI, T2WI, and gradient recalled-echo sequences. A total 17 patients (8 with hemorrhagic transformation and 9 with contrast staining; 8 men and 9 women; mean age, 72.00 ± 10.91 years; range, 52–90 years) who underwent mechanical thrombectomy for acute ischemic stroke and showed newly appearing hyperdense lesions on immediate (<24 hours) postinterventional nonenhanced CT scans were included in this study. Immediate postinterventional DWI of patients were compared.

RESULTS: In the phantom study, iodinated contrast agents diluted with normal saline showed minimal signal drop, while those diluted with arterial blood demonstrated dark signal intensity in the T2WI and gradient recalled-echo sequences. In the patient study, all hemorrhagic transformations and none of the contrast staining demonstrated dark or low signal (<gray matter) intensities similar to those of the vessel in the B_0 -DWI and gradient recalled-echo images.

CONCLUSIONS: According to our preliminary results, contrast staining might be differentiated from hemorrhagic transformation using an immediate postinterventional DWI protocol including gradient recalled-echo sequences. It might be possible to expedite establishment of postinterventional medical treatment strategy.

ABBREVIATIONS: CT_{FU} = postinterventional (24–72 hours) follow-up nonenhanced brain CT; CT_{imme} = postinterventional (<24 hours) nonenhanced brain CT; GRE = gradient recalled-echo; IODBL = iodinated contrast agents diluted with arterial blood; IODNS = iodinated contrast agents diluted with normal saline

After endovascular treatment in patients with acute ischemic stroke, newly developed parenchymal hyperdensity is frequently encountered in immediate postinterventional CT images (31%–61%).^{1–3} Although a large proportion (73%–79%) of the parenchymal hyperdensity represents contrast staining, the rest is associated with hemorrhagic transformation. During intra-arterial thrombolysis or thrombectomy, not only the underlying isch-

emic change but also the intra-arterial thrombolytics and mechanical injury could cause disruption of the blood-brain barrier. Additionally, a large number of concentrated iodinated contrast agents promote breakdown of the blood-brain barrier via chemical irritation.^{4,5} It is possible for contrast agents to escape from the vessels when the blood-brain barrier breaks down, but cellular components of the blood, such as red blood cells, cannot leak from the vessels. This phenomenon is called contrast staining, contrast enhancement, or contrast extravasation.^{3,5–7} It is not a risk factor for hemorrhagic transformation; therefore, the rapid introduction of antiplatelet agents is possible to prevent re-occlusion in patients with acute infarction.^{2,3} In contrast, if the basal lamina and the blood-brain barrier are degraded by more severe injury, hemorrhagic transformation may occur. Under such circumstances, antiplatelet agents should not be administered to prevent the progression of the hemorrhage. Therefore, early differentiation of contrast staining from hemorrhagic transforma-

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tion is critical to establish an optimal postinterventional treatment strategy using antiplatelet agents.

In principle, it is difficult to differentiate parenchymal hyperdensity resulting from contrast staining from hemorrhagic transformation on immediate postinterventional CT (<24 hours) due to the similar Hounsfield densities of the lesions.^{1,2,8} Although early diagnosis of hemorrhagic transformation after endovascular treatment is crucial, it may be differentiated from contrast staining only via follow-up CT (24–48 hours). In this study, we were interested in differentiating contrast staining from hemorrhagic transformation using DWI and gradient recalled-echo (GRE) imaging. The negative susceptibility and T2-shortening effect of iodinated contrast agents have been demonstrated in previous phantom and animal studies.⁹ However, no studies have compared the signal intensities of iodinated contrast agents diluted with normal saline (IODNS) representing contrast staining and those diluted with arterial blood (IODBL) representing hemorrhagic transformation. Additionally, the usefulness of the immediate postinterventional DWI protocol for differentiating contrast staining and hemorrhagic transformation has not yet been elucidated using patient data. The aim of the present study was to compare the MR signal intensities of iodinated contrast agents mixed with normal saline and arterial blood in a phantom model. We also aimed to validate the usefulness of an immediate postinterventional DWI protocol, including B_0 and GRE imaging to discriminate contrast staining and hemorrhagic transformation using retrospective patient imaging data.

MATERIALS AND METHODS

Phantom Model

Forty-two 5-mL cylindric plastic tubes were prepared for the phantom. The diameter and height of the tubes were 10 and 50 mm, respectively. The inner walls of the tubes were coated with heparin.

Thirty-five cells of the phantom were filled with 5 different kinds of nonionic iodinated contrast agents (Visipaque, iohexanol, 320 I mg/mL, 2.5 I mol/L, iso-osmolar, GE Healthcare, Piscataway, New Jersey; Omnipaque, iohexol, 350 I mg/mL, 2.8 I mol/L, low-osmolar, GE Healthcare; Xenetix, iobitridol, 300 I mg/mL, 2.4 I mol/L, low-osmolar, Guerbet, Roissy, France; Iomeron, iomeprol, 300 I mg/mL, 2.4 mol/L, low-osmolar, Bracco, Milan, Italy; and Pamiray, iopamidol, 300 I mg/mL, 2.4 mol/L, low-osmolar, Dongkook Pharm, Seoul, Korea) diluted with normal saline (0.9% sodium chloride) at 7 different concentrations (0, 0.1, 0.4, 0.6, 1.2, 2, and 2.4 I mol/L). The remaining 7 cells were filled with one of the nonionic iodinated contrast agents (Visipaque) diluted with arterial blood at 7 different concentrations (0, 0.1, 0.4, 0.6, 1.2, 2, and 2.4 I mol/L). In a previous pilot study, the aforementioned 5 nonionic iodinated contrast agents showed the same tendency toward magnetic fields regardless of their different side chains. Therefore, we diluted a representative contrast agent with human arterial blood for the phantom of IODBL.

MR Imaging Acquisition and Analysis of Phantom

The phantom with IODNS and IODBL was scanned by a 3T MR imaging unit (Tim Trio; Siemens, Erlangen, Germany) using spin-echo acquisitions with T1WI (TR/TE, 500/10 ms), T2WI (TR/TE, 6000/115 ms), and GRE (TR/TE, 535/15 ms) sequences.

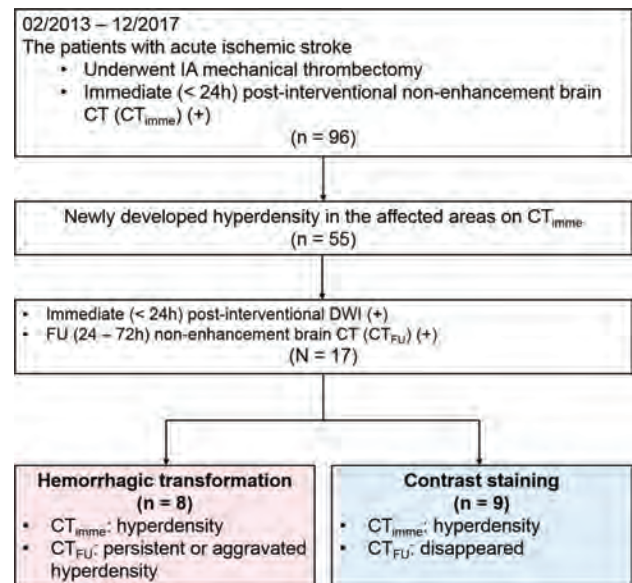


FIG 1. Study design.

The T1WI, T2WI, and GRE sequences were scanned in a visual analysis; then, another T2WI was performed after changing the TE (8.4–185 ms, TR fixed at 2500 ms, 1 single acquired FOV of 123 × 250 mm, and a matrix of 256 × 126) to measure the T2-relaxation time. All the blood-containing tubes were replaced with new tubes containing newly sampled arterial blood and the same concentration of iodinated contrast agents to maintain the same chemical status of hemoglobin. Finally, another T1WI was acquired after changing the TR (180–250 ms, TE fixed at 8.7 ms, 1 single acquired FOV of 123 × 250 mm, and a matrix of 256 × 126).

After reading the DICOM data from the MR imaging system, the T1- and T2-relaxation times for the phantom were calculated using a software for analyzing functional neuroimaging data.

Patients

This retrospective study was approved by the institutional review board of Korea University Anam Hospital. Informed consent was waived because of its retrospective nature. Between February 2013 and December 2017, ninety-six consecutive patients with ischemic stroke underwent intra-arterial mechanical thrombectomy, followed by immediate (<24 hours) postinterventional nonenhanced brain CT (CT_{imme}). The Solitaire (Covidien, Irvine, California) was used as a stent-retriever system for all the patients. Among them, patients who satisfied the following criteria were included in this study: 1) patients who showed newly developed hyperdensity in the affected areas on CT_{imme} ; 2) patients who underwent DWI including B_0 and GRE sequences within 24 hours after intra-arterial mechanical thrombectomy; and 3) patients who underwent follow-up nonenhanced brain CT (CT_{FU}) between 24 and 72 hours after thrombectomy. Based on previous studies,^{5,10} hemorrhagic transformation was defined as a parenchymal hyperdensity in the infarcted area on CT_{imme} that persisted on CT_{FU} . On the other hand, contrast staining was defined as a parenchymal hyperdensity on CT_{imme} that had disappeared on CT_{FU} . The patients were divided into 2 groups based on the findings on CT_{imme} and CT_{FU} (Fig 1). Among them, 14 patients

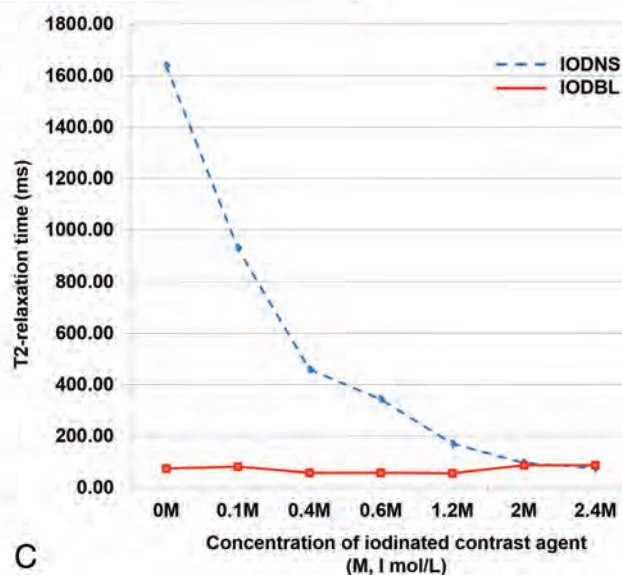
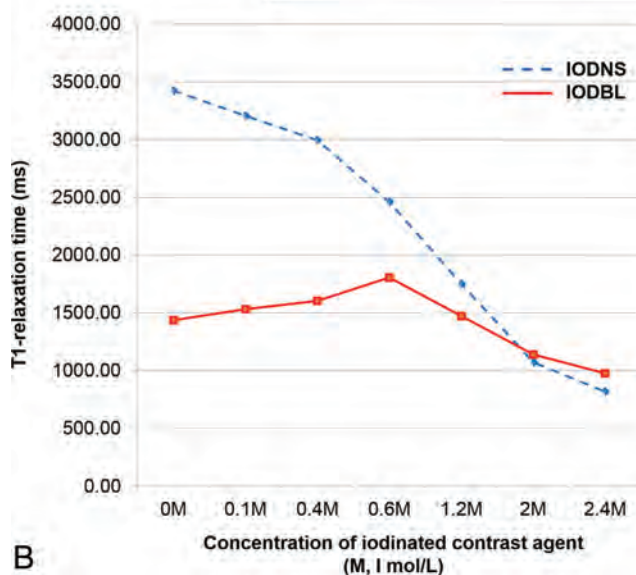
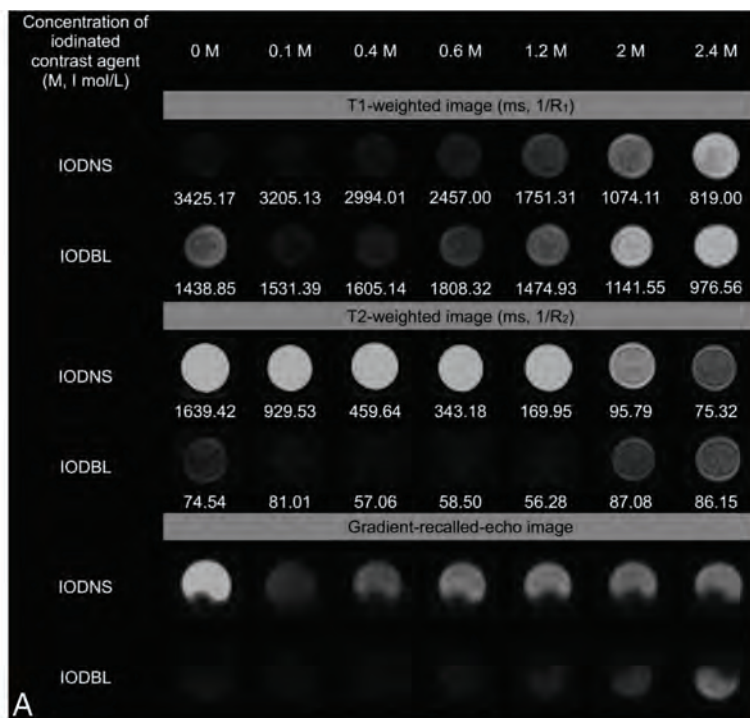


FIG 2. MR signal intensity of IODNS and IODBL on T1-weighted, T2-weighted, and gradient recalled-echo images. **A**, Images from the phantom. **B**, T1-relaxation times of IODNS and IODBL at different concentrations. **C**, T2-relaxation times of IODNS and IODBL according to the concentration of iodinated contrast agents. Visipaque (iodixanol, 320 I mg/mL, 2.5 I mol/L, iso-osmolar) was used as the iodinated contrast agent in this phantom.

(14/17 [82.35%]) also underwent conventional MR imaging, including T1WI and T2WI within 24 hours after intra-arterial mechanical thrombectomy. The type of the hemorrhagic transformation was evaluated on the basis of the European-Australasian Acute Stroke Study (ECASS) criteria.¹¹ Symptomatic intracerebral hemorrhage was defined according to ECASS II.¹² The fate of contrast staining was analyzed using the last imaging study before the discharge.

MR Imaging Acquisition and Analysis of Patients

MR images were acquired using four 3T MR imaging scanners (Prisma, Skyra, and Trio Tim, Siemens; and Achieva, Philips Healthcare, Best, the Netherlands) with a 32- or 64-channel head

coil. Imaging sequences included DWI (B_0 , $b=1000$), GRE imaging, T2WI, and T1WI. The MR imaging parameters were as follows: single-shot echo-planar imaging sequence; TR/TE/matrix = 3590–5970 ms/57–91 ms/128 × 120–192 × 192, $b=0$ and 1000 s/mm², bandwidth = 920–2374 Hz per voxel, 3 signals acquired for DWI; TR/TE/flip angle/matrix = 543–819 ms/12–15 ms/18°–20°/244 × 244–320 × 240 for GRE imaging; TR/TE/flip angle/matrix = 3000–6450 ms/80–118 ms/90°–150°/368 × 353–512 × 358 for spin-echo T2WI; TR/TE/flip angle/matrix = 578–1850 ms/10–12 ms/90°–120°/224 × 224–384 × 269 for fast spin-echo T1WI; section thickness, 4–5 mm (with a gap of 0.5–0.8 mm); and FOV = 179 × 220 or 220 × 220 mm.

Table 1: MR signal intensities of hemorrhagic transformation and contrast staining in B₀ and GRE image^a

	Hemorrhagic Transformation (n = 8)	Contrast Staining (n = 9)	Total (n = 17)	P
B ₀				<.001
Score 1	8 (100.00%)	0 (0.00%)	8 (47.06%)	
Score 2	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Score 3	0 (0.00%)	3 (33.33%)	3 (17.65%)	
Score 4	0 (0.00%)	6 (66.67%)	6 (35.29%)	
GRE				<.001
Score 1	8 (100.00%)	0 (0.00%)	8 (47.06%)	
Score 2	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Score 3	0 (0.00%)	6 (66.67%)	6 (35.29%)	
Score 4	0 (0.00%)	3 (33.33%)	3 (17.65%)	

^a Values are numbers of patients with percentages in parentheses. Score 1, signal intensity was similar to that of the vessel; score 2, signal intensity was lower than that of the gray matter; score 3, signal intensity was similar to that of the gray matter; score 4, signal intensity was higher than that of the gray matter.

Table 2: MR signal intensities of hemorrhagic transformation and contrast staining in T1WI and T2WI^a

	Hemorrhagic Transformation (n = 6)	Contrast Staining (n = 8)	Total (n = 14)	P
T1WI				.042
Score 1	1 (16.67%)	0 (0.00%)	1 (7.14%)	
Score 2	5 (83.33%)	3 (37.50%)	8 (57.14%)	
Score 3	0 (0.00%)	5 (62.50%)	5 (35.71%)	
Score 4	0 (0.00%)	0 (0.00%)	0 (0.00%)	
T2WI				.001
Score 1	6 (100.00%)	0 (0.00%)	6 (42.86%)	
Score 2	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Score 3	0 (0.00%)	3 (37.50%)	3 (21.43%)	
Score 4	0 (0.00%)	5 (62.50%)	5 (35.71%)	

^a Values are numbers of patients with percentages in parentheses. Score 1, signal intensity was similar to that of the vessel; score 2, signal intensity was lower than that of the gray matter; score 3, signal intensity was similar to that of the gray matter; score 4, signal intensity was higher than that of the gray matter.

The imaging analyses for dividing the groups were performed by 1 neuroradiologist (S.-H.Y. with 7 years of clinical experience) using the CT_{imme} and CT_{FU} images. Analyses of the immediate postinterventional MR images were performed by 2 neuroradiologists (B.K.K. and B.K. with 8 and 13 years of clinical experience, respectively) who were blinded to the CT_{FU} data. B₀, DWI, and GRE images of all patients were analyzed and T1WI/T2WI of those who underwent conventional MR imaging were reviewed. MR images, CT_{imme} images, and information concerning the target location were provided to the 2 reviewers. Two reviewers performed visual analysis based on the following criteria that we devised for the study: score 1, signal intensity similar to that of the vessel; score 2, signal intensity lower than that of the gray matter; score 3, signal intensity similar to that of the gray matter; and score 4, signal intensity higher than that of the gray matter.

Statistical Analysis

The Mann-Whitney *U* test was used to compare the medians of continuous variables that were nonparametrically distributed (NIHSS and mRS scores) and ordinal variables (TICI scores, hemorrhagic transformation, and MR signal intensity score), while the unpaired *t* test was used to compare the means of continuous variables (age) between the 2 groups. The Fisher exact test was used to compare categorical variables between the groups. All statistical analyses were performed using SPSS Statistics for Windows, Version 20.0 (IBM, Armonk, New York). A *P* value < .05 was considered statistically significant.

RESULTS

MR Signal Intensities of Various Iodinated Contrast Agents

The MR signal intensities and relaxation times of the 5 different IODNSs in the T1-weighted, T2-weighted, and GRE images are shown in On-line Figs 1–3. All 5 iodinated contrast agents showed a similar tendency of signal intensity change at each concentration. T1- and T2-shortening effects were commonly observed, which became more prominent at high iodine concentrations. At the lowest concentration (0.1 I mg/mL), the T1 values of the 5 different IODNSs ranged from 3205 to 3704 ms. As the concentration increased, the T1-relaxation times progressively decreased to a range of 819–1144 ms at the highest concentration (2.4 I mg/mL). The T2 values of the 5 different IODNSs ranged from 1030–1913 ms at the lowest concentration (0.1 I mg/mL). As the concentration increased, the T2-relaxation times were progressively reduced in all the iodinated contrast agents and ranged from 52–78 ms at the highest concentration (2.4 I mg/mL). In the GRE images, the signal intensity did not show a specific trend according to concentration of the contrast agents.

Comparison of MR Signal Intensities between IODNS and IODBL

MR signal intensities and relaxation times of IODNS and IODBL in the T1-weighted, T2-weighted, and GRE images are shown in Fig 2. At most iodine concentration ranges (0.1–1.2 I mol/L), IODNS could be differentiated from IODBL visually in the T2-weighted and GRE images. On T2WI, the T2 signal intensities of IODBL were darker than those of IODNS in visual assessment. The T2-relaxation times of IODBL (56–87 ms) were lower than those of IODNS (96–1639 ms) at most iodine concentrations (range, 0.1–2.0 I mg/mL) (Fig 2A, -B). On GRE images, IODBL showed dark signal intensity and IODNS showed intermediate signal intensity. There was no specific trend of signal change according to the concentration of the contrast agent (Fig 2A). On T1WI, it was impossible to differentiate IODNS and IODBL (Fig 2C).

Baseline Characteristics of Patients

The clinical characteristics of patients are summarized in On-line Table 1. Among the 17 patients, 8 were classified as having hemorrhagic transformation, and 9, as having contrast staining. No significant difference was observed between the 2 groups. One of 8 patients (12.50%) in the hemorrhagic transformation group showed symptomatic intracerebral hemorrhage. The final outcomes of areas of contrast staining were infarction in 7 patients (7/9 [77.78%]) (On-line Table 2).

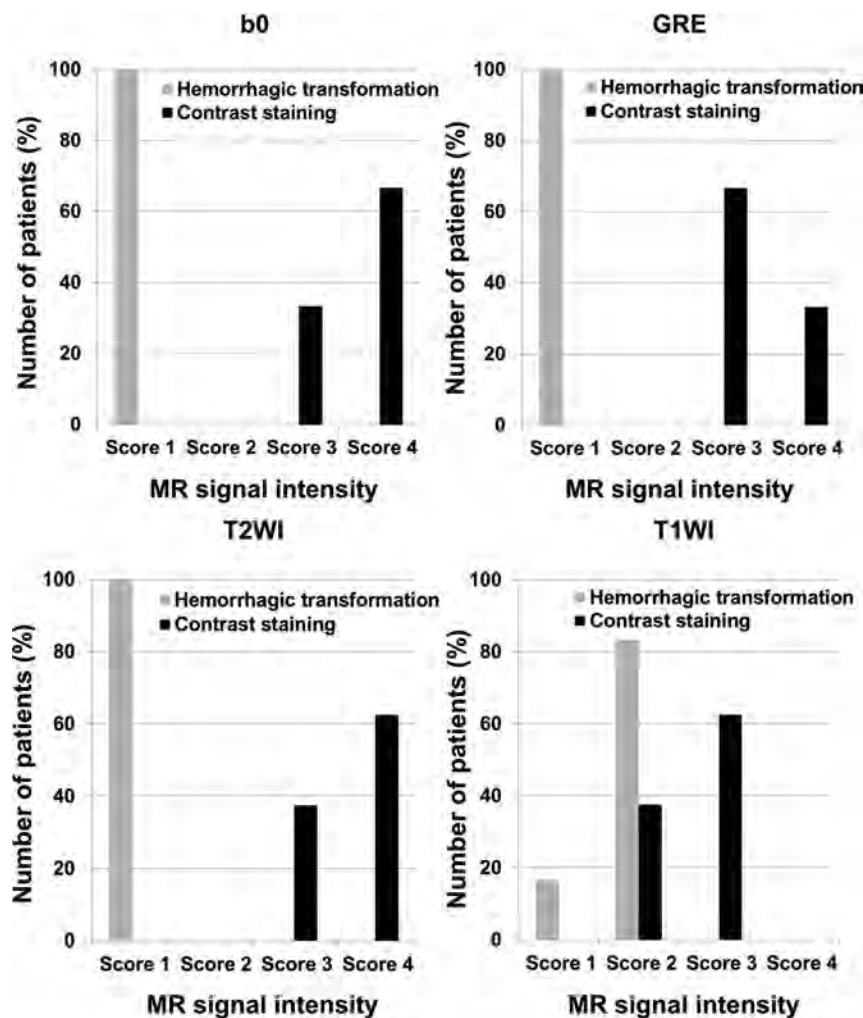


FIG 3. Magnetic signal intensity score of hemorrhagic transformation and contrast staining on B₀, gradient recalled-echo, T2-weighted, and T1-weighted imaging. Score 1, signal intensity was similar to that of the vessel; score 2, signal intensity was lower than that of the gray matter; score 3, signal intensity was similar to that of the gray matter; and score 4, signal intensity was higher than that of the gray matter.

MR Signal Intensities of Hemorrhagic Transformation and Contrast Staining

The MR signal intensity scores of hemorrhagic transformation and contrast staining are summarized in Tables 1 and 2 and Fig 3. Hemorrhagic transformation showed significantly lower visual scores than contrast staining in all MR imaging sequences (B₀, GRE, T1WI, and T2WI) ($P < .05$). All hemorrhagic transformations had a score of 1 (signal intensity was similar to that of the vessel) on B₀, GRE, and T2WI. However, all contrast staining had scores of 3 or 4 (signal intensity was similar to or higher than that of the gray matter). Representative MR images, including B₀, GRE, T2WI, and T1WI, are shown in Fig 4. Hemorrhagic transformation showed a dark signal intensity similar to that of the vessel, and contrast staining demonstrated an iso- or hyper-signal intensity compared with that of the normal gray matter on B₀, GRE, and T2WI.

DISCUSSION

In the present phantom study, the T2WI and GRE sequences could differentiate IODBL from IODNS at most of the iodine

concentrations (0.1–1.2 mol/L). In the exploratory patient study, immediate postinterventional B₀ and GRE images enabled differentiation of contrast staining from hemorrhagic transformation in patients with acute ischemic stroke who underwent endovascular thrombectomy.

The use of DWI for differentiating contrast staining from hemorrhagic transformation has 3 clinical advantages: First, MR imaging is available in almost all hospitals that treat acute ischemic stroke, and DWI and GRE are widely used sequences. Although the usefulness of dual-energy CT for differentiating these entities has been revealed in several previous studies, it cannot be applied in some types of CT scanners.^{6,7,13} Second, B₀-DWI may be used as an alternative to T2WI with a shorter scan time and at a lower cost. Our results demonstrated that B₀ imaging was not inferior to T2WI in differentiating hemorrhagic transformation and contrast staining. Third, $b = 1000$ -DWI could offer information about final infarction size, which influences treatment outcomes of endovascular thrombectomy.

In T2WI and B₀-DWI, contrast staining could be differentiated from hemorrhagic transformation. IODNS demonstrated a T2-shortening effect, but IODBL showed a much stronger T2-shortening effect. These results correspond well with those of earlier studies.^{9,14,15} The mechanism of the T2-shortening effect of the iodinated

contrast agent is not well-known, but the bound water effect and dipole-dipole interaction theories have been suggested as the most important mechanisms.^{16,17} In general, the T2-shortening effect is explained by 3 major mechanisms: paramagnetism, bound water effect, and dipole-dipole interaction.¹⁸ The paramagnetic effect could be excluded because iodinated contrast agents are classified as diamagnetic materials that do not have unpaired electrons.¹⁹ The bound water effect could be the cause of the T1- and T2-shortening effects. This is because neither the iodine nor the benzene ring could influence the relaxation process of water molecules; however, the hydrophilic hydroxyl-containing portion of the iodinated contrast agent can form a hydrogen bond with water.¹⁹ Bound water shows more rapid relaxation than free water; therefore, the bound water effect of the contrast agent may lead to T2-shortening.¹⁸ A dipole-dipole interaction that occurs between 2 adjacent molecules that have different degrees of electronegativity could influence T2-shortening because iodinated contrast agents and water have different degrees of electronegativity. In the phantom study, IODBL showed a much

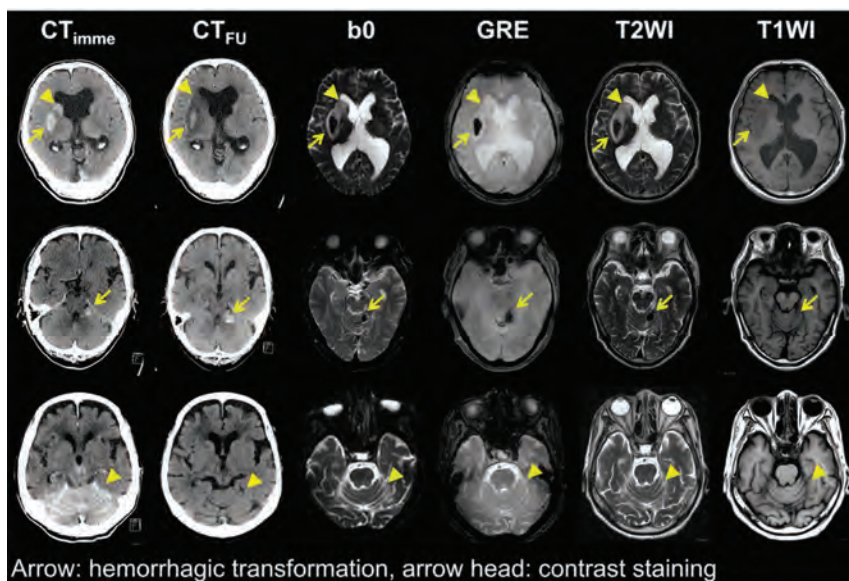


FIG 4. Representative images of hemorrhagic transformation and contrast staining in 3 patients with acute ischemic stroke. *First row:* images of a 66-year-old man with infarction in the territory of the right middle cerebral artery. A persistent hyperdense lesion in the right lentiform nucleus, presumed to be a hemorrhagic transformation (arrow), shows dark signal intensity in the B_0 , gradient recalled-echo, and T2-weighted images. In contrast, a hyperdense lesion in the right caudate nucleus, which is washed out on the follow-up nonenhanced brain CT and presumed to be contrast staining (arrowhead), demonstrates a high signal intensity in the B_0 , GRE, and T2-weighted images. This patient was grouped into the hemorrhagic transformation group, and the lesion in the lentiform nucleus was analyzed. *Middle row:* images of a 68-year-old man with infarction in the region of the right superior cerebellar artery. A persistent hyperdense lesion in the left cerebellum, presumed to be hemorrhagic transformation (arrow), shows dark signal intensity in the B_0 , GRE, and T2-weighted images. *Lower row:* images of an 88-year-old woman with bilateral cerebellar infarction. A hyperdense lesion in the bilateral upper cerebellum, which disappeared on CT_{FU} and was presumed to be contrast staining (arrowhead), demonstrates iso-signal intensity in the B_0 , GRE, and T2-weighted images.

stronger T2-shortening effect than IODNS. These results could be explained by 2 hypotheses^{9,14,15}: First, the T2-shortening effect of blood caused by the paramagnetic mechanism was much stronger than that of the bound water and dipole-dipole interaction effects of the iodinated contrast agent. Second, the bound water and dipole-dipole interaction effects of the iodinated contrast agent were weaker in the blood-mixed environment than in the water-mixed environment. Under these mechanisms, the more powerful T2-shortening effect of IODBL made it possible to distinguish IODNS from IODBL. In patient data, this effect also applied not only to T2WI but also to B_0 -DWI; thus, hemorrhagic transformation and contrast staining could be differentiated using immediate postinterventional DWI.

In the GRE images, hemorrhagic transformation could be differentiated from contrast staining by its strong positive susceptibility. IODNS showed a more minimal signal drop than pure water in the phantom study. This effect did not show a specific trend according to the concentration or kind of contrast agent. This phenomenon is difficult to explain because iodinated contrast agents are classified as diamagnetic materials that do not have unpaired electrons. One hypothesis is that diamagnetic materials are repelled by magnetic fields. Therefore, these materials possibly reduce the intensity of the magnetic fields only minimally and cause a minimal signal drop. However, this minimal signal drop could not be visualized on patients' imaging data. This result agrees with that of a previous animal study.⁹

Because blood has strong positive susceptibility, hemorrhagic transformation was well-distinguished from contrast staining in the GRE images.

Five kinds of commonly used non-ionic iodinated contrast agents were evaluated to reveal the effect of the side chains that are different in each contrast agent. Our study showed no significant difference in the T1 and T2 values among the different contrast agents at the same concentration. This is in concordance with the results of previous studies.^{9,16} The absence of a definite difference in the T1 and T2 values is probably because all kinds of iodinated contrast agents used in our study were nonionic. A minor difference in signal intensity among the contrast agents may be caused by their different side chains.

Several studies have reported the clinical relevance of newly developed parenchymal hyperdensity after mechanical thrombectomy, which is not associated with poor prognosis or symptomatic hemorrhage.^{3,10} In our study, the median mRS score at 90 days in the overall population that underwent mechanical thrombectomy ($n = 86/96$; 10 patients lost to follow-up) was 3.0 (interquartile range, 2.0–5.0). It is similar

to that in our final study population, which demonstrated newly developed parenchymal hyperdensity (3.0 [interquartile range 2.0–3.0]). In addition, only 1 of 17 cases showed symptomatic intracerebral hemorrhage in the present study. Regarding the longitudinal outcomes of areas of contrast staining, approximately 80% finally progressed to infarction in this study. This result is in close agreement with those of the other studies.^{10,20}

Our study has several limitations. First, the number of patients included in our retrospective study was small. Large-scale prospective studies are needed to validate the findings of this study. Second, oxygen saturation was not measured in our study; hence, the exact chemical status of blood could not be presented. Third, we cannot predict the effect of anticoagulating agents, such as heparin, present in the tubes containing the blood samples on MR imaging.

CONCLUSIONS

According to our preliminary results, contrast staining might be differentiated from hemorrhagic transformation using an immediate postinterventional DWI protocol including GRE imaging.

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REFERENCES

1. Payabvash S, Qureshi MH, Khan SM, et al. **Differentiating intraparenchymal hemorrhage from contrast extravasation on post-procedural noncontrast CT scan in acute ischemic stroke patients undergoing endovascular treatment.** *Neuroradiology* 2014;56:737–44 [CrossRef Medline](#)
2. Nikoubashman O, Reich A, Gindullis M, et al. **Clinical significance of post-interventional cerebral hyperdensities after endovascular mechanical thrombectomy in acute ischaemic stroke.** *Neuroradiology* 2014;56:41–50 [CrossRef Medline](#)
3. Parrilla G, García-Villalba B, Espinosa de Rueda M, et al. **Hemorrhage/contrast staining areas after mechanical intra-arterial thrombectomy in acute ischemic stroke: imaging findings and clinical significance.** *AJNR Am J Neuroradiol* 2012;33:1791–96 [CrossRef Medline](#)
4. Rudd MA, Johnstone M, Rabbani L, et al. **Thrombolytic therapy causes an increase in vascular permeability that is reversed by 1-deamino-8-D-vasopressin.** *Circulation* 1991;84:2568–73 [CrossRef Medline](#)
5. Yoon W, Seo JJ, Kim JK, et al. **Contrast enhancement and contrast extravasation on computed tomography after intra-arterial thrombolysis in patients with acute ischemic stroke.** *Stroke* 2004;35:876–81 [CrossRef Medline](#)
6. Phan CM, Yoo AJ, Hirsch JA, et al. **Differentiation of hemorrhage from iodinated contrast in different intracranial compartments using dual-energy head CT.** *AJNR Am J Neuroradiol* 2012;33:1088–94 [CrossRef Medline](#)
7. Gupta R, Phan CM, Leidecker C, et al. **Evaluation of dual-energy CT for differentiating intracerebral hemorrhage from iodinated contrast material staining.** *Radiology* 2010;257:205–11 [CrossRef Medline](#)
8. Dekeyser S, Nikoubashman O, Lutin B, et al. **Distinction between contrast staining and hemorrhage after endovascular stroke treatment: one CT is not enough.** *J Neurointerv Surg* 2017;9:394–98 [CrossRef Medline](#)
9. Nikoubashman O, Jablawi F, Dekeyser S, et al. **MRI appearance of intracerebral iodinated contrast agents: is it possible to distinguish extravasated contrast agent from hemorrhage?** *AJNR Am J Neuroradiol* 2016;37:1418–21 [CrossRef Medline](#)
10. Lummel N, Schulte-Altdorneburg G, Bernau C, et al. **Hyperattenuated intracerebral lesions after mechanical recanalization in acute stroke.** *AJNR Am J Neuroradiol* 2014;35:345–51 [CrossRef Medline](#)
11. Fiorelli M, Bastianello S, von Kummer R, et al. **Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort.** *Stroke* 1999;30:2280–84 [CrossRef Medline](#)
12. Larrue V, von Kummer R, Müller A, et al. **Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II).** *Stroke* 2001;32:438–41 [CrossRef Medline](#)
13. Tijssen M, Hofman P, Stadler A, et al. **The role of dual energy CT in differentiating between brain haemorrhage and contrast medium after mechanical revascularisation in acute ischaemic stroke.** *Eur Radiol* 2014;24:834–40 [CrossRef Medline](#)
14. Morales H, Lu A, Kurosawa Y, et al. **Variable MR and pathologic patterns of hemorrhage after iodinated contrast infusion in MCA occlusion/reperfusion model.** *J Neurointerv Surg* 2017;9:1248–52 [CrossRef Medline](#)
15. Yedavalli V, Sammet S. **Contrast extravasation versus hemorrhage after thrombectomy in patients with acute stroke.** *J Neuroimaging* 2017;27:570–76 [CrossRef Medline](#)
16. Hergan K, Doring W, Längle M, et al. **Effects of iodinated contrast agents in MR imaging.** *Eur J Radiol* 1995;21:11–17 [CrossRef Medline](#)
17. Jenkins JR, Robinson JW, Sisk L, et al. **Proton relaxation enhancement associated with iodinated contrast agents in MR imaging of the CNS.** *AJNR Am J Neuroradiol* 1992;13:19–27 [Medline](#)
18. Boulby PA, Rugg-Gunn F. *T2: The Transverse Relaxation Time.* West Sussex: John Wiley & Sons; 2003
19. Bae KT. **Intravenous contrast medium administration and scan timing at CT: considerations and approaches.** *Radiology* 2010;256:32–61 [CrossRef Medline](#)
20. Amans MR, Cooke DL, Vella M, et al. **Contrast staining on CT after DSA in ischemic stroke patients progresses to infarction and rarely hemorrhages.** *Interv Neuroradiol* 2014;20:106–15 [CrossRef Medline](#)

Functional MRI as an Objective Measure of Olfaction Deficit in Patients with Traumatic Anosmia

W.-J. Moon, M. Park, M. Hwang, and J.K. Kim



ABSTRACT

BACKGROUND AND PURPOSE: While posttraumatic anosmia is not uncommon, the olfactory function evaluation has strongly relied on subjective responses given by patients. We aimed to examine the utility of fMRI as an objective tool for diagnosing traumatic anosmia.

MATERIALS AND METHODS: Sixteen patients (11 men and 5 women; mean age, 42.2 ± 10.4 years) with clinically diagnosed traumatic anosmia and 19 healthy control subjects (11 men and 8 women; mean age, 29.3 ± 8.5 years) underwent fMRI during olfactory stimulation with citral (a pleasant odor) or β -mercaptoethanol (an unpleasant odor). All patients were subjected to a clinical olfactory functional assessment and nasal endoscopic exploration. Two-sample *t* tests were conducted with age as a covariate to examine group differences in brain activation responses to olfactory stimulation (false discovery rate–corrected $P < .05$).

RESULTS: Compared with healthy control subjects, patients with traumatic anosmia had reduced activation in the bilateral primary and secondary olfactory cortices and the limbic system in response to β -mercaptoethanol stimulation, whereas reduced activation was observed only in the left frontal subgyral region in response to citral stimulation.

CONCLUSIONS: Brain activation was decreased in the bilateral primary and secondary olfactory cortices as well as the limbic system in response to olfactory stimulation in patients with traumatic anosmia compared with healthy control subjects. These preliminary results may shed light on the potential of fMRI for the diagnosis of traumatic anosmia.

ABBREVIATIONS: BME = β -mercaptoethanol; BOLD = blood oxygen level–dependent; CC-SIT = Cross-Cultural Smell Identification Test; HC = healthy control; KVSS = Korean Version of the Sniffin' Sticks; MNI = Montreal Neurological Institute

Traumatic anosmia is not uncommon, affecting an estimated 5%–14.5% of patients with head trauma.¹ The main mechanism of olfactory dysfunction after closed head trauma is thought to involve damage to the olfactory nerve and associated nerve centers.² Traumatic anosmia can significantly affect quality of life,

reducing food appreciation and impairing an individual's ability to detect environmental hazards.^{1,3} Traumatic anosmia is most commonly diagnosed through a psychophysical olfactory function test that primarily relies on patient self-reporting using questionnaires and simple odorant sticks or solutions. This semi-objective psychophysical test thus requires patient cooperation and intact cognition.⁴ In addition to olfactory loss, odor memory may also affect test results,⁴ which limits the diagnostic accuracy in patients with impaired cognition. Furthermore, due to its self-reporting nature, the psychophysical test is also vulnerable to manipulation by malingering patients involved in compensation litigation.⁵ Several studies have evaluated systematic and objective tools for assessing olfactory function in patients; in particular, previous work has examined the diagnostic utility of single-photon emission CT and MR imaging. Previous MR imaging studies in patients diagnosed with traumatic anosmia based on the clinical olfactory test have found that 61%–88% of the study population had gross damage to the olfactory system, which differed according to the degree of trauma.^{6–8} Studies using SPECT have detected abnormalities that were previously undetectable on MR

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imaging in traumatic anosmia; however, patients with traumatic normosmia exhibited similar abnormalities, limiting the diagnostic utility of SPECT.^{9,10}

Functional MR imaging is a method that noninvasively evaluates the working human brain by detecting changes in blood oxygen level–dependent (BOLD) signal arising from neuronal responses to recurrent stimulation. Odor-stimulated or olfactory fMRI was first introduced by Yousem et al¹¹ and is now used for the study of olfactory deficits in neurodegenerative diseases, schizophrenia, and congenital hyposmia.^{12–16} However, the exact utility of olfactory fMRI for the evaluation of traumatic anosmia is unclear. The aim of this study was to compare brain activation between patients with traumatic anosmia and healthy control subjects during olfactory fMRI with 2 different olfactory stimuli (a pleasant odor and an unpleasant odor) to determine whether fMRI can be used to objectively measure olfactory function in a diagnostic capacity.

MATERIALS AND METHODS

Participants

This prospective study was approved by the ethics committee of Konkuk University Medical Center. Patients with traumatic anosmia were recruited from the otorhinolaryngology department from November 2012 to February 2015. We enrolled 16 patients with traumatic anosmia (11 men and 5 women; mean age, 42.2 ± 10.4 years). The inclusion criteria for patients with traumatic anosmia were as follows: 1) recent head injury, 2) criteria for anosmia met on the basis of the Korean Version of the Sniffin' Sticks (KVSS) II test, and 3) age between 18 and 65 years. Patients did not have any previous olfactory impairment, a history of sinonasal disease, or current nasal symptoms. Additionally, patients completed psychophysical olfactory testing, including the Cross-Cultural Smell Identification Test (CC-SIT), the KVSS I, and the KVSS II, and underwent nasal endoscopy to preclude the possibility of obstructive olfactory loss. Each participant provided written informed consent before study participation.

We also recruited 19 healthy control (HC) subjects (11 men and 8 women; mean age, 29.3 ± 8.5 years) from the local community. The inclusion criteria for HC participants were as follows: 1) normal olfactory function, 2) no brain lesions or prior substantial head trauma, and 3) no history of psychiatric or neurologic disease. All study participants were right-handed.

Clinical Olfactory Assessment

An otorhinolaryngologist with 17 years of clinical experience administered an examination to all patients that included an endoscopic examination of the nasal cavity and clinical olfactory performance testing to ensure that patients met the criteria for anosmia. Clinical olfactory performance measures included the CC-SIT, the KVSS I, and the KVSS II.¹⁷ The KVSS test is a modified Sniffin' Sticks test optimized for Korean patients, including the use of odors familiar to Korean individuals.^{17,18} The KVSS I is a test for rapid screening, and the KVSS II is the Korean equivalent of the Sniffin' Sticks test.^{17,18} Clinical diagnosis of anosmia was based on the KVSS II score, in which total scores of 0–20 were classified as anosmia, scores of 20.25–27 were classified as hyposmia, and scores of 27.25–48 were classified as normosmia.^{17,18}

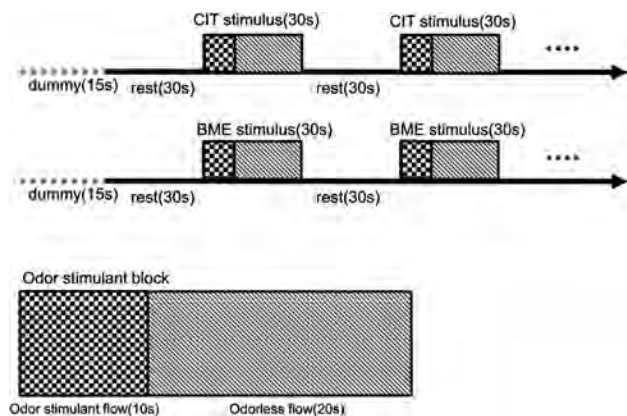


FIG 1. Task design of the citral (CIT) and β -mercaptoethanol (BME)-stimulated olfactory tasks.

MR Imaging Data Acquisition

All participants underwent MR imaging with a 3T scanner (Signa HDxT; GE Healthcare, Milwaukee, Wisconsin) using an 8-channel head coil. High-spatial-resolution T1-weighted 3D anatomic images were obtained in the axial plane using a fast-spoiled gradient-recalled sequence (TR, 7.8 ms; TE, 3.0 ms; matrix, 256×256 ; flip angle, 13° ; number of sections, 134; FOV, 240×240 mm²; section thickness, 1.3 mm).

The sequence for functional images was gradient recalled echo-planar imaging (TR, 3000 ms; TE, 35 ms; matrix, 64×64 ; flip angle, 90° ; FOV, 240×240 mm²; section thickness, 3.5 mm with no gap). A total of 100 brain volume sequences were collected during 5 minutes. Slices were aligned parallel to the anterior/posterior commissure line.

Functional images were subsequently obtained in a block design consisting of 5 odor exposure blocks ("on-period") and 5 normal breathing blocks ("off-period"). Odors were presented to participants via a custom-built olfactometer with continuous air flow (4 L/min) (Fig 1). During the 30 seconds on-period, odors were delivered to both nostrils for 10 seconds followed by 20 seconds of odorless air with 50% relative humidity at room temperature. However, it takes 3 seconds for the odor to travel through the tube from the odor container to the nasal piece; therefore, the on-period, in effect, consisted of the initial 3 seconds of odorless flow, 10 seconds of odor-stimulant flow, followed by 17 seconds of odorless flow. During the 30 seconds off-period, the subject also continuously received odorless air with 50% relative humidity at room temperature. By infusing the odorants for only 10 of the 30 seconds in the on-period, we aimed to reduce the possibility of olfactory habituation.

In the first session, 0.2 mL of 10 mmol/L citral (ie, the representative pleasant odor) was presented via the olfactometer. Subjects were instructed to follow the auditory instructions for breathing and to breathe regularly without sniffing.^{19,20} Subjects were not trained to become familiar with the stimulation paradigm before the experiment; instead, before odor delivery at the start of each session, subjects were given 15 seconds to become familiar with the auditory respiration instructions. After the citral stimulation, 0.2 mL of 1 mmol/L β -mercaptoethanol (BME) (ie, the representative unpleasant odor) was presented in the same fashion. There was a time interval of at least 30 minutes between

the citral and BME sessions, to avoid possible habituation. The room was dark, with only dimmed light, with no other stimulation besides the odorants. After the fMRI examination, the subjects were asked to describe what the odor smelled like and to judge its pleasantness. All control subjects detected the odors, either citral or BME. All subjects with anosmia reported that they did not detect any odors during the examination.

Before undertaking this prospective study, to determine the odor concentration for the fMRI examination, we presented 2 healthy subjects with serial dilutions of citral or BME by the ascending method.²¹ Thus, detection and recognition thresholds were determined, and we set the recognition threshold as the stimulant concentration for our study.

fMRI Data Analysis

fMRI data preprocessing was performed with SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12>). The first 4 volumes of each dataset were discarded to allow equilibration effects. Echo-planar images were corrected for slice-time differences and realigned to the first scan by rigid body transformation to correct for head movement. EPI and structural scans were normalized to the EPI standard template in the Montreal Neurological Institute (MNI) space (MNI: International Consortium for Brain Mapping) using linear and nonlinear transformations and were finally smoothed with a Gaussian kernel of 8-mm full width at half maximum.

Structural MR Imaging Analysis

A neuroradiologist with 20 years of experience assessed the structural abnormality of the brain, blinded to the clinical data, using images from the T1-weighted fast-spoiled gradient-recalled sequence. For assessment, multiplanar reformatted images and original axial images were used. When tissue loss was present, the maximal size of the tissue loss was measured.

Statistical Analysis

To compare clinical variables between patients with anosmia and HC subjects, we used the nonparametric Mann-Whitney *U* test in consideration of our small sample size. *P* values < .05 were considered statistically significant. Data represent the mean $\pm$ SD unless otherwise indicated. These statistical analyses were performed using the Statistical Package for the Social Sciences, Version 23.0. (SPSS; IBM, Armonk, New York).

Statistical analysis for fMRI was performed using general linear modeling implemented on SPM8 software. To provide a descriptive overview of the activation pattern (cluster size, ≥ 5 voxels) of each group in each fMRI condition, we performed 1-sample *t* tests with a false discovery rate–corrected threshold of *P* < .05. We then tested group differences using 2-sample *t* tests with age as a covariate in each stimulation condition, using the same statistical threshold. The voxels representing active structures were overlaid on 3D T1-weighted anatomic images in MNI coordinates.

RESULTS

Clinical Characteristics and Results of Olfactory Testing

There was a significant difference in age between the anosmia group (42.2 ± 10.4 years) and the HC group (29.3 ± 8.5 years)

(*P* < .001); however, there was no between-group difference in sex ratio. The mean time between head injury and clinical consultation was 11.5 months (range, 10 days to 9 years) in the anosmia group. Four of 16 patients exhibited focal tissue loss on either side of the orbitofrontal cortex on structural MR imaging, with the size of the loss varying from <1.0 cm in 3 patients to approximately 3.0 cm in 1 patient. In patients with anosmia, the mean CC-SIT score was 2.69 ± 1.96 , the mean KVSS I score was 2.0 ± 1.1 , and the mean KVSS II score was 3.2 ± 2.9 , indicating that all patients met the diagnostic criteria for anosmia.

fMRI Activation in the HC Group

Citral stimulation produced activation in some olfaction-related structures, including the bilateral medial orbitofrontal gyri and left inferior frontal gyrus (On-line Figure). BME stimulation produced more robust activation in multiple olfactory structures, including the amygdala, piriform cortex, insula, and orbitofrontal cortex (Fig 2A). We also observed significant recruitment of the superior temporal gyrus, middle temporal gyrus, inferior parietal lobule, and precuneus.

fMRI Activation in the Anosmia Group

Citral stimulation produced activation in the orbitofrontal cortex and insula and multiple bilateral cortical association areas, including the prefrontal cortex, supramarginal gyrus, and superior temporal gyrus (On-line Figure). In contrast to the HC group, no significant clusters were identified in response to BME stimulation in the anosmia group (Fig 2B).

Between-Group Comparison of fMRI Activation

In the between-group comparison, there were more prominent differences in activation in response to BME stimulation compared with citral stimulation, with differences identified in multiple olfactory structures and associated cortices in the BME condition (On-line Table 1). In contrast, between-group differences in the citral condition were only observed in small clusters in the left inferior frontal gyrus and right superior frontal gyrus.

Correlation between BOLD Activation and the KVSS-II Score

A correlation analysis was performed on KVSS II scores and fMRI brain responses to both citral and BME stimulation in the anosmia group. In both conditions, a weak-but-significant positive correlation was identified between BOLD activation in the left insula and the KVSS-II score (uncorrected *P* < .001) (On-line Table 2).

DISCUSSION

The present study demonstrates that fMRI may have utility for detecting olfactory dysfunction after closed head trauma. Compared with HC subjects, patients with traumatic anosmia exhibited reduced BOLD activation in multiple olfactory structures and associated cortices. Furthermore, these changes were most clearly observed in response to the unpleasant odor stimulation with BME.

Since the introduction of olfactory fMRI by Yousem et al in

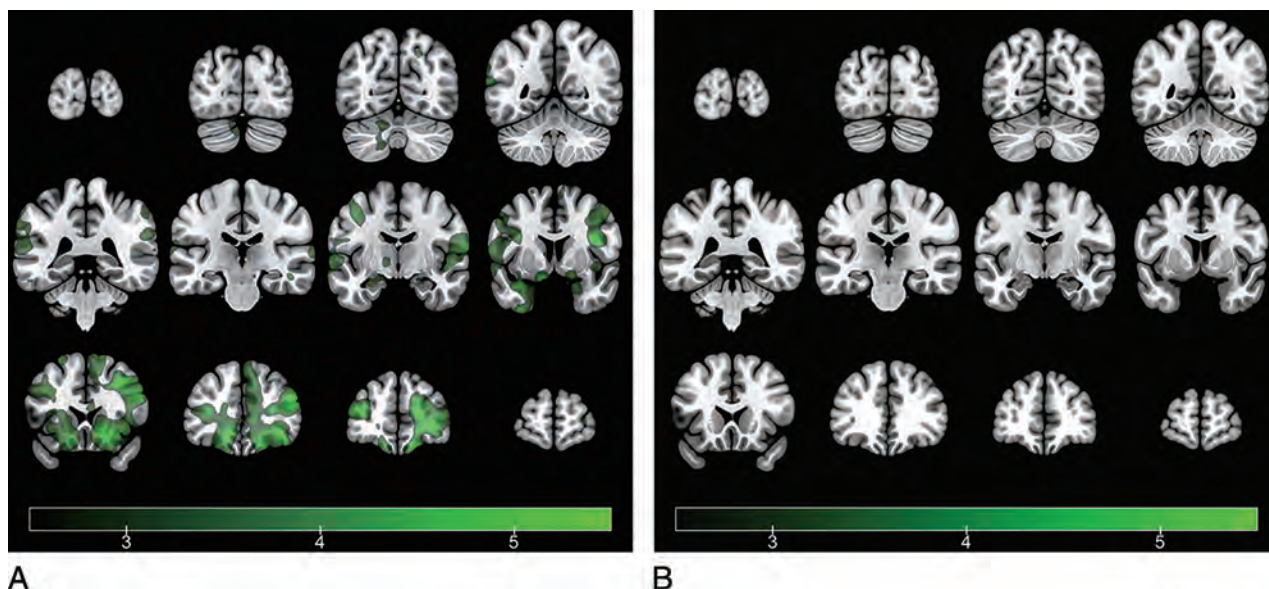


FIG 2. Representation of average brain-activation maps of the healthy control group (A) and the traumatic anosmia group (B) in response to the β -mercaptoethanol stimuli (1-sample t test, voxelwise threshold false discovery rate–corrected $P < .05$) (t values in a color scale). While the healthy control group shows activation in multiple olfactory structures and other associated brain regions, the traumatic anosmia group shows no activation in response to BME stimuli. The left side of the brain is presented on the left side of the image, according to neurologic convention.

1997,¹¹ fMRI has become increasingly used as a reliable tool for assessing olfactory function and brain responses to olfactory stimulation in a number of disease states.^{15,16,22,23} In our study, we identified significant impairment in brain activation on the surface of the uncus housing the primary olfactory cortex²⁴ and the orbitofrontal cortex as the secondary olfactory cortex as well as the insular cortex, which is associated with the processing of emotional aspects of odors,²⁵ in patients with traumatic anosmia. A previous study similarly reported that unpleasant odors produced stronger activation in the left insula of right-handed subjects compared with pleasant odors, suggesting that insular activation is related to the subjective hedonic or aversive perception of odors.²⁶

Our finding of decreased brain activation in the bilateral temporal cortex and left superior parietal lobule of patients with traumatic anosmia in response to an unpleasant odor is consistent with previous observations.^{27–29} Although olfaction primarily functions as a means for odor perception and identification, it also serves an additional function in understanding and integrating multimodal actions.²⁷ A previous fMRI study that used visual and olfactory stimuli reported increased activation in the middle temporal gyrus and parietal cortex (areas of multisensory integration) during stimulation, supporting the idea that olfaction serves multiple functions.²⁸ Furthermore, activation in the temporoparietal cortex has also been associated with odor-recognition memory, a task with a high cognitive demand.³⁰

The observation of a clear discrepancy in brain activation between the HC and anosmia groups in the unpleasant odor condition but not the pleasant odor condition can be explained by several different observations and hypotheses. First, our result is consistent with those of previous psychophysiological studies showing that unpleasant odors produce a greater degree of brain activation than pleasant odors.^{31,32} Second, previous studies have shown that the piriform cortex and other parts of the primary

olfactory cortex are only briefly activated in response to odor stimulation (<10 – 15 seconds), with BOLD signal decreasing to baseline shortly thereafter.^{27,33} Although our study design used a brief 10-second odor stimulus, a habituation effect would still be possible and may have obscured differences between the HC and anosmia groups in the pleasant odor condition (ie, in the condition evoking inherently weaker activation). Finally, while the unpleasant olfactory stimulation we used in this study is not known to cause trigeminal stimulation, clearly the pleasant odor of citral is related to trigeminal stimulation to a certain degree.³⁴ Thus, mild activation of olfactory areas by citral may be related to intranasal trigeminal stimulation of citral instead of olfactory stimulation. This hypothesis is supported by our observation that citral stimulation in the anosmia group caused activation in multiple bilateral association areas, including the prefrontal cortex, supramarginal gyrus, and superior temporal gyrus, because these areas are involved in trigeminal stimulation.³⁵

In contrast, the unpleasant BME invoked absolutely no activation in subjects with traumatic anosmia, thereby demonstrating an absence of trigeminal stimulation (if the trigeminal pathway could be stimulated at all in subjects with anosmia, we would have observed at least some activation in brain regions following BME applications). This result implies that the unpleasant BME odor may be a more suitable stimulant for detecting true subjects with anosmia because trigeminal stimulation can result in false-positive findings in the diagnosis of anosmia and should be minimized to decrease any activation not related to olfactory stimulation.

Finally, we observed a weak-but-significant positive correlation between activation in the left insular cortex and the KVSS II score in the pleasant and unpleasant stimulus conditions in the anosmia group. It is known that olfactory processes are lateralized in accordance with function in certain brain areas. Left hemispheric areas such as the orbitofrontal cortex, insula, piriform cortex, amygdala, and superior frontal cortex are primarily in-

volved with emotional responses, whereas right hemispheric areas are more involved with memory or familiarity ratings of olfaction.^{26,36} Therefore, left-sided activation of the insular cortex may be specific to the emotional processing or subjective perception of an unpleasant olfactory stimulus. Consistent with this hypothesis, a previous histopathologic study identified axonal projections from the primary and secondary olfactory cortical areas to the insula,³⁷ and other fMRI studies have corroborated a relationship between olfaction and insular activation.³⁸

The present study had several limitations. First, the statistical power of our results was rather limited by the small sample size. Therefore, future studies should confirm our findings in a larger cohort to determine the exact relationship between fMRI brain activation and clinical parameters in patients with traumatic anosmia. Second, the difference in age between groups might have contributed to reduced brain activation observed in the anosmia group because olfactory function is known to decline with increasing age.³⁹ Thus, we treated age as a covariate in our analysis. Although age is reportedly related to olfactory function, age decline has not been noted until 60 years of age.^{20,39} In addition, some studies have argued that the ability to identify unpleasant odors is unrelated to age.³¹ Therefore, we believe that a between-group age difference did not affect our study results.

Although more expensive and less accessible than subjective psychophysical testing, fMRI has an important potential for objectively detecting alterations in brain activity related to olfaction. Of note, psychophysical test results can be compromised when patients with posttraumatic anosmia exhibit associated cognitive symptoms or malingering due to secondary gain, so fMRI may be more reliable in patients with traumatic anosmia. Olfactory event-related potentials have also been suggested as an objective assessment tool for identifying olfactory deficits³⁶; however, this electrophysiologic approach lacks a methodology capable of producing a selective and controlled stimulation of the olfactory system.⁴⁰ Olfactory bulb volumetry using high-resolution structural imaging (<0.5-mm resolution) can be one of the objective measures of olfactory dysfunction. However, the normative value of olfactory bulb volume has not been established yet, and the assessment is mainly dependent on the subjective visual analysis by experts.⁴¹ In this regard, a further study of a larger sample group, including both ultra-high-resolution structural imaging for olfactory volumetry and olfactory fMRI, will be needed.

CONCLUSIONS

Our findings support the utility of olfactory fMRI for the objective visualization of deficits in olfaction-related brain activation in patients with traumatic anosmia. Future studies should confirm our preliminary findings regarding the diagnostic utility of olfactory fMRI.

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REFERENCES

- Costanzo RM, Miwa T. **Posttraumatic olfactory loss.** *Adv Otorhinolaryngol* 2006;63:99–107 Medline
- Miao X, Yang L, Gu H, et al. **Evaluation of post-traumatic anosmia with MRI and chemosensory ERPs.** *Eur Arch Otorhinolaryngol* 2015; 272:1945–53 CrossRef Medline
- Schofield PW, Moore TM, Gardner A. **Traumatic brain injury and olfaction: a systematic review.** *Front Neurol* 2014;5:5 CrossRef Medline
- Murphy C, Morgan CD, Geisler MW, et al. **Olfactory event-related potentials and aging: normative data.** *Int J Psychophysiol* 2000;36: 133–45 CrossRef Medline
- Bailie JM, Rybalsky KA, Griffith NM, et al. **The susceptibility of olfactory measures to malingering.** *Chemosensory Perception* 2008;1: 168–73 CrossRef
- Yousem DM, Geckle RJ, Bilker WB, et al. **Posttraumatic olfactory dysfunction: MR and clinical evaluation.** *AJNR Am J Neuroradiol* 1996;17:1171–79 Medline
- Sigurdardottir S, Jerstad T, Andelic N, et al. **Olfactory dysfunction, gambling task performance and intracranial lesions after traumatic brain injury.** *Neuropsychology* 2010;24:504–13 CrossRef Medline
- Ciofalo A, De Vincentiis M, Iannella G, et al. **Mild traumatic brain injury: evaluation of olfactory dysfunction and clinical-neurological characteristics.** *Brain Inj* 2018;32:550–56 CrossRef Medline
- Newton MR, Greenwood RJ, Britton KE, et al. **A study comparing SPECT with CT and MRI after closed head injury.** *J Neurol Neurosurg Psychiatry* 1992;55:92–94 CrossRef Medline
- Atighechi S, Salari H, Baradaran MH, et al. **A comparative study of brain perfusion single-photon emission computed tomography and magnetic resonance imaging in patients with post-traumatic anosmia.** *Am J Rhinol Allergy* 2009;23:409–12 CrossRef Medline
- Yousem DM, Williams SC, Howard RO, et al. **Functional MR imaging during odor stimulation: preliminary data.** *Radiology* 1997;204: 833–38 CrossRef Medline
- Levy LM, Henkin RI, Lin CS, et al. **Odor memory induces brain activation as measured by functional MRI.** *J Comput Assist Tomogr* 1999;23:487–98 CrossRef Medline
- Schneider F, Habel U, Reske M, et al. **Neural substrates of olfactory processing in schizophrenia patients and their healthy relatives.** *Psychiatry Res* 2007;155:103–12 CrossRef Medline
- Westermann B, Wattendorf E, Schwerdtfeger U, et al. **Functional imaging of the cerebral olfactory system in patients with Parkinson's disease.** *J Neurol Neurosurg Psychiatry* 2008;79:19–24 Medline
- Wang J, Eslinger PJ, Doty RL, et al. **Olfactory deficit detected by fMRI in early Alzheimer's disease.** *Brain Res* 2010;1357:184–94 CrossRef Medline
- Vasavada MM, Martinez B, Wang J, et al. **Central olfactory dysfunction in Alzheimer's disease and mild cognitive impairment: a functional MRI study.** *J Alzheimers Dis* 2017;59:359–68 CrossRef Medline
- Cho JH, Jeong YS, Lee YJ, et al. **The Korean version of the Sniffin' stick (KVSS) test and its validity in comparison with the cross-cultural smell identification test (CC-SIT).** *Auris Nasus Larynx* 2009;36: 280–86 CrossRef Medline
- Hong SC, Yoo YS, Kim ES, et al. **Development of KVSS test (Korean version of Sniffin' sticks test).** *Korean J Otolaryngol-Head Neck Surg* 1999;42:855–60
- Sobel N, Prabhakaran V, Desmond JE, et al. **Sniffing and smelling: separate subsystems in the human olfactory cortex.** *Nature* 1998; 392:282–86 CrossRef Medline
- Yousem DM, Maldjian JA, Hummel T, et al. **The effect of age on odor-stimulated functional MR imaging.** *AJNR Am J Neuroradiol* 1999;20:600–08 Medline
- Doty RL, Smith R, McKeown DA, et al. **Tests of human olfactory function: principal components analysis suggests that most measure a common source of variance.** *Percept Psychophys* 1994;56: 701–07 CrossRef Medline
- Henkin RI, Levy LM. **Functional MRI of congenital hyposmia: brain activation to odors and imagination of odors and tastes.** *J Comput Assist Tomogr* 2002;26:39–61 CrossRef Medline
- Hummel T, Fließbach K, Abele M, et al. **Olfactory fMRI in patients**

- with Parkinson's disease. *Front Integr Neurosci* 2010;4:125 [CrossRef Medline](#)
24. Zelano C, Bensafi M, Porter J, et al. **Attentional modulation in human primary olfactory cortex.** *Nat Neurosci* 2005;8:114–20 [CrossRef Medline](#)
 25. Katata K, Sakai N, Doi K, et al. **Functional MRI of regional brain responses to 'pleasant' and 'unpleasant' odors.** *Acta Otolaryngol Suppl* 2009;85–90 [Medline](#)
 26. Royet JP, Plailly J. **Lateralization of olfactory processes.** *Chem Senses* 2004;29:731–45 [CrossRef Medline](#)
 27. Vedaai F, Fakhri M, Harirchian MH, et al. **Methodological considerations in conducting an olfactory fMRI study.** *Behav Neurol* 2013; 27:267–76 [CrossRef Medline](#)
 28. Tubaldi F, Turella L, Pierno AC, et al. **Smelling odors, understanding actions.** *Soc Neurosci* 2011;6:31–47 [CrossRef Medline](#)
 29. Savic I. **Processing of odorous signals in humans.** *Brain Res Bull* 2001;54:307–12 [CrossRef Medline](#)
 30. Savic I, Gulyas B, Larsson M, et al. **Olfactory functions are mediated by parallel and hierarchical processing.** *Neuron* 2000;26:735–45 [CrossRef Medline](#)
 31. Konstantinidis I, Hummel T, Larsson M. **Identification of unpleasant odors is independent of age.** *Arch Clin Neuropsychol* 2006;21: 615–21 [CrossRef Medline](#)
 32. Alaoui-Ismaili O, Vernet-Maury E, Dittmar A, et al. **Odor hedonics: connection with emotional response estimated by autonomic parameters.** *Chem Senses* 1997;22:237–48 [CrossRef Medline](#)
 33. Poellinger A, Thomas R, Lio P, et al. **Activation and habituation in olfaction: an fMRI study.** *Neuroimage* 2001;13:547–60 [Medline](#)
 34. Doty RL, Brugger WE, Jurs PC, et al. **Intranasal trigeminal stimulation from odorous volatiles: psychometric responses from anosmic and normal humans.** *Physiol Behav* 1978;20:175–85 [CrossRef Medline](#)
 35. Albrecht J, Kopietz R, Frasnelli J, et al. **The neuronal correlates of intranasal trigeminal function-an ALE meta-analysis of human functional brain imaging data.** *Brain Res Rev* 2010;62:183–96 [CrossRef Medline](#)
 36. Barresi M, Ciurleo R, Giacoppo S, et al. **Evaluation of olfactory dysfunction in neurodegenerative diseases.** *J Neurol Sci* 2012;323:16–24 [CrossRef Medline](#)
 37. Jones-Gotman M, Zatorre RJ. **Olfactory identification deficits in patients with focal cerebral excision.** *Neuropsychologia* 1988;26:387–400 [CrossRef Medline](#)
 38. Fulbright RK, Skudlarski P, Lacadie CM, et al. **Functional MR imaging of regional brain responses to pleasant and unpleasant odors.** *AJNR Am J Neuroradiol* 1998;19:1721–26 [Medline](#)
 39. Doty RL, Kamath V. **The influences of age on olfaction: a review.** *Front Psychol* 2014;5:20 [CrossRef Medline](#)
 40. Rombaux P, Mouraux A, Bertrand B, et al. **Assessment of olfactory and trigeminal function using chemosensory event-related potentials.** *Neurophysiol Clin* 2006;36:53–62 [CrossRef Medline](#)
 41. Chung MS, Choi WR, Jeong HY, et al. **MR imaging-based evaluations of olfactory bulb atrophy in patients with olfactory dysfunction.** *AJNR Am J Neuroradiol* 2017 Dec 21. [Epub ahead of print] [CrossRef Medline](#)

Interaction of Developmental Venous Anomalies with Resting-State Functional MRI Measures

 B. Sundermann,  B. Pfeleiderer,  H. Minnerup,  K. Berger, and  G. Douaud



ABSTRACT

BACKGROUND AND PURPOSE: Functional MR imaging of the brain, used for both clinical and neuroscientific applications, relies on measuring fluctuations in blood oxygenation. Such measurements are susceptible to noise of vascular origin. The purpose of this study was to assess whether developmental venous anomalies, which are frequently observed normal variants, can bias fMRI measures by appearing as true neural signal.

MATERIALS AND METHODS: Large developmental venous anomalies (1 in each of 14 participants) were identified from a large neuroimaging cohort ($n = 814$). Resting-state fMRI data were decomposed using independent component analysis, a data-driven technique that creates distinct component maps representing aspects of either structured noise or true neural activity. We searched all independent components for maps that exhibited a spatial distribution of their signals following the topography of developmental venous anomalies.

RESULTS: Of the 14 developmental venous anomalies identified, 10 were clearly present in 17 fMRI independent components in total. While 9 (52.9%) of these 17 independent components were dominated by venous contributions and 2 (11.8%) by motion artifacts, 2 independent components (11.8%) showed partial neural signal contributions and 5 independent components (29.4%) unambiguously exhibited typical neural signal patterns.

CONCLUSIONS: Developmental venous anomalies can strongly resemble neural signal as measured by fMRI. They are thus a potential source of bias in fMRI analyses, especially when present in the cortex. This could impede interpretation of local activity in patients, such as in presurgical mapping. In scientific studies with large samples, developmental venous anomaly confounds could be mainly addressed using independent component analysis–based denoising.

ABBREVIATIONS: BOLD = blood oxygen level–dependent; DVA = developmental venous anomaly; IC = independent component; ICA = independent component analysis; rsfMRI = resting-state fMRI

Functional MR imaging of the brain is extensively used for task-specific presurgical functional mapping^{1–3} and for task-based

group studies.⁴ Analyses of spontaneous brain activity and connectivity by resting-state fMRI (rsfMRI)^{5–9} have been more recently introduced as a potential clinical tool, both in presurgical motor^{10,11} and language mapping,^{10,12–15} particularly in patients less able to adhere to task instruction, and mapping of epileptogenic foci.⁸ Additionally, rsfMRI combined with automatic machine learning shows promise for individual diagnosis and prognosis estimation in large datasets, especially in psychiatric and neurodegenerative disorders,^{16–19} as well as for genome-wide association studies.²⁰ fMRI is based on blood oxygen level–dependent (BOLD) contrast and thus provides indirect measures of neural activity. BOLD changes are attributed predominantly to both extravascular tissue and local capillaries and veins.²¹ Consequently, there are various sources of potential bias to the BOLD

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signal measured by fMRI, including global and local perfusion as well as vascular architecture.²¹

Incidental findings and normal variants are frequently encountered in brain MR imaging.^{22–26} While debates on the management of incidental findings in scientific studies mostly focus on participant safety,²⁷ little is known about potential biases of particular findings on measures of scientific or clinical interest (putative correlates of neural signals) in fMRI.

Developmental venous anomalies (DVAs)²⁸ are frequent (around 2% prevalence^{29,30}) and are usually clinically irrelevant but can be associated, in rare circumstances, with other vascular lesions, such as cavernous malformations, or with abnormalities of neuronal migration.^{28,31} DVAs can also exhibit signs of venous congestion.³² The normal venous drainage of the cerebral hemispheres can be divided into 2 systems: 1) The superficial system drains blood from cortical and immediately subcortical capillaries into pial veins; and 2) the deep system drains large parts of the deep white matter and basal ganglia into deep veins (the internal cerebral veins and the basal vein of Rosenthal). The cerebellum features a comparable, 2-system venous angioarchitecture.³¹ The term DVA describes variants in which a superficial venous territory drains into deep veins or a deep venous territory drains toward either the superficial pial veins or directly into a dural venous sinus.³¹

The detectability of DVAs depends largely on the imaging techniques used. However, DVAs are characterized by very typical morphologic imaging features. These are large collector veins crossing the brain parenchyma in locations where usually only capillaries and small veins are expected, and radially contributing veins resulting in a typical caput medusae appearance.^{29,31} These veins drain blood from an atypical territory. The presence of a DVA thus potentially undermines common assumptions about the origin of observed BOLD signal fluctuations in gray matter regions.

The purpose of this study was to assess if and how DVAs bias fMRI measures by assessing the similarity of DVA correlates in rsfMRI to typical patterns of neural activity in a large, community-based imaging population.³³ If such similarity exists, then the presence of DVAs might lead to misinterpretations of local activity patterns in presurgical mapping and confound conclusions in group studies and new rsfMRI-based diagnostic approaches.

MATERIALS AND METHODS

Subjects

This analysis is based on subjects with large DVAs identified during routine radiologic review and quality assessment of brain MR imaging for the BiDirect cohort study.^{33,34} They were selected from a mixed sample of patients with depression and population-dwelling controls ($n = 814$). The study was approved by the local ethics committee, and all subjects gave their written informed consent. Demographic characteristics of the BiDirect cohort and the imaging sample used here are presented in On-line Table 1.

MR Imaging Data Acquisition

Structural and functional MR imaging data were acquired using a 3T scanner (Intera with an Achieva upgrade; Philips Healthcare,

Best, the Netherlands) and a standard transmit/receive head coil. Full details on the imaging protocol have been published separately.³³

The main analyses were based on the following sequences: a 3D T1-weighted gradient-echo sequence with an inversion prepulse—turbo field echo, TR/TE = 7.26/3.56 ms, TI = 404 ms, flip angle = 9°, sagittal orientation, matrix = 256 × 256 mm, field of view = 256 × 256 × 160 mm, voxel size = 1 × 1 × 2 mm reconstructed to 1 × 1 × 1 mm by zero-filling in the k -space; rsfMRI using a T2*-weighted echo-planar imaging technique—fast-field echo, TR/TE = 3000/38 ms, flip angle = 90°, 72 volumes, matrix dimensions = 64 × 64, FOV = 230 × 230 mm, 36 axial slices, thickness = 3.6 mm, pixel size = 3.6 × 3.6 mm.

Additional information about DVA morphology was obtained from the following: FLAIR—TR/TE = 11,000/80 ms, TI = 2600 ms, flip angle = 90°, matrix dimensions = 352 × 206, FOV = 230 × 186 mm, 27 axial slices, thickness = 4 mm, gap = 1 mm, reconstructed pixel size = 0.45 × 0.45 mm; and a T2*-weighted fast-field echo sequence—TR/TE = 574/16 ms, flip angle = 18°, matrix dimensions = 256 × 164, FOV = 230 × 183 mm, 27 axial slices, thickness = 4 mm, gap = 1 mm, reconstructed pixel size = 0.45 × 0.45 mm.

DVA Identification

Suspected DVAs were confirmed in a separate step after initial screening during visual data-quality assessment based on T1-weighted images using the following criteria: 1) a large vessel crossing the brain parenchyma, and 2) a typical caput medusae appearance of feeding vessels. Finally, a typical hypointense appearance was confirmed on T2* fast-field echo. We excluded subjects with signs of other associated vascular lesions, for example, cavernous malformations. FLAIR images were inspected for surrounding hyperintensity as a potential sign of venous congestion.³² Demographic information about all subjects selected for the DVA analysis as well as DVA locations is presented in On-line Table 2.

Resting-State fMRI Data Analysis with Independent Component Analysis

Spatial independent component analysis (ICA) refers to a range of data-driven analysis techniques decomposing time-series data into a set of spatially independent components (ICs) characterized by spatial maps and signal time courses. ICA is particularly popular for the analysis of rsfMRI data because it can isolate separate representations of well-known functionally relevant brain networks.³⁵ In addition to these components related to the signal of interest originating from the gray matter, further components represent distinct sources of noise such as arterial or CSF pulsations or movement artifacts.³⁶ ICA is therefore very suitable for identifying and characterizing such biasing influences. ICA can identify general sources of noise independent of specific model assumptions in other fMRI analysis techniques. Thus, findings from ICA generalize to other analysis techniques and to task-fMRI data. Indeed, it can reveal potential biases that might have otherwise not been directly visible despite potentially significantly influencing results and conclusions. ICA is therefore increasingly applied as a preprocessing step for noise clean-up of both rsfMRI

and task-fMRI data before performing further analyses (see the Discussion for details).^{36–38}

Two types of components representing venous signal fluctuations are particularly relevant for DVAs: those showing mainly the venous sinuses and large veins and those putatively representing transmedullary and subependymal veins (traditionally referred to as white matter components). Given the partially venous origin of the BOLD signal of interest, venous noise components can exhibit temporal characteristics that greatly resemble signal components.³⁶ Thus, additional spatial features (eg, based on sinus masks) have to be used in automatic noise-classification tools,³⁷ but the underlying spatial assumptions behind these predefined masks could be broken in the presence of a large DVA.

Single-session analyses of the rsfMRI time-series data were conducted using the FMRIB Software Library (FSL, Version 5.0.9; <http://www.fmrib.ox.ac.uk/fsl>).^{39,40} Preprocessing included motion correction,⁴¹ non-brain tissue masking,⁴² spatial smoothing using a Gaussian kernel (full width at half maximum = 7 mm), and high-pass temporal filtering (cutoff period = 100 seconds). The resulting image time-series were then decomposed using probabilistic ICA with automatic dimensionality estimation as implemented in MELODIC (Version 3.15; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC>).^{35,43–45}

Identification of DVAs in the ICA Decomposition of rsfMRI

To help with the identification of the presence of DVAs in our ICA, we linearly registered ICA spatial maps to the T1-weighted anatomic images using boundary-based registration.⁴⁶ ICA spatial maps were thresholded at $|Z| = 2.3$ and overlaid with anatomic images with FSleyes (Version 0.9.11; <https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSleyes>). Components were individually assessed for contributions spatially corresponding to the courses of the DVAs (B.S.). Those ICs that were identified as containing DVA rsfMRI signal correlates were subsequently evaluated for whether they exhibited contributions of neural signal of interest or artifacts (eg, motion or arterial pulsations) by taking spatial maps, time courses, and power spectra into account.³⁶

RESULTS

General DVA Characteristics

Sixteen DVAs without an associated second vascular lesion were identified in 16 subjects. None of the DVAs exhibited associated hyperintensities on FLAIR, kinking of the draining vein, or other indirect signs of venous congestion. Two of these findings located in the cerebellum were excluded from further analyses because they were partially cut by the fMRI acquisition volume.

DVA Occurrence in the ICA Decomposition of rsfMRI

All of the 14 DVAs subsequently included were present in at least 1 IC. Ten DVAs (71.4%) had unique local presence, closely following their spatial distribution in at least 1 IC per subject and up to 4 ICs per subject. The remaining 4 DVAs had less specific spatial coverage. In other words, it could not be determined whether alterations in ICs corresponding to these 4 DVAs (at least 1 IC per subject) were directly related to the DVA or whether these alterations represented signal fluctuations of interest in the surrounding tissue or other sources of noise.

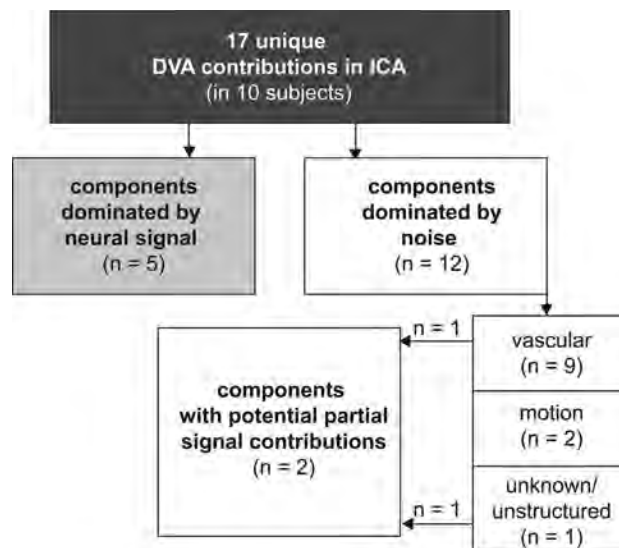


FIG 1. Overview of dominant effects represented by the independent components which included unique contributions of DVAs.

In total, 43 ICs thus covered spatial locations specific to DVAs across subjects. Seventeen of these ICs (39.5%) exhibited unique contributions following the spatial distribution of the DVAs, while a further 26 ICs (60.5%) were less specific, with their spatial distribution only partially overlapping that of the DVAs.

Characteristics of rsfMRI ICs Containing DVAs

Among the 17 ICs closely following the spatial distribution of the DVAs, 9 (52.9%) were ICs with predominantly vascular patterns and clear contributions of venous sinuses, deep cerebral veins, or subependymal veins (white matter components), one of which exhibited partial signal contribution. Two ICs (11.8%) were dominated by motion artifacts. Most important, 5 ICs (29.4%) in 3 subjects exhibited dominant patterns typical of true neural signal. Three of these 5 ICs had clean low-frequency power spectra, while contamination in the higher frequency range was present in 2 ICs. One final IC was unstructured in its overall spatial distribution but showed partial overlap with neural signal (see Fig 1 for an overview of these results).

Illustrative cases are presented in Figs 2 and 3. A full list of the sample including DVA-related findings is presented in On-line Table 2. All 17 ICs distinctly following the spatial distribution of the DVAs are presented in On-line Figs 1–10.

DISCUSSION

In summary, most DVAs clearly appeared in ≥ 1 component on the basis of ICA decomposition of the rsfMRI data. While some of these ICs demonstrated unambiguous venous ICs including the venous sinuses, some of the DVAs were present in ICs that mostly exhibited typical features of neural signal ICs or that could not be unambiguously classified as noise. These findings show that signal fluctuations in DVAs can contribute to the fMRI signal in the brain and thus have the potential to bias conclusions in both clinical and scientific fMRI analyses if not appropriately considered, especially in a superficial/cortical location. DVAs could thus lead to pseudoactivations in presurgical mapping, biasing the possible extent of subsequent tumor resection if not recognized.

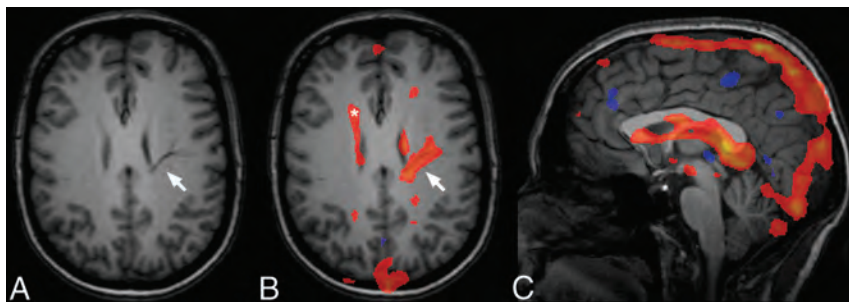


FIG 2. An example of a unique contribution of a DVA with deep drainage in an IC dominated by venous pulsations (subject 5). Typical anatomic features of the DVA (arrow, A) with a caput medusae appearance, unique contribution following the course of the DVA through the parenchyma (arrow, B) and contributions attributable to normal subependymal veins in the periventricular white matter (asterisk, B). C, Midsagittal view representing the typical venous character of this component, including venous sinuses and deep veins.

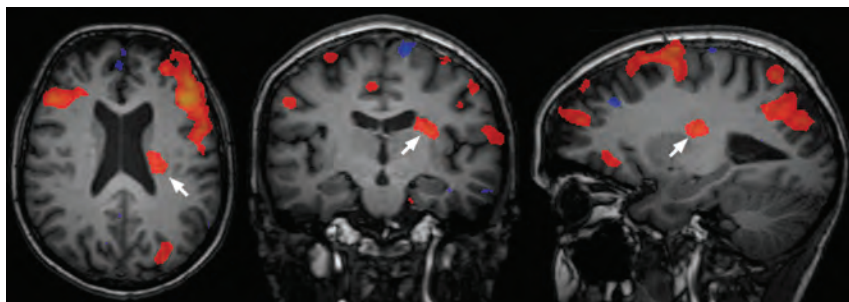


FIG 3. An example of a unique contribution of a DVA (arrows) in an IC exhibiting typical characteristics of a neural signal component (subject 3).

Local pseudoactivity might also bias conclusions in the rsfMRI group studies, focusing on disease mechanisms, particularly in small samples. Finally, altered activity patterns may lead to false individual diagnostic decisions in highly automated diagnostic modeling, for example, when a classifier (supervised learning) is applied to rsfMRI data biased by a DVA in a single subject.

Potentially strong biases of vascular abnormalities on fMRI measures are well-known from imaging in patients with arteriovenous malformations, which are high-flow lesions.^{1,47} Our findings demonstrate that such biases can also be caused by usually clinically irrelevant low-flow lesions such as DVAs. Perfusion imaging in DVAs has revealed a diverse pattern: The large collector veins typically present as strictly local hyperperfusion compared with the surrounding brain parenchyma. Surrounding brain tissue can either exhibit normal perfusion patterns⁴⁸ or show signs of venous congestion with delayed perfusion and increased cerebral blood volume extending beyond the visible transparenchymal vessels.^{32,48-52} Such venous congestion may be due to a rare stenosis of the draining vein³¹ and could further invalidate assumptions of fMRI in the affected area. We did not observe indirect signs of such venous congestion in our sample. Evidence of a more widespread influence of DVAs on adjacent brain tissue is provided by findings of reduced uptake of fluorodeoxyglucose in a subset of subjects with DVAs, suggesting hypometabolism.⁵³

In addition to identification of interpretable signal components,³⁶ ICA has a practical application for reduction of such biases. Indeed, it can be used to separate signals of interest from noise in fMRI data based on either hand classification of ICs^{36,54} or by using automated IC classification tools.^{36,37,55-65} Our results

suggest that biasing signal fluctuations in DVAs can not only be identified but also addressed by ICA-based denoising in most cases. However, our results also demonstrate that a non-negligible proportion of DVAs cannot be reasonably separated from the neural signal of interest and may contaminate clear signal ICs, as well as unclear ICs (which are typically not removed from the dataset with these cleaning methods). The co-occurrence of DVA signal and typical neural signal patterns might be mainly based on similarly low (and potentially aliased) frequencies of the BOLD signal fluctuations in the temporal domain. We therefore believe that this observation points to the typical problem that the indirect measurement of neural activity by BOLD fMRI can be confounded by vascular sources of noise.⁵⁵ In our opinion, this aspect is underappreciated in many fMRI and particularly rsfMRI studies, and both researchers and clinical personnel should be more aware of this general issue.

Another practically important finding is that the significant signal alterations related to DVAs strictly followed the spatial distribution of the collecting vein and large tributaries. This finding supports the idea that a potential bias is relatively local, though subthreshold alterations in the immediate vicinity cannot be excluded.

An important-but-controversial differential diagnostic aspect is the rare observation of arteriovenous malformations draining into DVAs or microshunts.^{66,67} While the latter is primarily an angiographic finding, whether the observation of DVA signal fluctuations with arteries, rather than with veins, might add to the diagnostic information in such cases remains to be evaluated. However, current temporal resolution typically below the frequency of arterial pulsations does not facilitate reliable diagnostic assessment of this issue due to aliasing.^{38,68}

Limitations

This analysis focused on large DVAs clearly identifiable by their typical branching morphology (ie, no hard size criterion). Because 3D susceptibility-weighted imaging or contrast-enhanced T1-weighted data were not available in this sample, the true DVA prevalence is probably underestimated. Thus, the sample size of 14 subjects with clear DVAs in this study is comparatively small. In particular, DVAs with a superficial drainage pattern were potentially underrepresented because they can be more difficult to identify by nonenhanced MR imaging. We expect superficial DVAs to be more problematic, even if smaller, because the spatial interpretation of the signal origin (cortex versus DVA) is more difficult in these cases. Because we did not observe rare DVAs with signs of venous congestion in our substantial cohort of 814 participants, we unfortunately could not assess how rsfMRI captures

this clinically relevant information. While focusing on ICA outputs might be perceived at first as a limitation, this analysis method actually provides an unbiased way to assess the true characteristics of the DVA signal and therefore its potential bias.

CONCLUSIONS

This work provides a proof of concept that DVAs can have features very similar to those of neural signal patterns and can thus potentially be a source of bias in fMRI analyses, probably especially when present in a superficial location involving the cortex. Thus, our study raises awareness of a potential issue that has been neglected so far. Although most effects of DVAs on fMRI signal were local and potentially amenable to dedicated noise-correction methods, there is evidence of more widespread alterations and a contamination of putative neural signal. In the clinical setting, physicians should be aware of potential “pseudoactivations” caused by DVAs, especially in the context of presurgical mapping, as well as potential biases these could cause in highly automated diagnostic approaches using supervised learning^{16–19} in big data and genome-wide association studies.²⁰ DVAs in brain regions of interest could bias conclusions in small-group studies and thus warrant exclusion on a case-by-case basis.

Even though DVAs are usually not a clinically relevant finding, they should thus be reported to researchers by radiologists or neuroradiologists involved in the routine evaluation of scientific MR images of the brain. Awareness of potential biases caused by these frequent normal variants is important not only for neuroscientists but also for correct interpretation of clinical fMRI data.

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REFERENCES

- Bartsch AJ, Homola G, Biller A, et al. **Diagnostic functional MRI: illustrated clinical applications and decision-making.** *J Magn Reson Imaging* 2006;23:921–32 CrossRef Medline
- Leuthardt EC, Allen M, Kamran M, et al. **Resting-state blood oxygen level-dependent functional MRI: a paradigm shift in preoperative brain mapping.** *Stereotact Funct Neurosurg* 2015;93:427–39 CrossRef Medline
- Gabriel M, Brennan NP, Peck KK, et al. **Blood oxygen level dependent functional magnetic resonance imaging for presurgical planning.** *Neuroimaging Clin N Am* 2014;24:557–71 CrossRef Medline
- Bandettini PA. **Twenty years of functional MRI: the science and the stories.** *Neuroimage* 2012;62:575–88 CrossRef Medline
- Zhang D, Raichle ME. **Disease and the brain's dark energy.** *Nat Rev Neurol* 2010;6:15–28 CrossRef Medline
- van den Heuvel MP, Hulshoff Pol HE. **Exploring the brain network: a review on resting-state fMRI functional connectivity.** *Eur Neuropsychopharmacol* 2010;20:519–34 CrossRef Medline
- Barkhof F, Haller S, Rombouts SA. **Resting-state functional MR imaging: a new window to the brain.** *Radiology* 2014;272:29–49 CrossRef Medline
- Lee MH, Smyser CD, Shimony JS. **Resting-state fMRI: a review of methods and clinical applications.** *AJNR Am J Neuroradiol* 2013;34:1866–72 CrossRef Medline
- Lv H, Wang Z, Tong E, et al. **Resting-state functional MRI: everything that nonexperts have always wanted to know.** *AJNR Am J Neuroradiol* 2018;39:1390–99 CrossRef Medline
- Leuthardt EC, Guzman G, Bandt SK, et al. **Integration of resting state functional MRI into clinical practice: a large single institution experience.** *PLoS One* 2018;13:e0198349 CrossRef Medline
- Hou BL, Bhatia S, Carpenter JS. **Quantitative comparisons on hand motor functional areas determined by resting state and task BOLD fMRI and anatomical MRI for pre-surgical planning of patients with brain tumors.** *Neuroimage Clin* 2016;11:378–87 CrossRef Medline
- Parker Jones O, Voets NL, Adcock JE, et al. **Resting connectivity predicts task activation in pre-surgical populations.** *Neuroimage Clin* 2016;13:378–85 CrossRef Medline
- Lu J, Zhang H, Hameed NU, et al. **An automated method for identifying an independent component analysis-based language-related resting-state network in brain tumor subjects for surgical planning.** *Sci Rep* 2017;7:13769 CrossRef Medline
- Branco P, Seixas D, Deprez S, et al. **Resting-state functional magnetic resonance imaging for language preoperative planning.** *Front Hum Neurosci* 2016;10:11 CrossRef Medline
- Kollndorfer K, Fischmeister FP, Kaspran G, et al. **A systematic investigation of the invariance of resting-state network patterns: is resting-state fMRI ready for pre-surgical planning?** *Front Hum Neurosci* 2013;7:95 CrossRef Medline
- Sundermann B, Herr D, Schwindt W, et al. **Multivariate classification of blood oxygen level-dependent fMRI data with diagnostic intention: a clinical perspective.** *AJNR Am J Neuroradiol* 2014;35:848–55 CrossRef Medline
- Wolfers T, Buitelaar JK, Beckmann CF, et al. **From estimating activation locality to predicting disorder: a review of pattern recognition for neuroimaging-based psychiatric diagnostics.** *Neurosci Biobehav Rev* 2015;57:328–49 CrossRef Medline
- Rathore S, Habes M, Iftikhar MA, et al. **A review on neuroimaging-based classification studies and associated feature extraction methods for Alzheimer's disease and its prodromal stages.** *Neuroimage* 2017;155:530–48 CrossRef Medline
- de Vos F, Koini M, Schouten TM, et al. **A comprehensive analysis of resting state fMRI measures to classify individual patients with Alzheimer's disease.** *Neuroimage* 2018;167:62–72 CrossRef Medline
- Elliott L, Sharp K, Alfaro-Almagro F, et al. **Genome-wide association studies of brain structure and function in the UK biobank.** *bioRxiv* 2018:178806 CrossRef
- Kim SG, Ogawa S. **Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals.** *J Cereb Blood Flow Metab* 2012;32:1188–206 CrossRef Medline
- Langner S, Buelow R, Fleck S, et al. **Management of intracranial incidental findings on brain MRI.** *Rofo* 2016;188:1123–33 CrossRef Medline
- Sandeman EM, Hernandez Mdel C, Morris Z, et al. **Incidental findings on brain MR imaging in older community-dwelling subjects are common but serious medical consequences are rare: a cohort study.** *PLoS One* 2013;8:e71467 CrossRef Medline
- Bos D, Poels MM, Adams HH, et al. **Prevalence, clinical management, and natural course of incidental findings on brain MR images: the population-based Rotterdam scan study.** *Radiology* 2016;281:507–15 CrossRef Medline
- Morris Z, Whiteley WN, Longstreth WT, Jr, et al. **Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis.** *BMJ* 2009;339:b3016 CrossRef Medline
- Vernooij MW, Ikram MA, Tanghe HL, et al. **Incidental findings on brain MRI in the general population.** *N Engl J Med* 2007;357:1821–28 CrossRef Medline
- Borra RJ, Sorensen AG. **Incidental findings in brain MRI research: what do we owe our subjects?** *J Am Coll Radiol* 2011;8:848–52 CrossRef Medline

28. Lasjaunias P, Burrows P, Planet C. **Developmental venous anomalies (DVA): the so-called venous angioma.** *Neurosurg Rev* 1986;9:233–42 CrossRef Medline
29. Lee M, Kim MS. **Image findings in brain developmental venous anomalies.** *J Cerebrovasc Endovasc Neurosurg* 2012;14:37–43 CrossRef Medline
30. Sarwar M, McCormick WF. **Intracerebral venous angioma: case report and review.** *Arch Neurol* 1978;35:323–25 CrossRef Medline
31. Ruiz DS, Yilmaz H, Gailloud P. **Cerebral developmental venous anomalies: current concepts.** *Ann Neurol* 2009;66:271–83 CrossRef Medline
32. Jung HN, Kim ST, Cha J, et al. **Diffusion and perfusion MRI findings of the signal-intensity abnormalities of brain associated with developmental venous anomaly.** *AJNR Am J Neuroradiol* 2014;35:1539–42 CrossRef Medline
33. Teuber A, Sundermann B, Kugel H, et al. **MR imaging of the brain in large cohort studies: feasibility report of the population- and patient-based BiDirect study.** *Eur Radiol* 2017;27:231–38 CrossRef Medline
34. Teismann H, Wersching H, Nagel M, et al. **Establishing the bidirectional relationship between depression and subclinical arteriosclerosis: rationale, design, and characteristics of the BiDirect study.** *BMC Psychiatry* 2014;14:174 CrossRef Medline
35. Beckmann CF, DeLuca M, Devlin JT, et al. **Investigations into resting-state connectivity using independent component analysis.** *Philos Trans R Soc Lond B Biol Sci* 2005;360:1001–13 CrossRef Medline
36. Griffanti L, Douaud G, Bijsterbosch J, et al. **Hand classification of fMRI ICA noise components.** *Neuroimage* 2017;154:188–205 CrossRef Medline
37. Salimi-Khorshidi G, Douaud G, Beckmann CF, et al. **Automatic denoising of functional MRI data: combining independent component analysis and hierarchical fusion of classifiers.** *Neuroimage* 2014;90:449–68 CrossRef Medline
38. Griffanti L, Salimi-Khorshidi G, Beckmann CF, et al. **ICA-based artefact removal and accelerated fMRI acquisition for improved resting state network imaging.** *Neuroimage* 2014;95:232–47 CrossRef Medline
39. Smith SM, Jenkinson M, Woolrich MW, et al. **Advances in functional and structural MR image analysis and implementation as FSL.** *Neuroimage* 2004;23(Suppl 1):S208–19 CrossRef Medline
40. Jenkinson M, Beckmann CF, Behrens TE, et al. **FSL.** *Neuroimage* 2012;62:782–90 CrossRef Medline
41. Jenkinson M, Bannister P, Brady M, et al. **Improved optimization for the robust and accurate linear registration and motion correction of brain images.** *Neuroimage* 2002;17:825–41 CrossRef Medline
42. Smith SM. **Fast robust automated brain extraction.** *Hum Brain Mapp* 2002;17:143–55 CrossRef Medline
43. Beckmann CF, Smith SM. **Probabilistic independent component analysis for functional magnetic resonance imaging.** *IEEE Trans Med Imaging* 2004;23:137–52 CrossRef Medline
44. Minka T. **Automatic choice of dimensionality for PCA: technical report 514.** MIT Media Lab Vision and Modeling Group. 2000. <https://tminka.github.io/papers/pca/minka-pca.pdf>. Accessed April 12, 2017
45. Hyvärinen A. **Fast and robust fixed-point algorithms for independent component analysis.** *IEEE Trans Neural Netw* 1999;10:626–34 CrossRef Medline
46. Greve DN, Fischl B. **Accurate and robust brain image alignment using boundary-based registration.** *Neuroimage* 2009;48:63–72 CrossRef Medline
47. Lehericy S, Biondi A, Sourour N, et al. **Arteriovenous brain malformations: is functional MR imaging reliable for studying language reorganization in patients? Initial observations.** *Radiology* 2002;223:672–82 CrossRef Medline
48. Kroll H, Soares BP, Saloner D, et al. **Perfusion-CT of developmental venous anomalies: typical and atypical hemodynamic patterns.** *J Neuroradiol* 2010;37:239–42 CrossRef Medline
49. Camacho DL, Smith JK, Grimmer JD, et al. **Atypical MR imaging perfusion in developmental venous anomalies.** *AJNR Am J Neuroradiol* 2004;25:1549–52 Medline
50. Hanson EH, Roach CJ, Ringdahl EN, et al. **Developmental venous anomalies: appearance on whole-brain CT digital subtraction angiography and CT perfusion.** *Neuroradiology* 2011;53:331–41 CrossRef Medline
51. Sharma A, Zipfel GJ, Hildebolt C, et al. **Hemodynamic effects of developmental venous anomalies with and without cavernous malformations.** *AJNR Am J Neuroradiol* 2013;34:1746–51 CrossRef Medline
52. Iv M, Fischbein NJ, Zaharchuk G. **Association of developmental venous anomalies with perfusion abnormalities on arterial spin labeling and bolus perfusion-weighted imaging.** *J Neuroimaging* 2015;25:243–50 CrossRef Medline
53. Larvie M, Timmerman D, Thum JA. **Brain metabolic abnormalities associated with developmental venous anomalies.** *AJNR Am J Neuroradiol* 2015;36:475–80 CrossRef Medline
54. Kelly RE Jr, Alexopoulos GS, Wang Z, et al. **Visual inspection of independent components: defining a procedure for artifact removal from fMRI data.** *J Neurosci Methods* 2010;189:233–45 CrossRef Medline
55. Murphy K, Birn RM, Bandettini PA. **Resting-state fMRI confounds and cleanup.** *Neuroimage* 2013;80:349–59 CrossRef Medline
56. Thomas CG, Harshman RA, Menon RS. **Noise reduction in BOLD-based fMRI using component analysis.** *Neuroimage* 2002;17:1521–37 CrossRef Medline
57. Beall EB, Lowe MJ. **Isolating physiologic noise sources with independently determined spatial measures.** *Neuroimage* 2007;37:1286–300 CrossRef Medline
58. Perlberg V, Bellec P, Anton JL, et al. **CORSICA: correction of structured noise in fMRI by automatic identification of ICA components.** *Magn Reson Imaging* 2007;25:35–46 CrossRef Medline
59. Sui J, Adali T, Pearlson GD, et al. **An ICA-based method for the identification of optimal FMRI features and components using combined group-discriminative techniques.** *Neuroimage* 2009;46:73–86 CrossRef Medline
60. Storti SF, Formaggio E, Nordio R, et al. **Automatic selection of resting-state networks with functional magnetic resonance imaging.** *Front Neurosci* 2013;7:72 CrossRef Medline
61. Bhaganagarapu K, Jackson GD, Abbott DF. **An automated method for identifying artifact in independent component analysis of resting-state FMRI.** *Front Hum Neurosci* 2013;7:343 CrossRef Medline
62. Tohka J, Foerke K, Aron AR, et al. **Automatic independent component labeling for artifact removal in fMRI.** *Neuroimage* 2008;39:1227–45 CrossRef Medline
63. De Martino F, Gentile F, Esposito F, et al. **Classification of fMRI independent components using IC-fingerprints and support vector machine classifiers.** *Neuroimage* 2007;34:177–94 CrossRef Medline
64. Sochat V, Supek K, Bustillo J, et al. **A robust classifier to distinguish noise from fMRI independent components.** *PLoS One* 2014;9:e95493 CrossRef Medline
65. Caballero-Gaudes C, Reynolds RC. **Methods for cleaning the BOLD fMRI signal.** *Neuroimage* 2017;154:128–49 CrossRef Medline
66. Pereira VM, Geibprasert S, Krings T, et al. **Pathomechanisms of symptomatic developmental venous anomalies.** *Stroke* 2008;39:3201–15 CrossRef Medline
67. Tomycz ND, Vora NA, Kanal E, et al. **Intracranial arterialized venous angioma: case report with new insights from functional brain MRI.** *Diagn Interv Radiol* 2010;16:13–15 CrossRef Medline
68. Lowe MJ, Mock BJ, Sorenson JA. **Functional connectivity in single and multislice echoplanar imaging using resting-state fluctuations.** *Neuroimage* 1998;7:119–32 CrossRef Medline

Peeking into the Black Box of Coregistration in Clinical fMRI: Which Registration Methods Are Used and How Well Do They Perform?

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ABSTRACT

BACKGROUND AND PURPOSE: Interpretation of fMRI depends on accurate functional-to-structural alignment. This study explores registration methods used by FDA-approved software for clinical fMRI and aims to answer the following question: What is the degree of misalignment when registration is not performed, and how well do current registration methods perform?

MATERIALS AND METHODS: This retrospective study of presurgical fMRI for brain tumors compares nonregistered images and 5 registration cost functions: Hellinger, mutual information, normalized mutual information, correlation ratio, and local Pearson correlation. To adjudicate the accuracy of coregistration, we edge-enhanced echo-planar maps and rated them for alignment with structural anatomy. Lesion-to-activation distances were measured to evaluate the effects of different cost functions.

RESULTS: Transformation parameters were congruent among Hellinger, mutual information, normalized mutual information, and the correlation ratio but divergent from the local Pearson correlation. Edge-enhanced images validated the local Pearson correlation as the most accurate. Hellinger worsened misalignment in 59% of cases, primarily exaggerating the inferior translation; no cases were worsened by the local Pearson correlation. Three hundred twenty lesion-to-activation distances from 25 patients were analyzed among nonregistered images, Hellinger, and the local Pearson correlation. ANOVA analysis revealed significant differences in the coronal ($P < .001$) and sagittal ($P = .04$) planes. If registration is not performed, 8% of cases may have a >3 -mm discrepancy and up to a 5.6-mm lesion-to-activation distance difference. If a poor registration method is used, 23% of cases may have a >3 -mm discrepancy and up to a 6.9-mm difference.

CONCLUSIONS: The local Pearson correlation is a special-purpose cost function specifically designed for T2*-T1 coregistration and should be more widely incorporated into software tools as a better method for coregistration in clinical fMRI.

ABBREVIATIONS: AFNI = Analysis of Functional Neuro Images; CR = correlation ratio; HEL = Hellinger; LAD = lesion-to-activation distance; LPC = local Pearson correlation; MI = mutual information; NMI = normalized mutual information; NR = nonregistered

Interpretation of fMRI depends on accurate functional-to-structural alignment. However, accurate placement of the activation area on the anatomic underlay is fraught with challenges. The images to be superimposed are acquired sequentially, not simultaneously, and patients are not always cooperative in holding still across the entire examination. Registration is then required to account for patient movement by placing the images back into the same reference space. Additionally, the image se-

quences are multimodal in that the anatomic data are T1-weighted gradient-echo, whereas the functional data are T2*-weighted echo-planar. The latter also has intrinsic geometric distortion with signal drop-out and is typically acquired at a lower resolution (Fig 1, upper row). Functional-to-structural misalignment may be subtle and not easily recognized (Fig 1, lower row). When functional-to-structural misalignment occurs, error is introduced when interpreting the functional significance of apparent gyrus activation and when judging lesion-to-activation distances (LADs), which can impact surgical risk assessment.

This coregistration between functional and structural images is an important postprocessing step that can affect the final interpretation, yet it is our observation that the registration step is not well-understood, even by most neuroradiologists experienced with functional imaging and vendor application specialists. Most publications only briefly remark that “images were coregistered” with no further elaboration. It seems to us that most fMRI users

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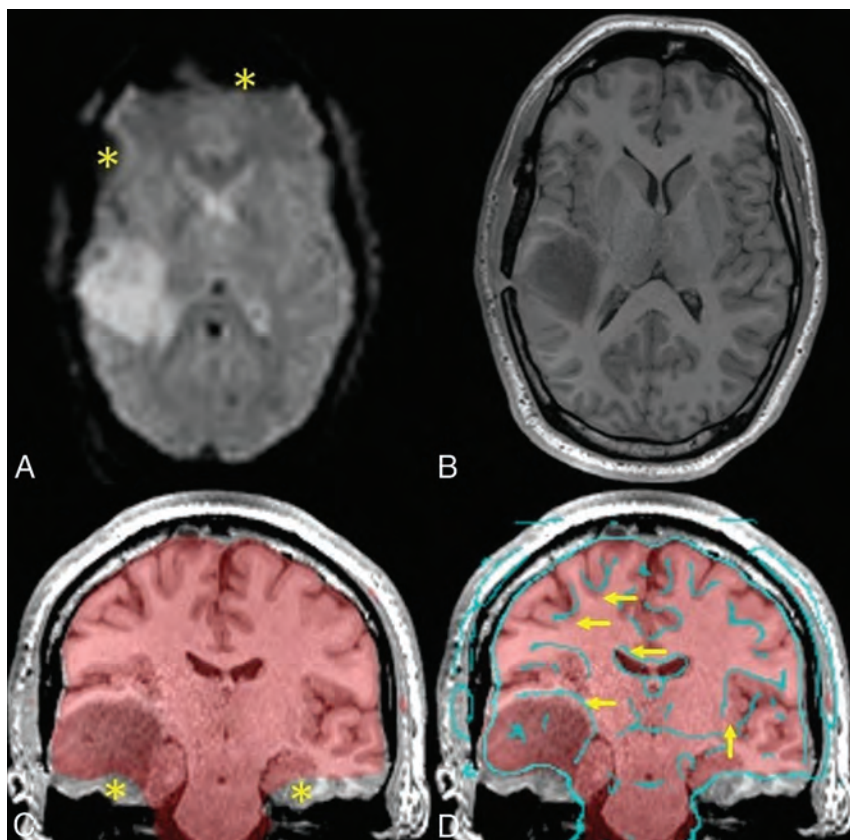


FIG 1. Sample patient with a right temporal lobe tumor. The upper row illustrates the challenge in functional-to-anatomic multimodal alignment between T2* EPI (A) and T1-weighted MPRAGE images (B). Note the inherently poor resolution of EPI. These images also show signal drop-out from susceptibility artifacts near the sinuses and craniotomy (asterisks). The lower row highlights the great difficulty in judging accurate alignment simply by visual inspection. The fusion image of the average EPI mask over the MPRAGE image (C) shows signal drop-out at the skull base (asterisks), which can potentially confound registration algorithms. The fusion image of edge-enhanced EPI (D) delineates structural boundaries in EPI data and reveals slight misalignment (arrows) due to patient motion between MPRAGE and EPI, primarily in the inferior-superior direction along with some rotation.

just assume that the coregistration step should work as intended without understanding what is actually happening. In our experience with presurgical fMRI studies, coregistration often seemed to underperform expectations; furthermore, there seemed to be too much variability in fMRI activation localization using different registration methods.

It is important to contextualize the aims of this study. While there is an inexhaustible number of possible ways to perform coregistration, our project has a distinct focus on the current state of clinical use. Thus, we are primarily interested in the performance of the coregistration step in FDA-approved commercial software. The cost functions evaluated in this study emerge from a survey of the current state of the industry.

A variety of research (Analysis of Functional Neuro Images [AFNI; <http://afni.nimh.nih.gov/afni/>]; FSL [<http://www.fmrib.ox.ac.uk/fsl/>]; statistical parametric mapping [SPM; <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>]) and FDA-approved commercial (Prism Clinical Imaging, <https://www.prismclinical.com/pages-output/prism-process/>; NordicNeuroLab, <http://www.nordicneurolab.com/>; Invivo, <http://www.invivocorp.com/>; Brainlab, <https://www.brainlab.com/>; Siemens, <https://usa.healthcare.siemens.com/magnetic-resonance-imaging/options-and-upgrades/>

clinical-applications/syngo-mr-neuro-fmri; GE Healthcare, <https://www.gehealthcare.com/products/advanced-visualization/all-applications/brainwave>) platforms are available for fMRI postprocessing. The following brief survey of the major commercial software packages illustrates the variety of approaches taken by the vendors. NordicNeuroLab, Invivo, Brainlab, Siemens, and GE Healthcare have a default workflow that automatically applies coregistration, and most also provide the option of manual nudging with 6 *df*. In these cases, only 1 cost function is available, it is chosen by the vendor, the choice is usually not obviously disclosed, it cannot be changed by the user, and it is applied universally to all modalities to be registered. Brainlab¹ and GE Healthcare use mutual information. Invivo and Siemens use normalized mutual information. NordicNeuroLab uses a variant of mutual information that uses adaptive sampling with an octree partition.² The workflow of Prism is more elaborate in several ways. It uses AFNI as its engine. It does not automatically coregister, though there is the option to activate formal coregistration, during which one may select the cost function from a list of choices, including Hellinger (default selection), local Pearson correlation, mutual information, normalized mutual information, correlation ratio, and least squares. A second cost

function (mutual information by default) runs in the background and warns the user about a discrepancy between the results of the primary and secondary cost functions. The primary and secondary metrics selected can be different for each pair of images to be registered. Last, manual nudging is allowed with 3 *df* for translation. (Compiled by personal e-mail communication with Chad Neller and Jim Reuss from Prism, Cathy Elsinger from NordicNeuroLab, Erik Peterson from Invivo, John Murray from BrainLab, David Carpenter from Siemens, and Olaf Roeder from GE. 12/12/2016–11/6/2017.)

This survey serves to illustrate the variability among vendors and that in most cases, the vendors make the decision for you. The presumption that the vendor has chosen the best registration algorithm may not necessarily be correct. There is always a need for more validation studies, and vendors are responsive to quality-improvement initiatives in partnership with physicians.

The most important work to date comparing cost functions against one another is by Cox et al³ and Saad et al,⁴ who introduced the local Pearson correlation (LPC) cost function specifically designed for T2*–T1 coregistration. They demonstrated that LPC outperforms mutual information, correlation ratio, and Hellinger across AFNI, FSL, and SPM platforms. Nevertheless,

this survey of commercial vendors reveals that only Prism makes LPC available, though not even by default.

The present study explores the performance of registration methods used by FDA-approved software for clinical fMRI and aims to answer the following question: What is the degree of misalignment when registration is not performed, and how well do current registration methods perform?

MATERIALS AND METHODS

Patient Selection

This is a retrospective evaluation of presurgical fMRI studies of consecutive patients scanned between April 2016 and March 2017. Inclusion criteria were fMRI studies with at least 1 motor or language task, the presence of brain tumor for the purpose of LAD measurement, and an activation area within 40 mm of the tumor margin. Studies were excluded if performed for indications other than tumor, if deemed clinically nondiagnostic due to gross patient motion or noncompliance with the task, or if no activation area was present within 40 mm of the tumor margin.

Scanning Technique

Images were acquired on a 3T Tim Trio scanner (Siemens, Erlangen, Germany). A 32-channel head coil was used. A sagittal 3D T1-weighted MPRAGE sequence was acquired with the following parameters: $1 \times 1 \times 1$ mm isotropic resolution, TR = 1690 ms, TI = 1100 ms, TE = 2.56 ms, flip angle = 12° , FOV = 256×224 mm, matrix = 256×224 , one hundred seventy-six partitions. Axial blood oxygen level–dependent fMRI was acquired by using T2* echo-planar imaging with the following parameters: $3.5 \times 3.5 \times 3.5$ mm isotropic resolution, no interslice gap, TR = 2100 ms, TE = 27 ms, flip angle = 77° , FOV = 224×224 mm, matrix = 64×64 , thirty-eight slices.

fMRI Tasks

Motor tasks used in these protocols included ≥ 1 of the following: finger motion, foot motion, or tongue motion, depending on the tumor location and the judgment of the supervising radiologist. Language tasks included ≥ 1 of the following: verb generation (in which a written noun is displayed and the patient is asked to covertly generate an appropriate verb), antonym generation (in which a written word is displayed and the patient is asked to covertly generate an appropriate antonym), and letter fluency (in which a written letter is displayed and the patient is asked to covertly generate words that begin with that letter). The block design consists of 21-second intervals, alternating between active and control blocks, totaling 3 minutes for the motor task and 4 minutes for each language task. Stimuli are presented by a projector-mirror system, and a finger response system is used to track patient participation.

Postprocessing

Postprocessing of blood oxygen level–dependent fMRI data was rendered automatically on a Prism Process (Prism Clinical Imaging) workstation following built-in steps that included within-series motion correction, spatial smoothing, and calculation of activation maps using a general linear model, which disregards EPI volumes deemed outliers and incorporates motion parameter

estimates as a nuisance covariate. This automated processing on the Prism workstation used default options for spatial smoothing (a modest amount of Gaussian blur with a full width at half maximum of 4 mm) and for spatial extent thresholds/clustering (a correlation coefficient threshold of 0.35 in conjunction with a cluster radius of 5 mm and a cluster volume of 210 mm^3), with additional statistical thresholding determined by the neuroradiologist during visual inspection of the activation maps.

The T1-weighted anatomic images were skull-stripped. No formal coregistration was performed at this initial processing step. These initial images are hereafter referred to as nonregistered (NR).

For assessing the effects of the registration method, we exported the NR images from Prism into the AFNI format for off-line coregistration. AFNI is the image-processing engine also used in Prism. The 3dAllineate function in AFNI was used to coregister EPI and T1-weighted images using Hellinger (HEL), mutual information (MI), normalized mutual information (NMI), correlation ratio (CR), and the local Pearson correlation (LPC) cost functions separately. We chose the default interpolation options of the 3dAllineate function, which uses linear interpolation internally during the steps of the alignment process (–interp option). As a weight function, we used a simple binary mask derived from the skull-stripped MPRAGE image.

Image Evaluation

The transformation parameters, consisting of 3 *df* in translation and 3 *df* in rotation, were automatically calculated by each registration algorithm. These transformation parameters were recorded for HEL, MI, NMI, CR, and LPC. Results were unambiguously congruent among the first 4 cost functions but notably divergent from LPC (see the Results section and Fig 2). Statistical analysis confirmed that LPC was significantly different from each of the other 4 methods, but neither HEL, MI, NMI, nor CR differed from one another. These results are not surprising because the first 4 cost functions belong to a category of information theory–based methods grounded in the joint histogram of the image intensities, whereas the modus operandi of the LPC method is entirely different. These results justify the use of HEL, which happens to be the default option in both AFNI and Prism, as a representative cost function for the category of information theory–based methods for further analysis against the LPC.

The NR, HEL, and LPC brain activation images were imported back into Prism to standardize the image display among the 3 methods. All images were resampled and cubic spline–interpolated to the 1-mm isotropic voxel size of the MPRAGE images. The blood oxygen level–dependent fMRI threshold level was visually optimized, as is routine practice in clinical work, by a board-certified neuroradiologist (F.D.R.) with 6 years of experience interpreting fMRI studies; but for each patient, the threshold level was held constant across all registration methods being compared. T1-weighted MPRAGE window-level settings were exaggerated for high contrast to easily delineate the tumor margin.

All activation areas located within 40 mm of the tumor margins were identified on any of the axial, coronal, and sagittal planes on either motor or language tasks. This distance was somewhat arbitrarily selected simply for collecting samples for subse-

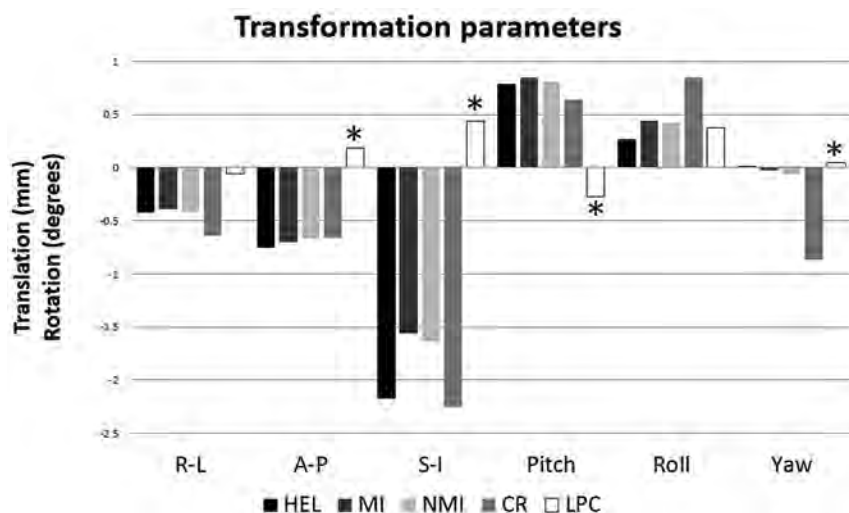


FIG 2. Graph plotting the average transformation parameters for translation and rotation as calculated by several metrics: Hellinger, mutual information, normalized mutual information, correlation ratio, and local Pearson correlation. The transformation effects of LPC are in the opposite direction (*asterisks*) for most translations and rotations, most notably the inferior translation and rotation in pitch. R-L indicates right-left; A-P, anterior-posterior; and S-I, superior-inferior.

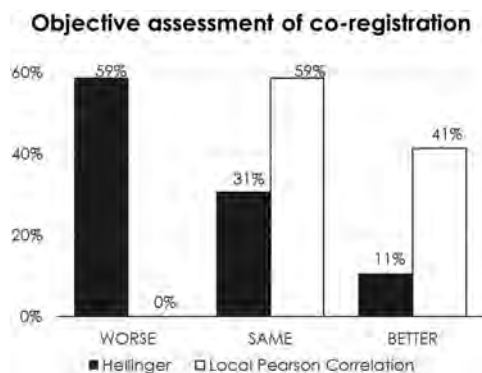


FIG 3. Histogram summarizing the objective assessment of coregistration using edge-enhanced images for both HEL and LPC compared with the initial nonregistered condition. In the case of the HEL metric, the accuracy of function-to-structural alignment actually worsens in 59% of cases and improves in 11% of cases. However, in the case of the LPC metric, none of the cases worsened and 41% improved.

quent analysis. The LAD was measured for each of these activation areas on all 3 registration methods.

To adjudicate the accuracy of spatial alignment among these 3 methods, the 3dedge3 function in AFNI was applied to the EPI data to create edge-enhanced EPI maps, which afford direct visual inspection of misalignment with respect to anatomic detail on the MPRAGE images. Following the work of a prior study,⁵ we rated these edge-enhanced versions of the NR, HEL, and LPC images for accurate alignment with the ventricular and sulcal margins using the following rating system: 1, grossly misaligned; 2, >5-mm error; 3, two- to five-millimeter error; and 4, zero- to two-millimeter error.

Statistical Analysis

Statistical analysis of the differences in transformation parameters among HEL, MI, NMI, CR, and LPC was performed using a repeated-measures ANOVA with the registration method and transformation parameter as levels of within factors. We per-

formed statistical analysis of the differences in LAD among NR, HEL, and LPC for each imaging plane separately using repeated-measures ANOVA, treating the registration method as the within-subject factor and subjects as levels of a between factor. Treating observations in each subject as coming from separate “groups” allows the modeling of a subject-by-method interaction effect and can help remove any bias in the main effect toward a particular method caused by a few subjects. Huynh-Feldt corrections to the number of *dfs* in the *F*-tests were used on the basis of a moderate departure from sphericity (Greenhouse-Geisser epsilon of >0.75).

RESULTS

Thirty consecutive patients undergoing presurgical fMRI were examined. Five patients were excluded because they

were scanned for indications other than tumor or were deemed clinically nondiagnostic. Of the patients included, 5 fMRI runs were excluded because there was no activation area within 40 mm of the tumor margin. Therefore, a total of 25 patients were evaluated with a combined total of 75 motor and language tasks. A total of 320 LADs were identified and measured, consisting of 56 in the axial plane, 112 in the coronal plane, and 152 in the sagittal plane.

The transformation parameters as calculated by each cost function were unambiguously congruent among HEL, MI, NMI, and CR but notably divergent from LPC (Fig 2). In fact, the transformation effects of the first 4 cost functions were in the opposite direction for most of the translations and rotations compared with LPC. The most notable discordance was inferior translation and rotation in pitch (ie, nodding the head). A repeated-measures ANOVA was performed with registration method and transformation parameters as levels of within factors. The analysis showed a highly significant effect of the registration method ($P < .001$). In Bonferroni-corrected pair-wise comparisons, the LPC method was significantly different from each of the other 4 methods ($P < .001$), whereas neither of HEL, MI, NMI, nor CR differed from one another at the $P < .05$ level. These results justify the use of HEL, which happens to be the default option in both AFNI and Prism, as a representative cost function for the category of information theory-based methods for further analysis against LPC. Direct visual inspection of edge-enhanced EPI revealed that HEL worsened misalignment with respect to NR in 59% of cases, primarily exaggerating inferior translation; no cases were worsened by LPC. HEL improved alignment in 11% of cases; LPC improved 41% of cases (Fig 3).

Figure 4 illustrates a typical case. The bottom row shows the edge-enhanced EPI superimposed on the anatomic T1-weighted images. Attention to the ventricular margin, tumor margin, and peripheral sulcal margins reveals alignment that is slightly too high on NR (rated 2 for 2- to 5-mm error), too low on HEL (rated 2 for >5-mm error), and just right on LPC (rated 4 for 0- to 2-mm

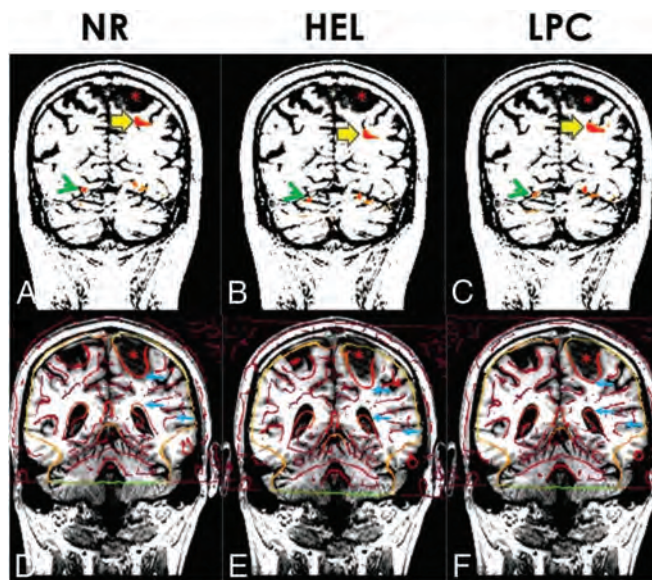


FIG 4. The upper row displays activation areas from the antonym task superimposed on coronal MPRAGE images (A–C). The high-contrast window-level setting helps demarcate the tumor in the left parietal lobe (asterisks). Lesion-to-activation distance between the tumor and the nearest activation area (large yellow arrows) is quite different: 2.6 mm in NR (A), 12.9 mm in HEL (B), and 7.4 mm in LPC (C). Notice that the activation area in the ventral temporo-occipital junction (green arrowheads) is displaced in the cerebellum in HEL (B). The lower row consists of edge-enhanced EPI superimposed on MPRAGE images (D–F). Visual inspection reveals that edge-enhanced EPI (small blue arrows) is too high in the initial NR (D), too low in HEL (E), but just right in LPC (F).

Differences in LAD between LPC, HEL, and NR

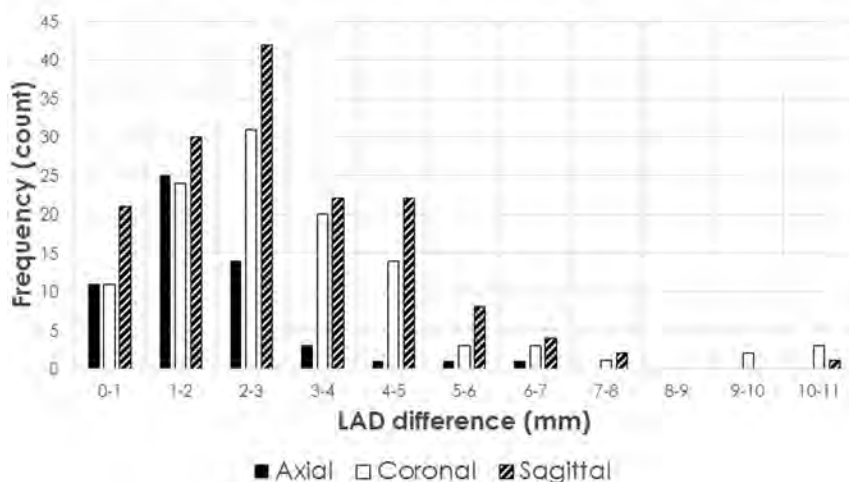


FIG 5. Histogram displaying the maximum differences in LAD among LPC, HEL, and NR. Data are also sorted by imaging plane. Notice that the LAD difference is <3 mm in most cases, and this is especially true in the axial plane. However, a nontrivial number of cases have a >3 mm discrepancy, particularly in the coronal and sagittal planes.

error). The upper row shows an activation area from the antonym task near the left parietal lobe tumor on a coronal section. The LADs were 2.6 mm for NR, 12.9 mm for HEL, and 7.4 mm for LPC. Incidentally, these images also show an activation area in the ventral temporo-occipital junction, which was inferiorly displaced with the HEL method and inadvertently localized below the tentorium within the cerebellum.

The 320 LADs were analyzed for differences among NR, HEL,

and LPC. The repeated-measures ANOVA test showed significant differences in the coronal ($P < .001$) and sagittal ($P = .04$) planes, but not in the axial plane ($P = .55$). Pair-wise comparisons between registration methods confirmed significant differences for LPC versus NR ($P < .001$) and for LPC versus HEL ($P < .001$) but not for HEL versus NR for those planes that exhibit a significant effect of method (coronal and sagittal).

Histogram analysis of differences in LAD measured among NR, HEL, and LPC (Fig 5) revealed that the maximum LAD difference was <3 mm in most cases; however, 105 (33%) cases had a >3 -mm discrepancy, almost all in the coronal and sagittal planes, even up to a 10.9-mm LAD difference. Figure 6 isolates the LAD differences between LPC, which is taken to represent accurate alignment based on the edge-enhanced analysis, and nonregistered. This contrast, therefore, reveals the degree of misalignment when registration is not performed. In this case, 27 (8%) cases have >3 mm discrepancy, almost all in the coronal and sagittal planes and up to a 5.6-mm LAD difference. Figure 7 isolates the LAD differences between LPC, which yields accurate alignment, and HEL, which has been shown to systematically introduce misregistration error. This contrast emphasizes the degree of misalignment that may result if a poor registration method is chosen. In this situation, 75 (23%) cases have a >3 -mm discrepancy, almost all in the coronal and sagittal planes, and up to a 6.9-mm LAD difference.

DISCUSSION

Registration consists of iterative algorithms that minimize an intensity-based cost function, which is a quantitative metric of how well 2 volumes are being aligned.⁵⁻⁷ The transformation model

may involve 6 *df* with 3 for translation and 3 for rotation (called rigid-body registration) or 9 *df* epsilons, adding 3 for scaling, or 12 *df* epsilons, adding 3 for shearing (called “full affine registration”), or >12 *df* epsilons, consisting of a diverse family of nonlinear algorithms. There is currently no consensus on which complex nonlinear registration techniques are reliable enough to guide clinical interpretations.

Rigid-body transformation remains the industry standard for

Differences in LAD between LPC and NR

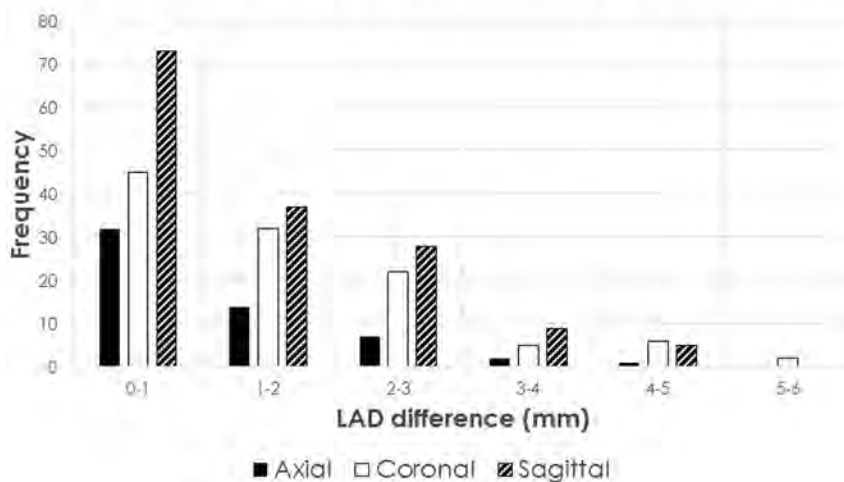


FIG 6. Histogram of the maximum differences in LAD between LPC and NR. Data are also sorted by imaging plane. Because edge-enhanced analysis has shown LPC to produce accurate alignment, the contrast between LPC and NR reveals the degree of misalignment when registration is not performed. The most pronounced LAD differences are found in the coronal and sagittal planes.

Differences in LAD between LPC and HEL

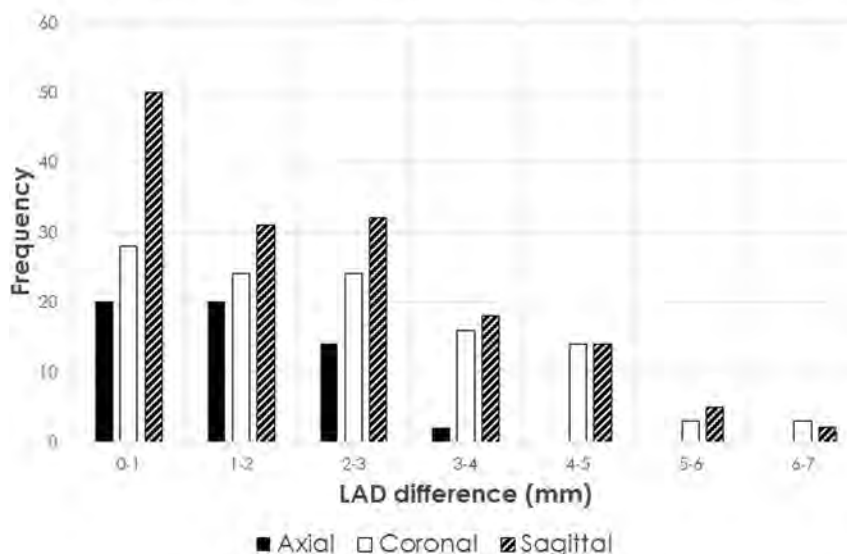


FIG 7. Histogram of the maximum differences in LAD between LPC and HEL. Data are also sorted by imaging plane. Because it has been shown that LPC produces accurate alignment and that HEL systematically introduces misregistration error, the contrast between LPC and HEL serves to illustrate the degree of misalignment that may result if a poor registration metric is chosen. The most pronounced LAD differences are found in the coronal and sagittal planes.

fMRI registration. This standard makes sense because we are aligning images taken from the same patient during the same session so that true structural differences between undistorted images with different weightings are not expected. However, in fMRI, the underlying T2* images are distorted nonuniformly, resulting in misalignment that rigid-body registration cannot fully correct. Proper alignment is also affected by signal drop-out in the T2* images due to air-tissue interfaces such as the nasal sinuses. The choice of metric or cost function is crucial but not yet stan-

dardized to obtain the best rigid-body registration despite the presence of these distortions. Most vendors supporting clinical software have made the choice of which cost function is used, usually mutual information or normalized mutual information, as reviewed earlier. In the case of Prism, the clinical imaging platform used at our institution, the default cost function is HEL, though alternative metrics are at least also available, including LPC. Validation of these choices is lacking.

Correct localization of fMRI activation is essential if LAD is to be used for prognostic value and risk assessment. Even a small amount of misalignment can lead to misinterpretation of the functional significance of fMRI activation, such as in the case of activation being classified as cerebellar instead of cerebral (Fig 4). Not only in the clinical setting but also in basic science research, correct anatomic localization of fMRI activation is an elementary expectation.

A number of publications have explored the significance of LAD for presurgical fMRI risk assessment. Concerning motor function, 1 study reported a higher risk of new postoperative deficits with an LAD of <5 mm, but complete resection without deficits was achieved for an LAD of >10 mm.⁸ For language function, Kundu et al⁹ found that the LAD with respect to the Broca area was 17.5 mm for the group with postoperative deficits but 26.8 mm for the group with no deficits. Similarly, the LAD with respect to the Wernicke area was 13.9 mm with deficits but 29.6 mm with no deficits. Wood et al¹⁰ found an overall correlation between LAD and mortality and furthermore reported that motor deficits increased linearly with a closer LAD but language deficits increased exponentially with a closer LAD (<20 mm), while leveling off and not further diminishing with farther LADs (>20 mm), which the authors posit may reflect the more distributed nature of lan-

guage networks. Bailey et al¹¹ found that the LAD, particularly for expressive language, failed to predict postoperative deficits. The authors suggested that their findings, though counterintuitive at first glance, actually corroborate the added value of presurgical fMRI because neurosurgeons would react appropriately and take a more cautious surgical approach to successfully minimize postoperative deficits. Another study scrutinized the accuracy of motor and language activation sites in fMRI when judged against the criterion standard of intraoperative electrocortical stimulation

and found that all such correlations were within 20 mm and 87% of correlations were within 10 mm.¹² The discrepancies likely reflect the combined error of technical factors, including spatial resolution, smoothing, geometric distortion, patient motion, misregistration, and stereotactic localization error and stimulation effects.

While these investigations into the prognostic value of LADs and the validity of fMRI results are meaningful, surprisingly, some references even neglected to mention the crucial postprocessing step of coregistration at all. This present study brings attention specifically to the choice of cost function because it has been underappreciated and its accurate implementation impacts image interpretation. Given that it matters which registration algorithm is applied, it is disconcerting that so many clinical (and basic science) fMRI articles give it so little attention. None of the studies cited above specified the cost function, presumably because the choice is thought to be “standard” and because better choices cannot be distinguished from poor choices. Two of them explained that EPI was manually nudged “for perceived optimal spatial coregistration.”^{9,10} However, visual checking and manual nudging are user-dependent and difficult to standardize.

In this study, the performance of several cost functions was compared alongside LPC. HEL was specifically chosen because this is the default cost function in AFNI and Prism, which is the FDA-approved postprocessing software used at our institution. HEL¹³ and the more common MI¹⁴ are both information theory-based cost functions and widely used for generic multitechnique registration.

LPC, introduced by Cox et al³ in 2008 and Saad et al⁴ in 2009, is a special-purpose cost function specifically designed for T2*-T1 coregistration by taking advantage of known differences in contrast between the 2 modalities, though it is not yet widely used. It exploits the strong negative correlation that CSF is bright on T2* images but dark on T1 images. This cost function is further distinguished by being more heavily weighted toward the CSF signal and by incorporating localized estimates with a scalar nonlinear stretching to accentuate larger correlations to accommodate non-uniformity artifacts. LPC was demonstrated to outperform a range of other cost functions, including MI, CR, and HEL.

An alternative rigid-body algorithm that bears similarities to LPC is boundary-based registration, which incidentally is made available in the FSL research platform. It, too, has proved superiority in T2*-T1 coregistration compared with the correlation ratio and normalized mutual information.¹⁵

Other groups have explored more exotic approaches using nonlinear techniques to correct the underlying geometric distortions inherent in EPI for the purpose of optimizing fMRI coregistration.¹⁶⁻¹⁸ Direct head-to-head comparisons between rigid and nonlinear techniques have been undertaken in both fMRI¹⁹ and PET/MR imaging.²⁰ In the fMRI study, the authors concluded that their particular nonlinear algorithm was superior to affine transformation, which happened to use normalized mutual information. In the PET/MR imaging study, of the limited selection of metrics evaluated, the 9-*df* transformation and the 12-*df* full affine transformation fared better than the 6-*df* rigid transformation or the 12+ -*df* nonlinear algorithm. However, neither LPC nor boundary-based registration was used in these analyses. For nonlinear registration algorithms to be validated, they must be

shown to reliably preserve accurate distances in patient scans. If this is shown to be the case at a future time, the option should exist for these algorithms to be placed alongside, or even in place of, the existing best standard for fMRI registration.

Our methodology has several potential limitations. Patient sample size was not large, and data collection was limited to a single institution. Moreover, only a select number of cost functions were compared, but as explained previously, this decision was influenced by the cost functions currently in clinical use and the options available in Prism (which uses an AFNI engine). For instance, AFNI does not offer boundary-based registration, and Prism cannot support FSL outputs. Second, evaluation of the tumor margin may be considered suboptimal on non-contrast-enhanced T1-weighted images so that tumor and edema were probably not perfectly differentiated. However, even on contrast-enhanced images, identifying nonenhancing tumor is still a problem, and regardless, the only detail pertinent to the current analysis is that the same tumor margin is used across all registration methods for consistent LAD measurements. Last, the activation areas were chosen on the basis of proximity, but their clinical significance was not considered and correlative intraoperative mapping was not available.

There are several future directions worth considering. The performance of the local Pearson correlation can be compared between different registration models, for instance 6-parameter rigid body versus 12-parameter full affine. Furthermore, a separately acquired field map can be used for correction of geometric distortion. Therefore, registration with and without field map-based correction can be assessed. Head-to-head comparison between LPC and boundary-based registration would also be interesting. Our results are preliminary in this regard and may serve as a catalyst for more definitive work.

CONCLUSIONS

Comparison of transformation parameters, visual inspection of edge-enhanced EPI, and statistical analysis of LAD differences in the different planes are all concordant with the fact that HEL and other similar cost functions introduce systematic error, primarily in terms of exaggerated inferior translation. This inferior shift is not surprising because registration algorithms must deal with missing data in the form of signal drop-out near the skull base from susceptibility artifacts in T2* echo-planar imaging. On the other hand, the LPC algorithm, which uses a different modulus operandi, performs superbly. On the basis of our patient series, we found that if formal coregistration is not performed in routine clinical fMRI, patient motion between EPI runs and between EPI and MPRAGE images (the dominant source of initial misalignment) causes up to a 5.6-mm error. If a poorer registration metric is used (ie, HEL instead of LPC), yet another source of misalignment may further muddle the situation, contributing up to a 6.9-mm error. It is important that fMRI users be aware of the limitations and variabilities in registration methods to avoid potential adverse outcomes, and that the LPC metric appears promising for routine T2*-T1 co-registration.

A few general recommendations follow. In the research world, while there are existing pipelines in both AFNI (using LPC) and FSL (using boundary-based registration) for optimal T2*-T1

coregistration, there is no guarantee that individual researchers using even these platforms will run the correct scripts. The peer-review process should have the expectation that one disclose the registration methodology, including cost function, *df*, software platform, and quality control. Our primary interest lies with commercial vendors supporting clinical fMRI. Thus, we note that Prism is the only software FDA-approved for clinical use that makes LPC available, though not by default. Vendors are encouraged to incorporate LPC (or perhaps boundary-based registration) as the default registration metric for T2*-T1 coregistration. fMRI users would also benefit if commercial software made available quality-control measures similar to the edge-enhanced rendering applied in this study. National organizations such as the American Society of Functional Neuroradiology and the Quantitative Imaging Biomarker Alliance fMRI section may consider incorporating recommendations for the standardization of the cost function and possibly specific quality-control measures to promote best practices. While there is no current industry standard for optimal functional-to-structural alignment, our results and review argue that there should be.

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REFERENCES

1. Grosu AL, Lachner R, Wiedenmann N, et al. **Validation of a method for automatic image fusion (BrainLAB System) of CT data and 11C-methionine-PET data for stereotactic radiotherapy using a LINAC: first clinical experience.** *Int J Radiat Oncol Biol Phys* 2003;56:1450–63 [CrossRef Medline](#)
2. Sundar H, Shen D, Biros G, et al. **Robust computation of mutual information using spatially adaptive meshes.** *Med Image Comput Assist Interv* 2007;10(Pt 1):950–58 [Medline](#)
3. Cox R, Saad Z, Glen D, et al. **False sense of EPI-to-structural alignment with common cross-modality registration methods.** In: *Proceedings of the Annual Meeting of the Organization for Human Brain Mapping*, Melbourne, Australia. June 15–19, 2008; 501
4. Saad ZS, Glen DR, Chen G, et al. **A new method of improving functional-to-structural MRI alignment using local Pearson correlation.** *Neuroimage* 2009;44:839–48 [CrossRef Medline](#)
5. Maintz JB, Viergever MA. **A survey of medical image registration.** *Med Image Anal* 1998;2:1–36 [Medline](#)
6. Zitova B, Flusser J. **Image registration methods: a survey.** *Image and Vision Computing* 2003;21:977–1000 [CrossRef](#)
7. Gholipour A, Kehtarnavaz N, Briggs R, et al. **Brain functional localization: a survey of image registration techniques.** *IEEE Trans Med Imaging* 2007;26:427–51 [CrossRef Medline](#)
8. Krishnan R, Raabe A, Hattingen E, et al. **Functional magnetic resonance imaging-integrated neuronavigation: correlation between lesion-to-motor cortex distance and outcome.** *Neurosurgery* 2004;55:904–15; discussion 914–15 [CrossRef Medline](#)
9. Kundu B, Penwarden A, Wood JM, et al. **Association of functional magnetic resonance imaging indices with postoperative language outcomes in patients with primary brain tumors.** *Neurosurg Focus* 2013;34:E6 [CrossRef Medline](#)
10. Wood JM, Kundu B, Utter A, et al. **Impact of brain tumor location on morbidity and mortality: a retrospective functional MR imaging study.** *AJNR Am J Neuroradiol* 2011;32:1420–25 [CrossRef Medline](#)
11. Bailey PD, Zacà D, Basha MM, et al. **Presurgical fMRI and DTI for the prediction of perioperative motor and language deficits in primary or metastatic brain lesions.** *J Neuroimaging* 2015;25:776–84 [CrossRef Medline](#)
12. Yetkin FZ, Mueller WM, Morris GL, et al. **Functional MR activation correlated with intraoperative cortical mapping.** *AJNR Am J Neuroradiol* 1997;18:1311–15 [Medline](#)
13. Pluim JP, Maintz JB, and Viergever MA. **F-information measures in medical image registration.** *IEEE Trans Med Imaging* 2004;23:1508–16 [CrossRef Medline](#)
14. Pluim JP, Maintz JB, Viergever MA. **F-information-based registration of medical images: a survey.** *IEEE Trans Med Imaging* 2003;22:986–1004 [CrossRef Medline](#)
15. Greve DN, Fischl B. **Accurate and robust brain image alignment using boundary-based registration.** *Neuroimage* 2009;48:63–72 [CrossRef Medline](#)
16. Villain N, Landeau B, Groussard M, et al. **A simple way to improve anatomical mapping of functional brain imaging.** *J Neuroimaging* 2010;20:324–33 [CrossRef Medline](#)
17. Studholme C, Constable RT, and Duncan JS. **Accurate alignment of functional EPI data to anatomical MRI using a physics-based distortion model.** *IEEE Trans Med Imaging* 2000;19:1115–27 [CrossRef Medline](#)
18. Renvall V, Witzel T, Wald LL, et al. **Automatic cortical surface reconstruction of high-resolution T1 echo planar imaging data.** *Neuroimage* 2016;134:338–54 [CrossRef Medline](#)
19. Gholipour A, Kehtarnavaz N, Briggs RW, et al. **Validation of non-rigid registration between functional and anatomical magnetic resonance brain images.** *IEEE Trans Biomed Eng* 2008;55:563–71 [CrossRef Medline](#)
20. Shan ZY, Mateja SJ, Reddick WE, et al. **Retrospective evaluation of PET-MRI registration algorithms.** *J Digit Imaging* 2011;24:485–93 [CrossRef Medline](#)

Isolated Internal Auditory Canal Diverticula: A Normal Anatomic Variant Not Associated with Sensorineural Hearing Loss

 D.C. Mihal,  Y. Feng,  M.L. Kodet,  C.M. Lohse,  M.L. Carlson, and  J.I. Lane

ABSTRACT

BACKGROUND AND PURPOSE: Bony internal auditory canal diverticula are relatively common, occurring in approximately 5% of temporal bone CTs. Internal auditory canal diverticula have historically been considered incidental; however, a recent publication reported that internal auditory canal diverticula are associated with sensorineural hearing loss. The objective of this study was to further characterize this potential association in a large cohort of patients.

MATERIALS AND METHODS: A total of 1759 patients undergoing high-resolution temporal bone CT were collected during a 6-year interval, and audiometric data were obtained from those with internal auditory canal diverticula. To assess any association of isolated internal auditory canal diverticula with sensorineural hearing loss, we excluded from further analysis patients with concomitant otosclerosis and bilateral diverticula and those without audiometric data, leaving 22 index cases. Audiometric data for the ear with a diverticulum was compared with that in the contralateral ear, to serve as an internal control.

RESULTS: Of 1759 patients, 82 (4.7%) had either unilateral ($n = 33$, 40%) or bilateral ($n = 49$, 60%) internal auditory canal diverticula. The co-incidence of otosclerosis and internal auditory canal diverticula was 34% ($n = 28$). There was no correlation between patient age and diverticulum size on either side. Among the index cases with isolated unilateral internal auditory canal diverticula and complete audiometric data, word recognition scores and the prevalence and severity of sensorineural hearing loss were not significantly different comparing the internal auditory canal diverticulum side to its contralateral control.

CONCLUSIONS: This study did not find a statistically significant association between ears with internal auditory canal diverticula and worsening sensorineural hearing loss or word recognition. Internal auditory canal diverticula most likely represent a normal anatomic variant in ears without otosclerosis.

ABBREVIATIONS: CHL = conductive hearing loss; HL = hearing loss; IAC = internal auditory canal; IQR = interquartile range, MHL = mixed hearing loss; SNHL = sensorineural hearing loss

An internal auditory canal (IAC) diverticulum (Fig 1) is a focal, well-demarcated lucency in the bone along the anteroinferior margin of the IAC fundus that may occur in cavitory otosclerosis or in isolation. This has also been referred to as “cupping” of the IAC in previous publications (Fig 2).^{1,2} IAC diverticula are relatively common, observed in approximately 5%–10%

of those undergoing high-resolution temporal bone CT.^{1,3,4} More recently, IAC diverticula have been reported to be associated with sensorineural hearing loss (SNHL) with or without concurrent otosclerosis.^{3,4} The purpose of this study was to elucidate whether isolated IAC diverticula are more commonly encountered as incidental findings as suggested by the pathologic literature or indicative of a pathologic process associated with SNHL.

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MATERIALS AND METHODS

Imaging Review

A retrospective review of all temporal bone CTs obtained during a nearly 6-year period (June 9, 2009, to March 8, 2015) in patients with research-use approval was performed by a single radiologist with a Certificate of Added Qualification in neuroradiology and >20 years of clinical experience. All patients with a focal lucency in the anteroinferior margin of the IAC fundus (IAC diverticulum) in one or both ears were collected into a database. Each

temporal bone CT scan in this cohort was obtained on CT scanners from the same manufacturer Siemens Definition and Siemens Flash (Siemens, Erlangen, Germany) with either 64- or 128-detector rows/slices. Measurement of the anteroposterior depth for each IAC diverticulum was recorded in addition to the presence of radiologic evidence of fenestral and retrofenestral otosclerosis. The indications for each study were also recorded, and the medical history was reviewed for the presence of clinical concern for hearing impairment at the time the CT scan was ob-

tained. Secondly, available MR images of the head in the 82 patients with CT findings of IAC diverticula were reviewed to assess for the presence of fluid signal within the diverticula.

Audiometry Review

All available audiometric data were collected and consisted of air conduction and bone conduction thresholds at set frequencies of 250, 500, 1000, 2000, 3000, and 4000 Hz, calculated 4-frequency pure tone averages (500, 1000, 2000, 4000), air-bone gap, word recognition scores, and a designation of SNHL, conductive hearing loss (CHL), mixed hearing loss (MHL), or normal hearing.

Statistical Analysis

Continuous features were summarized with means and SDs when approximately normally distributed and with medians and interquartile ranges (IQRs) otherwise; categorical features were summarized with frequency counts and percentages. IAC diverticula sizes were compared between patients with and without otosclerosis using a Wilcoxon rank sum test. Potential associations between patient age and diverticulum size were evaluated using Spearman rank correlation coefficients. Comparisons of hearing classification and audiometric data between ears with and without IAC diverticula in the same patient were

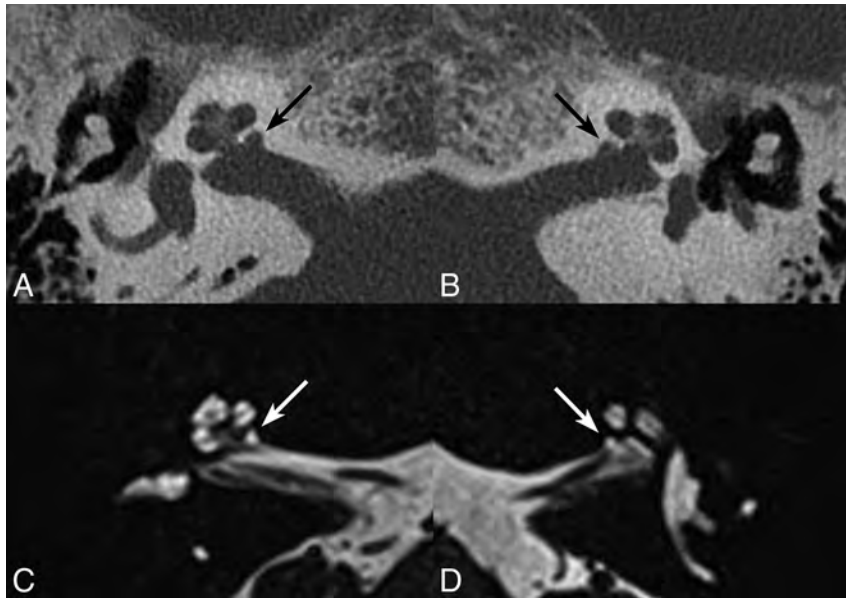


FIG 1. Axial CT (A and B) and axial 3D FSE T2 MR (C and D) images of right and left anterior wall IAC diverticula (black and white arrows) in the same patient with unilateral hearing loss.

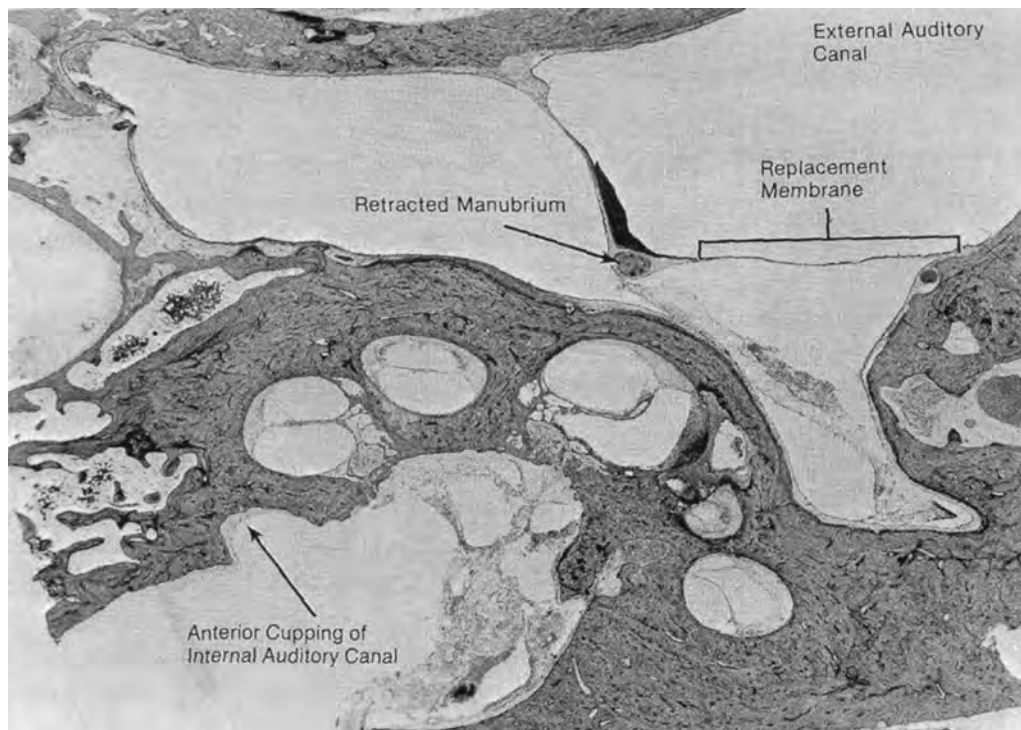


FIG 2. Histologic micrograph demonstrating the typical location of IAC diverticulum (ie, IAC cupping). Reproduced with permission from the third edition of *Guyula and Schucknecht's Anatomy of the Temporal Bone with Surgical Implications*.¹

evaluated using the McNemar and Wilcoxon signed rank tests to account for the paired nature of the data. Statistical analyses were performed using Version 9.4 of the SAS software package (SAS Institute; Cary, North Carolina). All tests were 2-sided, and P values $< .05$ were considered statistically significant.

RESULTS

A total of 1759 patients were scanned during the nearly 6-year study interval. Eighty-two of these patients (4.7%) had a focal lucency along the anteroinferior margin of the IAC fundus unilaterally ($n = 33$, 40%) or bilaterally ($n = 49$, 60%) on dedicated temporal bone CT scans. The median age for these 82 patients was 54 years, ranging from 1 to 91 years of age, and 57% ($n = 47$) were men and 43% ($n = 35$) women. Indications provided for CT scans noted hearing impairment in 52% of cases. Review of each patient's electronic medical record revealed that 88% of the study population had a history of hearing impairment at the time the CT was performed. The discrepancy between the two is attributable to the common scenario of incomplete medical histories provided in the indications for radiologic studies or provided indications that are associated with hearing loss without explicitly stating it.

Forty-one of the 82 (50%) also had MR imaging of the diverticula available at the time of review. Of those patients, 22 (54%) had corresponding fluid signal within the presumed IAC diverticulum and 19 (46%) did not. Notably, 15/18 (83%) patients showed fluid signal when the slice thickness of the MR imaging was ≤ 1 mm, but only 7/23 (30%) showed fluid signal when the slice thickness was 3–5 mm.

Twenty-eight (34%) of the 82 patients with either unilateral or bilateral IAC diverticula also had otosclerosis. Bilateral IAC diverticula were observed in 20/28 (71%) with otosclerosis in contrast to 29/54 (54%) patients without otosclerosis. The median size of the IAC diverticulum in patients without otosclerosis was 1.1 mm (IQR, 0.9–1.3 mm) compared with ears with otosclerosis having a median size of 1.4 mm (IQR, 1.2–1.9 mm) ($P < .001$); the maximum size from the right and left sides was used for patients with bilateral IAC diverticula. There was no correlation found between patient age and the size of the diverticula on either side (right-sided IAC diverticula: Spearman rank correlation coefficient, 0.12; $P = .35$; and left-sided IAC diverticula: Spearman rank correlation coefficient, -0.05 ; $P = .70$).

Nine patients without audiometric data were excluded from subsequent analysis, leaving 73 patients with complete radiographic and audiometric data for both ears. Bilateral IAC diverticula were present in 42 (58%) of these remaining patients, and unilateral IAC diverticula were present in 31 patients (42%). For further subanalysis from these 31 patients, we excluded 8 with coexisting otosclerosis by radiologic assessment and 1 with otosclerosis by clinical assessment to avoid potential confounders that might increase the incidence of hearing loss and the possibility of underlying cavitary otosclerosis producing the focal lucency, leaving 22 patients. The mean age for this subset of 22 patients was 48.2 ± 20.1 years and included 14 (64%) men and 8 (36%) women. There were 13 (59%) with right-sided diverticula and 9 (41%) with left-sided diverticula, with a mean size of 1.0 ± 0.2 mm (range, 0.6–1.4 mm).

Table 1: Comparison of the number of patients in each hearing classification category based on audiometric hearing assessment among those with unilateral IAC diverticula in the absence of otosclerosis ($N = 22$)

IAC Diverticulum	Control Side (No IAC Diverticulum)			
	Normal	CHL	MHL	SNHL
Normal	6	0	0	1
CHL	1	1	1	0
MHL	1	0	0	4
SNHL	2	0	2	3

This final group of 22 patients with isolated unilateral IAC diverticula and complete audiometric data for both ears provided 22 IAC diverticula and 22 nondiverticula internal controls. A comparison of hearing in the affected and unaffected ears is shown in Table 1. Within this subset, 6 patients had normal hearing in both ears and 11 patients had abnormal hearing (defined as CHL, MHL, or SNHL) in both ears. Four (18%) patients had abnormal hearing in the ear with the IAC diverticulum, but normal hearing in the unaffected ear; in contrast, 1 (5%) patient had normal hearing in the ear with the IAC diverticulum, but abnormal hearing in the unaffected ear ($P = .18$; McNemar test). The P value for the comparison of the prevalence of normal/CHL versus MHL/SNHL between affected and unaffected ears was .65.

Audiometric data comparing the ear with an IAC diverticulum with the contralateral side without an IAC diverticulum are shown in Table 2. The median air conduction pure tone average in the presence of an IAC diverticulum was 31 dB hearing level (HL) (IQR, 20–75 dB HL) compared with 20 dB HL (IQR, 9–41 dB HL) in the control ear. The median difference between the two measurements, calculated as IAC minus non-IAC, was 4 dB HL (IQR, 1–29 dB HL; $P = .056$). Median word recognition scores were 100 in both ears, resulting in a median difference of 0 ($P = .55$).

DISCUSSION

Previously published histopathologic studies of IAC diverticula, alternatively known as IAC cupping, demonstrated that these are well-margined concavities along the anteroinferior wall of the IAC fundus with normal bone around the periphery of the concavity.^{1,2} The cases of isolated IAC diverticula in this study correlate well with the published histology, being characterized on CT by intact cortical, trabecular, and labyrinthine bone adjacent to the concavity and, in most cases with volumetric 3D T2-weighted imaging, by normal CSF extending into the diverticulum (Fig 1). Historically, IAC diverticula have been referred to as normal variants, with a warning not to confuse them with pathology.^{1,2} Despite the evidence in the literature characterizing the benign nature of these diverticula, a recent publication has found an association between these lesions and SNHL.⁴ In the current study, we did not identify a statistically significant association with SNHL or word recognition score loss. These findings corroborate our anecdotal clinical observation and prior pathology-based studies that showed isolated IAC diverticula (ie, those not associated with cavitary otosclerosis) should be considered benign normal variants.

The etiology of IAC diverticula or cupping remains uncertain. Possible explanations include developmental variations in the in-

Table 2: Comparison of audiometric data in ears for patients with unilateral IAC diverticula in the absence of otosclerosis (N = 22)^a

	No. ^b	IAC Diverticulum	No IAC Diverticulum	Difference ^c	P Value ^d
Bone conduction pure tone average	22	22.5 (13–41)	17 (8–35)	1 (–4–17)	.31
BC 250 Hz (dB)	20	17.5 (7.5–25)	12.5 (7.5–20)	2.5 (–5–15)	.19
BC 500 Hz (dB)	21	20 (10–40)	15 (10–25)	5 (0–20)	.14
BC 1000 Hz (dB)	20	22.5 (10–40)	15 (5–27.5)	0 (–2.5–25)	.17
BC 2000 Hz (dB)	19	30 (10–50)	20 (10–45)	0 (–10–15)	.50
BC 3000 Hz (dB)	18	25 (7.5–47.5)	20 (10–55)	0 (–10–15)	.63
BC 4000 Hz (dB)	21	25 (10–50)	35 (15–60)	0 (–5–5)	.97
Air conduction pure tone average	22	31 (20–75)	20 (9–41)	4 (1–29)	.06
AC 250 Hz (dB)	22	22.5 (15–60)	17.5 (10–35)	2.5 (–5–20)	.19
AC 500 Hz (dB)	22	25 (15–75)	22.5 (10–40)	2.5 (–5–20)	.30
AC 1000 Hz (dB)	22	27.5 (15–75)	20 (5–40)	5 (0–30)	.06
AC 2000 Hz (dB)	22	32.5 (15–70)	20 (5–50)	10 (0–30)	.10
AC 3000 Hz (dB)	20	37.5 (15–60)	20 (12.5–62.5)	5 (–5–25)	.34
AC 4000 Hz (dB)	22	40 (20–85)	37.5 (15–70)	5 (–5–40)	.22
Air-bone gap	22	5 (0–12)	0 (0–5)	2 (0–9)	.37
Word recognition (%)	17	100 (85–100)	100 (95–100)	0 (–15–0)	.55

Note:—AC indicates air conduction; BC, bone conduction.

^a Data are median and IQR.

^b Summarized for a subset of patients with data for both ears.

^c Calculated as IAC minus non-IAC.

^d Determined using Wilcoxon signed rank tests.

terface between the 14 periotic enchondral growth plates and the adjacent sites of secondary bone formation of the surrounding skull base. Considering that the IAC extends across the transition zone between primary enchondral bone and secondary bone formation, variations in this transition may explain the consistent location of the diverticulum in the anteroinferior margin of the IAC fundus. Bast and Anson,⁵ in their seminal temporal bone textbook, *The Temporal Bone and the Ear*, claimed that residual cartilaginous tissue, such as that seen in fissula ante fenestram, can be found elsewhere within the otic capsule and may explain the distribution of otosclerosis involving the labyrinthine bone. If the anteroinferior margin of the IAC fundus represents one of these residual cartilaginous rests, then its resorption may result in the concavity observed in this and other studies. Persistence of the cartilaginous rest might also serve as a focus of pericochlear otosclerosis, contributing to the appearance of what has been reported in the literature as cavitory otosclerosis involving this segment of the IAC fundus.^{6–8} Otoposgiotic bone superimposed on a pre-existing congenital diverticulum might also explain the difference in diverticular size between the otospongiotic and nonotospongiotic groups.

The observed association between IAC diverticula and SNHL reported by Pippin et al⁴ could have arisen due to the potentially confounding effects of the inherent selection bias present when retrospectively examining a population of temporal bone CTs because these examinations have a much higher probability of being performed in patients with hearing loss. This inherent selection bias is exemplified by 88% of our patients with unilateral or bilateral IAC diverticula having either clinical concerns for or a reported history of hearing impairment in 1 or both ears at the time of their temporal bone CT scans. Our study design attempts to address the inherent selection bias issue by examining the subset of patients with unilateral IAC diverticula and without otosclerosis and by using the contralateral ear as an internal control. Because cochlear otosclerosis is defined as an SNHL due to involvement of the cochlear capsule, eliminating cases with cochlear otosclerosis should eliminate this as a potential confounder that

could otherwise artificially increase the prevalence of SNHL in the study population.⁸ Using these criteria, we found that there is no statistically significant correlation of IAC diverticula with SNHL or decline in word recognition scores. Diverticula were shown to be present more often and were larger in patients with concurrent otosclerosis, but in patients without otosclerosis, though the IAC diverticula varied in size, there did not appear to be a pattern of progression with age. This observation, in combination with the benign-appearing osseous margins, as demonstrated on temporal bone histology (Fig 2), further supports the notion that IAC diverticula are congenital rather than acquired and do not progress with time.

This normal variant can usually be distinguished from cavitory otosclerosis, which classically involves the anteroinferior wall of the IAC fundus and occurs in conjunction with pericochlear and fenestral otosclerosis (Fig 3).^{6–8} An anterior wall IAC concavity with density greater than that in the adjacent CSF and with ill-defined bony margins should raise concern for cavitory otosclerosis. Patients with cavitory otosclerosis will almost always have radiographic evidence of fenestral and/or retrofenestral otosclerosis in addition to audiometric evidence of a conductive or mixed hearing loss. Thus, finding a focal lucency in the anterior wall of the IAC should raise suspicion for cavitory otosclerosis if these findings are also present.

IAC diverticula are relatively common (approximately 5% prevalence), and cavitory otosclerosis involving the anteroinferior wall of the IAC fundus is comparatively quite rare.^{4,6,8} Discerning the difference between the two is clearly of clinical importance. In profound SNHL secondary to pericochlear otosclerosis, the presence of cavitory otosclerosis may predispose to electrode array extrusion during cochlear implant insertion.⁷ The absence of concurrent otosclerosis, as was seen in most (54/82, 66%) of our patients, should be reassuring that such a finding does not represent the sequelae of disease. Furthermore, the presence of a well-margined lucency in the anteroinferior wall of the IAC fundus in the absence of surrounding otospongiotic bone should heavily favor an isolated IAC diverticulum over cavitory otosclerosis.

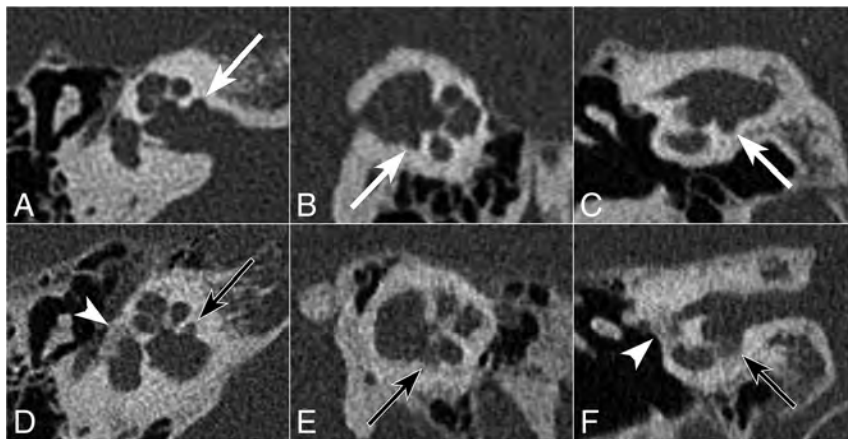


FIG 3. Right temporal bone axial (A and D), Pöschl (B and E), and coronal (C and F) views of an IAC diverticulum (upper row) versus cavitary otosclerosis (lower row). Note the well-demarcated margins of a lucent IAC diverticulum (white arrow) compared with the ill-defined spongiotic bone composing the otosclerotic focus along the anterior wall of the IAC (black arrow), with indistinct bony margins between this lesion and the basal turn of the cochlea (E and F). Also note the presence of fenestral otosclerosis (white arrowhead in D and F).

Correlation with clinical presentation, surgical history, and audiometric findings also remains important in assessing the potential importance of this finding. In the absence of other temporal bone derangement or findings to support an alternative diagnosis, an isolated well-demarcated lucency in the anteroinferior wall of the IAC fundus likely represents a normal variant and is unlikely to be of clinical importance. Conversely, attributing SNHL to the presence of these diverticula could lead a clinician to overlook other treatable causes of SNHL, which could, in turn, lead to permanent hearing loss.

Our study is limited by its retrospective approach, the lack of a true healthy control group, minor variations due to the use of CT scanners with different slice intervals despite a common manufacturer, and the use of a single neuroradiologist for interpretation. The population size in relation to the power of the study and the observed effect sizes raises the question of whether we would have been able to observe the difference asserted by an even smaller previous study.⁴ However, this remains the largest study of this radiographic entity to date, and the findings are in agreement with historical observations.^{1,2} Furthermore, the observed differences in frequency-specific bone conduction thresholds (ie, SNHL) and word recognition between the involved ear and contralateral control ear were small (median difference ranged between 0 and 5 dB in bone conduction thresholds; median word recognition score difference, 0%), suggesting that even if differences were found to be statistically significant in a study with much larger patient numbers, this small difference would still not be considered clinically relevant (Table 2). We have attempted to address some of the inherent weaknesses of a retrospective analysis and lack of true healthy controls with our case selection and

use of internal controls. Based on our limited number of cases in which volumetric CT and MR imaging were available for review, further research comparing high-resolution MR imaging with audiometric data would be useful in corroborating our findings. Future studies might also attempt to objectively demonstrate which features best distinguish these IAC diverticula from cavitary otosclerosis in a population of patients with otosclerosis.

CONCLUSIONS

No statistically significant association was found between isolated IAC diverticula and SNHL or word recognition score loss. Our data support historical observations that these most likely represent a normal anatomic variant.^{1,2} In

the absence of radiographic evidence of fenestral or pericochlear otosclerosis, the presence of IAC diverticula should bear no relationship to the clinical history of hearing loss.

ACKNOWLEDGMENTS

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REFERENCES

1. Gulya AJ, Schuknecht HF. **The inner ear.** In: Gulya AJ, ed. *Gulya and Schuknecht's Anatomy of the Temporal Bone with Surgical Implications*. 3rd ed. New York: Informa Healthcare USA; 2007:168–69
2. Kollias SS. **Imaging of the congenitally malformed temporal bone.** In: Lemmerling M, Kollias SS, eds. *Radiology of the Petrous Bone*. Berlin: Springer-Verlag; 2004:121
3. Hoeberigs MC, Postma AA, Waterval JJ, et al. **Prevalence of anterior internal auditory canal “diverticulum” on high resolution CT in patients with otosclerosis.** In: *Proceedings of the Radiological Society of North America Scientific Assembly and Annual Meeting*, Chicago, Illinois; November 25–30, 2012
4. Pippin KJ, Muelleman TJ, Hill J, et al. **Prevalence of internal auditory canal diverticulum and its association with hearing loss and otosclerosis.** *AJNR Am J Neuroradiol* 2017;38:2167–71 [CrossRef Medline](#)
5. Bast TH, Anson BJ. *The Temporal Bone and the Ear*. Springfield: CC Thomas; 1949
6. Bou-Assaly W, Mukherji S, Srinivasan A. **Bilateral cavitary otosclerosis: a rare presentation of otosclerosis and cause of hearing loss.** *Clin Imaging* 2013;37:1116–18 [CrossRef Medline](#)
7. Makarem AO, Hoang TA, Lo WW, et al. **Cavitating otosclerosis: clinical, radiologic, and histopathologic correlations.** *Otol Neurotol* 2010;31:381–84 [CrossRef Medline](#)
8. Makarem AO, Linthicum FH. **Cavitating otosclerosis.** *Otol Neurotol* 2008;29:730–31 [CrossRef Medline](#)

The Unwound Cochlea: A Specific Imaging Marker of Branchio-Oto-Renal Syndrome

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ABSTRACT

BACKGROUND AND PURPOSE: Branchio-oto-renal syndrome is an important syndromic cause of hearing loss. Our aim was to determine the test characteristics of the unwound cochlea on temporal bone CT for the diagnosis of branchio-oto-renal syndrome in a cohort of children with hearing loss.

MATERIALS AND METHODS: Patients were identified retrospectively with a clinical diagnosis of branchio-oto-renal syndrome and CT imaging of the temporal bones. Age-matched controls were also identified with sensorineural hearing loss not related to a diagnosis of branchio-oto-renal syndrome and CT imaging of the temporal bones. All examinations were reviewed by 2 neuroradiologists blinded to the diagnosis of branchio-oto-renal syndrome versus controls for the absence/presence of an unwound cochlea defined as anteromedial rotation and displacement of the middle and apical turns away from the basal turn.

RESULTS: The final study group comprised 9 patients with branchio-oto-renal syndrome (age range, 1–14 years; mean age, 8.0 ± 4.3 years) and 50 control patients (age range, 1–16 years; mean age, 7.9 ± 4.1 years). The cochlea was subjectively abnormal in all 9 patients. In 8 patients (89%), imaging demonstrated a typical unwound cochlear morphology. By contrast, none of the control subjects demonstrated an unwound cochlea on either side. Statistically, the unwound cochlea was significantly more frequent in the branchio-oto-renal group compared with controls ($P < .001$). The unwound cochlea was 89% sensitive and 100% specific for the diagnosis of branchio-oto-renal syndrome.

CONCLUSIONS: The unwound cochlea is a specific imaging marker of branchio-oto-renal syndrome. These findings further support the diagnostic accuracy and therefore the utility of temporal bone imaging in the diagnosis of this disorder.

ABBREVIATION: BOR = branchio-oto-renal syndrome

Branchio-oto-renal syndrome (BOR) is a rare autosomal dominant disorder that manifests as hearing loss, branchial fistulas, malformations of the ear, and renal anomalies.¹ It is one of the most common syndromic causes of hearing loss, with an estimated prevalence of 1:40,000.^{2–4} In the absence of family history, the diagnosis of BOR is made on the basis of the identification of 3 major criteria (second branchial arch anomalies, hearing loss, preauricular pits, auricular malformation, and renal anomalies) or 2 major and 2 minor criteria (preauricular tags or anomalies of the external auditory canal, middle ear, or inner ear). Expression of these findings is variable, however, resulting in the potential for a delayed or missed diagnosis, which can adversely impact the language and social development of these children.^{2,5–7} In addition,

though frequently silent at presentation, renal anomalies are a substantial cause of morbidity during the life span of these individuals.⁸ An early and definitive diagnosis prompting a search for associated anomalies would therefore be of great value in the management of these patients. In this regard, genetic testing for mutations in the *EYA1*, *SIX1*, and *SIX5* genes represents a promising adjunct.^{2,7,9} Currently, however, only approximately 50% of affected individuals have detectable gene mutations.^{2,7,10} Furthermore, an index of suspicion is required to justify the cost of such analyses, especially in light of the rarity of this disorder among all patients presenting with abnormal hearing. Given that most patients with BOR manifest hearing loss, temporal bone imaging represents an appealing opportunity to make the diagnosis.^{7,11,12} Unfortunately previous reports are heterogeneous, and the specificity of imaging findings for this syndrome is only rarely reported.¹⁰ As a result, temporal bone anomalies currently constitute minor criteria for the diagnosis.⁸ Robson³ reported that a distinctive “unwound appearance” of the cochlea, characterized

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by an anterior offset of the hypoplastic middle and apical turns away from a tapered basal turn, is characteristic of BOR. The diagnostic accuracy of this particular cochlear finding, however, is yet to be assessed. The goal of this study, therefore, was to determine the test characteristics of the unwound cochlea on temporal bone CT for the diagnosis of branchio-oto-renal syndrome in a cohort of children with hearing loss.

MATERIALS AND METHODS

Subjects

This Health Insurance Portability and Accountability Act–compliant study was approved by the local institutional review board. Informed consent was waived. This article conforms to Standards for Reporting of Diagnostic Accuracy Studies guidelines for reporting diagnostic accuracy.¹³ Consecutive patients were identified retrospectively from a search of existing patient data at a single institution. Inclusion in this study was based on the following criteria: 1) a diagnosis of BOR based on the reference standard: clinical evaluation by a member of the department of otorhinolaryngology according to standard criteria⁸; and 2) available CT imaging of the temporal bones. Control patients were identified with the following inclusion criteria: 1) sensorineural hearing loss (documented by a formal audiologic evaluation) deemed not related to a diagnosis of BOR after evaluation by an otorhinolaryngologist, and 2) available CT imaging of the temporal bones.

Imaging

Representative CT imaging protocol was the following: volumetric acquisition from above the ear to below the base of skull; 120 kV(peak); 220 mA (0–11 years of age) or 230 mA (12–18 years of age). Reconstructions were the following: 1-mm-slice axial and coronal reformats in a standard FOV (22 cm) and 0.5-mm-slice bilateral temporal bone axial and coronal reformats in FOV of 9.6 cm.

Image Review and Analysis

All imaging examinations were reviewed by 2 neuroradiologists, each with approximately 10 years of subspecialty experience in pediatric neuroimaging. Review was performed blinded to the diagnosis of BOR versus controls. The primary measure in this study was a subjective assessment of the absence/presence of an unwound cochlea. In particular, the unwound cochlear dysmorphology consists primarily of anteromedial angulation and displacement of the middle and apical turns of the cochlea away from the basal turn (Fig 1). In addition, the basal-middle turn interval was measured as the maximal distance between the basal (any part) and middle (any part) turns of the cochlea on axial CT images of the temporal bone. This measurement was performed in an attempt to quantify what we believe to be the fundamental dysmorphology of the unwound cochlea and, thereby, corroborate the subjective assessment. Finally, the presence of any other cochlear and inner ear abnormalities was assessed and tabulated.

The frequency of the unwound cochlea in patients with BOR was compared with that in control subjects using the Wilcoxon rank sum test. The sensitivity, specificity, and positive predictive value of an unwound cochlea for the diagnosis of BOR were calculated in a standard fashion. Agreement between readers was

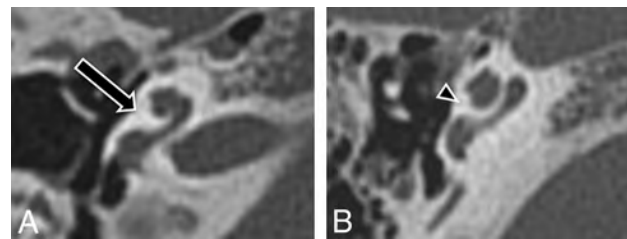


FIG 1. Unwound cochlea. A, Axial CT image through the right cochlea of a patient with BOR demonstrates characteristic unwound dysmorphology with anteromedial rotation and displacement of the middle turn away from a tapered basal turn (arrow). B, Axial CT image through a normal right cochlea demonstrates normal apposition of the middle and basal turns (arrowhead).

measured using the Cohen κ . Inconsistencies were settled by consensus re-review.

RESULTS

Patients

The final study group comprised 9 patients with a diagnosis of branchio-oto-renal syndrome (age range, 1–14 years; mean age, 8.0 ± 4.3 years; 6 boys, 3 girls). All patients underwent CT imaging from July 2013 through May 2017. All patients with BOR had hearing loss at a formal audiologic evaluation. The control group consisted of 50 patients (age range, 1–16 years; mean age, 7.9 ± 4.1 years; 26 boys, 24 girls) imaged for sensorineural hearing loss between December 2015 and August 2017. Although most of the control patients manifested isolated hearing loss, other relevant diagnoses in this cohort included the following: Usher syndrome ($n = 2$), meningitis ($n = 2$), Waardenburg syndrome ($n = 1$), congenital cytomegalovirus infection ($n = 1$), chronic otitis media ($n = 1$), and auditory neuropathy spectrum disorder ($n = 1$).

Imaging Findings

Imaging findings in patients with branchio-oto-renal syndrome are summarized in Table 1. The cochlea was subjectively abnormal bilaterally in all 9 patients. In 8 patients (89%), imaging demonstrated typical unwound cochlear dysmorphology with anteromedial rotation and displacement of the middle and apical turns away from the basal turn bilaterally (Fig 2). In the remaining patient with BOR (11%), CT demonstrated complete absence of the middle and apical turns bilaterally (Fig 3). Notably, these findings were symmetric side-to-side in all patients with BOR. By contrast, none of the control subjects demonstrated an unwound cochlea on either side. Cochlear and other inner ear abnormalities identified in control subjects are presented in Table 2. Statistically, the unwound cochlea was significantly more frequent in the BOR group compared with the control group for both reader 1 (8/9 BOR versus 0/50 controls; $P < .001$) and reader 2 (7/9 BOR versus 0/50 controls; $P < .001$). Test characteristics of the unwound cochlea for the diagnosis of branchio-oto-renal syndrome are presented in Table 3.

With regard to identification of an unwound cochlea, there was almost perfect agreement between the 2 readers ($\kappa = 0.93$), with discrepant interpretations in only 1 of 59 (1.6%) cases. The single discrepant interpretation occurred in a patient with BOR with an unwound cochlea by consensus re-review (Fig 4).

The mean basal-middle turn interval was 2.5 ± 0.13 mm in the

Table 1: Summary of inner ear findings in patients with branchio-oto-renal syndrome

Patients with BOR	Hearing Loss	Unwound Cochlea (Reader 1)	Unwound Cochlea (Reader 2)	Other Inner Ear Abnormalities
1	B Mixed	Bilateral	Bilateral	R vestibular aqueduct enlargement; B medialized facial nerve; B funnel IAC
2	B Mixed	Bilateral	Bilateral	B hypoplastic apical turn/modiolus; right hypoplastic posterior semicircular canal; B funnel IAC
3	B Conductive	Bilateral	Bilateral	B medialized facial nerve; B funnel IAC
4	B Conductive	Bilateral	Bilateral	B vestibular aqueduct enlargement; B funnel IAC
5	B Conductive	Bilateral	Bilateral	L vestibular aqueduct enlargement; B hypoplastic lateral semicircular canal; L medialized facial nerve; B funnel IAC
6	B Sensorineural	Bilateral	Bilateral	B hypoplastic apical turn/modiolus; B cochlear aperture stenosis; B vestibular aqueduct enlargement; B medialized facial nerve; L funnel IAC
7	B Sensorineural	No	No	B cochlear hypoplasia with absent middle and apical turns; B medialized facial nerve
8	B Mixed	Bilateral	No	B medialized facial nerve
9	B Sensorineural	Bilateral	Bilateral	B hypoplastic apical turn/modiolus; B vestibular aqueduct enlargement; B medialized facial nerve; B funnel IAC

Note:—IAC indicates internal auditory canal; R, right side; L, left side; B, bilateral.

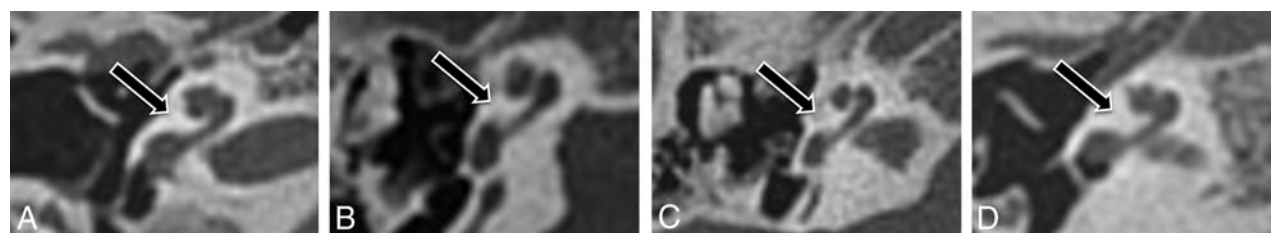


FIG 2. Cochlear morphology in patients with branchio-oto-renal syndrome. Axial CT images through the right temporal bone in 4 representative patients (A–D) with unwound cochleae.

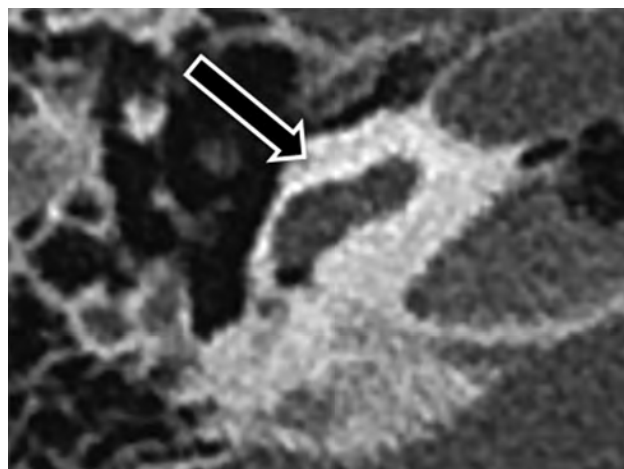


FIG 3. Branchio-oto-renal syndrome without the unwound cochlea. Axial CT image through the right temporal bone demonstrates a truncated basal turn with complete absence of the middle and apical turns of the cochlea.

BOR group compared with 1.4 ± 0.17 mm in the control group. For both readers, measurements of the basal-middle turn interval were significantly larger in the BOR group compared with controls for both the right ($P < .001$) and left ($P < .001$) cochleae.

DISCUSSION

We report the following main findings in a cohort of children with hearing loss: The unwound cochlea is a frequent finding in patients with branchio-oto-renal syndrome; this finding was not observed in patients with hearing loss not related to BOR. There

was near-perfect agreement between readers regarding the presence/absence of this subjective finding. Together, these results suggest that the unwound cochlea is a specific and reliable imaging marker of branchio-oto-renal syndrome.

Although the association between hearing loss and branchial anomalies has been recognized for more than a century, the pathogenesis of BOR remains incompletely understood. Clinical features point to a developmental defect occurring between 4 and 10 weeks of embryogenesis.¹⁴ During this interval, the inner ear develops from a pair of surface placodes that appear in human development during week 4. These placodes fold inward to form fluid-filled sacs called vesicles; each vesicle sinks into the regional mesenchyme to form the otic capsule. The epithelium of the otic capsule then undergoes a series of morphologic changes to form the primitive membranous labyrinth, which ultimately differentiates into the cochlea and vestibular apparatus by week 8.¹⁰ During this same time, the ossicles develop from the neural crest-derived cells of the first and second branchial arches, while the external auditory canal and middle ear cavity derive from the first branchial cleft and pouch, respectively; normally, elements of the branchial apparatus disappear by approximately week 8 of development. During this time, *EYA1*, the most commonly identified gene mutation underlying BOR, functions to promote cell survival within the developing ear.¹⁵ Interaction of *EYA1* with the DNA-binding proteins SIX1 and SIX5 results in the recruitment of DNA repair (rather than proapoptotic) machinery in response to genetic damage during organogenesis.¹⁶ *EYA1* has been shown to be prominently expressed by the cochlear and vestibular epithelium as well as by the mesenchyme of the otic capsule and

Table 2: Abnormalities of the cochlea and inner ear in control patients with hearing loss not associated with branchio-oto-renal syndrome

Cochlear Abnormality	Other Inner Ear Abnormalities
Incomplete partition defect type 2 (<i>n</i> = 3)	Posterior semicircular canal hypoplasia (<i>n</i> = 1)
Cochlear aperture stenosis (<i>n</i> = 1)	Posterior semicircular canal dehiscence (<i>n</i> = 1)
Labyrinthitis ossificans (<i>n</i> = 1)	Vestibular aqueduct enlargement (<i>n</i> = 1)
	Funnel-shaped internal auditory canal (<i>n</i> = 2)

Table 3: Test characteristics of the unwound cochlear morphology for a clinical diagnosis of branchio-oto-renal syndrome^a

Reader	Sensitivity	Specificity	PPV	NPV
1	0.89 (0.51–0.99)	1.0 (0.91–1.0)	1.0 (0.60–1.0)	0.98 (0.88–1.0)
2	0.78 (0.40–0.96)	1.0 (0.91–1.0)	1.0 (0.56–1.0)	0.96 (0.86–0.99)

Note:—NPV indicates negative predictive value; PPV, positive predictive value.

^a Numbers in parentheses are 95% CIs.

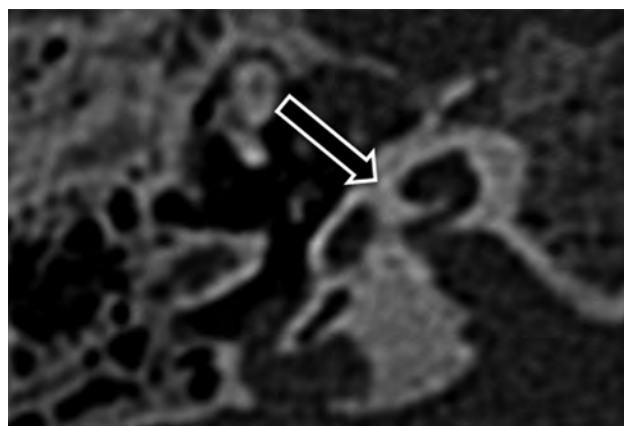


FIG 4. Interreader disagreement. Axial CT images through the right temporal bone in the single patient with BOR with interreader discrepancy. This cochlea was considered unwound at consensus re-review.

middle ear during early development.¹⁴ These findings support a direct role for *EYA1* in the development of all components of the middle and inner ear, consistent with the diversity of ear findings reported in patients with BOR.¹⁴ Most interesting, *EYA1* is also prominently expressed during development by the metanephric cells surrounding the ureteric branches of the kidney, consistent with a role in kidney morphogenesis.¹⁴

Branchio-oto-renal syndrome continues to present a diagnostic challenge, mainly due to its clinical and genetic heterogeneity. Given that it has become a mainstay in the evaluation of patients with hearing loss, temporal bone imaging represents an intuitively appealing opportunity to make the diagnosis. Unfortunately, studies investigating temporal bone findings at CT have yielded inconsistent results. Cochlear anomalies are the most frequently reported, typically hypoplasia of the apical turn, with a prevalence that has ranged widely across cohorts from 30%¹⁷ to 100%.^{10,18} Further complicating potential application to clinical practice, the specificity of temporal bone findings has only rarely been reported.¹⁰ In response to these deficiencies, Propst et al¹⁰ compared the appearance of the temporal bones in a large cohort of patients with BOR with that of subjects with normal hearing. With regard to the cochlea, they observed isolated hypoplasia of the apical turn with a deficient modiolus in all patients with BOR, but none of the healthy controls. Consistent with their findings, we observed apical turn hypoplasia and deficiency of the modio-

lus in our cohort, though only in 3 of 9 patients. Ultimately, direct comparison with Propst et al on our primary end point—the diagnostic accuracy of the unwound cochlea for BOR—is not possible because their report predates the earliest mention of the unwound co-

chlea that we could find in the imaging literature.

Other frequently reported inner ear anomalies in BOR include an abnormal course of the facial nerve, a dysmorphic internal auditory canal, dysplasia of the lateral and/or posterior semicircular canals, vestibular aqueduct enlargement, and cochlear aperture stenosis.^{10,17–19} These imaging findings, however, have been reported in other syndromes as well as in isolated forms of hearing loss.^{3,17} Most interesting, Propst et al¹⁰ observed a characteristic medialized course of the facial nerve (medial to the cochlea) in most patients with BOR but in none of the healthy controls. Consistent with their results, we observed a medialized facial nerve in 7 of 9 patients with BOR but in none of the patients with other causes of hearing loss. The combination of this finding with the unwound cochlea would have resulted in a sensitivity and specificity of 100% in our cohort. This observation raises the possibility that the optimal diagnosis of BOR on temporal bone CT would be based on a combination of findings, rather than a single imaging marker. Finally, our results are consistent with the original assertion by Robson³ that unwound cochlear morphology is characteristic of BOR. Our study adds to the literature by measuring the diagnostic accuracy of this finding in a cohort of children with hearing loss.

This study has several limitations. First, this was a small cohort of patients with BOR. However, the statistical power for the specificity of this finding was driven by the number of control patients, and we observed a relatively narrow confidence interval for specificity (91%–100%). Still, a study with a larger cohort would be of value, especially with regard to defining the optimal combination of findings to identify these patients within the overall population of children with hearing loss. Second, genetic testing was not performed. It therefore cannot be assumed that this cohort captures the spectrum of mutations associated with BOR. This feature is particularly notable, given the observation that genotype may be related to the prevalence of inner ear anomalies.¹⁶ Third, our results reflect cochlear findings on temporal bone CT, which is the standard test performed for hearing loss at our institution. However, MR imaging has become increasingly popular in this clinical setting, especially in light of the risks of ionizing radiation in children. Application of this finding to MR imaging will require further study. Finally, this study was not designed to evaluate the unwound cochlea as a potential causative factor in hearing loss. In fact, this finding was identified in patients without a detectable sensorineural component of hearing loss at formal audiologic evaluation. The unwound cochlear morphology may therefore reflect anomalous development of the inner ear in these patients, which is independent, at least in some cases, of the features that determine sensorineural hearing loss.

CONCLUSIONS

We report, in a cohort of children with hearing loss, that the unwound cochlea, characterized by anteromedial rotation and

displacement of the middle and apical turns away from the basal turn, was a specific and reliable imaging marker of branchio-oto-renal syndrome. These findings further support the diagnostic accuracy and therefore the utility of temporal bone imaging in the diagnosis of this challenging disorder.

REFERENCES

1. Ginat DT, Ferro L, Gluth MB. **Anatomic and quantitative temporal bone CT for preoperative assessment of branchio-oto-renal syndrome.** *Clin Neuroradiol* 2016;26:481–83 CrossRef Medline
2. Lindau TA, Cardoso AC, Rossi NF, et al. **Anatomical changes and audiological profile in branchio-oto-renal syndrome: a literature review.** *Int Arch Otorhinolaryngol* 2014;18:68–76 CrossRef Medline
3. Robson CD. **Congenital hearing impairment.** *Pediatr Radiol* 2006;36:309–24 CrossRef Medline
4. Huang BY, Zdanski C, Castillo M. **Pediatric sensorineural hearing loss, Part 2: syndromic and acquired causes.** *AJNR Am J Neuroradiol* 2012;33:399–406 CrossRef Medline
5. Huang BY, Zdanski C, Castillo M. **Pediatric sensorineural hearing loss, Part 1: practical aspects for neuroradiologists.** *AJNR Am J Neuroradiol* 2012;33:211–17 CrossRef Medline
6. Bellini C, Piaggio G, Massocco D, et al. **Branchio-oto-renal syndrome: a report on nine family groups.** *Am J Kidney Dis* 2001;37:505–09 CrossRef Medline
7. Morisada N, Nozu K, Iijima K. **Branchio-oto-renal syndrome: comprehensive review based on nationwide surveillance in Japan.** *Pediatr Int* 2014;56:309–14 CrossRef Medline
8. Chang EH, Menezes M, Meyer NC, et al. **Branchio-oto-renal syndrome: the mutation spectrum in EYA1 and its phenotypic consequences.** *Hum Mutat* 2004;23:582–89 CrossRef Medline
9. Song MH, Kwon TJ, Kim HR, et al. **Mutational analysis of EYA1, SIX1 and SIX5 genes and strategies for management of hearing loss in patients with BOR/BO syndrome.** *PLoS One* 2013;8:e67236 CrossRef Medline
10. Propst EJ, Blaser S, Gordon KA, et al. **Temporal bone findings on computed tomography imaging in branchio-oto-renal syndrome.** *Laryngoscope* 2005;115:1855–62 CrossRef Medline
11. Chen A, Francis M, Ni L, et al. **Phenotypic manifestations of branchio-oto-renal syndrome.** *Am J Med Genet* 1995;58:365–70 CrossRef Medline
12. Fraser FC, Sproule JR, Halal F. **Frequency of the branchio-oto-renal (BOR) syndrome in children with profound hearing loss.** *Am J Med Genet* 1980;7:341–49 CrossRef Medline
13. Cohen JF, Korevaar DA, Altman DG, et al. **STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration.** *BMJ Open* 2016;6:e012799 CrossRef Medline
14. Abdelhak S, Kalatzis V, Heilig R, et al. **A human homologue of the Drosophila eyes absent gene underlies branchio-oto-renal (BOR) syndrome and identifies a novel gene family.** *Nat Genet* 1997;15:157–64 CrossRef Medline
15. Cook PJ, Ju BG, Telese F, et al. **Tyrosine dephosphorylation of H2AX modulates apoptosis and survival decisions.** *Nature* 2009;458:591–96 CrossRef Medline
16. Sanggaard KM, Rendtorff ND, Kjaer KW, et al. **Branchio-oto-renal syndrome: detection of EYA1 and SIX1 mutations in five out of six Danish families by combining linkage, MLPA and sequencing analyses.** *Eur J Hum Genet* 2007;15:1121–31 CrossRef Medline
17. Kemperman MH, Koch SM, Joosten FB, et al. **Inner ear anomalies are frequent but nonobligatory features of the branchio-oto-renal syndrome.** *Arch Otolaryngol Head Neck Surg* 2002;128:1033–38 CrossRef Medline
18. Ceruti S, Stinckens C, Cremers CW, et al. **Temporal bone anomalies in the branchio-oto-renal syndrome: detailed computed tomographic and magnetic resonance imaging findings.** *Otol Neurotol* 2002;23:200–07 CrossRef Medline
19. Ostri B, Johnsen T, Bergmann I. **Temporal bone findings in a family with branchio-oto-renal syndrome (BOR).** *Clin Otolaryngol Allied Sci* 1991;16:163–67 Medline

Retrospective Review of Otic Capsule Contour and Thickness in Patients with Otosclerosis and Individuals with Normal Hearing on CT

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ABSTRACT

BACKGROUND AND PURPOSE: Otosclerosis is commonly identified on CT as a focus of hypodensity in the otic capsule anterior to the oval window. However, otosclerosis can have a sclerotic phase approximating the density of normal bone, making diagnosis challenging. This study assesses differences in otic capsule contour and thickness anterolateral to the anterior margin of the oval window in patients with otosclerosis compared with individuals with normal hearing.

MATERIALS AND METHODS: Axial CT of 104 ears with clinically diagnosed otosclerosis and 108 consecutive ears of audiometrically normal individuals were retrospectively reviewed. Two radiologists independently evaluated the pattern of otosclerosis, otic capsule contour, and bone thickness on standardized axial images at the level of the oval window and cochleariform process. Measurements were made from the posterolateral margin of the cochlea to the apex of the otic capsule convex contour just anterolateral to the anterior margin of the oval window. In the absence of a convex contour, the sulcus between the oval window and the cochleariform process was identified, and measurement to the depth of the sulcus was used. Receiver operating characteristic analysis determined the best cutoff value of otic capsule thickness.

RESULTS: Mean otic capsule thickness (2 SDs) was 3.08 (0.93) mm and 1.82 (0.31) mm in patients with otosclerosis and individuals with normal hearing, respectively ($P < .001$), with excellent interobserver agreement. Otic capsule thickness of >2.3 mm had 96.2% sensitivity, 100% specificity, 100% positive predictive value, and 96.4% negative predictive value for otosclerosis. A bulging/convex contour of the otic capsule had 68.3% sensitivity, 98.1% specificity, 97.3% positive predictive value, and 76.3% negative predictive value.

CONCLUSIONS: Patients with otosclerosis have significantly thicker bone abutting the oval window than individuals with normal hearing.

ABBREVIATIONS: CBCT = conebeam CT; MDCT = multidetector row CT

Otosclerosis is a primary osteodystrophy of the otic capsule, and a cause of progressive conductive hearing loss in adults. Severe cases of otosclerosis can result in a combination of sensorineural and conductive hearing loss.¹ Otosclerosis can be categorized on the basis of the extent of involvement into fenestral and retrofenestral types,

and on the phase of disease, into spongiotic (active) or sclerotic (inactive).¹ The otic capsule just anterior to the oval window is the typical site of manifestation. Disease limited to this area is referred to as fenestral otosclerosis and is most commonly lucent on CT due to resorption of the enchondral bone during the spongiotic (active) phase.²⁻⁵ As the disease progresses to the inactive or sclerotic phase, these lesions undergo remineralization and can become indistinguishable on CT from the normal dense otic capsule.¹⁻³ Notably, otosclerotic foci are usually larger in volume than the bone they replace, causing thickening of the affected otic capsule.¹

Diagnosis of otosclerosis is classically based on history, physical examination, and audiometric testing.^{6,7} High-resolution CT is the technique of choice to confirm the diagnosis and evaluate alternate diagnoses or coexisting diseases and for preoperative anatomic assessment.^{2,3,6,8} The aforementioned variable disease activity and the presence of sclerotic foci mimicking normal bone can make diagnosis of otosclerosis by CT challenging.

The purpose of this study was to assess the qualitative and quantitative differences in otic capsule contour and thickness just

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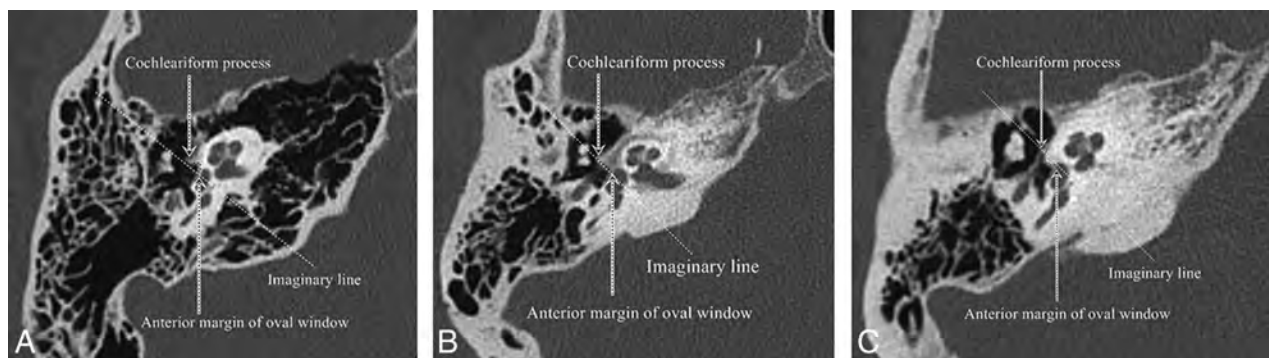


FIG 1. Qualitative description of the otic capsule contour relative to an imaginary line drawn from the anterior margin of the oval window to the cochleariform process. *A*, Normal temporal bone with a concave contour. *B*, Lucent phase of fenestral and retrofenestral otosclerosis with a flattened contour. *C*, Sclerotic phase of fenestral otosclerosis with a bulging or convex contour.

anterolateral to the anterior margin of the oval window in patients with otosclerosis and individuals with normal hearing on CT. We hypothesized that patients with otosclerosis have measurably thicker otic capsules near the oval window than individuals with normal hearing on CT.

MATERIALS AND METHODS

Subjects

All CT studies of the temporal bone including multidetector row CT (MDCT) and conebeam CT (CBCT) performed at Massachusetts Eye and Ear Infirmary between January 2016 and June 2017 were retrospectively reviewed following institutional review board approval. Consecutive CTs of 58 patients with clinically diagnosed otosclerosis (104 ears) were included. Consecutive CTs of 54 patients (108 ears) with normal audiogram findings who underwent temporal bone CT for other indications (tinnitus, dizziness, vertigo, and facial palsy) were included. CTs of children (younger than 18 years of age) and CTs with motion degradation were excluded. Individual ears in both the otosclerosis and control groups were counted because some CBCT studies were performed unilaterally.

Image Acquisition

MDCT (Discovery 750 HD; GE Healthcare, Milwaukee, Wisconsin) of the temporal bone was performed with 120 kV(peak), 240 mA, 0.6-mm slice thickness, and 0.2-mm gap. CBCT (3D Accuitomo; J. Morito Mfg, Kyoto, Japan) of the temporal bone was performed with a 90-kVp, 8-mA, high-resolution mode with exposure time = 30.8 seconds, FOV = 60 × 60 mm, and slice thickness = 0.5 mm. Axial reformats of the temporal bones were created for both MDCT and CBCT studies in a plane parallel to the lateral semicircular canal.

Reader Assessment

Two radiologists independently determined the location of involvement (fenestral, and/or retrofenestral) for patients with otosclerosis. A subjective subgroup analysis was performed to characterize the phase of otosclerosis into sclerotic, mixed sclerotic-lucent, and lucent disease. The sclerotic phase of disease was characterized as disease that was similar to or near the density of the unaffected otic capsule, while lucent disease was characterized by disease that approached the density of the facial nerve. Mixed lucent sclerotic disease was grouped subjectively between the lucent and sclerotic phases of disease. Qualitative and quantitative

assessments of the otic capsule were evaluated with the readers blinded to patient information, including presenting symptoms, audiogram results, and clinical diagnosis. Axial reconstructions through the temporal bone parallel to the entire lateral semicircular canal were confirmed in all cases.

Qualitative Assessment of the Otic Capsule

At the level of the oval window and cochleariform process, the otic capsule contour was classified into bulging or convex and flattened or concave configurations relative to an imaginary line drawn from the anterior margin of the oval window to the cochleariform process (Fig 1).

Quantitative Assessment of the Otic Capsule

To quantitatively assess the otic capsule thickness using axial reformatted images that were parallel to the plane of lateral semicircular canal for standardization purposes, we chose the axial image at the level of oval window and cochleariform process. Measurements were made from the posterolateral margin of the cochlea closest to the middle ear (junction of the basal and middle turns) to the apex of the convex contour of the otic capsule just anterolateral to the anterior margin of the oval window (Fig 2). In the absence of a convex contour, the sulcus formed between the cochleariform process and oval window was identified, and a measurement was made to the depth of the sulcus, anterior to the oval window (Fig 3).

Statistical Analysis

The data were analyzed using R statistical and computing software, Version 3.3.3 (<http://www.r-project.org/>). The Fisher exact test was used to analyze differences in patient demographics between the patients with otosclerosis and those with normal hearing. A χ^2 test with a Yates correction was used for the otic capsule contour 2-by-2 table. Mean thickness of the otic capsule and mean age of the patient populations were compared using the Student *t* test. A 1-way ANOVA test was used to evaluate differences in mean thickness among the subgroups of otosclerosis. A χ^2 test in a 2-by-3 table was used to evaluate differences between the phases of otosclerosis and the presence of a bulging/convex or flattened/concave contour. *P* < .05 indicated a statistically significant difference. A receiver operating characteristic curve analysis was used to determine the cutoff

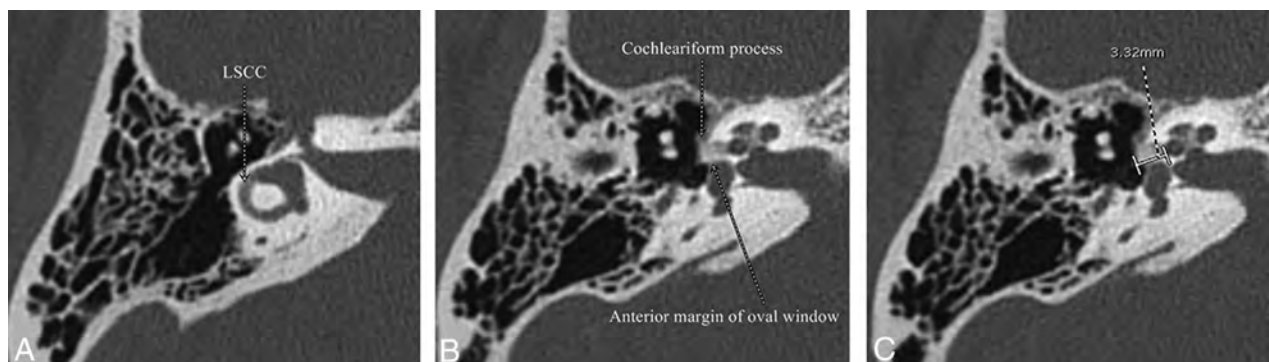


FIG 2. Measurement of otic capsule thickness from the posterolateral margin of the cochlea at the junction between the basal and middle turns to the most convex contour. *A*, Axial images parallel to the plane of the lateral semicircular canal (LSCC) are created. *B*, The axial slice at the level of the cochleariform process and anterior margin of the oval window is chosen. *C*, Measurement from the posterolateral margin of the cochlea at the junction of the basal and middle turns to the apex of the convex contour of the otic capsule is performed.

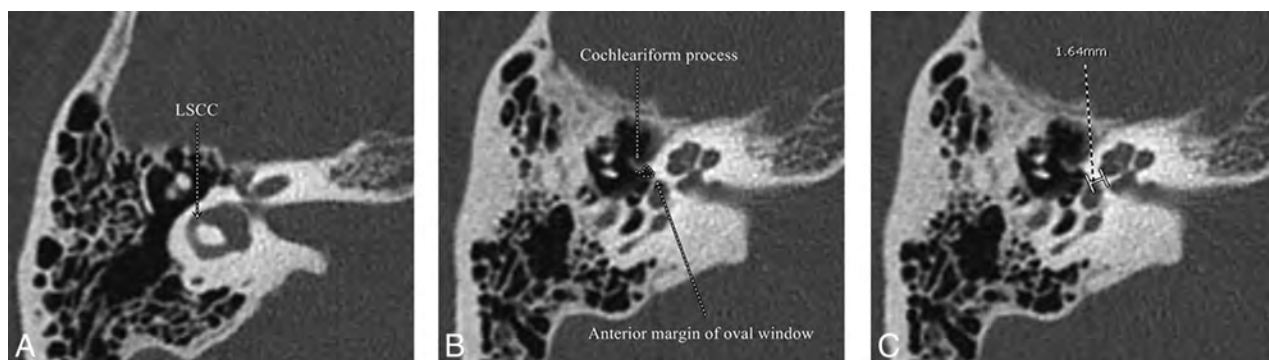


FIG 3. Measurement of otic capsule thickness in a patient without a convex contour of the otic capsule. *A*, Axial images parallel to the plane of the lateral semicircular canal (LSCC) are created. *B*, The axial slice at the level of the cochleariform process and anterior margin of the oval window is chosen. The sulcus between the cochleariform process and the anterior margin of the oval window is shown (white dashed line). *C*, Measurement from the posterolateral margin of the cochlea at the junction of the basal and middle turns to the depth of the sulcus anterior to the oval window is performed.

Table 1: Characteristics of the study groups

Patient Characteristics	Otosclerosis	Normal Hearing
No. of Patients	58	54
No. of Ears	104	108
Sex		
Male (%)	21 (36.2)	14 (25.9)
Female (%)	37 (63.8)	40 (74.1)
<i>P</i> value		.31
Mean age (yr)	49.7	38.5
Age (SD) (yr)	13.9	13.7
<i>P</i> value		<.001
CT modalities		
MDCT (%)	35 (60.3)	44 (81.5)
CBCT (%)	23 (39.7)	10 (18.5)
<i>P</i> value		.02
Otosclerosis involvement (%)		
Fenestral only	71 (68.3)	—
Fenestral and retrofenestral	31 (29.8)	—
Isolated round window	2 (1.9)	—
Otosclerosis phase of disease (%)		
Sclerotic disease	25 (24.0)	—
Mixed sclerotic lucent disease	34 (32.7)	—
Lucent disease	45 (43.3)	—

Note: — indicates not applicable.

value of the otic capsule thickness that had the best combination of sensitivity and specificity for differentiating patients with otosclerosis from individuals with normal hearing. Interobserver

Table 2: Otic capsule contour

Contour	Otosclerosis	Normal Hearing	Total
Bulging/convex	71	2	73
Flattened/concave	33	106	139
Total	104	108	212
Two-tailed <i>P</i> value	<.001		

reliability was evaluated using the Pearson product-moment correlation coefficient.

RESULTS

Study Groups

The enrolled population characteristics, CT modalities, and types of otosclerosis are shown in Table 1.

Qualitative Assessment of the Otic Capsule

Otic capsule contour in otosclerosis and normal hearing patients is shown in Table 2. Bulging or convex contour had 68.3% sensitivity, 98.1% specificity, 97.3% positive predictive value, and 76.3% negative predictive value (Table 3).

Quantitative Assessment of the Otic Capsule

Patients with otosclerosis had significantly thicker otic capsules near the oval window ($P < .001$) measured from the posterolateral margin of the cochlea lumen closest to the middle ear (junc-

Table 3: Otic capsule contour and thickness for diagnosis of otosclerosis

Diagnostic Performance	Bulging/Convex Contour ^a	Otic Capsule Thickness >2.3 mm ^b
Sensitivity (%)	68.3	96.2
Specificity (%)	98.1	100
Positive predictive value (%)	97.3	100
Negative predictive value (%)	76.3	96.4

^a Bulging/convex contour across an imaginary line between the anterior margin of the oval window and the cochleariform process.

^b Otic capsule thickness measured from the posterolateral margin of the cochlea closest to the middle ear (junction of the basal and middle turns) to the most convex contour.

Table 4: Mean otic capsule thickness in millimeters (2 SDs)

Study Groups	Radiologist 1	Radiologist 2	Overall
Otosclerosis (<i>n</i> = 104)	3.09 (0.92)	3.06 (0.97)	3.08 (0.93)
Normal hearing (<i>n</i> = 108)	1.87 (0.32)	1.78 (0.33)	1.82 (0.31)

Table 5: Overall mean otic capsule thickness in millimeters (2 SDs) and percentage of patients with a bulging/convex contour by phase of otosclerosis

Phase of Otosclerosis	Mean Thickness	Bulging/Convex Contour (%)	Flattened/Concave Contour (%)
Sclerotic (<i>n</i> = 25)	3.02 (0.82)	64.0	36.0
Mixed (<i>n</i> = 34)	3.20 (1.08)	70.6	29.4
Lucent (<i>n</i> = 45)	3.06 (0.82)	68.9	31.1
<i>P</i> value	.26 ^a		.86 ^b

^a *P* value calculated with a 1-way ANOVA test.

^b *P* value calculated with a 2 × 3 table χ^2 test.

tion of the basal and middle turns) to the apex of the convex contour (Table 4).

Interobserver agreement was excellent with the Pearson product-moment correlation coefficient = 0.93 for measurement of otic capsule thickness in patients with otosclerosis and individuals with normal hearing.

In addition, a subgroup analysis based on a subjective phase of otosclerosis was performed (Table 5). There was no statistically significant difference between otic capsule thickness or contour type based on the phase of otosclerosis.

Furthermore, we determined the cutoff value of otic capsule thickness using a receiver operating characteristic curve analysis. Otic capsule thickness of >2.3 mm showed the best trade-off between sensitivity and specificity to distinguish otosclerosis from individuals with normal hearing (Table 3). The area under the receiver operating characteristic curve was 0.99.

DISCUSSION

The otic capsule is composed of an inner layer of endosteum, a middle layer of persistent primary enchondral bone, and an outer layer of periosteum. Normally, the otic capsule does not undergo postdevelopmental remodeling.¹ However, during the active or spongiotic phase of otosclerosis, the dense middle layer of enchondral bone is resorbed and replaced by spongy vascular bone, resulting in lower density on CT.^{1,5,9} During the inactive phase, the affected areas of otosclerosis undergo new bone formation, thus mimicking the density of normal bone on CT.^{2,9} Our study hypothesis is based on the pathophysiology that otosclerotic foci undergo continuous resorption and remodeling, eventually resulting in production of more mature bone, often larger than the

original affected area, thus leading to focal thickening of the otic capsule.^{1,9} Thus, our study included all consecutive patients with clinically diagnosed otosclerosis regardless of the phase of disease. Because the otic capsule adjacent to the anterior margin of the oval window is expected to enlarge with remodeling, this bone should be thicker in patients with otosclerosis compared with individuals with normal hearing regardless of the phase of disease. Our study demonstrated that there was no significant difference between the phase of otosclerosis and the thickness of the otic capsule contour. In addition, there was no significant difference between the phase of otosclerosis and the presence of a bulging/convex contour.

We found that a bulging or convex contour of the otic capsule across an imaginary line drawn from the anterior margin of the oval window to the cochleariform process had 98.1% specificity and 97.3% positive predictive value. The high specificity suggests that individuals with normal hearing are unlikely to have a bulging or convex contour and that this technique is a good diagnostic tool to rule in disease. Although predictive values are influenced by prevalence, this high positive predictive value can imply that patients with a bulging or convex contour have a high probability of otosclerosis. This finding is consistent with the bone remodeling, deposition, and thickening of the otic capsule seen in otosclerosis on histology.¹ In addition, this finding is compatible with the clinical symptoms of conductive hearing loss as the normal sulcus immediately anterolateral to the oval window is lost, resulting in stapes fixation and impedance of sound.

For quantitative assessment, otosclerosis resulted in a significantly thicker otic capsule near the oval window than in individuals with normal hearing (*P* < .001). Otic capsule thickness of >2.3 mm of the most convex contour provided the best trade-off between sensitivity and specificity and is also >3 SDs from the average otic capsule thickness in individuals with normal hearing. This finding is an objective evaluation with excellent interobserver agreement of 93%, high discriminative power, and an area under the receiver operating characteristic curve of 0.99. Using a cutoff of otic capsule thickness of >2.3 mm from the posterolateral margin of the cochlea lumen closest to the middle ear (junction of the basal and middle turns) to the most convex contour resulted in high values of all statistical measures including 96.2% sensitivity, 100% specificity, 100% positive predictive value, and 96.4% negative predictive value. Retrospective review of the imaging in the 4 ears with otosclerosis and false-negative results on CT based on the 2.3-mm cutoff revealed small lucent fenestral lesions in 3 ears and 1 ear that had only round window disease present. Overall, this standardized measurement value of 2.3 mm is a good diagnostic tool to help recognize patients with otosclerosis.

Our otosclerosis population corresponds well to previous reports in terms of sex and age predilection as well as type of otosclerosis.^{1-4,10-14} There were no significant differences between the patients with otosclerosis and those with normal hearing in terms of sex. There was a significant difference in terms of age between the 2 groups with the normal-hearing group being younger than the patients with otosclerosis. However, otosclerosis is a disorder of the enchondral bone,¹ and the enchondral bone of the otic capsule anterior to the oval window is expected to be largely ossified by term infancy with the exception of the cartilage

immediately surrounding the fissula ante fenestram, which is one of the last parts of the otic capsule to ossify.¹⁵ Small pericochlear lucencies can be seen in children,^{16,17} but these would not be expected to affect the otic capsule contour or the overall thickness of the otic capsule. Because our patients were adults, we would not have expected differences related to the age of the patients. Most interesting, 1.9% of patients with otosclerosis had isolated round window lesions without associated disease anterior to the oval window, a higher percentage than reported in prior literature.¹⁸ Although imaging may not be necessary in the diagnosis of patients who present with characteristic clinical findings and typical audiometric test findings,⁹ imaging is helpful for the diagnosis in cases of sensorineural or mixed hearing loss, evaluating other differential diagnoses or coexisting diseases, and preoperative anatomic assessment.^{2,3,6,8} Most of our patients underwent imaging for preoperative evaluation before stapes prosthesis and cochlear implant insertion for fenestral and retrofenestral otosclerosis, respectively.

There was a statistically significant difference between patients with otosclerosis who underwent CBCT versus MDCT in patients with normal hearing. This was expected because there is a trend at our institution to perform more CBCT for patients with conductive hearing loss. MDCT is preferred at our institution for the entities commonly seen in the normal-hearing population, including facial paralysis and vertigo. We would not expect a difference in terms of measurement based on the 2 modalities.

Prior literature has suggested that MDCT and CBCT are limited in cases of tiny foci of <1 mm, superficial foci, inactive disease, and density variation of <200 HU.¹⁹⁻²² In addition, CBCT has been found to have a 0% sensitivity for detection of otosclerosis in the sclerotic phase; however, detection was based on a visual grading system with no standardized measurement techniques used.¹⁹ As in our study, Swartz et al²³ described the presence of a bony excrescence or a bulging contour of the otic capsule anterior to the oval window as a helpful finding in otosclerosis; however, the interval improvement in MDCT technology now enables reproducible quantitative measurements in standardized planes, improving accuracy and reproducibility. A recent systematic review suggests that high-resolution CT has a low sensitivity of 58%, high specificity of 95%, and a high positive predictive value of 92% but is limited in submillimeter disease, retrofenestral disease, and dense sclerotic lesions.²⁴ Our study improves the sensitivity and specificity for the diagnosis of otosclerosis using a standardized plane and clearly defined landmarks for quantitative assessment of the otic capsule, regardless of phase of disease.

A limitation of this study was that there was no histologic confirmation of disease as a definitive diagnosis of the degree of disease activity. However, our patients met clinical features sufficient to confirm otosclerosis. In addition, the characterization of the phase of disease was subjective on the basis of perceptual differences in otic capsule density. While there are currently no quantitative measures of CT density to define the different phases of disease, our study shows that the thickness of the otic capsule and the presence of a bulging contour are independent of the phase of disease. In addition, our patients with otosclerosis had undergone either an MDCT or CBCT but not both; thus, we could

not compare the 2 modalities. Additional study may provide this information to support decision-making for the choice of CT imaging modalities. In addition, submillimeter foci of otosclerosis may be too small to result in a contour bulge or significant thickening of the otic capsule; however, these lesions may be less likely to result in conductive hearing loss. Another limitation is that this study was performed at 1 institution. While our study showed excellent interobserver reliability, further studies at other institutions may help confirm reproducibility. Finally, other osteodysplasias could produce a bulging contour, though entities such as Paget disease would not be expected to involve only the area anterior to the oval window.

CONCLUSIONS

Using a standardized axial plane parallel to the lateral semicircular canal, a bulging or convex contour of the otic capsule relative to a line drawn between the anterior margin of the oval window and the cochleariform process occurred with high specificity and positive predictive value in patients with otosclerosis. The otic capsule along the anterior margin of the oval window at the level of the cochleariform process is significantly thicker in patients with otosclerosis compared with individuals with normal hearing. Use of a quantitative assessment of the otic capsule may help the radiologist accurately diagnose otosclerosis.

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REFERENCES

- Merchant SN, Nadel JB Jr, Schuknecht HF. **Disorders of bone.** In: Merchant SN, Nadol JB, eds. *Schuknecht's Pathology of the Ear*. 3rd ed. Shelton: People's Medical Publishing House; 2010:716–37
- Juliano AF, Ginat DT, Moonis G. **Imaging review of the temporal bone, Part II: traumatic, postoperative, and noninflammatory non-neoplastic conditions.** *Radiology* 2015;276:655–72 [CrossRef Medline](#)
- Purohit B, Hermans R, Op de beeck K. **Imaging in otosclerosis: a pictorial review.** *Insights Imaging* 2014;5:245–52 [CrossRef Medline](#)
- Schuknecht HF, Barber W. **Histologic variants in otosclerosis.** *Laryngoscope* 1985;95:1307–17 [Medline](#)
- Swartz JD, Mandell DW, Wolfson RJ, et al. **Fenestral and cochlear otosclerosis: computed tomographic evaluation.** *Am J Otol* 1985;6:476–81 [Medline](#)
- Gredilla Molinero J, Mancheño Losa M, Santamaría Guinea N, et al. **Update on the imaging diagnosis of otosclerosis** [in Spanish and English]. *Radiologia* 2016;58:246–56 [CrossRef Medline](#)
- Handzel O, McKenna MJ. **Surgery for otosclerosis.** In: Gulya AJ, Minor LB, Poe DS, eds. *Glasscock-Shambaugh Surgery of the Ear*. 6th ed. Shelton: People's Medical Publishing House; 2010:529–46
- Sepúlveda I, Schmidt Putz T, Platin E. **Use of cone beam computed tomography in the diagnosis of otosclerosis.** *J Radiol* 2017;128:224–27
- Sakai O, Curtin HD, Hasso AN, et al. **Otosclerosis and dysplasias of the temporal bone.** In: Som PM, Curtin HD, eds. *Head and Neck Imaging*. 5th ed. St. Louis: Mosby; 2011:1231–56
- Nager FR. **Zur Klinik und Pathologischen Anatomie der Otoklerose.** *Acta Oto-Laryngologica* 1939;27:542–51 [CrossRef](#)

11. Cawthorne T. **Otosclerosis.** *J Laryngol Otol* 1955;69:437–56 CrossRef Medline
12. Larsson A. **Otosclerosis: a genetic and clinical study.** *Acta Otolaryngol Suppl* 1960;154:1–86 Medline
13. Schmidt E. **Erblichkeit und Gravidität bei der Otosklerose.** *European Archives of Oto-Rhino-Laryngology* 1933;136:188–201 CrossRef
14. Shambaugh GE Jr. **Fenestration operation for otosclerosis: experimental investigations and clinical observations in 2,100 operations over a period of ten years.** *Acta Otolaryngol Suppl* 1949;79:1–101
15. Bast TH, Anson BJ. **The otic capsule.** In: Bast TH, Anson BJ, eds. *The Temporal Bone and the Ear.* Springfield: CC Thomas;1949:205–46
16. Pekkola J, Pitkaranta A, Jappel A, et al. **Localized pericochlear hypoattenuating foci at temporal-bone thin-section CT in pediatric patients: nonpathologic differential diagnostic entity?** *Radiology* 2004;230:88–92 CrossRef Medline
17. Chadwell JB, Halsted MJ, Choo DI, et al. **The cochlear cleft.** *AJNR Am J Neuroradiol* 2004;25:21–24 Medline
18. Mansour S, Nicolas K, Ahmad HH. **Round window otosclerosis: radiologic classification and clinical correlations.** *Otol Neurotol* 2011;32:384–92 CrossRef Medline
19. Liktor B, Révész P, Csomor P, et al. **Diagnostic value of cone-beam CT in histologically confirmed otosclerosis.** *Eur Arch Otorhinolaryngol* 2014;271:2131–38 CrossRef Medline
20. Virk JS, Singh A, Lingam RK. **The role of imaging in the diagnosis and management of otosclerosis.** *Otol Neurotol* 2013;34:55–60 CrossRef Medline
21. Révész P, Liktor B, Liktor B, et al. **Comparative analysis of preoperative diagnostic values of HRCT and CBCT in patients with histologically diagnosed otosclerotic stapes footplates.** *Eur Arch Otorhinolaryngol* 2016;273:63–72 CrossRef Medline
22. Lagleyre S, Sorrentino T, Calmels MN, et al. **Reliability of high-resolution CT scan in diagnosis of otosclerosis.** *Otol Neurotol* 2009;30:1152–59 CrossRef Medline
23. Swartz JD, Faerber EN, Wolfson RJ, et al. **Fenestral otosclerosis: significance of preoperative CT evaluation.** *Radiology* 1984;151:703–07 CrossRef Medline
24. Kanzara T, Virk JS. **Diagnostic performance of high resolution computed tomography in otosclerosis.** *World J Clin Cases* 2017;5:286–91 CrossRef Medline

Long-Term Ultrasound Follow-Up of Incidentally Detected Thyroglossal Duct Cysts in Adults

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ABSTRACT

BACKGROUND AND PURPOSE: There has been no previous study that used ultrasonography for longitudinal changes of thyroglossal duct cysts, to our knowledge. We assessed the prevalence and interval changes in incidentally detected thyroglossal duct cysts in adults.

MATERIALS AND METHODS: From January 2010 to December 2016, we identified 796 ultrasonography radiologic reports from 513 subjects that contained the words “thyroglossal” or “TGDC” among 54,369 participants. Of 513 subjects, 172 (M/F = 103:69, mean age, 53 ± 11 years) who underwent ≥ 2 sonography studies were enrolled. Two reviewers determined ultrasonography features, including maximal diameter, location, internal echogenicity, wall thickness, and the presence of posterior enhancement, internal septa, and solid components.

RESULTS: The mean follow-up time of total 172 lesions was 2.01 ± 1.13 years. Thyroglossal duct cysts ranged from 2 to 32 mm (mean, 8.77 ± 3.83 mm) on the initial ultrasonography examination. On follow-up ultrasonography studies, 14 lesions (8.2%) increased by >2 mm, while most thyroglossal duct cysts (133 lesions, 77.3%) remained stable in size. During the follow-up period, 31 lesions (18.0%) showed interval changes in ultrasonography features. There was no significant relationship between the presence of ultrasonography feature changes and size changes ($P = .12$).

CONCLUSIONS: On ultrasonography, 0.9% of adults had incidental thyroglossal duct cysts. Most did not increase in size with time despite changes in various ultrasonography features. Therefore, we recommend performing an observation at long intervals of 2–3 years for asymptomatic thyroglossal duct cysts, and we suggest that fine-needle aspiration can be suspended unless suspicious findings of malignancy are detected.

ABBREVIATIONS: TGDC = thyroglossal duct cyst; US = ultrasonography

Thyroglossal duct cyst (TGDC) is the most common congenital neck mass, accounting for approximately 70% of congenital lesions of the neck. TGDCs typically present before 20 years of age; however, they present in adults as well. Although the reported prevalence of TGDCs varies among studies, it is generally estimated that 7% of the population has a TGDC and persistent remnants.¹ High-resolution ultrasonography (US) is a readily available, noninvasive imaging technique commonly used for the initial investigation of the neck in daily practice. This has resulted in the incidental detection of TGDCs on neck US examinations. Due to the benign nature of TGDCs, it is recommended that most

patients in whom a TGDC is incidentally detected be observed only if they develop related symptoms or any suspicious findings consistent with a coexisting malignancy.

Prior studies have reported that TGDCs have a variable sonographic appearance ranging from typical anechoic to pseudo-solid.^{2–5} Nevertheless, to the best of our knowledge, no previous study has used sonography to follow changes in TGDCs.

In this study, we assessed the prevalence and interval changes in incidentally detected TGDCs with a largest diameter of ≥ 3 mm in asymptomatic adults who underwent thyroid US examinations.

MATERIALS AND METHODS

This retrospective study was approved by the review boards of Seoul National University Hospital; informed consent was waived.

Adults 20–96 years of age who had undergone thyroid sonography during a comprehensive health screening examination from January 2010 to December 2016 were considered eligible for

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enrollment in our study. During the study period, 105,293 thyroid sonographic studies were performed in 54,369 consecutive subjects. Of 54,369 patients, 26,456 subjects were men and 27,913 were women. Among them, we identified 796 US radiologic reports from 513 subjects that contained the words “thyroglossal” or “TGDC.” Of the 513 participants, 329 subjects underwent a single US examination, 103 subjects underwent 2 US studies, and the remaining subjects underwent ≥ 3 US examinations during the study period. Among the 184 subjects who underwent ≥ 2 US studies, 12 subjects were excluded because US images were not available. Finally, a total of 172 subjects (M/F = 103:69, mean age, 53 ± 11 years) with a TGDC were enrolled in our study.

US Images

Real-time gray-scale US was performed by various radiologists assigned arbitrarily according to the daily schedule of the hospital. Images were obtained using an 8- to 15-MHz transducer (Acuson Sequoia; Siemens Medical Solutions, Mountain View, California), or a 5- to 14-MHz linear array transducer (iU22; Philips Medical Systems, Bothell, Washington).

Two US examinations were selected per subject. The first US study on which a TGDC was reported was designated the initial US study. The presence or absence of morphologic changes was then determined on follow-up US studies. The final study was defined as the most recent study if there were no morphologic changes, while if there were morphologic changes, the US study that first documented the changes was considered the final study. Two radiologists (S.C.K. and H.Y.S., with 5 and 3 years of experience in thyroid imaging) retrospectively reviewed static US images from 2 sets of US studies using a PACS and a consensus approach. Sonographic images were evaluated for the following features: maximal diameter, location of the mass, internal echogenicity, wall thickness, presence of posterior enhancement, internal septa, solid components, and presence or absence of the thyroid gland and any fistulous communication. Internal echogenicity was characterized as anechoic (definitely no internal echoes), homogeneously hypoechoic (hypoechoic relative to the strap muscle), homogeneously hyperechoic or pseudosolid (more echogenic than the strap muscle), or heterogeneous. The location was recorded as midline or lateral and at the suprahyoid/hyoid or infrahyoid level. Wall thickness was defined as imperceptible, thin (1–2 mm), or thick (≥ 2 mm). Internal septa were classified as no septa, 1–3 septa, and ≥ 4 internal septa.

Statistical Analysis

Interval size changes between the initial and final US studies were calculated. We then classified subjects into the following 3 groups: 1) a decreased group, in which the interval size decrease was >2 mm; 2) a stable group, in which the interval size change was ≤ 2 mm; and 3) an increased group, in which the interval size increase was >2 mm. We used either the χ^2 or the Kruskal-Wallis H test with Bonferroni correction to test for differences in demographic and US characteristics among the 3 groups. All analyses were performed with SPSS, Version 20 (IBM, Armonk, New York). $P < .05$ indicated a statistically significant difference.

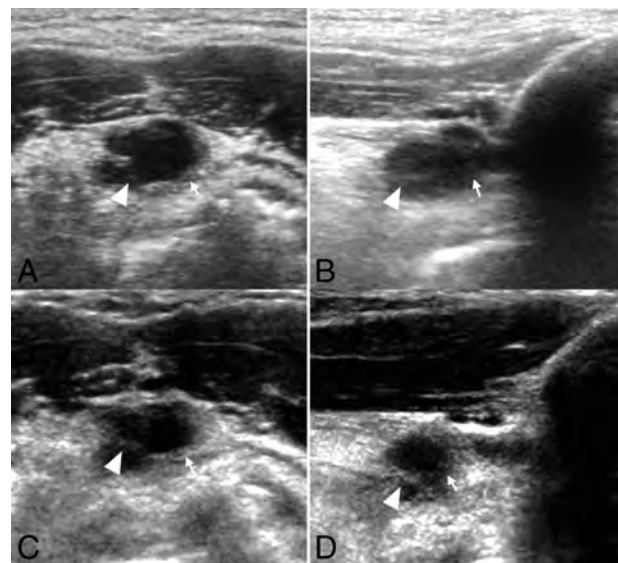


FIG 1. An 86-year-old man with an incidentally detected midline mass on US. Transverse (A) and longitudinal (B) sonograms show a uniformly anechoic thyroglossal duct cyst with few internal septa (arrowheads) and thin walls (white arrows). On follow-up US studies (C and D) at 2.5 years, the TGDC decreased by 4 mm. There were no interval changes in US features.

RESULTS

The mean follow-up time between the initial and final US examination was 2.01 ± 1.13 years with a range of 0.42–6.83 years. The follow-up time between the initial and the last US examination was <1 year for 61 lesions (35.5%), between 1 and 2 years for 63 lesions (36.6%), between 2 and 3 years for 41 lesions (23.8%), and ≥ 4 years for 7 lesions (4.1%).

US Features on Initial US Examinations

TGDCs ranged from 2 to 32 mm (mean, 8.77 ± 3.83 mm) on the initial US examination. Among all lesions, 50 (29.1%) were >10 mm. One hundred sixty-five TGDCs (95.9%) had a midline location. Eight TGDCs (4.7%) presented at the infrahyoid level. Among them, 7 lesions were located at the lateral aspect.

Of the 172 lesions, 154 lesions (89.5%) were truly anechoic, while 16 lesions (9.3%) were homogeneously hypoechoic. One lesion (0.6%) showed hyperechoic/pseudosolid echogenicity, and 1 lesion (0.6%) had heterogeneous internal echoes. Regarding wall thickness, 20 lesions (11.6%) had thin walls, while the walls of the other 152 lesions (88.4%) were imperceptible. None of the 172 lesions had a wall thicker than 2 mm.

Fifty lesions had 1–3 septa, while most TGDCs (121 lesions, 70.3%) had no internal septa. One TGDC had >4 internal septa. Among 172 TGDCs, 146 lesions (84.9%) showed posterior enhancement. Two TGDCs (1.2%) had solid components.

No fistulous tracts were identified by sonography. All 172 individuals had thyroid glands in the normal location.

Interval Changes on Follow-Up US Examinations

On follow-up US studies, 25 TGDCs (14.5%) decreased by >2 mm (Fig 1), while 14 lesions (8.2%) increased by >2 mm. Most TGDCs (133 lesions, 77.3%) remained stable in size (Fig 2). There were significant differences in follow-up intervals ($P = .009$)

among the 3 groups (decreased versus stable versus increased groups, Table). In post hoc analysis, the follow-up intervals of the decreased group were shorter than those of the stable group ($P = .005$). Similarly, there were significant differences in initial diameters between the decreased and stable groups ($P = .011$), but there were no significant differences between the decreased/stable and increased groups ($P = .31$).

During the follow-up period, 31 lesions (18.0%) showed interval changes in US features (Table). Eight lesions (4.7%) showed changes in echogenicity; 11 lesions (6.4%), in wall thickness; 14 lesions (8.1%), in the presence of posterior enhancement; and 4 lesions (2.3%), in internal septa. There was no case that showed a change in internal solid components. There were no significant differences in the presence of US feature changes among the 3 groups ($P = .12$). Furthermore, there was no significant relationship between the type of US feature change and group identity ($P = .27$).

Clinicopathologic Results

During the study period, fine-needle aspirations were performed for 2 lesions that had a solid component; for both cases, whitish

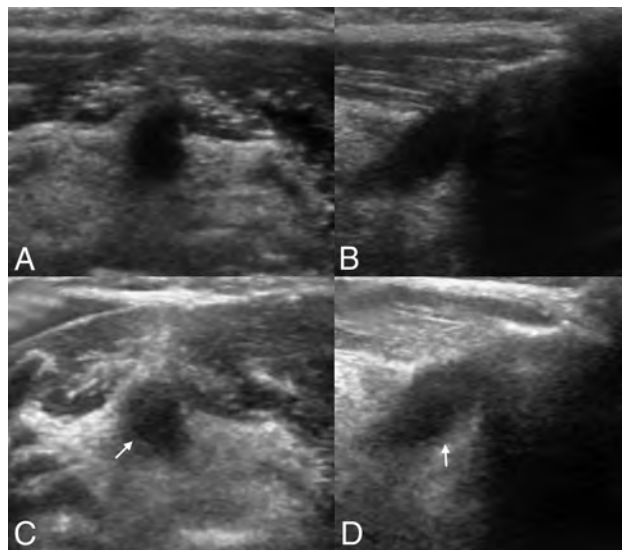


FIG 2. A 59-year-old man with an incidentally detected midline mass on US. Transverse (A) and longitudinal (B) sonograms demonstrate a uniformly anechoic thyroglossal duct cyst without a perceptible wall. On follow-up US (C and D) at 6 years, the TGDC remained the same size, while there were interval changes in US features. White arrows indicate the thin walls of the TGDC.

Interval changes on follow-up US examinations^a

	Decreased Group (n = 25)	Stable Group (n = 133)	Increased Group (n = 14)	P Value
Follow-up intervals (mo)	18.2 ± 10.6 ^b	25.2 ± 13.3 ^b	29.9 ± 14.1	.009
Maximal diameter on initial US (mm)	10.8 ± 5.8 ^c	8.3 ± 3.2 ^c	9.3 ± 4.2	.042
US feature changes of	8 (32%)	20 (15%)	3 (21.4%)	.12
Internal echogenicity	0	5	3	
Wall thickness	2	8	1	.27
Presence of posterior enhancement	4	9	1	
Internal septa	2	2	0	
Solid component	0	0	0	

^a Continuous variables are presented as means. Categorical variables are presented as numbers (percentages).

^b and ^c Post hoc analysis was evaluated by the Bonferroni correction method. The same letters indicate a significant difference between groups.

mucinous fluid was aspirated and no malignant cells were detected. Two subjects underwent Sistrunk operations because their TGDCs increased in size and caused neck discomfort (Fig 3). Pathologic examination revealed cystic lesions lined by pseudostratified ciliated columnar epithelium, consistent with thyroglossal duct cysts.

DISCUSSION

Kurt et al⁶ reported that 15% of 80 adult cadavers had a TGDC, while Ellis and van Nostrand,⁷ on the basis of microscopic examination of 200 adult larynges, reported thyroglossal duct remnants in 7% of specimens. Yim et al⁸ reported a 0.1% prevalence of incidentally detected TGDCs among 60,663 CT and MR imaging scans of pediatric patients. In the present study, 513 of 54,369 subjects had TGDCs (0.9%). We assume that some TGDCs were not described in radiologic reports because they were too small to detect or overlooked on screening thyroid US examinations. The prevalence of TGDCs will likely vary on the basis of the particular clinical setting, study population, and detection method. Our data therefore represent only the prevalence of incidental TGDCs on high-resolution US examinations of asymptomatic adults. Most TGDCs in our study were located at the suprahyoid/hyoid level rather than the infrahyoid level as in the study of Yim et al and other previous studies.⁸⁻¹⁰ Differences among studies in the methods used to detect TGDCs likely account for differences in their reported locations.

Ahuja et al¹¹ reported that <30% of a total of 40 TGDCs were truly anechoic in adults. However, almost all TGDCs in our study presented as a purely anechoic mass without any internal septa or solid components but with posterior enhancement, consistent with the typical sonographic description.^{2-5,12} This is likely because the TGDCs in the present study were relatively small and incidentally detected during screening of asymptomatic adults.

During the study period, >90% of TGDCs remained the same size or decreased in size, even if there were interval changes in US features. Moreover, there was no correlation between the US feature that changed and whether size was stable, decreased, or increased. Previous studies indicated that a complex echo pattern accompanied by coarse internal debris and septa was due to the proteinaceous content of the cyst secreted by the cyst lining.¹¹ On the basis of this description, we believe that the US feature changes of TGDCs are more likely related to changes in the internal content or infection than to progression with time. Thus, we found no specific US feature that predicted an increase in the size of the TGDCs. Therefore, we believe that US can be implemented at long intervals of 2–3 years for asymptomatic TGDCs, even if there is a change in US features.

This study had some limitations. The most important one was that we enrolled TGDCs by clinicoradiologic diagnoses, not pathologic diagnoses. Although most TGDCs were clinically diagnosed and followed up without pathologic confirmation, Rayess et al¹³ reported co-existing malignancies in TGDCs incidentally

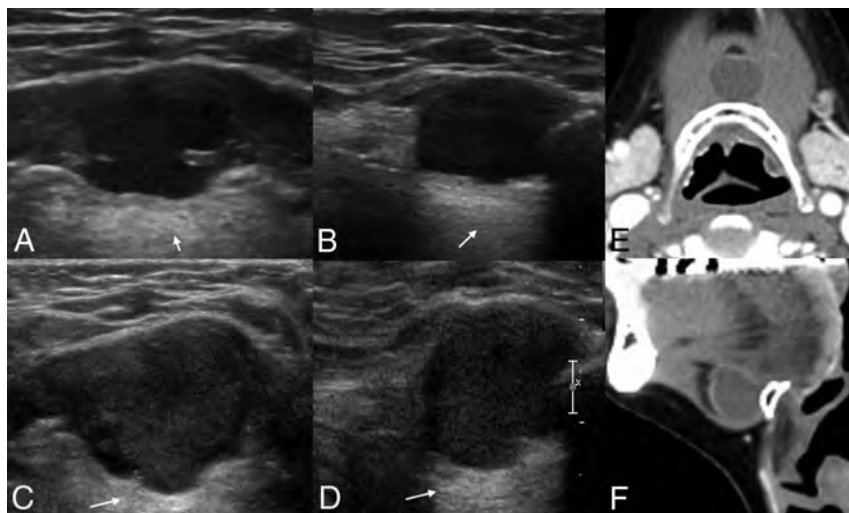


FIG 3. A 54-year-old man with an incidentally detected midline mass on US. Transverse (A) and longitudinal (B) sonograms depict a truly anechoic thyroglossal duct cyst with posterior enhancement (white arrows). On follow-up US (C and D) at 1 year, the TGDC shows a gradual increase of 5 mm and a pseudosolid appearance. He underwent a Sistrunk operation due to neck discomfort. Preoperative CT images (E and F) demonstrate a uniformly hypoechoic cystic mass at the hyoid bone level. The TGDC was confirmed by pathologic examination of the surgical specimen, which showed no inflammation or hemorrhage.

tally diagnosed on the basis of the final pathologic analysis. Therefore, strictly speaking, we did not evaluate the development of TGDC carcinoma or its relationship to US feature changes on follow-up US images. However, no patient developed solid components or a mural mass with associated microcalcifications during the follow-up period; these are suspicious findings for malignancy.^{13,14} In addition, there was no evidence of malignancy in the 3 subjects who underwent pathologic diagnosis (2 who underwent operations due to a size increase and symptom development, and 1 individual who underwent fine-needle aspiration due to a size increase) during the follow-up period. Moreover, after the study period, we additionally evaluated follow-up US images of 5 individuals (among total 14 patients except 2 who underwent surgery, 5/12, 41.7%) who had a TGDC that increased in size during the study period. None of the 5 lesions showed interval changes in size or developed solid components during the additional follow-up period of 1 year. Therefore, we argue that the possibility of a carcinoma arising within a TGDC was very low in the present study, as in prior studies.^{13–15} Furthermore, based on the results that no cancer was found at pathologic diagnosis and, even in cases of increased size of TGDCs, no newly suspicious findings for cancer at follow-up developed, we believe that size increase does not require the implementation of fine-needle aspiration. Nevertheless, our follow-up for the evaluation of malignant TGDCs was relatively short. Further studies with a longer follow-up and pathologic confirmation are needed.

CONCLUSIONS

TGDCs incidentally detected on high-resolution US examinations in adults are not uncommon. Most of these TGDCs do not increase in size with time despite changes in various US features. Therefore, we recommend performing an observation at long intervals of 2–3 years for asymptomatic TGDCs, and we suggest that fine-needle aspiration can be suspended unless suspicious findings of malignancy are detected.

REFERENCES

1. Ewing CA, Kornblut A, Greeley C, et al. **Presentations of thyroglossal duct cysts in adults.** *Eur Arch Otorhinolaryngol* 1999;256:136–38 [CrossRef Medline](#)
2. Wadsworth DT, Siegel MJ. **Thyroglossal duct cysts: variability of sonographic findings.** *AJR Am J Roentgenol* 1994;163:1475–77 [CrossRef Medline](#)
3. Foley DS, Fallat ME. **Thyroglossal duct and other congenital midline cervical anomalies.** *Semin Pediatr Surg* 2006;15:70–75 [CrossRef Medline](#)
4. Koch BL. **Cystic malformations of the neck in children.** *Pediatr Radiol* 2005;35:463–77 [CrossRef Medline](#)
5. Choi HI, Choi YH, Cheon JE, et al. **Ultrasonographic features differentiating thyroglossal duct cysts from dermoid cysts.** *Ultrasonography* 2018;37:71–77 [CrossRef Medline](#)
6. Kurt A, Ortug C, Aydar Y, et al. **An incidence study on thyroglossal duct cysts in adults.** *Saudi Med J* 2007;28:593–97 [Medline](#)
7. Ellis PD, van Nostrand AW. **The applied anatomy of thyroglossal tract remnants.** *Laryngoscope* 1977;87:765–70 [CrossRef Medline](#)
8. Yim MT, Tran HD, Chandy BM. **Incidental radiographic findings of thyroglossal duct cysts: prevalence and management.** *Int J Pediatr Otorhinolaryngol* 2016;89:13–16 [CrossRef Medline](#)
9. Moore KL, Persaud TV. *The Developing Human: Clinically Oriented Embryology.* Philadelphia: W.B. Saunders;1993:200–03
10. Thompson LD, Herrera HB, Lau SK. **A clinicopathologic series of 685 thyroglossal duct remnant cysts.** *Head Neck Pathol* 2016;10:465–74 [CrossRef Medline](#)
11. Ahuja AT, King AD, King W, et al. **Thyroglossal duct cysts: sonographic appearances in adults.** *AJNR Am J Neuroradiol* 1999;20:579–82 [Medline](#)
12. Ballenger JJ, Snow JB. *Otorhinolaryngology: Head and Neck Surgery.* Baltimore: Williams and Wilkins;1996:211–12
13. Rayess HM, Monk I, Svider PF, et al. **Thyroglossal duct cyst carcinoma: a systematic review of clinical features and outcomes.** *Otolaryngol Head Neck Surg* 2017;156:794–802 [CrossRef Medline](#)
14. Cignarelli M, Ambrosi A, Marino A, et al. **Three cases of papillary carcinoma and three of adenoma in thyroglossal duct cysts: clinical-diagnostic comparison with benign thyroglossal duct cysts.** *J Endocrinol Invest* 2002;25:947–54 [CrossRef Medline](#)
15. Page CP, Kammerer WT, Haff RC, et al. **Thyroid carcinomas arising in thyroglossal ducts.** *Ann Surg* 1974;180:799–803 [CrossRef Medline](#)

Value of *BRAF* V600E in High-Risk Thyroid Nodules with Benign Cytology Results

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ABSTRACT

BACKGROUND AND PURPOSE: Limitations of ultrasound-guided fine-needle aspiration include nondiagnostic, indeterminate cytology and false-negative results. The *BRAF* V600E mutation is a specific biomarker for papillary thyroid carcinoma. This study aimed to investigate the additional diagnostic role of the *BRAF* V600E mutation in high-risk thyroid nodules with benign cytology results.

MATERIALS AND METHODS: A total of 787 high-risk nodules in 720 patients underwent ultrasound–fine-needle aspiration. A subsequent *BRAF* V600E mutation test was performed on thyroid nodules with benign cytology. Final pathology confirmed thyroid nodules with benign cytology that were positive for the *BRAF* V600E mutation. Ultrasound was performed on thyroid nodules with benign cytology results that were negative for the *BRAF* V600E mutation. Fine-needle aspiration was repeated on thyroid nodules with enlarged size or changed ultrasound features.

RESULTS: Among the 787 nodules, 292 thyroid nodules had benign cytology results with 256 nodules negative for the *BRAF* V600E mutation and 36 nodules positive for the *BRAF* V600E mutation. Thirty-one nodules positive for the *BRAF* V600E mutation were confirmed malignant, and 5 nodules were confirmed benign by pathology. Fine-needle aspiration was repeated on 11 enlarged thyroid nodules with benign cytology findings that were negative for the *BRAF* V600E mutation. The results of repeat fine-needle aspiration were 4 benign nodules, 2 follicular neoplasms or suspected follicular neoplasms, 3 suspected malignancies, and 2 malignant nodules. Among the 36 thyroid nodules positive for the *BRAF* V600E mutation, 25 (69.4%) had ≥ 2 suspicious ultrasound features and 11 (30.6%) nodules had 1 suspicious ultrasound feature.

CONCLUSIONS: The *BRAF* V600E mutation test can detect papillary thyroid carcinomas that might be missed by fine-needle aspiration. We recommend that fine-needle aspiration be routinely accompanied by the *BRAF* V600E mutation test in high-risk thyroid nodules with ≥ 2 suspicious ultrasound features.

ABBREVIATIONS: FNA = fine-needle aspiration; PCR = polymerase chain reaction; PTC = papillary thyroid carcinoma; US = ultrasound

Thyroid nodules are commonly found in clinical practice. Although most thyroid nodules are benign, the differentiation between malignant and benign lesions remains a challenge for clinicians. Ultrasound (US) has been established as the first detection tool in thyroid studies.¹ The expected malignancy risk of high-risk thyroid nodules is 50%–90% based on the presence of ≥ 1 suspicious finding.² Fine-needle aspiration (FNA) cytology

represents the criterion standard for determining the nature of thyroid nodules.^{2,3} Fine-needle aspiration is a reliable method with good sensitivity and specificity. However, the limitations of ultrasound-guided fine-needle aspiration include nondiagnostic, indeterminate cytology and false-negative and false-positive results, which are 10%–40% of all cytology results.^{4–6} The conventional practice is US monitoring or repeat FNA when a mismatch is determined between radiology and cytology findings.^{2,3}

Molecular testing of thyroid fine-needle aspirates has emerged as a tool to complement routine cytopathologic examinations.^{7,8} The *BRAF* V600E mutation is used as a specific biomarker for

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papillary thyroid carcinoma (PTC) and has a high positive predictive value (95.5%–100.0%).^{9,10}

Considering the false-negative rate of 3.6%–21% in US-FNA^{11,12} and the high-risk rate of malignancy in thyroid nodules with suspicious US features, this study investigated the additional diagnostic role of the *BRAF* V600E mutation in high-risk thyroid nodules with benign cytology findings and compared the clinical US features of thyroid nodules with benign cytology results and tests positive for the *BRAF* V600E mutation with nodules that had tests negative for the *BRAF* V600E mutation.

MATERIALS AND METHODS

This was a prospective study. It was approved by the Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University. All study participants provided written informed consent before undergoing US-FNA and *BRAF* V600E mutation tests. The study conformed to the Declaration of Helsinki.

Patients

A total of 787 high-risk thyroid nodules in 720 patients underwent US-FNA from October 2015 to March 2017 in our hospital. On the basis of the Bethesda System for Reporting Thyroid Cytopathology, FNA cytology results were categorized as nondiagnostic, benign, atypia of undetermined significance/follicular lesion of undetermined significance, follicular neoplasm or suspicious follicular neoplasm, suspected malignancy, and malignant. A subsequent *BRAF* V600E mutation test was performed on 292 patients with benign cytology results of thyroid nodules. A total of 36 thyroid nodules were positive for the *BRAF* V600E mutation, and 256 thyroid nodules were negative for the *BRAF* V600E mutation. The 36 thyroid nodules positive for the *BRAF* V600E mutation underwent an operation. US monitoring was performed on thyroid nodules with benign cytology results and negative for the *BRAF* V600E mutation every 6 months. The follow-up duration for patients was >1 year. Repeat fine-needle aspiration biopsy was conducted on thyroid nodules that met at least 1 of the following criteria: The nodule grew during follow-up (>50% change in volume or a 20% increase in at least 2 nodule dimensions with a minimal increase of 2 mm in solid nodules or in the solid portion of mixed cystic-solid nodules). The patients underwent an operation if the results of repeat cytology were follicular neoplasm or suspicious follicular neoplasm, suspected malignancy, or malignant, and continued follow-up US every 6 months if the results of repeat cytology were nondiagnostic, benign, or atypia of undetermined significance/follicular lesion of undetermined significance.

US and US-FNA

Two radiologists with 10 years of experience in thyroid imaging performed US examinations using a 5- to 12-MHz linear array transducer (EZU-MT28-S1; Hitachi Medical, Tokyo, Japan). Radiologists interpreted US findings on the basis of the internal composition, echogenicity, margin, calcification, and shape. Subsequently recorded US features were reclassified on the basis of the updated American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi guidelines.² Highly suspicious US features indicative of thyroid cancer included ≥ 1 of the following

features: marked hypoechogenicity (confer prethyroid muscles), spiculated or microlobulated margins, microcalcifications, taller-than-wide shape, evidence of extrathyroidal growth, or pathologic adenopathy.²

FNAs were performed under US guidance with a 23-ga needle attached to a 2-mL syringe. Each lesion was aspirated in 2–3 passes in different directions. The aspirates were expelled on glass slides, smeared, and immediately placed in 95% alcohol and were sent for cytologic analysis by 2 experienced cytologists. The 1 remaining pass of material was rinsed in 180- μ L cytology liquid and was stored at -20°C for subsequent *BRAF* V600E mutation testing.

DNA Isolation and *BRAF* V600E Detection

BRAF V600E mutation analysis was performed on the remaining extracted DNA from FNA cells after cytologic evaluation. DNA extraction was successfully completed in all samples following the manufacturer's instructions with a commercially available kit (ADx-Amplification Refractory Mutation System [ADx-ARMS]; AmoyDX, Xiamen, China). The quantity of isolated DNA was assessed using a NanoDrop2000 spectrophotometer (Thermo Fisher Scientific, Waltham, Massachusetts, USA). All samples in this study were adequate for genetic detection. The samples were analyzed by applying the ADx-ARMS technique. Briefly, each polymerase chain reaction (PCR) mixture contained 5 μ L of extracted DNA and other chemicals available in a kit (ADx-ARMS; AmoyDX) that contained oligonucleotide primers, Taq DNA polymerase, oligonucleotide probes, nucleotides, and buffers. PCR reaction was conducted on a qRT-PCR machine (ABI 7500; Applied Biosystems, Foster City, California) with an initial denaturation step at 94°C for 5 minutes, 15 annealing cycles at 95°C for 25 seconds, 64°C for 20 seconds, and 72°C for 20 seconds, followed by 31 extension cycles at 93°C for 25 seconds, 60°C for 35 seconds, and 72°C for 20 seconds.

Statistical Analysis

The comparison of variables between the 2 groups was analyzed with Student *t* and Mann-Whitney *U* tests. Qualitative variables were evaluated with a χ^2 test. Analyses were performed with Statistical Package for Social Sciences, Version 19.0 (IBM, Armonk, New York). A confidence interval of 95% and a significance level of 5% were used.

RESULTS

A total of 787 high-risk nodules in 720 patients (653 patients had a single nodule and 67 patients had 2 nodules; 511 women, 209 men; mean age, 46.2 ± 11.7 years; range, 15–83 years) were included in the study and underwent US-FNA. A subsequent *BRAF* V600E mutation test was performed on 292 patients with benign cytology results. A total of 36 thyroid nodules with benign cytology results were positive for the *BRAF* V600E mutation and 256 thyroid nodules with benign cytology results were negative for the *BRAF* V600E mutation. Figure 1 represents the clinical course of 292 thyroid nodules with benign cytology results. Of the 36 thyroid nodules with benign cytology results and positive for the *BRAF* V600E mutation, 10 were in men and 26 were in women. The mean age of patients was 44.7 ± 11.3 years and ranged from 18 to 75 years. The mean size of the thyroid nodules was 9.4 mm

and ranged from 5.3 to 25 mm. All 36 patients underwent thyroidectomy. Nodules in 31 of 36 patients were confirmed malignant by surgical pathology. Twelve nodules were PTC, and 19 were papillary thyroid microcarcinomas (Fig 2). Twenty-three of 36 nodules measured <1 cm, whereas the remaining 13 were >1 cm (Table 1). Among the patients, 11 had 1 suspicious US feature, 17 had 2 suspicious US features, 7 had 3 suspicious US features, and 1 had 4 suspicious US features (Table 1). Among the 256 patients with thyroid nodules with benign cytology results and negative for the *BRAF* V600E mutation, 27 were men and 229 were women. The mean age of patients was 47.3 ± 13.9 years and ranged from 15 to 83 years. The mean size of thyroid nodules was 11.8 mm and ranged from 5.7 to 39 mm (Table 1). Eleven patients had enlarged nodules during follow-up and underwent repeat FNA. Nodules of 4 patients were still benign during repeat FNA, and the patients continued follow-up US. Two patients had fol-

licular neoplasms or suspicious follicular neoplasms, 3 nodules were suspicious for malignancy, and 2 patients with malignancy on repeat FNA underwent an operation. One of the 7 nodules was confirmed as a follicular adenoma, one was follicular thyroid carcinoma, and the other 5 were confirmed as PTC based on pathology.

No statistically significant differences were observed in mean age, mean size, and US features such as echogenicity and margins between the nodules positive for the *BRAF* V600E mutation and nodules negative for the *BRAF* V600E mutation (Table 1). Statistically significant differences were observed in sex, the number of suspicious US features, and other US features such as calcification and shape between the 2 groups (Table 1).

Five of the 36 thyroid nodules with benign cytology results and positive for the *BRAF* V600E mutation had benign results on surgical pathology (Table 2). Among the patients, 2 nodules were confirmed as nodular goiter with underlying lymphocytic thyroiditis (Fig 3), 2 nodules were nodular goiter, and 1 was a fibrotic nodule with calcification. Three of 5 nodules measured <1 cm, whereas the remaining 2 were >1 cm. Among the patients, 2 had 1 suspicious US feature, 2 had 2 suspicious US features, and 1 had 3 suspicious US features.

DISCUSSION

Sonography is a sensitive available technique that enables clinicians to detect thyroid nodules with their dimensions and sonographic features suggestive of malignancy. According to the 2016 American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi guidelines, the estimated risks of malignancy were 50%–90% for thyroid nodules with highly suspicious US features.²

FNA is currently the reliable nonsurgical approach for the diagnosis of thyroid nodules. However, thyroid FNA is not an accurate test. A review of the lit-

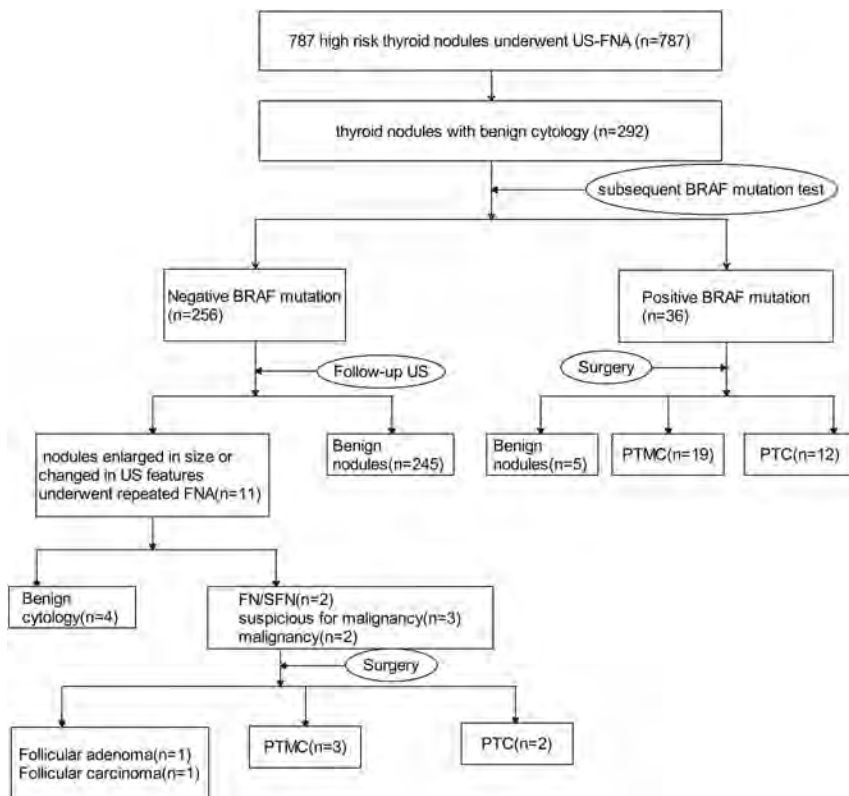


FIG 1. Diagram of the study group. PTMC indicates papillary thyroid microcarcinoma.

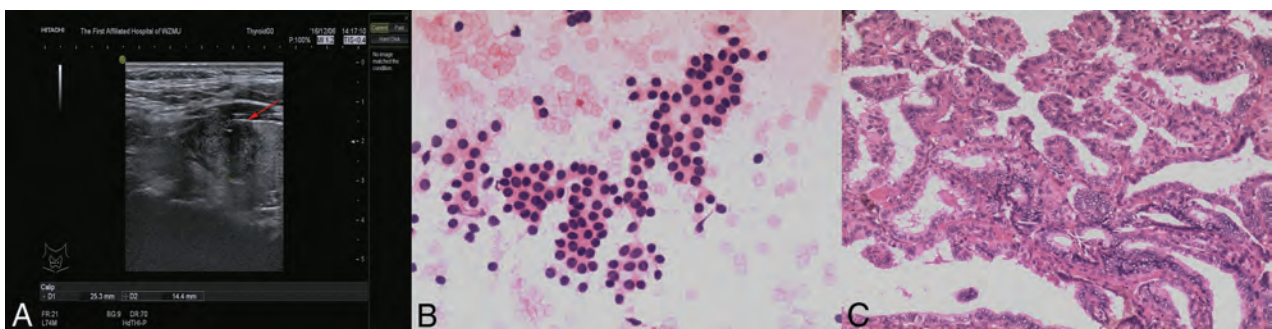


FIG 2. Right thyroid with a palpable lesion in a 20-year-old man. US scan of the right thyroid reveals a 25-mm hypoechoic nodule (arrow) with an irregular margin and microcalcification (A). The cytologic diagnosis from US-FNA is benign (B, HE stain, magnification 4X10) and positive for the *BRAF* V600E mutation. The nodule is confirmed as PTC by surgical pathology (C, HE stain, magnification 10X10).

erature revealed thyroid nodules with overall false-negative rates in FNA (malignant histology of a nodule with benign cytology) that ranged from <1% to 12%.^{13,14} Other studies have observed higher false-negative rates in nodules of ≥ 3 or 4 cm (10%–13% in larger nodules compared with 5%–6% in smaller nodules).^{15,16} By contrast, Shrestha et al¹³ reported that false-negative rates for FNA were 7.0% overall, 15.8% in nodules that ranged between 0.5 and 0.9 cm, 6.3% in nodules that ranged between 1.0 and 3.9 cm, and 7.1% in nodules of ≥ 4.0 cm. Shrestha's study showed a tendency toward a high false-negative rate in subcentimeter nodules. False-negative results complicated the subsequent clinical management of patients. The conventional practice was US monitoring or repeat FNA when a mismatch occurred between radiology and cytology findings.

The *BRAF* V600E mutation is commonly found in PTC. In China, its mutation rate is up to 69%–85.3% in patients with PTC.^{10,17} The *BRAF* V600E mutation analysis has proved valuable and accurate as an adjunctive diagnostic tool on US-FNA in providing additional information in the differential diagnosis of

PTC that shows nondiagnostic or indeterminate cytology results.^{8,18–20} However, what role does the *BRAF* V600E mutation analysis play in thyroid nodules with highly suspicious US features and negative FNA findings? A review of the literature revealed that few studies focused on the role of molecular testing in false-negative FNA results. Proietti et al²¹ reported 54 cases of false-negative cytology results among 1347 PTCs. *BRAF* V600E mutations were found in 6 cases (11%), and *Ras* alterations were present in 16 cases (29.6%). Consequently, the authors suggested that preoperative molecular assessment was valuable for benign nodules. Kim et al²² observed 31 nodules with benign cytology findings and positive for the *BRAF* V600E mutation. Among the cases, 17 underwent thyroidectomy. Fifteen of 17 nodules were malignant, and 2 were benign. However, 14 nodules were not confirmed with resection, and whether the cytology results were false-negative or the *BRAF* V600E mutation results were false-positive was undetermined.

In our prospective study, we observed 292 patients who had high-risk thyroid nodules with benign cytology findings who underwent subsequent *BRAF* V600E mutation testing. Among them, 256 patients had nodules negative for the *BRAF* V600E mutation and 36 patients had nodules positive for the *BRAF* V600E mutation. Thirty-six patients who had nodules with highly suspicious US features and were positive for the *BRAF* V600E mutation underwent thyroidectomy. Nodules of thirty-one of 36 patients were confirmed malignant by surgical pathology, and *BRAF* V600E mutation analysis decreased the false-negative rate of FNA. These results supported the high specificity of the *BRAF* V600E mutation (31/36, 86.1%) in thyroid nodules, and *BRAF* V600E analysis played a role in thyroid nodules that showed highly suspicious US features with benign cytology results. Among the 31 cases confirmed by pathology, 22 (71.0%) cases had ≥ 2 suspicious US features and 9 (29.0%) had 1 suspicious US feature. Follow-up US was performed in 256 patients who had thyroid nodules with benign cytology results and were negative for the *BRAF* V600E mutation. During the follow-up, 11 patients had enlarged nodules and underwent repeat FNA. Nodules of 4 patients were still benign on repeat FNA, and the 7 remaining patients underwent an operation, in which 2 nodules were follicular neoplasm or suspicious follicular neoplasm, 3 were suspicious for malignancy, and 2 were malignant on repeat FNA. One of the 7 nodules was confirmed as follicular adenoma, 1 was follicular thyroid carcinoma, and the other 5 were confirmed as PTC on the basis of pathology. On the basis of our results, we recommended diagnostic lobectomy in the management of thyroid nodules that showed highly suspicious US features, especially for a nodule with ≥ 2 suspicious US features with benign cytology results but positive for the *BRAF* V600E mutation. However, we determined that results negative for the *BRAF* V600E mutation

Table 1: Clinical and US features and characteristics of thyroid nodules with benign cytology

	Positive for <i>BRAF</i> V600E Mutation	Negative for <i>BRAF</i> V600E Mutation	P
No. of nodules	36	256	
Diagnosis			<.001
Malignant	31	6	
Benign	5	250	
Age (mean) (yr)	44.7 $\pm$ 11.3	47.3 $\pm$ 13.9	.31
Sex			<.001
F	2	229	
M	10	27	
Mean size of nodules (mm)	9.4 $\pm$ 3.7	11.8 $\pm$ 4.1	.41
5–10	23	145	
>10	13	112	
No. of suspicious US features			<.001
1	11	243	
2	17	12	
3	7	1	
4	1	0	
Echogenicity			.11
Hyper- or isoechoic	1	15	
Hypoechoic	30	229	
Marked hypoechoic	5	12	
Margin			.18
Circumscribed	15	137	
Not circumscribed	21	119	
Calcification			<.001
No calcifications	12	161	
Microcalcification	21	72	
Macrocalcification	3	23	
Shape			<.01
Parallel	16	167	
Taller-than-wide	20	89	
Evidence of extrathyroidal growth	0	0	
Pathologic adenopathy	2	0	

Table 2: Demographics of 5 patients whose nodules had benign cytology results and were positive for the *BRAF* V600E mutation

No.	Age (yr)	Sex	No. of Suspicious US Features	Size of the Nodules (mm)	Pathology Results
1	48	F	1	5.3	Nodule goiter
2	39	F	2	11	Fibrotic nodule with calcification
3	45	M	2	9	Nodule goiter
4	45	M	1	6	Nodule goiter with underlying lymphocytic thyroiditis
5	69	F	3	13	Nodule goiter with underlying lymphocytic thyroiditis

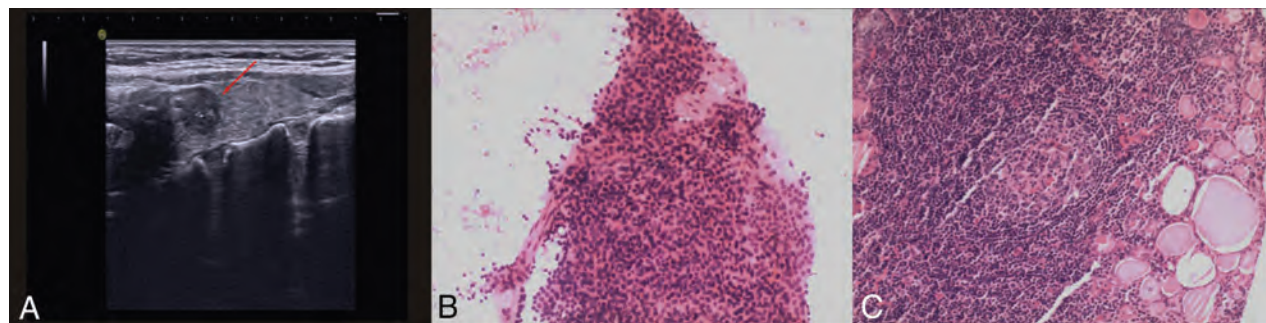


FIG 3. An incidentally found nodule in a 69-year-old woman during US screening. US scans reveal a 13-mm hypoechoic nodule (arrow) with microcalcification in the right thyroid (A). The cytologic diagnosis from US-FNA is benign (B, HE stain, magnification 4X10) and positive for the *BRAF* V600E mutation using direct DNA sequencing. The nodule is confirmed as a nodular goiter with underlying lymphocytic thyroiditis (C, HE stain, magnification 10X10).

did not rule out malignancy with benign cytology results. Five cases of PTC and 1 follicular thyroid carcinoma were missed by FNA and *BRAF* V600E mutation tests.

In our institution, *BRAF* V600E mutation analysis was performed using ADx-ARMS, which is a real-time PCR. Real-time PCR was more sensitive than traditional methods such as DNA sequencing and pyrosequencing because real-time PCR detected the *BRAF* V600E mutation in a small amount of mutant DNA.^{23–25} High-sensitivity ADx-ARMS method suggested its diagnostic significance for detecting the *BRAF* V600E mutation in thyroid samples. Studies of highly sensitive diagnostic methods for detecting the *BRAF* V600E mutation have rarely reported false-positive mutations in the literature. Kim et al¹⁹ reported 5 false-positive cases in 2010, and DiLorenzo et al²⁶ reported 1 false-positive case. The 2 studies stated that the sensitive *BRAF* V600E molecular testing using dual priming oligonucleotide–based multiplex PCR was the cause of the false-positive results. Kim et al²³ also compared real-time PCR and pyrosequencing for the detection of the *BRAF* V600E mutation in FNA; 6 false-positive cases were detected by real-time PCR, whereas 4 false-positive cases were detected by pyrosequencing. We also observed 5 false-positive cases among the 36 nodules treated by thyroidectomy. Two were confirmed as nodular goiter with underlying lymphocytic thyroiditis, 2 were nodular goiter, and 1 was a fibrotic nodule with calcification by surgical pathology.

CONCLUSIONS

The *BRAF* V600E mutation test detected PTC missed by FNA. We recommend that fine-needle aspiration be routinely accompanied by *BRAF* V600E mutation testing in high-risk thyroid nodules with ≥ 2 suspicious US features. The combination of *BRAF* V600E mutation testing and cytologic diagnosis improved the sensitivity and accuracy of detection.

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REFERENCES

- Sipos JA. Advances in ultrasound for the diagnosis and management of thyroid cancer. *Thyroid* 2009;19:1363–72 [CrossRef Medline](#)
- Gharib H, Papini E, Garber JR, et al; AACE/ACE/AME Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules: 2016 Update. *Endocr Pract* 2016;22:622–39 [CrossRef Medline](#)
- Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management. *Thyroid* 2016;26:1–133 [CrossRef Medline](#)
- Yoon JH, Moon HJ, Kim E-K, et al. Inadequate cytology in thyroid nodules: should we repeat aspiration or follow-up? *Ann Surg Oncol* 2011;18:1282–89 [CrossRef Medline](#)
- Yoon JH, Kim EK, Moon HJ, et al. Is follow-up *BRAF*(V600E) mutation analysis helpful in the differential diagnosis of thyroid nodules with negative results on initial analysis? *PLoS One* 2013;8:e58592 [CrossRef Medline](#)
- Moon HJ, Son E, Kim EK, et al. The diagnostic values of ultrasound and ultrasound-guided fine needle aspiration in subcentimeter-sized thyroid nodules. *Ann Surg Oncol* 2012;19:52–59 [CrossRef Medline](#)
- Kim SK, Hwang TS, Yoo YB, et al. Surgical results of thyroid nodules according to a management guideline based on the *BRAF*(V600E) mutation status. *J Clin Endocrinol Metab* 2011;96:658–64 [CrossRef Medline](#)
- Moon HJ, Kim E-K, Chung WY, et al. Diagnostic value of *BRAF*(V600E) mutation analysis of thyroid nodules according to ultrasonographic features and the time of aspiration. *Ann Surg Oncol* 2011;18:792–99 [CrossRef Medline](#)
- Koh J, Choi JR, Han KH, et al. Proper indication of *BRAF*(V600E) mutation testing in fine-needle aspirates of thyroid nodules. *PLoS One* 2013;8:e64505 [CrossRef Medline](#)
- Zhang Y, Xu T, Cui D, et al. Value of TIRADS, BSRTC and FNA-*BRAF* V600E mutation analysis in differentiating high-risk thyroid nodules. *Sci Rep* 2015;5:16927 [CrossRef Medline](#)
- Lew JI, Snyder RA, Sanchez YM, et al. Fine needle aspiration of the thyroid: correlation with final histopathology in a surgical series of 797 patients. *J Am Coll Surg* 2011;213:188–94; discussion 194–95 [CrossRef Medline](#)
- Yeh MW, Demircan O, Ituarte P, et al. False-negative fine-needle aspiration cytology results delay treatment and adversely affect outcome in patients with thyroid carcinoma. *Thyroid* 2004;14:207–15 [CrossRef Medline](#)
- Shrestha M, Crothers BA, Burch HB. The impact of thyroid nodule size on the risk of malignancy and accuracy of fine-needle aspiration: a 10-year study from a single institution. *Thyroid* 2012;22:1251–56 [CrossRef Medline](#)
- Cavallo A, Johnson DN, White MG, et al. Thyroid nodule size at ultrasound as a predictor of malignancy and final pathologic size. *Thyroid* 2017;27:641–50 [CrossRef Medline](#)
- McCoy KL, Jabbour N, Ogilvie JB, et al. The incidence of cancer and rate of false-negative cytology in thyroid nodules greater than or

- equal to 4 cm in size. *Surgery* 2007;142:837–44; discussion 844.e1–3 [CrossRef Medline](#)
16. Agcaoglu O, Aksakal N, Ozcinar B, et al. **Factors that affect the false-negative outcomes of fine-needle aspiration biopsy in thyroid nodules.** *Int J Endocrinol* 2013;2013:126084 [CrossRef Medline](#)
 17. Lu ZZ, Zhang Y, Wei SF, et al. **Outcome of papillary thyroid microcarcinoma: study of 1,990 cases.** *Mol Clin Oncol* 2015;3:672–76 [CrossRef Medline](#)
 18. Cohen Y, Rosenbaum E, Clark DP, et al. **Mutational analysis of BRAF in fine needle aspiration biopsies of the thyroid: a potential application for the preoperative assessment of thyroid nodules.** *Clin Cancer Res* 2004;10:2761–65 [CrossRef Medline](#)
 19. Kim SW, Lee JI, Kim JW, et al. **BRAFV600E mutation analysis in fine-needle aspiration cytology specimens for evaluation of thyroid nodule: a large series in a BRAFV600E-prevalent population.** *J Clin Endocrinol Metab* 2010;95:3693–700 [CrossRef Medline](#)
 20. Xing M, Tufano RP, Tufaro AP, et al. **Detection of BRAF mutation on fine needle aspiration biopsy specimens: a new diagnostic tool for papillary thyroid cancer.** *J Clin Endocrinol Metab* 2004;89:2867–72 [CrossRef Medline](#)
 21. Proietti A, Borrelli N, Giannini R, et al. **Molecular characterization of 54 cases of false-negative fine-needle aspiration among 1347 papillary thyroid carcinomas.** *Cancer Cytopathol* 2014;122:751–59 [CrossRef Medline](#)
 22. Kim SY, Kim EK, Kwak JY, et al. **What to do with thyroid nodules showing benign cytology and BRAF(V600E) mutation? A study based on clinical and radiologic features using a highly sensitive analytic method.** *Surgery* 2015;157:354–61 [CrossRef Medline](#)
 23. Kim WY, Kim H, Hwang TS. **Comparison between real-time PCR and pyrosequencing for detection of BRAF V600E mutation in thyroid fine-needle aspirates.** *Appl Immunohistochem Mol Morphol* 2017;25:358–65 [CrossRef Medline](#)
 24. Ellison G, Donald E, McWalter G, et al. **A comparison of ARMS and DNA sequencing for mutation analysis in clinical biopsy samples.** *J Exp Clin Cancer Res* 2010;29:132 [CrossRef Medline](#)
 25. Huang T, Zhuge J, Zhang WW. **Sensitive detection of BRAF V600E mutation by Amplification Refractory Mutation System (ARMS)-PCR.** *Biomarker Res* 2013;1:3 [CrossRef Medline](#)
 26. DiLorenzo M, Miller J, Tuluc M, et al. **False-positive FNA due to highly sensitive BRAF assay.** *Endocr Pract* 2014;20:e8–10 [CrossRef Medline](#)

Imaging and Surgical Findings in Patients with Hemi-Laryngopharyngeal Spasm and the Potential Role of MRI in the Diagnostic Work-Up

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ABSTRACT

BACKGROUND AND PURPOSE: Hemi-laryngopharyngeal spasm is a recently discovered condition characterized by episodic coughing and unilateral throat contractions that may lead to severe stridor. These symptoms are caused by a vascular compression of the ipsilateral vagus nerve, typically the PICA. Microvascular decompression of the vagus nerve has been demonstrated to be a potential cure for this neurovascular compression syndrome. The main aim of this study was to clarify the role of MR imaging in the diagnostic work-up of this rare condition.

MATERIALS AND METHODS: We describe the imaging and surgical findings of 3 patients from our prospective case series of patients with hemi-laryngopharyngeal spasm from 2015 to 2017. Second, the imaging data of 100 patients (control cohort) with symptoms unrelated to hemi-laryngopharyngeal spasm were reviewed to investigate the rate and degree of neurovascular conflict of the vagus nerve.

RESULTS: All patients with hemi-laryngopharyngeal spasm reported to date have had vascular compression of the vagus nerve due to the PICA. In the control cohort, there was a good interrater agreement in scoring the “contact” and “compression” of the vagus nerve ($\kappa = 0.73$, $P = < .001$). The frequency of contact or compression of the vagus nerve was approximately 50%. The PICA was the most frequent vessel involved in 74%.

CONCLUSIONS: The presence of unilateral neurovascular contact or compression of the vagus nerve does not confirm the diagnosis of hemi-laryngopharyngeal spasm. The MR imaging finding of ipsilateral vascular compression of the vagus nerve is a necessary but not sufficient finding for the diagnosis of hemi-laryngopharyngeal spasm.

ABBREVIATIONS: HELPS = hemi-laryngopharyngeal spasm; MVD = microvascular decompression

Hemi-laryngopharyngeal spasm (HELPS) is a recently discovered condition characterized by episodic coughing and unilateral throat contractions that may lead to severe stridor. These symptoms are caused by a vascular compression of the ipsilateral vagus nerve, typically by the tonsillomedullary segment of the PICA. Similar to hemifacial spasm, the motor component of HELPS (ipsilateral pharyngeal or laryngeal contractions) does not respond to medications but can be ameliorated with ipsilateral botulinum toxin. Microvascular decompression (MVD) of the vagus nerve has been demonstrated to be a potential cure for this neurovascular compression syndrome.^{1,2} The diagnosis of the

more common neurovascular compression syndromes, such as trigeminal neuralgia, glossopharyngeal neuralgia, and hemifacial spasm, often relies on MR imaging of the brain with a 3D balanced steady-state gradient-echo sequence to demonstrate the cranial nerve anatomy and the offending compressing vessel. Many studies have reported a surprisingly high incidence of neurovascular compression of the trigeminal and facial nerves in asymptomatic patients.^{3–5} There is currently no information about the incidence of vascular compression of the vagus nerve, to our knowledge. As HELPS begins to be more widely recognized, we sought to clarify the role of MR imaging in its diagnosis. The aims of this study were the following: 1) to correlate the imaging and surgical findings of patients with HELPS, 2) to estimate the incidence of neurovascular conflict of the vagus nerve in the general population, and 3) to clarify the role of MR imaging in the diagnostic work-up of this rare condition.

MATERIALS AND METHODS

The clinical research ethics board of the University of British Columbia approved this study (H17–03466). First, we describe the

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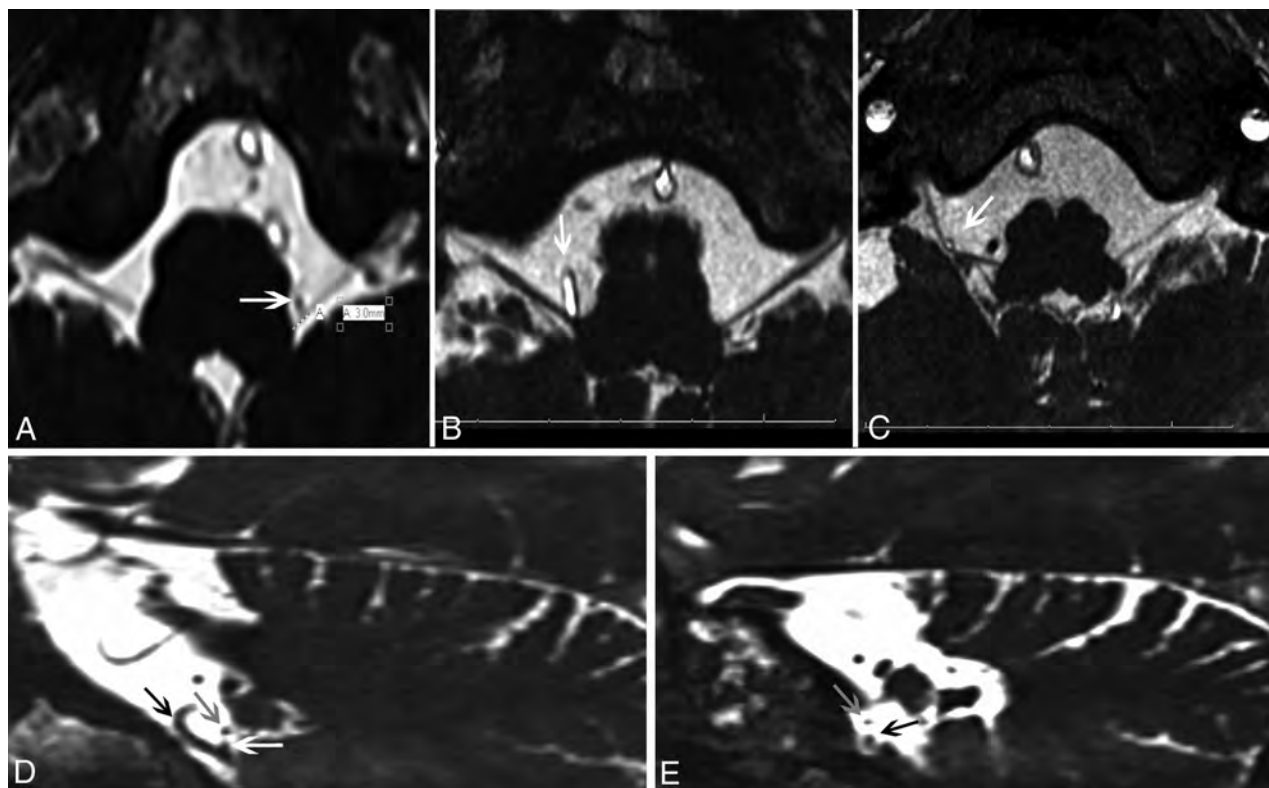


FIG 1. Grading system. The vagus nerve was rated separately for the proximal (3 mm from the brain stem) and the distal portions. A, Grade I: “no vessel contact” (white arrow). B, Grade II: “contact,” which was defined as no visible CSF between the blood vessel and the nerve but no displacement of the normal trajectory of the nerve (white arrow). C, Grade III: “compression,” which was defined as displacement of the normal trajectory of the nerve (white arrow). D, Grade I: Oblique projection showing the vagus nerve (white arrow) in contact with the PICA (black arrow). The glossopharyngeal nerve (gray arrow) is shown above the vagus nerve. E, Oblique projection of the IX/X complex close to the jugular foramen. It was possible to see the upper glossopharyngeal nerve more anteriorly and superiorly moving lateral into the foramen, and the vagus nerve branches were below this.

imaging and surgical findings of 3 patients from our prospective case series of patients with HELPS from 2015 to 2017. The full clinical description of 3 of these patients has been recently published.² These patients were effectively treated with unilateral MVD of the vagus nerve. Second, the imaging data of 100 patients (control cohort) with symptoms unrelated to HELPS were reviewed to investigate the rate and degree of neurovascular conflict of the vagus nerve. These patients (48 men and 52 women) ranged from 24 to 91 years of age and had undergone 1.5T MR imaging of the cerebellopontine angle cisterns with a 3D balanced steady-state gradient-echo sequence (or FIESTA) during 2017 for the following symptoms: tinnitus, headache, isolated facial contractions not consistent with hemifacial spasm, and facial pain not consistent with trigeminal or glossopharyngeal neuralgia. The inclusion criteria for this control cohort of 100 consecutive patients were those with a 3D-CISS or FIESTA sequence on MR imaging with clear visualization of the cerebellomedullary region, no evidence of tumor or vascular malformations, no history of head trauma or surgical procedures in the posterior fossa, and no signs on the FLAIR sequence of multiple sclerosis or other inflammatory or demyelinating conditions.

Neurovascular Conflict Assessment

Posterior fossa images were acquired on a 1.5T platform using a 3D balanced steady-state gradient-echo sequence. The voxel size

was 0.4 mm, the slice thickness was 0.5 mm with no gap or overlap, and slice interpolation was used in the z-axis. TE and TR were approximately 2.73 and 5.94 ms, respectively. Two researchers (M.G.K., J.A.-C.) evaluated and rated 200 vagus nerves looking for the presence and degree of neurovascular conflict. The grading scale was as follows: grade 1, “no vessel contact”; grade 2, “contact,” which was defined as no visible CSF between the blood vessel and the nerve but no displacement of the normal trajectory of the nerve; and grade 3, “compression,” which was defined as displacement of the normal trajectory of the nerve (Fig 1A–D).^{6,7} The rating was performed separately for the transitional zone of the vagus nerve (within 3 mm from the brain stem) and the cisternal portion of the nerve (henceforth referred to as the proximal and distal portions of the nerve, respectively).^{8,9} The vagus nerve was evaluated along its entire course from the brain stem to the jugular foramen in oblique, axial, and coronal planes. The glossopharyngeal nerve could be identified as the most anterior and superior nerve in the jugular foramen, with the vagus nerve inferior (or caudal) to it (Fig 1E). In a small number of patients (~5%), it was not possible to visualize these nerves as separate entities. When this issue occurred, they were evaluated as an IX/X complex. In patients with “contact” or “compression,” we recorded the offending vessel and its direction of compression against the vagus nerve. We also simultaneously graded the neurovascular conflict of the trigeminal nerve to determine its rate of

Clinical and demographic data of our patients with HELPS

Patient No.	Age/Sex	Symptoms	Offending Vessel	Grading of NVC
1	65/M	Episodic throat contractions and coughing	Left PICA	2
2	43/F	Episodic throat contractions, coughing, and vocal changes	Right PICA	3
3	32/F	Episodic left-sided throat contractions, choking, and vocal changes	Left PICA	2

Note:—NVC indicates neurovascular conflict.

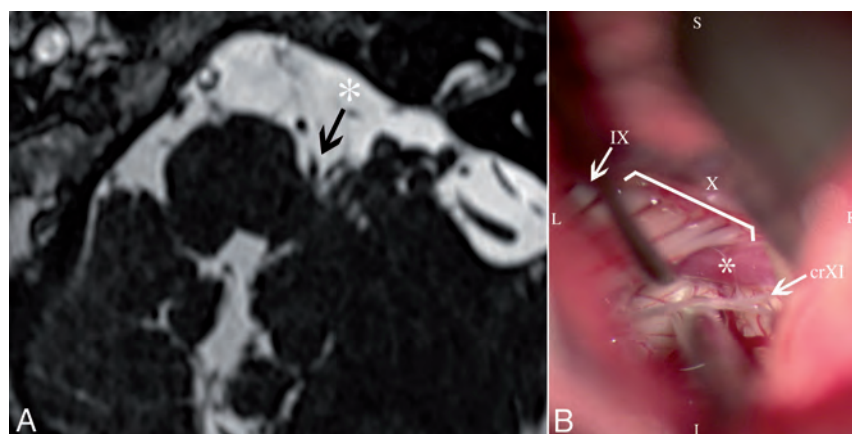


FIG 2. Patient 1. *A*, MR imaging shows neurovascular conflict of the PICA (arrow) with the proximal part of the vagus nerve. *B*, Intraoperative findings show the loop of the PICA (asterisk) pulsating against the caudal rootlets of the vagus nerve (X). IX indicates glossopharyngeal nerve; crXI, cranial root of the accessory nerve; S, superior; I, inferior; R, right; L, left.

contact/compression as a control to compare our cohort with the other patient groups previously reported in the literature.

Statistical Analysis

The frequencies for each grade of compression, the offending vessel, and the direction of compression were calculated. The Cohen κ coefficient was calculated to determine the level of interrater agreement. A κ value < 0.4 was considered poor agreement, between 0.40 and 0.59 was a fair agreement, between 0.60 and 0.74 was a good agreement, and ≥ 0.75 was excellent agreement. We used the SPSS software package 22.0 (IBM, Armonk, New York), and a P value $< .05$ was considered significant.

RESULTS

All patients with HELPS reported to date have had vascular compression of the vagus nerve due to the PICA. The clinical and demographic data of 3 patients are presented in the Table, and their surgical and imaging findings are demonstrated in Figs 2–4. In the control cohort, there was good interrater agreement in scoring the contact and compression of the vagus nerve ($\kappa = 0.73$, $P = < .001$). The proximal portion of the left vagus nerve had 10% contact and 11% compression, and the right side had 10% contact and 1% compression. The distal portion of the left vagus nerve had 16% contact and 16% compression, and the right side had 20% contact and 15% compression. The total frequency of contact or compression for the entire left or right vagus nerve was therefore approximately 50%. The vessel in contact or compressing the vagus nerve was the PICA in 74%, the AICA in 14%, the vertebral artery in 6%, and a vein in 6%. The direction of the contact/compression relative to the nerve was from anterior in

52%, posterior in 24%, inferior in 13%, and superior in 11%. There was excellent interrater agreement in scoring the neurovascular conflict of the trigeminal nerve ($\kappa = 0.83$, $P = < .001$). There was 54% (grade 2, 44%; grade 3, 10%) contact or compression of the left trigeminal nerve and 52% (grade 2, 42%; grade 3, 10%) of the right trigeminal nerve.

DISCUSSION

Patients with hemi-laryngopharyngeal spasm have unilateral neurovascular compression of the vagus nerve. In all our patients, the offending vessel was the PICA and patients were cured following MVD. The 3 examples presented in this study showed neurovascular conflict caused by a PICA loop impacting the vagus nerve from inferior and anterior. Two patients had vascular contact with the proximal portion of the vagus nerve, and 1 had contact with the distal portion of the nerve. According to the grading system used in this study, 2 patients presented with contact, and 1 patient, with compression of the vagus nerve. In this study, we also report that asymptomatic

or incidental vascular contact or compression of the vagus nerve was common in our control cohort ($\sim 50\%$). We also noted that identification of neurovascular conflict of the vagus nerve is more difficult than for the trigeminal or facial nerve because the vagus nerve rootlets can be in close relationship with the cerebellar tonsil for a variable length of its trajectory. The degree of contrast between the vagus nerve rootlets and the tonsil is much less than between the trigeminal nerve and the CSF.

Three of the first 4 patients successfully treated for HELPS had unilateral compression of the vagus nerve primarily involving the more caudal rootlets.^{1,2} Compression of the rostral rootlets is likely possible, but because of the close proximity of the glossopharyngeal nerve, the resulting clinical presentation is likely to be a combination of painful glossopharyngeal neuralgia and HELPS. We have treated 1 such patient (Prof Christopher Honey Presentation: ESSFN 2018 Oral presentation, September 27, 2018, unpublished results) who had unilateral vagus and glossopharyngeal nerve compression from anterorostrally.

We dichotomized the location of the vagus nerve contact or compression into proximal and distal at 3 mm from the brain stem. Guclu et al⁹ reported that the transitional zone of the vagus nerve can vary between 0.45 and 4.2 mm. Our experience with trigeminal neuralgia led us to believe that the vagus nerve could be pathologically affected by a vessel anywhere along its course, but the degree of contact/compression required may be much less where the nerve is tethered proximally. The number of affected patients is too small to comment on this feature, but the data will be available for future analysis. The vagus nerve emerges at the retro-olivary groove in the medulla as several rootlets that ulti-

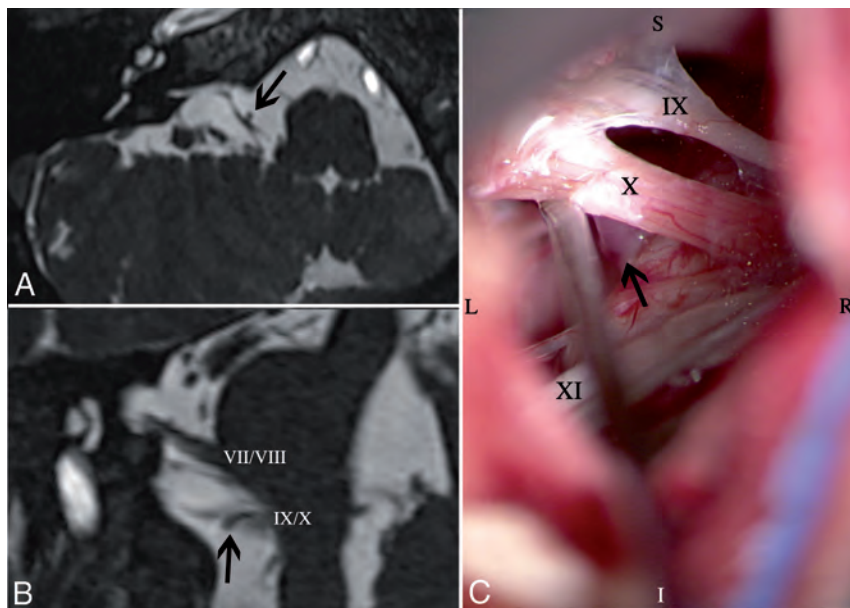


FIG 3. Patient 2. A, Axial view of MR imaging shows compression of the vagus nerve by the right PICA from the anterior direction (arrow). B, The coronal-oblique plane shows the vessel loop of the PICA (arrow). VII/VIII indicates the facial and vestibulocochlear nerve complex; IX/X, the glossopharyngeal and vagus nerve complex. C, Intraoperative findings confirm that the vessel loop of the PICA (arrow) is pulsating against the anterior aspect of the vagus nerve (X). IX indicates the glossopharyngeal nerve; XI, the accessory nerve; S, superior; I, inferior; R, right; L, left.

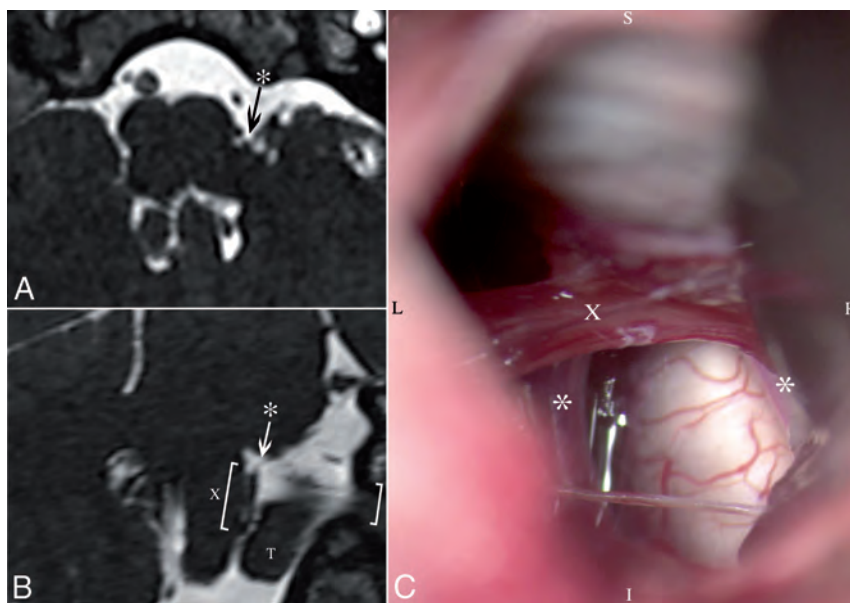


FIG 4. Case 3. A, Axial view of MR imaging shows neurovascular conflict of the left PICA (asterisk) and the vagus nerve. B, The coronal-oblique plane shows the loop of the left PICA (asterisk) in contact with the proximal part of the rootlets of the vagus nerve (X), which is also in contact with the left cerebellar tonsil (T). C, Intraoperative findings. After gentle retraction of the cerebellum and part of the left tonsil, the left PICA loop (asterisk) is found in contact with the proximal part of the vagus nerve (X). S indicates superior; I, inferior; R, right; L, left.

mately enter the jugular foramen after a cisternal trajectory. The proximal portion of the nerve is in close proximity with the tonsil and is therefore poorly visualized with standard MR imaging.¹⁰ 3T MR imaging may be able to delineate the vagus nerve better because of its high signal-to-noise ratio.¹¹ Another challenge with the current MR imaging protocols for detecting neurovascular

compression is their lack of dynamic information. A vessel loop with its convex apex contacting a nerve will pulsate against it with every heartbeat, while another with its apex directed away from the nerve will not. Both would be reported as “contact” in this and other studies. It remains to be seen whether new dynamic or cine MR imaging sequences will clarify neurovascular compression as they have clarified the dynamics of spinal cord syrinx. There will always be a patient-specific nerve vulnerability to vascular compression that may partially explain why few patients develop symptoms despite the high incidence of neurovascular compression. Our control cohort had approximately 50% of patients with contact or compression of the trigeminal nerve. This was within the range of the previously reported studies by Antonini et al (17%),¹² Chun-Cheng et al (32%),⁵ and Peker et al (87.5%).⁴ Although our control cohort was being imaged because of unexplained neurologic symptoms, these subjects probably reflect the incidence of vascular contact/compression of the vagus nerve in the general population.

During the past 20 years, our center has evaluated >1500 patients with trigeminal neuralgia and hemifacial spasm. MR imaging plays an important role in their surgical evaluation. Once the diagnosis is confirmed by history and physical examination, the presence of arterial compression of the appropriate nerve triggers a discussion of MVD with the patient. It also provides critical information for the surgeon to plan the procedure and anticipate the intraoperative findings. Absence of compression halts the consideration of MVD because there is nothing to decompress. The MR imaging documentation of neurovascular compression is therefore a necessary but not sufficient finding to justify MVD of the nerve. We believe the MR imaging investigation of patients with HELPS will be similar. The high incidence of asymptomatic vascular contact/compression of the vagus nerve (~50%)

means that its presence cannot be used as a definitive test for this condition. The absence of a contact/compression, however, can be used to rule out the condition.

Limitations of our study include the small number of patients with HELPS; the simplicity of our rating scheme not distinguishing different degrees of compression, including possible dis-

tortion or atrophy of the nerve; and the study being performed on a 1.5T MR imaging platform, rather than at 3T (which may have allowed better vessel-to-nerve characterization).

CONCLUSIONS

Clinicians should be aware that the presence of unilateral neurovascular contact or compression of the vagus nerve does not confirm the diagnosis of HELPS because 50% of the general population may have such a finding. An accurate clinical history with a unilateral beneficial response to botulinum toxin in the vocal fold and ipsilateral vascular contact/compression of the vagus nerve should prompt a discussion about MVD. The MR imaging finding of ipsilateral vascular compression of the vagus nerve is therefore a necessary but not sufficient finding for the diagnosis of this rare condition.

REFERENCES

1. Honey CR, Gooderham P, Morrison M, et al. **Episodic hemilaryngopharyngeal spasm (HELPS) syndrome: case report of a surgically treatable novel neuropathy.** *J Neurosurg* 2017;126:1653–56 CrossRef Medline
2. Honey CR, Morrison M, Heran MKS, et al. **Hemi-laryngopharyngeal spasm (HELPS): a novel cause of inducible laryngeal obstruction with a surgical cure.** *J Neurosurg* 2018 Jul 20:1–5. [Epub ahead of print] CrossRef Medline
3. Suzuki M, Yoshino N, Shimada M, et al. **Trigeminal neuralgia: differences in magnetic resonance imaging characteristics of neurovascular compression between symptomatic and asymptomatic nerves.** *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015;119:113–18 CrossRef Medline
4. Peker S, Dinçer A, Necmettin Pamir M. **Vascular compression of the trigeminal nerve is a frequent finding in asymptomatic individuals: 3-T MR imaging of 200 trigeminal nerves using 3D CISS sequences.** *Acta Neurochir (Wien)* 2009;151:1081–88 CrossRef Medline
5. Chun-Cheng Q, Qing-Shi Z, Ji-Qing Z, et al. **A single-blinded pilot study assessing neurovascular contact by using high-resolution MR imaging in patients with trigeminal neuralgia.** *Eur J Radiol* 2009;69:459–63 CrossRef Medline
6. Leal PR, Hermier M, Froment JC, et al. **Preoperative demonstration of the neurovascular compression characteristics with special emphasis on the degree of compression, using high-resolution magnetic resonance imaging: a prospective study, with comparison to surgical findings, in 100 consecutive patients who underwent microvascular decompression for trigeminal neuralgia.** *Acta Neurochir (Wien)* 2010;152:817–25 CrossRef Medline
7. Zhou Q, Liu ZL, Qu CC, et al. **Preoperative demonstration of neurovascular relationship in trigeminal neuralgia by using 3D FIESTA sequence.** *Magn Reson Imaging* 2012;30:666–71 CrossRef Medline
8. Słoniewski P, Korejwo G, Zieliński P, et al. **Measurements of the Obersteiner-Redlich zone of the vagus nerve and their possible clinical applications.** *Folia Morphol (Warsz)* 1999;58:37–41 Medline
9. Guclu B, Sindou M, Meyronet D, et al. **Cranial nerve vascular compression syndromes of the trigeminal, facial and vago-glossopharyngeal nerves: comparative anatomical study of the central myelin portion and transitional zone—correlations with incidences of corresponding hyperactive dysfunctional syndromes.** *Acta Neurochir (Wien)* 2011;153:2365–75 CrossRef Medline
10. Sarrazin JL, Toulgoat F, Benoudiba F. **The lower cranial nerves: IX, X, XI, XII.** *Diagn Interv Imaging* 2013;94:1051–62 CrossRef Medline
11. Garcia M, Naraghi R, Zumbunn T, et al. **High-resolution 3D-constructive interference in steady-state MR imaging and 3D time-of-flight MR angiography in neurovascular compression: a comparison between 3T and 1.5T.** *AJNR Am J Neuroradiol* 2012;33:1251–56 CrossRef Medline
12. Antonini G, Di Pasquale A, Cruccu G, et al. **Magnetic resonance imaging contribution for diagnosing symptomatic neurovascular contact in classical trigeminal neuralgia: a blinded case-control study and meta-analysis.** *Pain* 2014;155:1464–71 CrossRef Medline

MRI, Magnetoencephalography, and Surgical Outcome of Oligodendrocytosis versus Focal Cortical Dysplasia Type I

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ABSTRACT

BACKGROUND AND PURPOSE: Abnormalities of oligodendrocytes have been reported in surgical specimens of patients with medically intractable epilepsy. The aim of this study was to compare the MR imaging, magnetoencephalography, and surgical outcome of children with oligodendrocytosis relative to focal cortical dysplasia I.

MATERIALS AND METHODS: Oligodendrocytosis included oligodendroglial hyperplasia, oligodendrogliosis, and oligodendroglial-like cells in the white matter, gray matter, or both from children with medically intractable epilepsy. Focal cortical dysplasia I included radial and tangential cortical dyslamination. The MR imaging, magnetoencephalography, type of operation, location, and seizure outcome of oligodendrocytosis, focal cortical dysplasia I, and oligodendrocytosis + focal cortical dysplasia I were compared.

RESULTS: Eighteen subjects (39.1%) had oligodendrocytosis, 21 (45.7%) had focal cortical dysplasia I, and 7 (15.2%) had oligodendrocytosis + focal cortical dysplasia I. There were no significant differences in the type of seizures, focal or nonfocal epileptiform discharges, magnetoencephalography, and MR imaging features, including high T1 signal in the cortex, high T2/FLAIR signal in the cortex or subcortical white matter, increased cortical thickness, blurring of the gray-white junction, or abnormal sulcation and gyration among those with oligodendrocytosis, focal cortical dysplasia I, or oligodendrocytosis + focal cortical dysplasia I ($P > .01$). There were no significant differences in the extent of resection (unilobar versus multilobar versus hemispherectomy), location of the operation (temporal versus extratemporal versus both), or seizure-free outcome of oligodendrocytosis, focal cortical dysplasia I, and oligodendrocytosis + focal cortical dysplasia I ($P > .05$).

CONCLUSIONS: Oligodendrocytosis shared MR imaging and magnetoencephalography features with focal cortical dysplasia I, and multilobar resection was frequently required to achieve seizure freedom. In 15% of cases, concurrent oligodendrocytosis and focal cortical dysplasia I were identified. The findings suggest that oligodendrocytosis may represent a mild spectrum of malformations of cortical development.

ABBREVIATIONS: EEG = electroencephalography; FCD = focal cortical dysplasia; ILAE = International League Against Epilepsy; MEG = magnetoencephalography; MEGSS = MEG spike sources; MOGHE = mild malformation of cortical development with oligodendroglial hyperplasia; PD = proton density; ST = slice thickness

Malformations of cortical development, including focal cortical dysplasia (FCD), are one of the most commonly encountered pathologic substrates in children with medically refractory epilepsy.^{1,2} White matter abnormalities including heterotopic

neurons, hypomyelination, and gliosis have been reported in patients with focal epilepsy, including epilepsy secondary to FCD.^{3,4} Oligodendrocytes are the myelinating cells of the central nervous system. Abnormalities of oligodendrocytes have been reported in surgical specimens of patients with medically intractable epilepsy, but without evidence of cortical dyslamination—that is, without evidence of FCD.^{5–11} As part of our institutional clinical epilepsy case conference and pathology review following an operation, we have noted reports of oligodendroglial hyperplasia, oligodendrogliosis, and oligodendroglial-like cells in the white matter and, in some cases, gray matter, which we collectively referred to as “oligodendrocytosis.” These cases frequently have white matter signal abnormality on MR imaging, a feature also seen in FCD type I.¹² As yet, it is not known whether there are clinical or imaging features that could distinguish oligodendrocytosis from FCD type I and whether surgical outcomes differ between these 2 entities. There are several studies that have focused mainly on the histopathologic findings of oligodendrocytosis,^{6,9,11}

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but a dearth of studies has systematically compared the presurgical investigations and outcomes of oligodendrocytosis with FCD I. The aim of this study was to compare the MR imaging, magnetoencephalography (MEG), and surgical outcome of oligodendrocytosis relative to FCD I in children with medically intractable epilepsy.

MATERIALS AND METHODS

Patients

This retrospective study had the approval of the research ethics board from The Hospital for Sick Children. All consecutive children who underwent an epilepsy operation from January 2001 to November 2016 and who had a histologic diagnosis of oligodendrocytosis and/or FCD I were retrospectively identified from the epilepsy surgery data base at our institution.

Histopathology

The surgical specimens were fixed in formalin and serially sectioned tangential to the surface of the cortex. Five-micrometer paraffin sections were stained with hematoxylin-eosin/Luxol fast blue, Periodic Acid Schiff, and Periodic Acid Schiff–diastase. For immunohistochemistry, 5- μ m sections were cut from paraffin blocks and mounted on positively charged slides. Immunodetection was performed with the automated BenchMark XT stainer (Ventana, Tucson, Arizona) using the ultraView Universal DAB Detection kit (Ventana). Slides were counterstained with the Hematoxylin II kit (Ventana). Anti-Olig2 antibody (diluted 1:200, Catalog No. AB9610; Millipore, Temecula, California) was used to identify oligodendrocytosis. Olig2 is strongly expressed in oligodendrocyte precursor cells/progenitors and weakly expressed in mature oligodendrocytes. Immunohistochemical staining of the neuronal nuclear antigen (NeuN, 1:2000; Chemicon, Temecula, California) and glial fibrillary acidic protein (GFAP, 1:2000; DakoCytomatin, Glostrup, Denmark) was also performed to distinguish neuronal cells and GFAP-positive astrocytic gliosis from oligodendrocytosis. The histology was assessed by a pediatric neuropathologist. A histologic diagnosis of oligodendrocytosis was confirmed if there was an increased population of cells with round nuclei and a scant amount of cytoplasm in the white matter, with or without gray matter involvement (Fig 1).¹¹

The histologic diagnosis of FCD I was confirmed if there was abnormal radial and/or tangential cortical lamination as per the International League Against Epilepsy (ILAE) criteria.¹³ Dysmorphic neurons or balloon cells were neither detectable on hematoxylin-eosin stains nor using immunohistochemistry for nonphosphorylated neurofilament proteins.

We also evaluated heterotopic neurons in the white matter and blurring of the gray-white matter junction on histology.

MR Imaging

Patients were scanned with 1.5T MR imaging before January 2008 ($n = 15$) and with 3T MR imaging after January 2008 ($n = 31$). The following MR imaging parameters were used on 1.5T Signa LX and CV/I magnets (GE Healthcare, Milwaukee, Wisconsin) with a quadrature head coil: volumetric T1 (TR/TE = 11/4.2 ms, slice thickness [ST] = 2 mm, FOV = 22 cm, matrix = 256×192), sagittal T1 (TR/TE = 566/14 ms, ST = 5 mm, FOV = 21 cm, matrix = 256×192), axial and coronal proton density (PD)/T2

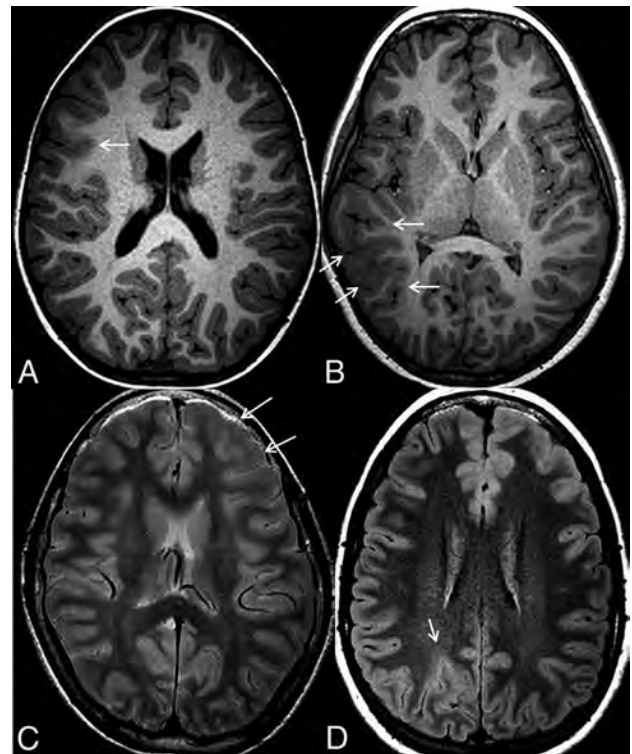


FIG 1. MR imaging features. Axial volumetric T1 shows high T1 signal in the cortex and blurring of the gray-white matter junction in the right inferior frontal gyrus (arrow, A) and thickening of the cortex, high T1 signal in the cortex, and an abnormal sulcation and gyration pattern (arrows, B) in the right temporal lobe. C, Axial proton-density sequence demonstrates high signal in the subcortical white matter (arrows) of the left frontal lobe. D, Axial FLAIR image shows high signal in the cortex (arrow) of the right parietal lobe.

(TR/TE = 4000/50/100 ms, ST = 5 mm, FOV = 22 cm, matrix = 384×224), and FLAIR (TR/TE = 9000/160 ms, ST = 5 mm, FOV = 22 cm, matrix = 256×192); and on a 1.5T Achieva scanner (Philips Healthcare, Best, Netherlands) with an 8-channel head coil: volumetric T1 (TR/TE = 10/4.6 ms, ST = 1 mm, FOV = 22 cm, voxel = 1 mm), axial and coronal FLAIR (TR/TE = 7000/140 ms, ST = 5 mm, FOV = 22 cm, matrix 276×189), and PD/T2 (TR/TE = 4000/20/100 ms, ST = 5 mm, FOV = 22 cm, matrix = 316×207). The following parameters were used on a 3T scanner (Achieva Magnet, Philips Healthcare) with an 8-channel head coil: volumetric T1 (TR/TE = 4.9/2.3 ms, ST = 0.9 mm, FOV = 22 cm, matrix = 220×220), axial and coronal FLAIR (TR/TE = 10,000/140 ms, ST = 3 mm, FOV = 22 cm, matrix = 316×290), and PD/T2 (TR/TE = 4200/40/80 ms, ST = 3 mm, FOV = 22 cm, matrix = 400×272).

The whole MR imaging study of each patient was reviewed by 2 assessors (D.M.-M and E.W.) independently. Discrepancy was resolved by consensus among the 2 assessors. The whole brain was visually inspected for the following MR imaging features: high T1 in the cortex, high T2/FLAIR in the cortex, high T2/PD/FLAIR in the subcortical white matter, increased cortical thickness, and blurring of the gray-white matter junction (Fig 1). The cerebral hemispheres were compared with each other for asymmetry with respect to these features, and suspected areas of abnormality were also compared with the remaining brain in the ipsilateral hemisphere. An abnormal sulcation and gyration pattern was also evaluated.

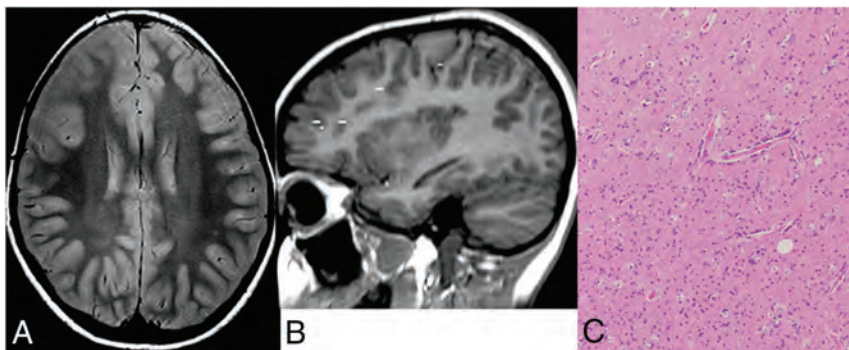


FIG 2. Case with oligodendrocytosis only. A, Axial proton density shows increased signal in the subcortical white matter of right frontal lobe. B, MEG demonstrates dipole scatter in the right frontal lobe. C, Hematoxylin-eosin stain magnification 10X demonstrates hypercellularity of oligodendroglial-like cells, with round nuclei and a scant amount of cytoplasm, in keeping with oligodendrocytosis.

Magnetoencephalography

MEG recordings were performed using a whole-head gradiometer-based Omega system (151 channels, CTF MEG; Coquitlam, British Columbia, Canada). The procedures for MEG recording and the methods for detecting, localizing, and analyzing interictal MEG spikes have been previously described.¹⁴⁻¹⁶ MEG spike sources (MEGSS) were coregistered onto volumetric T1 MR imaging. An MEGSS cluster was defined as ≥ 6 MEGSS with ≤ 1 cm between each spike source; scatters consisted of groups of either < 6 spike sources regardless of the distance between the spike sources or groups of spike sources with > 1 cm between each spike source, regardless of the number of spike sources in the group.^{14,15} We assessed the location of the MEGSS cluster and whether the cluster was concordant with the surgical resection site. We also evaluated whether there was a spike and wave pattern on the MEG and whether the peak of the MEGSS preceded the peak of electroencephalography (EEG) spike.

Surgical Treatment and Outcome

Surgery-related data collected included invasive monitoring, type of operation (focal/lobar resection, multilobar resection, or hemispherectomy), and location of the operation (temporal, extratemporal, or both). Seizure outcome was classified using the International League Against Epilepsy classification as follows: class 1, completely seizure-free; class 2, only auras, no other seizures; class 3, 1-3 seizure days per year $\pm$ an aura; class 4, 4 seizure days per year to 50% reduction of baseline seizure days $\pm$ auras; class 5, $< 50\%$ reduction of baseline seizure days $\pm$ auras; and class 6, $> 100\%$ increase of baseline seizure days $\pm$ an aura.¹⁷ Subsequently, patients were classified as seizure-free (ILAE I) or having persistent seizures (ILAE II-VI) as well as good (ILAE I-IV) versus poor (ILAE V-VI) seizure outcomes.

Analysis and Statistics

Statistical analyses were performed using JMP Pro 13 (SAS Institute, Cary, North Carolina). A P value $< .01$ was considered significant to account for multiple comparisons. We conducted the analysis in 2 steps: First, we compared the clinical variables, MR imaging, video-EEG, and MEG features, as well as outcomes across the 3 groups, oligodendrocytosis, FCD I, and oligodendrocytosis + FCD I using ANOVA for continuous variables or the χ^2 test for categorical data. For

those variables that were significant in the above analysis, we then compared oligodendrocytosis versus FCD I using a t test for continuous variables or the χ^2 test or Fisher exact test for categorical data.

RESULTS

Subjects

Forty-six patients (age at the operation = 10.6 ± 5.3 years, male = 24 [52.2%], age at seizure onset = 4.7 ± 4.6 years, duration of epilepsy = 6.4 ± 3.9 years) were included in this study. Of these, 18 (39.1%) patients had oligodendrocytosis (Fig 2), 21 (45.7%) had FCD I, and 7 (15.2%) had oligodendrocytosis + FCD I (Fig 3 and Table 1). There was no significant difference

in age at the operation between patients with oligodendrocytosis, FCD I, and oligodendrocytosis + FCD I ($P = .71$). Patients who had oligodendrocytosis + FCD I had a relatively younger age at seizure onset (2.44 ± 1.7 years) and a longer duration of epilepsy (10.4 ± 5.6 years) compared with those with only oligodendrocytosis (6.2 ± 4.8 years and 6.3 ± 3.9 years, respectively) or FCD I (4.6 ± 4.9 years and 6.5 ± 4.1 years, respectively), though the years were not statistically significant (all $P > .01$). There were no significant differences in preoperative seizure frequency or the number of antiepileptic drugs across the 3 groups (all $P > .01$). There was no significant difference in the type of seizures among those with oligodendrocytosis, FCD I, or oligodendrocytosis + FCD I ($P = .60$). Fifteen patients (83%) with oligodendrocytosis, 17 (81%) with FCD I, and 6 (86%) with oligodendrocytosis + FCD I had focal epileptiform discharges ($P = .95$).

Of 18 patients with only oligodendrocytosis, 5 (27.7%) showed oligodendrocytes only in white matter; 1 (5.6%), only in gray matter; and 12 (66.7%), in both gray and white matter. Of 7 patients with oligodendrocytosis + FCD I, 4 (57.1%) showed oligodendrocytes only in white matter; 1 (14.3%), only in gray matter; and 2 (28.6%), in both gray and white matter. Heterotopic neurons were identified in the subcortical white matter in 6 (33.3%) with oligodendrocytosis, 4 (57.1%) with oligodendrocytosis + FCD I, and 10 (47.6%) with FCD I. Blurring of the gray-white matter junction on histology was present in 3 (16.7%) with oligodendrocytosis, 1 (14.3%) with oligodendrocytosis + FCD I, and 2 (9.5%) with FCD I.

MEG

There was no significant difference across the 3 groups regarding the MEG features, including the presence of an MEGSS cluster, concordance of the MEGSS cluster with surgical resection, spike and wave patterns on MEG, and the peak of MEGSS preceding EEG spike (all $P > .01$) (Table 2). Twelve (67%) patients with oligodendrocytosis had an MEGSS cluster that was concordant with the surgical resection in all 12 patients (100%). Eighteen (86%) patients with FCD I had an MEGSS cluster that was concordant with the surgical resection site in 17 patients (94%). Five (71%) patients with oligodendrocytosis + FCD I had an MEGSS cluster that was concordant with the surgical resection in all 5 patients (100%).

MR Imaging

Nine patients (3 with oligodendrocytosis, 5 with FCD I, and 1 with oligodendrocytosis + FCD I) had normal MR imaging find-

ings; 6 (66.7%) scans were performed on 3T, and 3 (33.3%), on a 1.5T magnet.

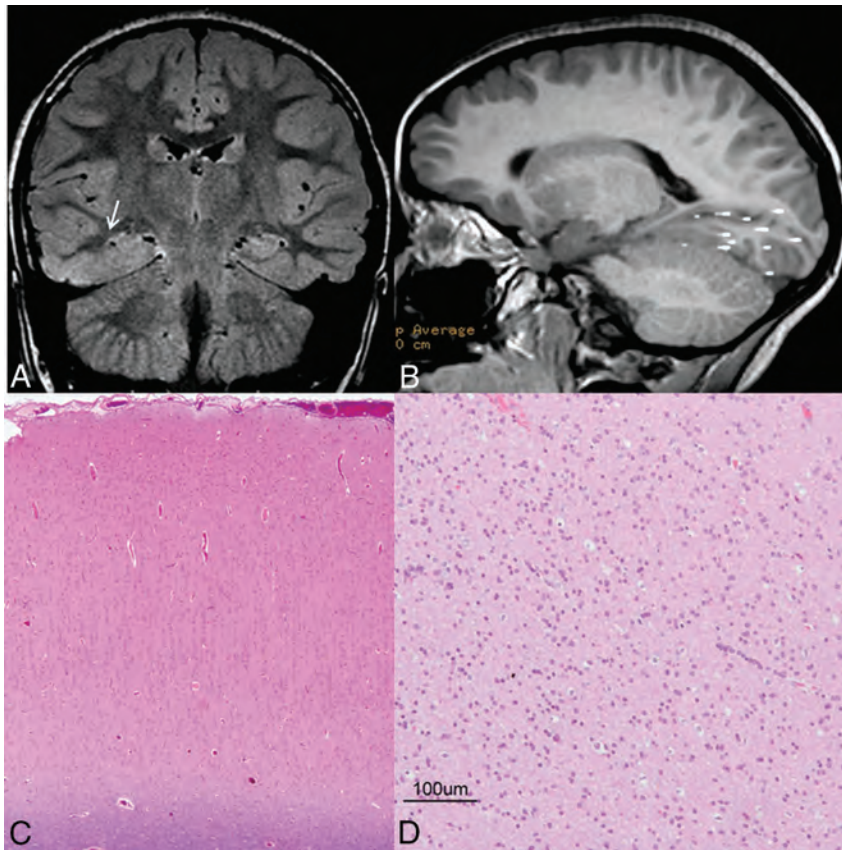


FIG 3. Case with oligodendrocytosis + focal cortical dysplasia type I. A, Coronal FLAIR shows increased FLAIR signal in the white matter of the right parahippocampal and fusiform gyri. B, MEG shows a dipole cluster in the right temporal and occipital lobes. Hematoxylin-eosin stain magnification 10X demonstrates abnormal radial cortical lamination, in keeping with FCD I (C), and hypercellularity of oligodendroglial-like cells with round nuclei and scant amount of cytoplasm (D), in keeping with oligodendrocytosis.

There were no significant differences among oligodendrocytosis, FCD I, and oligodendrocytosis + FCD I with respect to high T1 signal in the cortex (28% versus 19% versus 43%, respectively; $P = .44$), high T2/FLAIR in the cortex (11% versus 29% versus 14%, respectively; $P = .40$), high T2/PD/FLAIR in the subcortical white matter (72% versus 67% versus 86%, respectively; $P = .57$), increased cortical thickness (0% versus 14% versus 29%, respectively; $P = .10$), blurring of gray-white matter junction (17% versus 14% versus 43%, respectively; $P = .24$), or abnormal sulcation and gyration pattern (6% versus 0% versus 29%, respectively; $P = .03$) (Table 2).

Surgical Treatment and Outcome

There were no significant differences in invasive monitoring ($P = .09$), extent of resection (unilobar versus multilobar versus hemispherectomy) ($P = .37$), or location of the operation (temporal versus extratemporal versus both) ($P = .10$) among patients with oligodendrocytosis, FCD I, and oligodendrocytosis + FCD I (Table 3). Seizure-free outcome at 1 year after the operation was not significantly different among patients with oligodendrocytosis (72%), FCD I (57%), and oligodendrocytosis + FCD I

Table 1: Patient characteristics

	Oligodendrocytosis (n = 18)	FCD I (n = 21)	Oligodendrocytosis + FCD I (n = 7)	P Value
Sex				.78
Male (%)	9 (50%)	12 (57.14%)	3 (42.9%)	
Female (%)	9 (50%)	9 (42.9%)	4 (57.1%)	
Age at operation (mean) (SD) (yr)	11.2 (4.6)	9.9 (6.0)	11.1 (5.6)	.71
Age at seizure onset (mean) (SD) (yr)	6.2 (4.8)	4.6 (4.9)	2.44 (1.7)	.18
Duration of epilepsy (mean) (SD) (yr)	6.3 (3.9)	6.5 (4.1)	10.4 (5.6)	.11
Frequency of seizures				.26
Daily (%)	8 (44.4%)	16 (76.2%)	5 (71.4%)	
Monthly (%)	3 (16.7%)	1 (4.8%)	0 (0%)	
Weekly (%)	7 (38.9%)	4 (19%)	2 (28.6%)	
Types of seizures				.60
FOWIA/FOWIA-BTCZ (%)	12 (66.7%)	10 (47.6%)	3 (42.9%)	
FOWA/ FOWA-BTCZ (%)	2 (11.1%)	4 (19.0%)	1 (14.3%)	
Epileptic spasms (%)	4 (22.2%)	5 (23.8%)	3 (42.9%)	
Generalized (%)	0 (0%)	2 (9.5%)	0 (0%)	
Epileptiform discharges on video-EEG				.95
Focal (%)	15 (83.3%)	17 (81.0%)	6 (85.7%)	
No focal (%)	3 (16.7%)	4 (19.0%)	1 (14.3%)	
No. of AEDs (mean) SD)	2 (0.8)	2.2 (0.7)	2.7 (0.8)	.13

Note:—AED indicates Anti-epileptic drugs; FOWIA, focal onset with impaired awareness; FOWIA-BTCZ, focal onset with impaired awareness of bilateral tonic clonic seizures; FOWA, focal onset with awareness; FOWA-BTCZ, focal onset with awareness of bilateral tonic clonic seizures.

Table 2: MRI and magnetoencephalography features

	Oligodendrocytosis (n = 18)	FCD I (n = 21)	Oligodendrocytosis + FCD I (n = 7)	P Value
MRI features				
High T1 in cortex (%)	5 (27.8)	4 (19.0)	3 (42.9)	.44
High T2/FLAIR in cortex (%)	2 (11.1)	6 (28.6)	1 (14.3)	.40
High T2/PD/FLAIR in subcortical white matter (%)	13 (72.2)	14 (66.7)	6 (85.7)	.57
Increased cortical thickness (%)	0 (0)	3 (14.3)	2 (28.6)	.10
Blurring of gray-white matter junction (%)	3 (16.7)	3 (14.3)	3 (42.9)	.24
Abnormal sulcation and gyration pattern (%)	1 (5.6)	0 (0)	2 (28.6)	.03
MEG features				
MEGSS cluster (%)	12 (66.7)	18 (85.7)	5 (71.4)	.19
Concordance of MEGSS cluster with surgical resection (%)	12 (100)	17 (94.4)	5 (100)	.30
Peak of MEGSS leading peak of EEG spike (%)	9 (50.0)	14 (66.7)	5 (71.4)	.19
Spike and wave (%)	10 (55.6)	14 (66.7)	4 (57.1)	.65

Table 3: Operation and seizure outcome

	Oligodendrocytosis (n = 18)	FCD I (n = 21)	Oligodendrocytosis + FCD I (n = 7)	P Value
Invasive monitoring				.09
Yes (%)	10 (55.6)	15 (71.4)	7 (100)	
No (%)	8 (44.4)	6 (28.6)	0 (0)	
Extension of resection				.37
Unilobar (%)	10 (55.6)	7 (33.3)	3 (42.9)	
Multilobar (%)	8 (44.4)	12 (57.2)	4 (57.1)	
Hemispherectomy (%)	0 (0)	2 (9.5)	0 (0)	
Location of operation				.10
Temporal (%)	8 (44.4)	3 (14.3)	0 (0)	
Temporal and extratemporal (%)	7 (38.9)	11 (52.4)	4 (57.1)	
Extratemporal (%)	3 (16.7)	7 (33.3)	3 (42.9)	
Seizure outcome at 1 yr				.58
Seizure-free (ILAE I) (%)	13 (72.2)	12 (57.1)	4 (57.1)	
Persistent seizures (ILAE II–VI) (%)	5 (27.8)	9 (42.9)	3 (42.9)	
Seizure outcome at 1 yr				.35
ILAE (I–IV)	18 (100)	16 (76.2)	7 (100)	
ILAE (V–VI)	0 (0)	5 (23.8)	0 (0)	

(57.1%) ($P = .58$). Good (ILAE I–IV) seizure outcome was not significantly different among (100%), FCD I (76.2%), and oligodendrocytosis + FCD I (100%) ($P = .35$) (Table 3).

DISCUSSION

To our knowledge, this is the first study that has systematically compared the MEG, MR imaging, and outcome data of oligodendrocytosis with FCD I. We have found that oligodendrocytosis has MR imaging, MEG, and surgical outcomes similar to those in patients with FCD I and some patients have oligodendrocytosis + FCD I. Approximately half of those with oligodendrocytosis underwent multilobar resection, similar to patients with FCD I. In addition, those with oligodendrocytosis have seizure-free surgical outcomes similar to those with FCD I.

Different terminology has been used to describe oligodendroglial abnormalities in the literature, including oligodendroglial hyperplasia,^{5,6,10} clusters of oligodendroglia,⁷ oligodendroglial hamartoma,⁸ and oligodendroglial-like cells.^{9,11} These lesions may represent a spectrum of the same abnormality. More recently, Schurr et al⁶ reported an increased in Olig2-immunoreactive oligodendroglial-like cells and increased proliferation activity in patients who had surgical resection for medically intractable epilepsy, which was termed “mild malformation of cortical development with oligodendroglial hyperplasia” (MOGHE). These patients also had blurring of gray-white matter boundaries due to

heterotopic neurons in the white matter on histology. In our study, an increased number of cells that stain for the anti-Olig2 antibody were used to identify oligodendrocytosis, which occurred in the white matter, with or without gray matter involvement. However, we did not include blurring of the gray-white matter junction, increased heterotopic neurons, or increased proliferation activity as criteria for oligodendrocytosis. Oligodendroglial-like cells have been reported in larger numbers in pediatric patients with medically intractable epilepsy compared with controls.⁹ Recurrent seizures in medically intractable epilepsy may promote oligodendrogenesis because oligodendrogenesis and differentiation are promoted by action potential firing.

¹⁸ However, whether oligodendrocytosis constitutes a cause or consequence of epilepsy is yet to be determined.

Oligodendrocytosis shared similar MR imaging features with FCD I. An abnormal sulcation and gyration pattern was seen in those with oligodendrocytosis or oligodendrocytosis + FCD I, but not in FCD I, though this was identified in only a small number of patients. None of the children with oligodendrocytosis in our study had cortical thickening, while a small proportion of those with FCD I and oligodendrocytosis + FCD I had cortical thickening, though it was not statistically significant. Although Schurr et al⁶ did not systematically compare the presurgical investigations of patients with MOGHE relative to FCD, they reported that the MR imaging of patients with MOGHE revealed blurring of the gray-white matter junction and signal abnormality in the subcortical white matter, which led to the presurgical hypothesis of an underlying FCD. Hamilton and Nesbit⁵ also reported a case of oligodendroglial hyperplasia with cortical thickening and indistinctness of the gray-white junction, which are features seen in FCD.

We have found that 15% of patients in our cohort have oligodendrocytosis and FCD I. Furthermore, there were no features that distinguish oligodendrocytosis from FCD I on MR imaging and MEG, suggesting that oligodendrocytosis may represent a spectrum of mild malformations of cortical development. In the

study by Schurr et al,⁶ none of the patients with oligodendroglial hyperplasia had abnormal radial microcolumns or horizontal dyslamination. However, the authors considered this entity a mild spectrum of malformations of cortical development and have labeled this MOGHE because the MR imaging features suggested FCD. Although Hamilton and Nesbit⁵ did not identify FCD I in their case of oligodendroglial hyperplasia, the authors suggested that this could be the mildest end of the spectrum of a neuronal migrational disorder or microdysgenesis. In a recent study, Scholl et al¹⁹ also identified oligodendroglial hyperplasia in malformations of cortical development, with the exception of FCD IIB and cortical tubers.

We found that patients with oligodendrocytosis frequently underwent multilobar resection, and about 40% of patients with oligodendrocytosis have combined temporal and extratemporal epilepsy, similar to those with FCD I. Sakuma et al⁹ reported increased oligodendroglial-like cells in children who underwent extratemporal (50%) and both temporal and extratemporal (40%) resection. Fifteen (50%) children with oligodendroglial-like cells underwent multilobar resections, indicating that these children have an extensive epileptogenic network. Schurr et al⁶ reported oligodendroglial hyperplasia in patients with frontal lobe epilepsy. However, only a third of their patients were seizure-free, suggesting that these patients have a wide epileptogenic network that was not completely resected. Seizure-free outcome in our patients was higher than that in the study by Schurr et al,⁶ likely related to more extensive surgical resection in our patient population.

There are some limitations to our study. We have not counted the number of cells in oligodendrocytosis. An increased number of oligodendroglial cells were based on visual assessment of histology by a pediatric neuropathologist. We believe that expert assessment of increased oligodendroglial cells has face validity. Schurr et al⁶ have semi-quantitatively measured the oligodendroglial cell densities from surgical specimens of patients with medically refractory epilepsy, whose neuropathology reports indicated an increased number of subcortical oligodendroglial cells. Findings in the neuropathology reports were based on visual assessment of histology, which was concordant with a semiquantitative measurement of increased oligodendroglial cell densities. We have compared the presurgical evaluation and surgical outcome of oligodendrocytosis with FCD I, but not with FCD II because FCD II is usually a more focal pathology compared with FCD I, requiring focal rather than multilobar resection, and has better surgical outcomes than FCD I.^{20–22} We may have underestimated the number of patients with oligodendrocytosis + FCD I because surgical sampling for histologic examinations may fail to identify areas of FCD I in patients with oligodendrocytosis, and vice versa.

Another limitation is related to the retrospective nature of the study, whereby inclusion of patients was dependent on surgical resection and a histologic diagnosis of FCD I and/or oligodendrocytosis. Patient selection for an operation is frequently dependent on the ability to identify a lesion on MR imaging and localize the epileptogenic zone with video-EEG and/or MEG. It is possible that some patients with oligodendrocytosis did not undergo an operation for a variety of reasons, such as subtle changes on MR

imaging, including a mild abnormal sulcation/gyration pattern, that were not detected or due to failure to localize the epileptogenic zone on video-EEG or MEG.

CONCLUSIONS

We have found that oligodendrocytosis shared similar MR imaging and MEG features with FCD I, and multilobar resection was required to achieve seizure freedom, similar to FCD I. In 15% of cases, we identified concurrent oligodendrocytosis + FCD I. The findings from this study lend support to the notion that oligodendrocytosis may represent a mild spectrum of malformation of cortical development, similar to FCD I.

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REFERENCES

1. Rubinger L, Chan C, D'Arco F, et al. **Change in presurgical diagnostic imaging evaluation affects subsequent pediatric epilepsy surgery outcome.** *Epilepsia* 2016;57:32–40 [CrossRef Medline](#)
2. Wyllie E, Comair YG, Kotagal P, et al. **Seizure outcome after epilepsy surgery in children and adolescents.** *Ann Neurol* 1998;44:740–48 [CrossRef Medline](#)
3. Shepherd C, Liu J, Goc J, et al. **A quantitative study of white matter hypomyelination and oligodendroglial maturation in focal cortical dysplasia type II.** *Epilepsia* 2013;54:898–908 [CrossRef Medline](#)
4. Mühlebner A, Coras R, Kobow K, et al. **Neuropathologic measurements in focal cortical dysplasias: validation of the ILAE 2011 classification system and diagnostic implications for MRI.** *Acta Neuropathol* 2012;123:259–72 [CrossRef Medline](#)
5. Hamilton BE, Nesbit GM. **MR imaging identification of oligodendroglial hyperplasia.** *AJNR Am J Neuroradiol* 2009;30:1412–13 [CrossRef Medline](#)
6. Schurr J, Coras R, Rössler K, et al. **Mild malformation of cortical development with oligodendroglial hyperplasia in frontal lobe epilepsy: a new clinico-pathological entity.** *Brain Pathol* 2017;27:26–35 [CrossRef Medline](#)
7. Inage Y, Halliday WC, Go C, et al. **Histopathology of cortex and white matter in pediatric epileptic spasms: comparison with those of partial seizures.** *Brain Dev* 2012;34:118–23 [CrossRef Medline](#)
8. Marucci G, Giulioni M, Martinoni M, et al. **Oligodendroglial hamartoma: a potential source of misdiagnosis for oligodendroglioma.** *J Neurooncol* 2011;101:325–28 [CrossRef Medline](#)
9. Sakuma S, Halliday WC, Nomura R, et al. **Increased population of oligodendroglia-like cells in pediatric intractable epilepsy.** *Neurosci Lett* 2014;566:188–93 [CrossRef Medline](#)
10. Burger PC, Scheithauer BW, Vogel FS. **The brain: surgery for seizures.** In: Burger PC, Scheithauer BW, Vogel FS. *Surgical Pathology of the Nervous System and Its Coverings*. 4th ed. Philadelphia: Churchill Livingstone; 2002:390–402
11. Sakuma S, Halliday WC, Nomura R, et al. **Increased subcortical oligodendroglia-like cells in pharmacoresistant focal epilepsy in children correlate with extensive epileptogenic zones.** *Epilepsia* 2016;57:2031–38 [CrossRef Medline](#)
12. Widjaja E, Otsubo H, Raybaud C, et al. **Characteristics of MEG and MRI between Taylor's focal cortical dysplasia (type II) and other cortical dysplasia: surgical outcome after complete resection of MEG spike source and MR lesion in pediatric cortical dysplasia.** *Epilepsy Res* 2008;82:147–55 [CrossRef Medline](#)
13. Blümcke I, Thom M, Aronica E, et al. **The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission.** *Epilepsia* 2011;52:158–74 [CrossRef Medline](#)
14. Iida K, Otsubo H, Matsumoto Y, et al. **Characterizing magnetic spike sources by using magnetoencephalography-guided neuronaviga-**

- tion in epilepsy surgery in pediatric patients. *J Neurosurg* 2005;102:187–96 [CrossRef Medline](#)
15. Iida K, Otsubo H, Mohamed IS, et al. **Characterizing magnetoencephalographic spike sources in children with tuberous sclerosis complex.** *Epilepsia* 2005;46:1510–17 [CrossRef Medline](#)
 16. Holowka SA, Otsubo H, Iida K, et al. **Three-dimensionally reconstructed magnetic source imaging and neuronavigation in pediatric epilepsy: technical note.** *Neurosurgery* 2004;55:1226 [Medline](#)
 17. Wieser HG, Blume WT, Fish D, et al; Commission on Neurosurgery of the International League Against Epilepsy (ILAE). **ILAE Commission Report: proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery.** *Epilepsia* 2001;42:282–86 [Medline](#)
 18. Stevens B, Porta S, Haak LL, et al. **Adenosine: a neuron-glial transmitter promoting myelination in the CNS in response to action potentials.** *Neuron* 2002;36:855–68 [CrossRef Medline](#)
 19. Scholl T, Mühlebner A, Ricken G, et al. **Impaired oligodendroglial turnover is associated with myelin pathology in focal cortical dysplasia and tuberous sclerosis complex.** *Brain Pathol* 2017;27:770–80 [CrossRef Medline](#)
 20. Xue H, Cai L, Dong S, et al. **Clinical characteristics and post-surgical outcomes of focal cortical dysplasia subtypes.** *J Clin Neurosci* 2016;23:68–72 [CrossRef Medline](#)
 21. Choi SA, Kim SY, Kim H, et al. **Surgical outcome and predictive factors of epilepsy surgery in pediatric isolated focal cortical dysplasia.** *Epilepsy Res* 2018;139:54–59 [CrossRef Medline](#)
 22. Isler C, Kucukyuruk B, Ozkara C, et al. **Comparison of clinical features and surgical outcome in focal cortical dysplasia type 1 and type 2.** *Epilepsy Res* 2017;136:130–36 [CrossRef Medline](#)

Critical Assessment of Myelography Practices: A Call for Rational Guideline Revision

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ABSTRACT

BACKGROUND AND PURPOSE: Patient preparation for myelography and postprocedural monitoring varies widely between practices, despite published guidelines. Our aim was to examine the current practice variations in discontinuing reportedly seizure threshold-lowering medications before myelography and to assess the reported incidence of postmyelographic seizures.

MATERIALS AND METHODS: An e-mail survey was sent to American Society of Neuroradiology members concerning the number of postmyelographic seizures experienced in the past 5 years, the presence of an institutional policy for discontinuing seizure threshold-lowering medications, and the type of myelographic contrast used. We compared the postmyelographic seizure frequency in the responses.

RESULTS: Of 700 survey responses, 57% reported that they do not discontinue seizure threshold-lowering medications before myelography. Most (97%) indicated never having a patient experience a seizure following myelography. The number of postmyelographic seizures between those who discontinue seizure threshold-lowering medications and those who do not was not statistically significant (OR = 2.13; 95% CI, 0.91–4.98; $P = .08$). Most (95%) reported using nonionic hypo-osmolar agents.

CONCLUSIONS: Survey results revealed widely variable practices for patient myelography preparation and postprocedural monitoring. We found no difference in reported seizures between those who discontinued seizure threshold-lowering medications and those who did not. In light of our findings, we propose that discontinuing reportedly seizure threshold-lowering medications is not warranted with the current nonionic water-soluble contrast agents and may be potentially harmful in some instances. This work supports revision of existing recommendations to withhold such medications before myelography.

ABBREVIATION: STLM = seizure threshold-lowering medications

Myelography with intrathecal injection of iodinated contrast remains a valuable imaging test for patients with neurologic deficits, particularly those having contraindications to MR imaging.¹ Potential complications of myelography include infection, hemorrhage, nerve injury, and, reportedly, postmyelographic seizures in patients taking certain medications. Published¹ and pending² American College of Radiology–American Society of Neuroradiology–Society of Pediatric Radiology (ACR-ASNR-SPR) clinical practice parameters, which are based on myelographic contrast agent package

inserts^{3,4} and case reports,^{5–27} recommend screening of the patient's medication list and discontinuation of those medications that reportedly lower the seizure threshold (phenothiazine derivatives, monoamine oxidase inhibitors, tricyclic antidepressants, CNS stimulants, and psychoactive drugs) to reduce the theoretic risk of postmyelographic seizures.

Adherence to these recommendations varies; some centers discontinue seizure threshold-lowering medications (STLMs) before myelography, while others do not. At many institutions, only anticoagulants are discontinued, and no extended postprocedural patient monitoring is performed. However, the common practice in many institutions is to stop STLMs up to 48 hours before and 24 hours after the myelogram and monitor patients at least 4 hours postprocedure. These recommendations are based on anecdotal evidence and literature based on the use of older iodinated contrast agents, now outdated, given the current widespread use of nonionic myelographic contrast agents.²⁸ There has been considerable clinical experience in safely performing myelography without complications using the newer, less neurotoxic iodine

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Summary of survey results^a

Type of Practice	Discontinue STLMs	Observed Postmyelographic Seizure	30-Min to 2-Hr Postmyelographic Monitoring	Nonionic Hypo-Osmolar Contrast	>15 Yr in Practice
Academic (<i>n</i> = 281)	59% (167)	4% (12)	69% (193)	93% (260)	46% (129)
Private practice (<i>n</i> = 316)	52% (163)	2.2% (7)	55% (175)	97% (304)	66% (207)
Hybrid (<i>n</i> = 100)	67% (67)	4% (4)	54% (54)	92% (92)	47% (47)

^a Percentage (No.) of practitioners in different practice group settings and whether they discontinued STLMs, observed a postmyelographic seizure, performed 30-min to 2-hr postmyelographic monitoring, used nonionic hypo-osmolar contrast, and have been in practice >15 yr.

ated contrast agents.²² Although there are a few case reports of complications, particularly seizures,^{6,19,21,25} it is not clear whether the seizure was an unrelated, idiosyncratic reaction due to the myelographic agent itself or due to a drug interaction with a reportedly STLM. There is no strong evidence supporting an increased risk of seizures after exposure to the current, nonionic myelographic contrast agents while the patient is on these medications.

Hundreds of commonly used medications fall into this category of STLMs, and the task of identifying and discontinuing these medications at least 24 hours before the myelography and then resuming them to the therapeutic levels after the procedure is challenging clinically and potentially harmful to the patient. Often the procedure has to be rescheduled after the patient arrives at the hospital if these STLMs have not been discontinued. This rescheduling causes direct and indirect financial burdens to the patients, and the potential for undertreating comorbid conditions while these medications are withheld. Cancelling and rescheduling procedures can also have a negative impact on the health care institution.²⁹ The patient may have emotional stress and a negative perception of the quality of care.

The purpose of this investigation was to study the practice variability of discontinuing STLMs before myelography by means of a survey of the ASNR membership. We compared the number of reported seizure events by practitioners who withhold these medications with the number of reported seizure events by those who do not withhold these medications. In addition, we reviewed the literature on which recommendations are based, to critically assess the risks and benefits of this practice.¹

MATERIALS AND METHODS

The myelogram survey was e-mailed to 6300 members of the American Society of Neuroradiology (with approval from the American Society of Neuroradiology Board of Directors) in December 2017 and was open until May 2018. The survey introduction stated the goals of this project: "The current clinical practice for myelography, including patient preparation and postprocedural monitoring, seems to vary widely among institutions. Although the ACR-ASNR-SPR clinical practice parameters suggest careful evaluation of the risk-benefit assessment, there is no clear evidence to support the discontinuation of the reported STLMs before myelography, particularly with the newer contrast agents. The purpose of this survey is to obtain the current practice patterns of neuroradiologists in different practice settings with the goal of updating practice parameters that help guide practitioners who perform these procedures." The survey was designed to be brief to increase the likelihood of completion and response. We estimated that this would take <2 minutes. It included questions on the number of reported postmyelographic seizures in the past

5 years, their practice of discontinuing STLMs (phenothiazine derivatives, monoamine oxidase inhibitors, tricyclic antidepressants, CNS stimulants, and psychoactive drugs), and the type of myelographic contrast used (On-line Table 1). We compared the number of reported postmyelographic seizures by members who routinely discontinued STLMs versus those who did not routinely discontinue STLMs.

Statistical Analysis

A 2 × 2 cross-tabulation table of the number of patients in an institution with postmyelographic seizures whose medications were stopped and the number of patients in an institution with postmyelographic seizures whose medications were not stopped was formulated. This was then tested for statistical significance using a χ^2 test.³⁰ Contingency tables with χ^2 tests were also performed among types of practices, years in practice, the method of patient preparation, and whether the practitioners observed a postmyelographic seizure. *P* < .05 was considered a statistically significant difference between groups, and analysis was conducted using STATA 15.1 (StataCorp, College Station, Texas).

RESULTS

There were 700 responses to the survey during 6 months, with a response rate of 11.1%. The summary of the survey results is listed in the Table. Of note, a few responders did not answer some of the questions, so the subsets of the questions combining these answers have fewer total numbers of responses. Most of those responding (398; 57%) reported that they do not routinely discontinue medications before myelography. Most (677; 97%) responders reported that they never had a patient who experienced a seizure following myelography. Most (422; 61%) respondents indicated that they monitored patients between 30 minutes and 2 hours following the myelographic procedure. Most (656; 94%) also reported using a nonionic hypo-osmolar agent (ie, Isovue-M [iopamidol; Bracco, Princeton, New Jersey] or Omnipaque [iohexol; GE Healthcare, Piscataway, New Jersey]). The iso-osmolar agent Visipaque (iodixanol; GE Healthcare) was used less frequently (37; 5.3%). Regarding the types of practice, 316 responders (45%) indicated that they were in private practice, while 282 responders (40%) reported that they were in an academic practice. Most respondents also reported being in practice for >15 years (383; 55%).

Twenty-three (3.3%) respondents indicated that they had observed at least 1 patient having a seizure after myelography in the past 5 years. Of these 23 practitioners reporting at least 1 seizure, 14 (61%) specified that they had stopped any seizure threshold-lowering medications before the procedure, and 9 (39%) did not stop those medications before the myelographic procedure. There was a 2.13 odds ratio (95% confidence interval, 0.91–4.98; *P* = .08) of a practitioner

reporting a seizure when STLMs were withheld compared with a practitioner who did not withhold medications, though the difference was not statistically significant. Most (15/23, 65%) of these respondents monitored patients for 30 minutes to 2 hours.

There was no statistically significant difference between the reported number of postmyelographic seizures and the type of nonionic contrast used—that is, hypo-osmolar or iso-osmolar ($P = .48$). No statistically significant difference was observed in the following comparisons: practice type and STLM discontinuation ($P = .14$), practice type and postmyelographic seizure observation ($P = .34$), years in practice and STLM discontinuation ($P = .62$), and years in practice and postmyelographic seizure observation ($P = .28$) (On-line Table 2).

DISCUSSION

The use of myelography has declined dramatically in the past 3 decades, but it remains a vital imaging technique for assessing patients with contraindications to MR imaging, for preoperative orthopedic surgical planning, for radiation treatment planning, and for possible demonstration of a cerebrospinal leak.^{1,2} Physicians must weigh the benefits of performing myelography with the theoretic risk of seizures in patients who must temporarily discontinue STLMs. A survey of the ASNR membership allowed us to collect data on the current practice variations among diverse practice settings and estimate the reported incidence of postmyelographic seizure among those practitioners who withhold these medications and those who do not. Our review of the literature provided insight into the origin of withholding STLMs.

Metrizamide (Amipaque; Nyegaard and Company, Oslo, Norway), the first nonionic water-soluble contrast medium for myelography, was introduced in the early 1970s.^{31,32} It was the first such agent to gain wide acceptance, replacing oil-soluble contrast agents such as iodophenylundecylic acid (Pantopaque (Lafayette Pharmacal Company); GlaxoSmithKline, Brentford, UK) and allowing examination of the entire spinal subarachnoid space with much less chance of subsequent arachnoiditis. The adverse effects of metrizamide were milder than those with the ionic water-soluble agents, consisting of mainly nausea and vomiting (10%–20% of cases), though there were reports of more serious adverse effects, including seizures (0.2%–0.6%), hallucinations, and aseptic meningitis.^{33,34} Complications from metrizamide are often dose-related, resulting from excessive intracranial concentrations of the drug.^{12,18,35–38} The mechanism of metrizamide neurotoxicity is postulated to be cerebral glucose metabolism interference.^{11,37,39} The recognized risk factors for metrizamide myelography were seizure disorder, STLMs, dehydration, diabetes, and age,⁴⁰ and these risk factors were not dose-dependent.^{33,41} Given such neurologic complications, withholding STLMs for at least 48 hours before metrizamide myelography was recommended.⁴²

Nonionic contrast media, such as iohexol (Omnipaque), iopamidol (Isovue-M), and iodixanol (Visipaque)^{43,44} have replaced metrizamide and are less neurotoxic than ionic, water-soluble contrast agents, causing fewer adverse effects than agents previously used to evaluate the spine and intrathecal contents.²² The reported cases of postmyelographic seizure with nonionic, water-soluble contrast in the past decade have been very rare. Although

animal studies have shown iopamidol to be more epileptogenic than metrizamide⁴⁵ and the excitative neurotoxic potential of iodixanol,⁴⁶ clinical trials of these newer nonionic agents have shown them to be safe and effective, with fewer adverse effects than metrizamide.^{8,16,22,47} The risk of seizure with the currently used contrast media is reported to be in the range of 0.093%–0.847%.^{19,48} Review of the literature revealed only case reports of seizure activity after myelography with iopamidol^{13,21} and iohexol (On-line Table 3).^{5,7,15,26} In patients with epilepsy, the risks and benefits of myelography, even with the newer agents, must be weighed against the risk of inducing seizures or status epilepticus because there have been reports of seizures induced by nonionic contrast myelographic agents in patients with epilepsy.^{13,19,20} Given the rare incidence of postmyelographic seizures with the newer contrast agents, it is difficult to perform a prospective randomized controlled study. In a 2005 survey of the ASNR membership on myelography practice patterns and complications, 88% of 351 respondents reported no seizures postmyelographic and 12% reported 1–2 seizures in the past 5 years.⁴⁹ In our ASNR survey, 23 (3.3%) of 700 respondents indicated that they had observed at least 1 patient having a postmyelographic seizure in the past 5 years.

Case reports have described seizures occurring <12 hours after the myelographic procedure.^{13,50} Nonionic, water-soluble radiographic contrast agents such as iohexol and metrizamide penetrate the CNS spaces and are eliminated from the subarachnoid space during 2–8 hours.³³ Most of the subjective reactions have occurred in the first 8 hours after cervical and thoracic myelography,⁵¹ while in a study on lumbar myelography, half of all subjective reactions occurred in the first 9 hours.²² Almost all electroencephalography changes after cervical and thoracic myelography occurred within 6 hours⁵¹ and at 24 hours after lumbar myelography. The Nakstad et al⁵¹ study describing electroencephalography changes did not indicate whether the patients were on STLMs, but the authors stated that patients continued to take other medications.⁵¹ More than half (61%) of the survey respondents indicated that they monitored patients for between 30 minutes and 2 hours following the myelographic procedure, which was the length of time that most (65%) of those reporting postmyelographic seizures described monitoring patients postmyelography.

Some case reports offered different rationales for postmyelographic seizures. In most reported cases of major motor seizures with nonionic myelographic media, ≥ 1 of the following factors was present: deviations from the recommended procedure, use in patients with a history of epilepsy, over-dosage,¹⁴ intracranial entry of a bolus or premature diffusion of a high concentration of the medium, failure to maintain elevation of the head during or postprocedure, and/or excessive patient movement or straining.⁵² In 1 case report of iopamidol 300 mol/L–induced seizures, the authors proposed that the patient's underlying alcoholism resulted in an increase in blood-brain barrier micropinocytic activity, with associated increased permeability to the myelographic iodinated material, and resulted in postmyelographic seizures.¹³ Some investigators have suggested that the incidence of complications such as meningeal and radicular irritation may be related to the dose of the contrast medium.^{10,24} On the other hand, Lipman et al²¹ reported 2 cases of seizure after iopamidol myelography

in a retrospective series of 236 consecutive patients with recommended doses.²¹ There may be a correlation between the upper level of visible contrast medium and the incidence of adverse reactions.¹⁰ Klein et al¹⁹ found a lower incidence of seizure induction for lumbar myelography than for myelography that included the cervical subarachnoid space. In a retrospective review of cervical myelograms performed with iopamidol-300 mol/L (~12 mL) between 2011 and 2016, however, we had no documentation of seizure activity within 24 hours of the procedure.⁵³ The higher incidence of neurologic complications with cervical myelography compared with lumbar myelography has been postulated to be caused by changes in the transmitter metabolism, resulting in overexcitability of the neurons,⁵⁴ and may not require breakdown of the BBB because contrast media may enter the extracellular space by passive diffusion through the pia mater.¹⁹

In many of these case reports describing postmyelographic seizures, it was either not specified whether the patients were on a reportedly STLM or no association was discussed. Two case reports of seizure activity with metrizamide and iohexol included the concomitant use of an agent that lowers the seizure threshold.^{7,17} However, several animal experiments^{23,45,55-57} have failed to demonstrate any excitative effect on the CNS after subarachnoid injection of iohexol, even after lowering of the seizure threshold with chlorpromazine.²³ Small scale, open-label, observational investigations, though flawed, did not show an association between the concomitant administration of contrast agents and STLMs and an increased risk of seizures.⁵⁸⁻⁶⁰ In a prospective, placebo-controlled trial, Standnes et al⁵⁹ evaluated the potentiation of seizures with neuroleptic drugs (ie, levomepromazine) in conjunction with metrizamide myelography and found electroencephalography deterioration in 22% of the patients, with no difference in electroencephalography results between the 2 groups. In a retrospective review of cervical myelography performed with iopamidol-300 mol/L, at the University of Utah, 40% (73/185) had documentation of at least 1 of the reportedly STLMs; however, no seizures were observed in either group.⁵³

Although there have been no well-designed studies to confirm an increased seizure risk in patients undergoing myelography who take STLMs, some practitioners recommend that such medications be avoided 48 hours before and 24 hours after administration of myelographic contrast medium.⁶¹ Many institutions have initiated protocols to withhold these medications preprocedure despite no high-level evidence to advocate this practice. A literature review by Fedutes and Ansani⁴⁸ recommended that any medication associated with seizure threshold lowering may potentially increase the risk of seizures with metrizamide or iohexol. However, they stated that the available data are anecdotal. The authors made this recommendation based on the studies showing that the nonionic, water-soluble contrast media agents themselves may lower the seizure threshold, and therefore, that there may be a potential increase in seizure risk when these contrast agents are administered concomitantly with medications that carry the same risk. Without providing any data, the authors recommended discontinuing medications associated with seizure activity before and immediately following myelography.⁴⁸

Expert opinions and practice patterns vary. Neurologists specializing in epilepsy management in some institutions consider

the current myelographic contrast agents to have a very low epileptogenic potential and do not prescreen for or withhold STLMs.⁶² They modify the procedure (eg, use a smaller volume of contrast material or avoid direct intracranial passage) when the patient reports being on such medications during the informed consent discussion.⁶² There is institutional variability in policies regarding discontinuing STLMs, with some having no published guidelines and others having internal or individual experiential policies. Together with community standards, these define regional standard of care. The authors in our study represent 3 institutions with varying practices regarding discontinuing STLMs. The 2005 ASNR myelography survey revealed that most of the seizures (88%) were in patients who were not taking potentially epileptogenic drugs and most (78%) occurred in practices that screen for such drugs.⁴⁹ The trend has changed in the past decade because more than half (57%) of the respondents in our recent ASNR survey indicated that they do not routinely discontinue these medications before myelography. Of the respondents in the 2005 survey whose patients experienced seizures, 40% indicated that these patients had a history of seizures and 14% reported that the patients had been taking potentially epileptogenic drugs. In our recent ASNR survey, there was no statistically significant difference between the reported number of postmyelographic seizures by those who discontinued STLMs and by those who did not. There were no greater odds of a practitioner reporting a seizure when STLMs were not withheld compared with when they were withheld (OR = 2.13, *P* = .08). That the number of postmyelographic seizures were reported more frequently (14/23, or 61%) when STLMs were withheld runs counter to the idea that holding such medications reduces the risk of seizures. Rather, it indicates that the seizure risk is the same regardless of the discontinuation of the STLMs and is supported by the lack of statistical significance in the difference between the groups.

The package inserts for iohexol and iopamidol do not recommend the concomitant use of the contrast agent and “drugs which lower the seizure threshold, especially phenothiazine derivatives, including those used for their antihistamine properties ...” and allow clinicians to make decisions for each patient individually, “while the contributory role of these medications has not been established, the use of such drugs should be based on physician evaluation of potential benefits and potential risks.”^{3,4} Such statements also do not make it easy to formulate a succinct list of medications to discontinue before myelography, which is particularly exasperating because new drugs that potentially decrease the seizure threshold are frequently introduced by the pharmaceutical industry. From informal discussions with radiologists at other institutions and survey responders, we believe the STLM list is not uniform. Adherence to the list may be impractical, and there may be health risks related to discontinuing medications used to treat comorbid conditions.⁶³ For example, abruptly discontinuing antipsychotic medications can cause abnormal motor syndromes and greater mood instability. Difficulty in compliance leads to many patients being rescheduled, resulting in delay of care, poor use of resources, and decreased patient and referring physician satisfaction.

Our study has a few limitations. With survey research, there may be a self-reporting bias because respondents may not feel

encouraged to provide accurate answers or responses that present them in an unfavorable manner. There may also be a recall bias, with responders not accurately recalling incidences of postmyelographic seizures. We had a relatively low response rate of 11% to the survey, which may be due to a limited number of ASNR members routinely performing myelograms. The members with myelography experience who did not respond may introduce a nonresponse bias.⁶⁴ Those responders to the survey may have different practice characteristics, which may not be representative of the ASNR membership or neuroradiologists in the community. This coverage error of discrepancy between all physicians performing myelography and the sampling frame may invalidate inferences about all myelographers. The average response rate for external surveys is 10%–15% and that of on-line surveys is 30%.⁶⁵ The response rate of our survey (11%) has a 95% $\pm$ 10% statistical accuracy. A further limitation of surveys is that respondents may not answer all questions, which we encountered. Although survey responders may perform a premyelography medication review, it is also conceivable that the patient's medication list is incomplete so that the radiologist may have been misled as to the use of STLMs. Another variability in practice is the postmyelographic observation time, which limits long-term follow-up in those who were not followed for >2 hours.

Given the rare occurrence of postmyelographic seizures, it is impractical to execute a randomized controlled trial or a prospective observational cohort study. The survey methodology of this study is a surrogate for an observational cohort study because it considers the experience of multiple practitioners from multiple institutions. An additional limitation of this study is the inaccuracy of estimating the real incidence of postmyelographic seizures. In our recent ASNR survey, 3.3% of the responders reported having observed a postmyelographic seizure in at least 1 patient. However, the total number of myelographic procedures that each respondent performs to estimate the true incidence is lacking. On the basis of data from the University of Utah where we performed 955 myelograms during 5 years (recognizing that this varies among institutions), we can estimate that the 700 survey respondents performed a total number of 668,500 myelographic procedures. Thus, we estimate that the incidence of postmyelographic seizures would be approximately a 0.003% incidence in a 5-year period.

The lack of high-level evidence in the literature combined with the objective analysis of data from the University of Utah and that from the multi-institutional survey leads us to propose that the theoretic increased seizure risk when a patient is on these reportedly STLMs does not outweigh the potential harm from temporary medication interruption. Furthermore, a revision of these recommendations would allow more patients access to diagnostic myelography, which is often important for clinical management. The results of this investigation will help guide local clinical practices.

CONCLUSIONS

Practice patterns for patient preparation and postmyelographic monitoring vary widely. Many practices screen for and withhold any of the hundreds of common medications that reportedly lower the threshold for seizure with concomitant myelographic contrast administration and perform extended postprocedural monitoring. This practice is based on anecdotal experience, case reports, and older contrast agents that are no longer used in most

institutions. There is no compelling evidence to support this practice. We challenge the recommendation to withhold these medications: a practice with potential to harm to the patient and institution without proved benefit. We base this challenge on the results of our recent multi-institutional ASNR survey, comprehensive review of the literature, and our extensive experience performing myelographic procedures in patients on STLMs without experiencing postmyelographic seizures. We propose that discontinuing reportedly seizure threshold-lowering medications is not warranted with the current nonionic water-soluble contrast agents and that these results support an examination and revision of the current guidelines and local practices.

REFERENCES

1. ACR-ASNR Practice Guideline for the Performance of Myelography and Cisternography 2013. <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/Myelog-Cisternog.pdf>. Accessed October 4, 2018
2. ACR-ASNR Practice Guideline for the Performance of Myelography and Cisternography 2018. In press.
3. OMNIPAQUE (iohexol) Injection by General Electric Healthcare. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018956s099lbl.pdf. Accessed August 23, 2018
4. ISOVUE-M (iopamidol) Injection. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018735s057lbl.pdf. Accessed August 23, 2018
5. Ahmed I, Pepple R, Jones RP. Absence status epilepticus resulting from metrizamide and Omnipaque myelography. *Clin Electroencephalogr* 1988;19:37–42 CrossRef Medline
6. Alimohammadi H, Abdalvand A, Safari S, et al. Status epilepticus after myelography with iohexol (Omnipaque). *Am J Emerg Med* 2012;30:2092.e1–3 CrossRef Medline
7. Altschuler EM, Segal R. Generalized seizures following myelography with iohexol (Omnipaque). *J Spinal Disord* 1990;3:59–61 Medline
8. Baccarini L, de Nicola D, Gasprini D, et al. Iopamidol (B 15000), a nonionic water-soluble contrast medium for neuroradiology, Part I: results of a clinical trial for myelography. *Neuroradiology* 1982;23:81–84 CrossRef Medline
9. Baker RA, Hillman BJ, McLennan JE, et al. Sequelae of metrizamide myelography in 200 examinations. *AJR Am J Roentgenol* 1978;130:499–502 CrossRef Medline
10. Bassi P, Cecchini A, Dettori P, et al. Myelography with iopamidol, a nonionic water-soluble contrast medium: incidence of complications. *Neuroradiology* 1982;24:85–90 CrossRef Medline
11. Bertoni JM, Schwartzman RJ, Van Horn G, et al. Asterixis and encephalopathy following metrizamide myelography: investigations into possible mechanisms and review of the literature. *Ann Neurol* 1981;9:366–70 CrossRef Medline
12. Butler MJ, Cornell SH, Damasio AR. Aphasia following pluridirectional tomography with metrizamide: the effect of patient position. *Arch Neurol* 1985;42:39–45 CrossRef Medline
13. Carchietti E, Baldassarre M, Penco T, et al. Iopamidol 300-induced epilepsy: intensive treatment and pathogenic hypothesis. *Neuroradiology* 1988;30:256–57 CrossRef Medline
14. Carella A, Federico F, Di Cuonzo F, et al. Adverse side effects of metrizamide and iopamidol in myelography. *Neuroradiology* 1982;22:247–49 CrossRef Medline
15. Dalen K, Kerr HH, Wang AM, et al. Seizure activity after iohexol myelography. *Spine (Phila Pa 1976)* 1991;16:384 CrossRef Medline
16. Drayer BP, Vassallo C, Sudilovsky A, et al. A double-blind clinical trial of iopamidol versus metrizamide for lumbosacral myelography. *J Neurosurg* 1983;58:531–37 CrossRef Medline
17. Hindmarsh T, Grepe A, Widen L. Metrizamide-phenothiazine interaction: report of a case with seizures following myelography. *Acta Radiol Diagn (Stockh)* 1975;16:129–34 CrossRef Medline

18. Killebrew K, Whaley RA, Hayward JN, et al. **Complications of metrizamide myelography.** *Arch Neurol* 1983;40:78–80 [CrossRef Medline](#)
19. Klein KM, Shiratori K, Knake S, et al. **Status epilepticus and seizures induced by iopamidol myelography.** *Seizure* 2004;13:196–99 [CrossRef Medline](#)
20. Levey AI, Weiss H, Yu R, et al. **Seizures following myelography with iopamidol.** *Ann Neurol* 1988;23:397–99 [CrossRef Medline](#)
21. Lipman JC, Wang AM, Brooks ML, et al. **Seizure after intrathecal administration of iopamidol.** *AJNR Am J Neuroradiol* 1988;9:787–88 [Medline](#)
22. Maly P, Bach-Gansmo T, Elmqvist D. **Risk of seizures after myelography: comparison of iohexol and metrizamide.** *AJNR Am J Neuroradiol* 1988;9:879–83 [Medline](#)
23. Maly P, Olivecrona H, Almén T, et al. **Interaction between chlorpromazine and intrathecally injected non-ionic contrast media in non-anaesthetized rabbits.** *Neuroradiology* 1984;26:235–40 [CrossRef Medline](#)
24. Noda K, Miyamoto K, Beppu H, et al. **Prolonged paraplegia after iohexol myelography.** *Lancet* 1991;337:681 [Medline](#)
25. Singh S, Rajpal C, Nannapneni S, et al. **Iopamidol myelography-induced seizures.** *MedGenMed* 2005;7:11 [Medline](#)
26. Tahta K, Ozgen T, Berker M, et al. **Status epilepticus following iohexol myelography.** *Neuroradiology* 1993;35:322–23 [CrossRef Medline](#)
27. Vossler DG, Wright SJ Jr. **Convulsive status epilepticus following intrathecal iopamidol administration.** *J Epilepsy* 1994;7:18–20 [CrossRef](#)
28. Hanus PM. **Metrizamide: a review with emphasis on drug interactions.** *Am J Hosp Pharm* 1980;37:510–13 [Medline](#)
29. Maimaiti N RA, Aghaie LA. **Economic impact of surgery cancellation in a general hospital, Iran.** *Ethiopian Journal of Health Development* <https://www.ajol.info/index.php/ejhd/article/view/167749>. Accessed August 23, 2018
30. Pepe MS. *The Statistical Evaluation of Medical Tests for Classification and Prediction.* New York: Oxford University Press; 2003
31. Skälpe IO, Amundsen P. **Thoracic and cervical myelography with metrizamide: clinical experiences with a water-soluble, non-ionic contrast medium.** *Radiology* 1975;116:101–06 [CrossRef Medline](#)
32. Skälpe IO, Amundsen P. **Lumbar radiculography with metrizamide: a nonionic water-soluble contrast medium.** *Radiology* 1975;115:91–95 [CrossRef Medline](#)
33. Junck L, Marshall WH. **Neurotoxicity of radiological contrast agents.** *Ann Neurol* 1983;13:469–84 [CrossRef Medline](#)
34. Centeno RS, Sovak M, Hackney DB, et al. **Brain changes on computed tomography following metrizamide myelography: significance and therapeutic implications.** *Spine (Phila Pa 1976)* 1986;11:509–12 [CrossRef Medline](#)
35. Drayer BP, Rosenbaum AE. **Metrizamide brain penetration.** *Acta Radiol Suppl* 1977;355:280–93 [Medline](#)
36. Ropper AH, Chiappa KH, Young RR. **The effect of metrizamide on the electroencephalogram: a prospective study in 61 patients.** *Ann Neurol* 1979;6:222–26 [CrossRef Medline](#)
37. Caillé JM, Guibert-Tranier F, Howa JM, et al. **Cerebral penetration following metrizamide myelography [in French].** *J Neuroradiol* 1980;7:3–12 [Medline](#)
38. Solti-Bohman L, Bentson JR. **Comparative advantages of small- and large-dose metrizamide myelography.** *AJR Am J Roentgenol* 1983;141:825–28 [CrossRef Medline](#)
39. Ekholm SE, Reece K, Coleman JR, et al. **Metrizamide: a potential in vivo inhibitor of glucose metabolism.** *Radiology* 1983;147:119–21 [CrossRef Medline](#)
40. Steiner E, Simon JH, Ekholm SE, et al. **Neurologic complications in diabetics after metrizamide lumbar myelography.** *AJR Am J Roentgenol* 1986;146:1057–60 [CrossRef Medline](#)
41. Skälpe IO. **Adverse effects of water-soluble contrast media in myelography, cisternography and ventriculography: a review with special reference to metrizamide.** *Acta Radiol Suppl* 1977;355:359–70 [Medline](#)
42. Meador K, Hamilton WJ, El Gammal TA, et al. **Irreversible neurologic complications of metrizamide myelography.** *Neurology* 1984;34:817–21 [CrossRef Medline](#)
43. Maly P, Sundgren P, Bååth L, et al. **Neural tolerance of the non-ionic dimers iodixanol and iotrolan and the non-ionic monomer iopamidol during myelography in non-anaesthetized rabbits.** *Acta Radiol* 1995;36:644–48 [Medline](#)
44. La Noce A, Bertani F, Lorusso V, et al. **Preclinical safety assessment of iomeprol for injection as contrast medium for myelography.** *Eur J Radiol* 1994;18(Suppl 1):S43–50 [CrossRef Medline](#)
45. Gonsette RE, Brucher JM. **Neurotoxicity of novel water-soluble contrast media for intrathecal application.** *Invest Radiol* 1980;15:S254–59 [CrossRef Medline](#)
46. Sundgren P, Bååth L, Maly P. **CNS-effects from subarachnoid injections of iohexol and the non-ionic dimers iodixanol and iotrolan in the rabbit.** *Acta Radiol* 1995;36:307–11 [Medline](#)
47. Witwer G, Cacayorin ED, Bernstein AD, et al. **Iopamidol and metrizamide for myelography: prospective double-blind clinical trial.** *AJR Am J Roentgenol* 1984;143:869–73 [CrossRef Medline](#)
48. Fedutes BA, Ansani NT. **Seizure potential of concomitant medications and radiographic contrast media agents.** *Ann Pharmacother* 2003;37:1506–10 [CrossRef Medline](#)
49. Sandow BA, Donnal JF. **Myelography complications and current practice patterns.** *AJR Am J Roentgenol* 2005;185:768–71 [CrossRef Medline](#)
50. Olsen J. **Seizures after myelography with iopamidol.** *Am J Emerg Med* 1994;12:329–30 [CrossRef Medline](#)
51. Nakstad P, Helgetveit A, Aaserud O, et al. **Iohexol compared to metrizamide in cervical and thoracic myelography: a randomized double blind parallel study.** *Neuroradiology* 1984;26:479–84 [CrossRef Medline](#)
52. Lin SM, Tsou MY, Chan KH, et al. **Myoclonic seizure in the postanesthesia care unit after thoracic laminectomy.** *Anesth Analg* 2002;95:777–79, table of contents [Medline](#)
53. Aldred B, Pierson N, Shah L. **Selective discontinuation of medications prior to myelography: Is it really necessary?** *American Society of Spine Radiology*, February 23–26, 2017; San Diego, CA. [Abstract](#)
54. Grunert P, Pendl G. **Cerebral seizure following lumbar myelography with iopamidol [in German].** *Radiologe* 1986;26:526–27 [Medline](#)
55. Maly P, Almén T, Golman K, et al. **Excitatory effects in anaesthetized rabbits from subarachnoidally injected iso- and hyperosmolar solutions of iohexol and metrizamide.** *Neuroradiology* 1984;26:131–36 [CrossRef Medline](#)
56. Golman K, Olivecrona H, Gustafson C, et al. **Excitation and depression of non-anaesthetized rabbits following injection of contrast media into the subarachnoid space.** *Acta Radiol Suppl* 1980;362:83–86 [Medline](#)
57. Sovak M, Ranganathan R, Kerber CW, et al. **Iotrol, a new myelographic agent, 2: comparative electroencephalographic evaluation by spectrum analysis.** *AJNR Am J Neuroradiol* 1983;4:319–22 [Medline](#)
58. Hauge O, Falkenberg H. **Neuropsychologic reactions and other side effects after metrizamide myelography.** *AJR Am J Roentgenol* 1982;139:357–60 [CrossRef Medline](#)
59. Standnes B, Oftedal SI, Weber H. **Effect of levomepromazine on EEG and on clinical side effects after lumbar myelography with metrizamide.** *Acta Radiol Diagn (Stockh)* 1982;23:111–14 [CrossRef Medline](#)
60. Gonsette RE, Liesenborghs L. **Iohexol: a new nonionic contrast medium for myelography and cisternography with markedly reduced neurotoxicity.** *Invest Radiol* 1985;20:S32–36 [Medline](#)
61. Smith RR. **Myelographic complications associated with drug interactions.** *AJR Am J Roentgenol* 2001;177:713 [Medline](#)
62. Eames FA, Cloft HJ. **Discontinuing patient medications prior to myelography.** *AJR Am J Roentgenol* 2005;184:695 [Medline](#)
63. Howland RH. **Potential adverse effects of discontinuing psychotropic drugs, Part 3: antipsychotic, dopaminergic, and mood-stabilizing drugs.** *J Psychosoc Nurs Ment Health Serv* 2010;48:11–14 [CrossRef Medline](#)

64. Fincham JE. **Response rates and responsiveness for surveys, standards, and the journal.** *Am J Pharm Educ* 2008;72:43 [CrossRef](#) [Medline](#)
65. Nulty DD. **The adequacy of response rates to online and paper surveys: what can be done?** *Assessment & Evaluation in Higher Education* 2008;33:301–14 [CrossRef](#)
66. Canbay O, Bal N, Akinici S, et al. **Rhabdomyolysis after intraoperative myelography.** *Paediatr Anaesth* 2004;14:509–13
67. Kelley BC, Roh S, Johnson PL, et al. **Malignant cerebral edema following CT myelogram using Isovue-M 300 intrathecal nonionic water-soluble contrast: a case report.** *Radiol Res Pract* 2011;2011:212516
68. Sobel DF, Rowe R, Zyroff J, et al. **Adverse reactions to iopamidol and iohexol myelography with special attention to headache: role of myelographic technique.** *Headache* 1989;29:519–22
69. Teasdale E, Macpherson P. **Guidelines for cervical myelography: lumbar versus cervical puncture technique.** *Br J Radiol* 1984;57:789–93

Percutaneous Radiofrequency Ablation of Spinal Osteoid Osteomas Using a Targeted Navigational Bipolar Electrode System

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ABSTRACT

SUMMARY: Safe and effective percutaneous CT-guided radiofrequency ablation of spinal osteoid osteomas can be performed using a targeted navigational bipolar electrode system. Articulating bipolar electrodes with built-in thermocouples along an electrode shaft and variable generator wattage settings allow optimal nidus access, particularly in challenging locations; provide precise real-time monitoring of ablation zone volume and geometry; and minimize the risk of undesired thermal injury.

ABBREVIATION: RF = radiofrequency

During the past decade, investigators have successfully used percutaneous radiofrequency (RF) ablation for definitive treatment of spinal osteoid osteomas using traditional unipolar straight electrodes with variable ablation times ranging from 4 to 30 minutes after reaching a desired plateau temperature (typically 90°C).^{1–4}

A recently introduced navigational bipolar RF ablation system has been successfully used for treatment of spinal metastases,⁵ which has several important advantages over traditional straight unipolar RF electrodes for the management of spinal lesions, particularly given the proximity of neural structures and the potential risk of undesired thermal injury. Most importantly, 2 built-in active thermocouples along the electrode shaft provide precise real-time monitoring of ablation zone volume and geometry and ensure that the entire nidus is safely ablated. Additionally, the articulating distal segment (tip) of the electrode can be curved in several directions, allowing optimal electrode positioning in different portions of the nidus from a single osseous entry site, particularly in larger lesions that would otherwise require more than one access points, and this feature is also advantageous for challenging-to-access lesions. Last, the bipolar electrode design eliminates the risk of thermal skin injury and obviates grounding pad placement.

In this report, we describe the initial experience using a targeted multidirectional bipolar RF ablation electrode system for the treatment of spinal osteoid osteomas.

MATERIALS AND METHODS

Institutional review board approval was obtained to retrospectively review the institutional data base for patients who underwent RF ablation for the treatment of spinal osteoid osteomas between May 2015 and April 2018. Clinical manifestations included focal pain, particularly at night, which improved with nonsteroidal anti-inflammatory medications; painful scoliosis; and spinal stiffness. Imaging characteristics were best evaluated on CT and included an osteolytic nidus with surrounding osseous sclerosis. Informed consent was waived for retrospective participation. Recorded data included patient age, sex, treated anatomic site, and histologic diagnosis. Preprocedural imaging was reviewed to determine the nidus size and the shortest distance of the nidus from the central canal or neuroforamen. Procedural notes were reviewed to determine the total ablation time, generator wattage settings, use of electrode distal segment articulation, and the type of thermal protection. A procedure was considered technically successful if ablations encompassing the entire nidus volume were performed. Procedural complications were documented according to the Society of Interventional Radiology classification,⁶ based on patients' symptoms and physical examinations. Patients were clinically evaluated 2 hours after each procedure for potential acute complications such as hematoma formation or neurologic injury. Patients were discharged the day of procedure. Telephone follow-up was documented by a musculoskeletal nurse coordinator at 1- and 6-week postprocedure time points. Duration of clinical follow-up was recorded, and elec-

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FIG 1. Navigational bipolar radiofrequency ablation electrode. The targeted multidirectional distal tip of the electrode (*large arrow*) can be articulated up to 90° by turning the gray knob (*small arrow*) on the handle in the direction of the printed white arrow on the handle. Laser etchings (*arrowheads*) along the device shaft mark the exit point and deployment point of the electrode from the introducer cannula. After desired positioning within the nidus, the RF electrode tip is fully extended by turning the white knob (*dotted arrow*) at the handle. There are 2 active thermocouples embedded within the electrode located 5 and 10 mm from the center of ablation zone, which allow precise real-time monitoring of ablation zone volume and geometry.

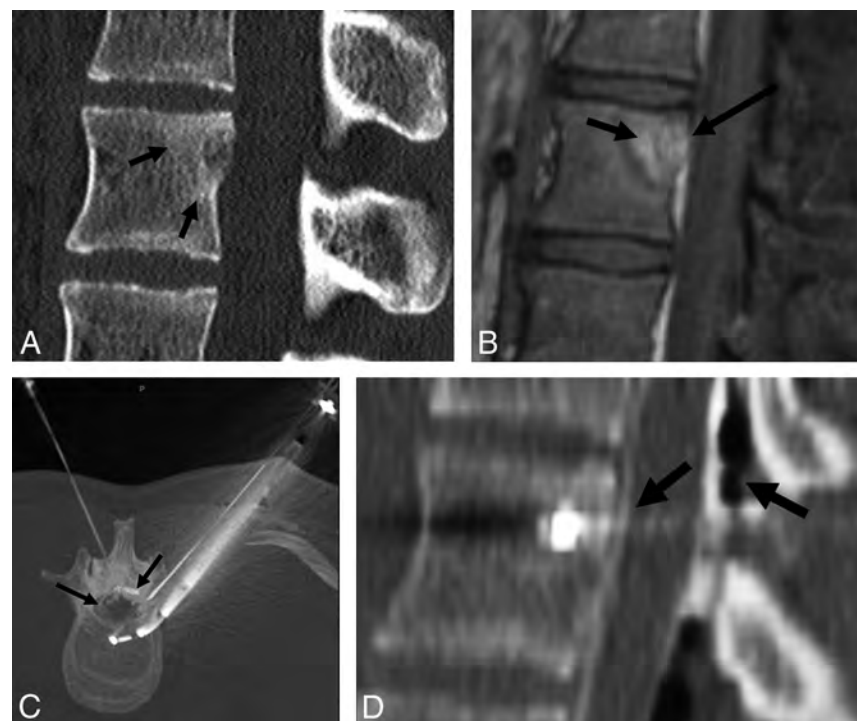


FIG 2. An 18-year-old woman with lumbar spine hypomobility and low back pain. This case highlights the advantages of articulating the distal electrode tip for challenging-to-access nidus location as well as real-time monitoring of ablation zone volume, considering the proximity to neural elements. Sagittal unenhanced CT (A) and sagittal T1-weighted fat-saturated gadolinium-enhanced MR imaging (B) show a partly mineralized nidus in the posterior L2 vertebral body abutting the posterior wall cortex and resulting in cortical thinning and slight convexity toward the central canal. Note surrounding reactive medullary sclerosis and reactive osteitis (A and B, *small arrows*) as well as partial obliteration of the anterior epidural space (B, *large arrow*). Prone maximum-intensity-projection axial CT (C) and sagittal CT (D) during radiofrequency ablation show articulation of the distal tip of the navigational RF electrode placed via a lateral transpedicular approach for optimal access to the nidus in the central posterior vertebral body, which would be challenging to reach with traditional straight RF electrodes. Note the epidural injection of carbon dioxide and 5% dextrose in water (diluted in iodinated contrast) for active thermal protection (C and D, *arrows*). An 18-ga spinal needle is placed in the neuroforamen (C) for passive thermal protection (temperature monitoring). Somatosensory and motor-evoked potential monitoring was performed during the procedure.

tronic medical records were reviewed for potential delayed complications, such as infection and persistent/recurrent pain.

Radiofrequency Ablation Equipment and Procedure

Procedures were performed under general anesthesia in pediatric patients and under conscious sedation in 1 adult patient under CT guidance after written informed consent was obtained.

The nidus was accessed using a 10-ga introducer needle. Nidus biopsy and channel creation for the electrode were then performed coaxially with a battery-powered hand drill and a 12-ga hollow biopsy needle (OnControl; Vidacare, Shavano Park, Texas). RF ablation was performed using the STAR Tumor Ablation System (Merit Medical Systems, South Jordan, Utah), consisting of the Spine STAR Ablation device and the MetaSTAR Generator. The ablation device is an articulating navigational bipolar RF electrode (The 5/10 STAR electrode), which contains 2 active thermocouples positioned 5 and 10 mm from the center of the ablation zone (Fig 1). Based on the manufacturer's thermal distribution curves, the dimensions of the ellipsoid ablation volume are 15 × 7 × 7 mm when the thermocouple located 5 mm from center of the ablation zone (distal thermocouple) reaches 50°C, and 20 × 15 × 15 mm when the thermocouple located 10

mm from center of ablation zone (proximal thermocouple) reaches 50°C. As a safety feature, RF energy automatically stops when the proximal thermocouple registers 50°C. There are laser etchings along the device that demarcate the exiting point of the electrode from the noninsulated working cannula to reduce the risk of ablating along the introducer tract (Fig 1). The MetaSTAR Generator provides 3-W, 5-W, 7.5-W, and 10-W power settings, which allow slow ablations. The generator also displays ablation time, impedance, and the 2 thermocouple temperature readings, which permit precise real-time monitoring of the ablation zone dimensions and geometry.

The navigational bipolar RF ablation electrode was subsequently positioned in the nidus center and articulated in different orientations, if needed, to ensure that the entire nidus was ablated (Figs 1 and 2).

Active and passive neural thermal protection techniques (Fig 2) were implemented and included an epidural or neuroforaminal injection of carbon dioxide and/or cooled 5% dextrose in water, achieved by placement of an 18-ga spinal needle in the epidural space or in the neuroforamen and coaxial placement of a thermocouple to measure temperatures.⁷ Intraprocedural somatosensory and motor-evoked potential monitoring was performed when procedures were performed

Patient, tumor, and RF ablation characteristics

Patient (No.)	Age/Sex (yr)	Anatomic Site	Nidus Size (mm)	Distance ^a (mm)	Ablation Time (min:sec)	Articulation	Wattage	Follow-Up (mo)
1 ^b	32/M	C5 lateral mass	8 × 7 × 5	5	6:09	Yes	3 and 5	27
2	16/M	C7 transverse process	10 × 8 × 7	1	5:23	Yes	3 and 5	26
3	15/F	L2 superior articular process	10 × 9 × 9	2	1:55	Yes	3 and 5	23
4	6/M	C7 superior articular process	13 × 9 × 8	0	5:41	No	3 and 5	19
5	13/M	T10 pedicle	19 × 15 × 13	0	9:04	No	3 and 5	11
6	18/F	L2 vertebral body	7 × 6 × 6	0	9:08	Yes	3 and 5	6
7	13/M	C5 superior articular process	10 × 9 × 7	4	9:57	No	3 and 5	1

^a Shortest distance from the central canal/neuroforamen. A distance of 0 mm indicates that the nidus involved the cortex, compromising the central canal or neuroforamen.

^b This patient's data have been previously published.⁸

with the patient under general anesthesia for early detection of potentially impending thermal nerve/spinal cord injury.⁷ Additionally, an immediate postablation prophylactic ipsilateral nerve root block was performed when the nidus abutted the neuroforamen with no intact cortex. This was achieved by neuroforaminal injection of 10 mg of dexamethasone to improve postablation inflammation.

RESULTS

Seven spinal osteoid osteomas were RF-ablated using the targeted multidirectional bipolar electrode system. All ablations were technically successful with no complications. All tumors were accessed via a single osseous channel. Biopsy was performed in 5 patients, and all were diagnostic of osteoid osteoma. No biopsy specimen was obtained in patient 3, and the nidus was not accessible using a transpedicular approach with a straight biopsy needle in patient 6 due to the central location in the posterior vertebral body. All patients had complete pain resolution following the procedures. Patient 4 developed slight intermittent pain 4 months following the procedure, which remained unchanged at the 19-month follow-up. Details of the patient cohort are summarized in the Table.

DISCUSSION

This initial report demonstrates that unique features of the targeted navigational bipolar STAR Tumor Ablation System successfully used to treat spinal metastases and primarily appendicular osteoid osteomas^{5,8-11} can also be used for safe and effective treatment of spinal osteoid osteomas. Radiofrequency ablation of spinal osteoid osteomas poses a unique challenge due to the proximity of neural structures, particularly considering the location of most lesions within the posterior spinal elements. Preserved spinal cortical bone, flow of CSF, and the epidural space have been described as protective factors against undesired RF energy propagation.¹² Our experience highlights the importance of precise real-time monitoring of ablation zone volume and geometry made possible by 2 active embedded thermocouples along the electrode, a feature that is a recent development in RF ablation electrode design technology. This allows the operator to ensure that sufficiently high temperature is generated over a volume that encompasses the entire nidus while minimizing the risk of undesired thermal injury, and it is vital when ablating close to the spinal cord or nerve roots.

CSF and vessels may result in convective cooling (heat-sink effect) that hinders RF energy deposition within the nidus. In our experience, variable power settings provided by the MetaSTAR Generator permit slow ramping of temperatures. We believe this results in reduction of heat sink and improvement of efficacy while minimizing undesired heat dispersion and impedance is-

sues, particularly in densely mineralized lesions. The 3 cases in this series in which the osteoid osteoma nidus was <1 mm from the closest neural element or with no intact interposing cortex demonstrate that these lesions can be safely ablated with appropriate neural protection and careful monitoring of ablation zone dimensions (Fig 2). We recommend that both passive and active neural thermal protective measures be implemented for radiofrequency ablation of spinal osteoid osteomas, particularly with lesions closer than 5 mm to the spinal cord or nerve roots.

Because the entire nidus must be ablated to ensure a definitive cure and a nidus of >12 mm has been described as an independent risk factor for recurrence, a larger nidus may require placement of more than one straight RF electrode to achieve sufficient overlapping ablation volume through separate osseous access sites, further compromising bone integrity and predisposing to potential fracture. The articulating distal segment of the navigational system affords electrode placement within any desired location within the nidus from a single bone-entry site, a characteristic that is particularly useful in larger lesions. This feature also facilitates access to difficult-to-reach nidus locations, particularly in the cervical spine and adjacent to the vertebral body posterior wall (Fig 2), where they would otherwise be challenging to access using traditional straight RF electrodes.

In addition, the risk of skin thermal injury inherent in unipolar electrodes due to inadequate dispersion of RF energy on the skin surface at the region of grounding pads is eliminated using a bipolar RF electrode design.

CONCLUSIONS

Safe and effective CT-guided radiofrequency ablation of spinal osteoid osteomas can be achieved using a targeted navigational bipolar electrode system.

Disclosures: Jack W. Jennings—RELATED: Consulting Fee or Honorarium: Merit Medical Systems, Comments: ablation training courses and consultation; UNRELATED: Consultancy: Bard Peripheral Vascular; Expert Testimony: Bard Peripheral Vascular.

REFERENCES

- Rybak LD, Gangi A, Buy X, et al. Thermal ablation of spinal osteoid osteomas close to neural elements: technical considerations. *AJR Am J Roentgenol* 2010;195:W293-98 [CrossRef Medline](#)
- Vidoni A, Grainger M, James S. Experience of neuroprotective air injection during radiofrequency ablation (RFA) of spinal osteoid osteoma. *Eur Radiol* 2018;28:4146-50 [CrossRef Medline](#)
- Vanderschueren GM, Obermann WR, Dijkstra SP, et al. Radiofrequency ablation of spinal osteoid osteoma: clinical outcome. *Spine (Phila Pa 1976)* 2009;34:901-04 [CrossRef Medline](#)
- Albisinni U, Facchini G, Spinnato P, et al. Spinal osteoid osteoma:

- efficacy and safety of radiofrequency ablation. *Skeletal Radiol* 2017; 46:1087–94 CrossRef Medline
5. Hillen TJ, Anchala P, Friedman MV, et al. **Treatment of metastatic posterior vertebral body osseous tumors by using a targeted bipolar radiofrequency ablation device: technical note.** *Radiology* 2014;273: 261–67 CrossRef Medline
 6. Ahmed M, Solbiati L, Brace CL, et al; International Working Group on Image-Guided Tumor Ablation; Interventional Oncology Sans Frontières Expert Panel; Technology Assessment Committee of the Society of Interventional Radiology; Standard of Practice Committee of the Cardiovascular and Interventional Radiological Society of Europe. **Image-guided tumor ablation: standardization of terminology and reporting criteria—a 10-year update.** *J Vasc Interv Radiol* 2014;25:1691–705.e4 CrossRef Medline
 7. Tomasian A, Gangi A, Wallace AN, et al. **Percutaneous thermal ablation of spinal metastases: recent advances and review.** *AJR Am J Roentgenol* 2018;210:142–52 CrossRef Medline
 8. Wallace AN, Tomasian A, Chang RO, et al. **Treatment of osteoid osteomas using a navigational bipolar radiofrequency ablation system.** *Cardiovasc Intervent Radiol* 2016;39:768–72 CrossRef Medline
 9. Wallace AN, Tomasian A, Vaswani D, et al. **Radiographic local control of spinal metastases with percutaneous radiofrequency ablation and vertebral augmentation.** *AJNR Am J Neuroradiol* 2016;37: 759–65 CrossRef Medline
 10. Greenwood TJ, Wallace A, Friedman MV, et al. **Combined ablation and radiation therapy of spinal metastases: a novel multimodality treatment approach.** *Pain Physician* 2015;18:573–81 Medline
 11. Anchala PR, Irving WD, Hillen TJ, et al. **Treatment of metastatic spinal lesions with a navigational bipolar radiofrequency ablation device: a multicenter retrospective study.** *Pain Physician* 2014;17: 317–27 Medline
 12. Dupuy DE, Hong R, Oliver B, et al. **Radiofrequency ablation of spinal tumors: temperature distribution in the spinal canal.** *AJR Am J Roentgenol* 2000;175:1263–66 CrossRef Medline

Application of 3D T1 Black-Blood Imaging in the Diagnosis of Leptomeningeal Carcinomatosis: Potential Pitfall of Slow-Flowing Blood

I read the publication “Application of 3D Fast Spin-Echo T1 Black-Blood Imaging in the Diagnosis and Prognostic Prediction of Patients with Leptomeningeal Carcinomatosis” by Oh et al¹ with a great interest. The authors concluded that black-blood imaging showed a significantly higher sensitivity than contrast-enhanced gradient recalled-echo and contrast-enhanced spin-echo imaging for detecting leptomeningeal carcinomatosis.

A variety of techniques can be used to achieve blood suppression on T1-weighted imaging. The most commonly used technique, which was also used by Oh et al,¹ is a variable flip angle refocusing pulse sequence in which the protons in the vessel lumen experience the slice-selective radiofrequency pulse but flow out of the imaging section before the refocusing pulse, resulting in blood-signal suppression. This technique is widely used in high-resolution intracranial vessel wall MR imaging; however, an important pitfall with this technique is that slow-flowing blood in leptomeningeal veins, dilated arteries, or leptomeningeal collaterals can cause incomplete or lack of suppression.^{2,3} Kato et al⁴ compared 3D fast spin-echo (sampling perfection with application-optimized contrasts by using different flip angle evolutions [SPACE; Siemens, Erlangen, Germany]) and 3D gradient-echo T1-weighted MPRAGE images in patients with small parenchymal brain metastasis. Lesion detectability was significantly higher on SPACE than on MPRAGE; however, vessels were falsely reported as metastasis using both techniques. I can only imagine that this pitfall will be aggravated when assessing leptomeningeal metastasis. One way to avoid these artifacts would be to use a double inversion recovery technique, which exploits both the flow

and T1 properties of blood to suppress its signal.² This technique requires a longer acquisition time, which is a limitation in high-resolution intracranial vessel wall MR imaging, given the need for very high spatial resolution; however, this should be less of a problem in the context of metastatic disease.

In conclusion, I agree with the authors that postcontrast T1 black-blood imaging is a promising technique for the detection of leptomeningeal carcinomatosis; however, it will require further investigation to determine the best technique for blood suppression to avoid the above-mentioned pitfall.

REFERENCES

1. Oh J, Choi SH, Lee E, et al. **Application of 3D fast spin-echo T1 black-blood imaging in the diagnosis and prognostic prediction of patients with leptomeningeal carcinomatosis.** *AJNR Am J Neuroradiol* 2018; 39:1453–59 CrossRef Medline
2. Mandell DM, Mossa-Basha M, Qiao Y, et al; Vessel Wall Imaging Study Group of the American Society of Neuroradiology. **Intracranial vessel wall MRI: principles and expert consensus recommendations of the American Society of Neuroradiology.** *AJNR Am J Neuroradiol* 2017; 38:218–29 CrossRef Medline
3. Lindenholz A, van der Kolk AG, Zwanenburg JJ, et al. **The use and pitfalls of intracranial vessel wall imaging: how we do it.** *Radiology* 2018;286:12–28 CrossRef Medline
4. Kato Y, Higano S, Tamura H, et al. **Usefulness of contrast-enhanced T1-weighted sampling perfection with application-optimized contrasts by using different flip angle evolutions in detection of small brain metastasis at 3T MR imaging: comparison with magnetization-prepared rapid acquisition of gradient echo imaging.** *AJNR Am J Neuroradiol* 2009;30:923–29 CrossRef Medline

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REPLY:

We appreciate Dr. Nabavizadeh's interest and comments on our article, "Application of 3D Fast Spin-Echo T1 Black-Blood Imaging in the Diagnosis and Prognostic Prediction of Patients with Leptomeningeal Carcinomatosis."¹ We agree that poorly suppressed blood vessels often mimic leptomeningeal enhancement on the black-blood imaging; in particular, slow-flowing blood in leptomeningeal veins, dilated arteries, or leptomeningeal collaterals can be incompletely suppressed using a variable flip angle refocusing pulse sequence.² However, we evaluated the consecutive sections of the images rather than the 1 image section, allowing anatomic differentiation between leptomeningeal vessels and leptomeningeal enhancement because the floating curvilinear enhancement pattern of leptomeningeal vessels is somewhat different from that in leptomeningeal carcinomatosis. The use of multiplanar reconstruction images may also be helpful in avoiding this kind of misinterpretation.

As Dr. Nabavizadeh has mentioned, among the various techniques for blood suppression on T1-weighted imaging, other methods such as the double inversion recovery technique may be an alternative to avoid this pitfall. However, the double inversion recovery technique requires longer acquisition times because of the time needed for spins to reach the null point.^{3,4} This disadvantage becomes more problematic as spatial coverage increases, and it can be difficult to use routinely in clinical practice. However, we agree that further investigation is warranted to determine the best technique for blood suppression to avoid the above-mentioned pitfall.

Our alternative suggestion is that 3D gradient-echo T1-weighted MPRAGE images can be used with black-blood imaging for better differentiation between leptomeningeal vessels and lep-

tomeningeal enhancement than with a single application of black-blood imaging, which also needs further study.

REFERENCES

1. Oh J, Choi SH, Lee E, et al. **Application of 3D fast spin-echo T1 black-blood imaging in the diagnosis and prognostic prediction of patients with leptomeningeal carcinomatosis.** *AJNR Am J Neuroradiol* 2018; 39:1453–59 CrossRef Medline
2. Kato Y, Higano S, Tamura H, et al. **Usefulness of contrast-enhanced T1-weighted sampling perfection with application-optimized contrasts by using different flip angle evolutions in detection of small brain metastasis at 3T MR imaging: comparison with magnetization-prepared rapid acquisition of gradient echo imaging.** *AJNR Am J Neuroradiol* 2009;30:923–29 CrossRef Medline
3. Mandell D, Mossa-Basha M, Qiao Y, et al; Vessel Wall Imaging Study Group of the American Society of Neuroradiology. **Intracranial vessel wall MRI: principles and expert consensus recommendations of the American Society of Neuroradiology.** *AJNR Am J Neuroradiol* 2017; 38:218–29 CrossRef Medline
4. Park J, Kim EY. **Contrast-enhanced, three-dimensional, whole-brain, black-blood imaging: application to small brain metastases.** *Magn Reson Med* 2010;63:553–61 CrossRef CrossRef

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Towards Reproducible Results: Validating CT Hemorrhage-Detection Algorithms on Standard Datasets

We read with great interest the work by Chang et al¹ entitled, “Hybrid 3D/2D Convolutional Neural Network for Hemorrhage Evaluation on Head CT.” Using a custom hybrid 3D/2D variant of the feature pyramid network, they have developed algorithms with excellent accuracy for detecting and classifying bleeds and quantifying bleed volumes. This study has the essential role of showing the importance of using a Convolutional Neural Network (CNN) for automated reporting of hemorrhages in CT of the brain. This would be useful in detecting traumatic brain injury-related bleeds and various spontaneous intracranial hemorrhages. The accuracy in distinguishing different types of bleeds is also impressive. The bleed identification time for the trained algorithm is 0.121 seconds, which is incredibly fast, given that a radiologist would take 3–5 minutes on average.

There is, however, a substantial drop in sensitivity of small intracerebral hemorrhages (ICHs) and extradural hematomas (EDHs) in the test datasets. This drop could be due to overfitting on the training dataset because the number of small (0.01–5.0 mL) ICHs and EDHs is relatively lower on the training set.

As the authors have pointed out, they have trained their algorithm limited to their institution imaging system, and performance of the tool may drop, given the heterogeneity in data ac-

quisition in various machines. This overfitting on the training dataset would delay adoption of the tool in other clinical settings.

Presentation of the results in standard publicly available test datasets (<http://headctstudy.qure.ai/dataset>) such as CQ500² would make the results more accurate and comparable. It would also be helpful if the authors could host the testing dataset used in the validation of their tool as a comparison for future studies in automated hemorrhage detection and quantification.

Disclosures: Gowtham R is an intern in Quantiphi Inc, India. This work is not related to his present work at Quantiphi Inc.

REFERENCES

1. Chang PD, Kuoy E, Grinband J, et al. **Hybrid 3D/2D convolutional neural network for hemorrhage evaluation on head CT.** *AJNR Am J Neuroradiol* 2018;39:1609–16 CrossRef Medline
2. Chilamkurthy S, Ghosh R, Tanamala S, et al. **Development and validation of deep learning algorithms for detection of critical findings in head CT scans.** *Computer Vision and Pattern Recognition*. <https://arxiv.org/abs/1803.05854>. Accessed August 5, 2018 arXiv: 1803.05854v2

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REPLY:

Thank you very much for your keen and insightful comments. We furthermore congratulate your team on both the incredibly large dataset and impressive results across various head CT findings in the reference that has been provided.¹

Looking back on our experimental data, we saw no difference in algorithm performance between the training dataset and each respective cross-validation fold across all hemorrhage sizes. Instead of overfitting, the slight relative drop in algorithm performance for small-volume (<5 mL) hemorrhage likely relates to the inherent difficulty in identifying subtle CT findings, as well as a degree of interpreter subjectivity in differentiating microhemorrhage from punctate high-density mimics (Fig 1C in our original article), especially without corresponding comparison studies, advanced imaging, or clinical history that may otherwise be available in routine practice. Furthermore, no statistically significant differences in performance were noted between cross-validation and test datasets, while acknowledging the overall low number of punctate ($n = 4$, <0.1 mL) and small ($n = 11$, <5 mL) test set hemorrhages.

However, while no significant overfitting was observed in our internal dataset, we agree that generalization of deep-learning algorithms remains an unsolved challenge for the Artificial Intelligence (AI) medical imaging community. To some extent, this relates to difficulty in the curation of large, diverse datasets shared among multiple institutions; in the United States, a number of logistic barriers and concerns for robust patient anonymization are key bottlenecks. To this end, we applaud the impressive curation effort and open-source release of data in the provided reference.¹

However, a large dataset alone does not guarantee generaliz-

ability. For true clinical relevance and widespread adoption, an AI tool must be flexible enough to generalize across use cases and clinical contexts. For example, the referenced dataset and corresponding trained algorithms¹ do not include any postoperative CT scans, patients with postsurgical changes or hardware, or pediatric patients. While this exclusion may make sense in certain clinical contexts (eg, community hospitals or outpatient clinics), these exclusion criteria account for a significant population at most large academic centers in the United States; algorithms trained using such a dataset may thus fail to generalize against hardware streak artifacts or other high-density mimics that are commonly seen in such a setting. Conversely, an algorithm optimized for high disease prevalence and rare entities seen at an academic center may produce too many false-positives in a more routine, healthy population.

This issue of generalizability and a number of other key practical considerations remain key unsolved problems that must be addressed before the potential of medical deep learning is realized on a large scale. To this end, we look forward to working alongside your capable team and the radiology deep-learning community across the world to identify solutions to these problems and together build the next generation of AI-enabled tools.

REFERENCE

1. Chilamkurthy S, Ghosh R, Tanamala S, et al. **Development and validation of deep learning algorithms for detection of critical findings in head CT scans.** March 13, 2018. <https://arxiv.org/pdf/1803.05854.pdf>. Accessed August 5, 2018

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Vessel Wall Enhancement in Treated Unruptured Aneurysms

We read with great interest the article “Vessel Wall Enhancement in Unruptured Intracranial Aneurysms: An Indicator for Higher Risk of Rupture? High-Resolution MR Imaging and Correlated Histologic Findings,” published in the *American Journal of Neuroradiology* by Larsen et al.¹ The authors found that wall enhancement in vessel wall MR imaging is associated with inflammatory cell invasion, neovascularization, and the presence of vasa vasorum, factors that provide valuable information for unruptured aneurysm risk stratification.¹ Previous studies have suggested that aneurysm wall inflammation may precede, rather than result from, rupture. In as much as inflammation affects aneurysm growth and rupture, vessel wall enhancement may be a marker of rupture risk.²

However, we would like to discuss the clinical importance of the presence of aneurysm wall enhancement, detected by high-resolution MR imaging after treatment. We present the case of a 68-year-old woman with an unruptured anterior cerebral artery aneurysm treated with a flow diverter. Follow-up 3T MR angiography 1 month after flow-diverter placement showed magnetic susceptibility artifacts in the A1 portion of the right anterior cerebral artery, secondary to the flow diverter. The aneurysm, which measured 1.7×1.5 cm, had a T1-hyperintense signal within it due to thrombosis or slow flow induced by the treatment. Subtraction of the precontrast from the postcontrast enhanced vessel wall images revealed a thin rim of enhancement around the aneurysm wall, without edema in the surrounding parenchyma (Figure). The patient was asymptomatic at the time of the examination and is being monitored as an outpatient.

A thin rim of circumferential contrast enhancement around a treated aneurysm is commonly seen in contrast-enhanced TOF-MR angiography following treatment and should be an expected finding. This contrast enhancement is thought to be attributed to a combination of organized peripherally distributed intra-aneurysmal thrombosis, vasa vasorum within the adventitial layer of the aneurysm wall, and/or growth of vascularized tissue into an implanted coil mass or flow diverter due to inflammation or healing.³

Guan et al⁴ described 3 patients with intracranial aneurysms

treated with flow diversion. Post treatment vessel wall high-resolution MR imaging to evaluate aneurysm obliteration revealed intra-aneurysm thrombus development, reduced aneurysm filling, and vessel wall enhancement of the aneurysm sac in all 3 patients. Although the authors did not discuss the significance of the wall enhancement detected by vessel wall imaging, all 3 patients were clinically well and in outpatient follow-up, like the case presented here. In such post treatment scenarios, vessel wall enhancement detected by high-resolution vessel wall MR imaging may be of no clinical significance and not a sign of elevated rupture risk, though this technique is more sensitive to inflammatory changes, atherosclerotic plaques, arterial dissection, and other causes of intracranial arterial narrowing than TOF-MR angiography.²

Hence, whereas vessel wall enhancement of nontreated intracranial aneurysms seen in high-resolution vessel wall imaging may be a marker of rupture risk,^{1,2} wall enhancement of a treated aneurysm may not necessarily be pathologic, though there is a lack of studies addressing the utility of vessel wall imaging in treated aneurysms in the literature.

REFERENCES

1. Larsen N, von der Brelie C, Trick D, et al. **Vessel wall enhancement in unruptured intracranial aneurysms: an indicator for higher risk of rupture? High-resolution MR imaging and correlated histologic findings.** *AJNR Am J Neuroradiol* 2018;39:1617–21 CrossRef Medline
2. Mandell DM, Mossa-Basha M, Qiao Y, et al; Vessel Wall Imaging Study Group of the American Society of Neuroradiology. **Intracranial vessel wall MRI: principles and expert consensus recommendations of the American Society of Neuroradiology.** *AJNR Am J Neuroradiol* 2017; 38:218–29 CrossRef Medline
3. Wallace RC, Karis JP, Partovi S, et al. **Noninvasive imaging of treated cerebral aneurysms, Part I: MR angiographic follow-up of coiled aneurysms.** *AJNR Am J Neuroradiol* 2007;28:1001–08 CrossRef Medline
4. Guan J, Karsy M, McNally S, et al. **High-resolution magnetic resonance imaging of intracranial aneurysms treated by flow diversion.** *Interdisciplinary Neurosurgery* 2017;10:69–74 CrossRef

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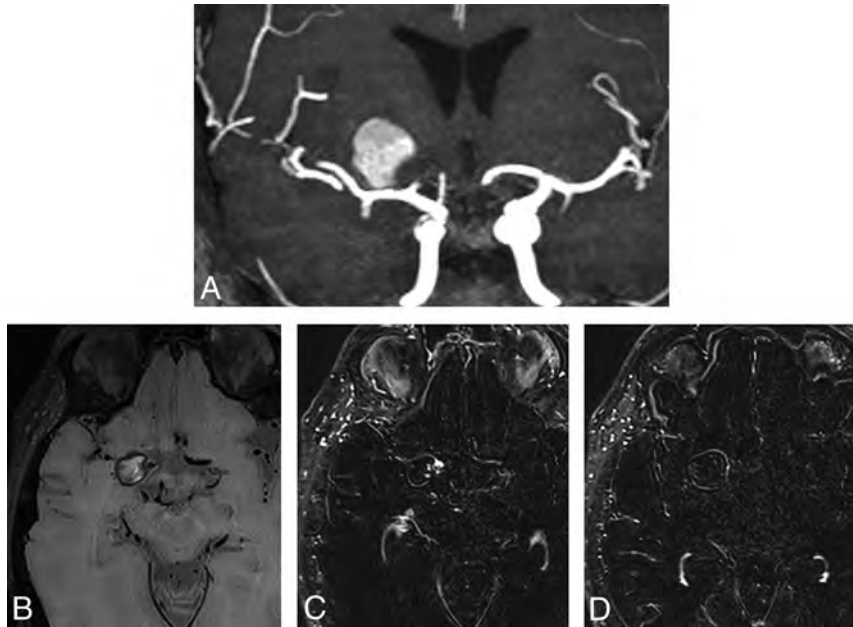


FIGURE. A, Maximum intensity projection of TOF-MR angiography shows an aneurysm adjacent to the A1 portion of the right anterior cerebral artery. B, T1 black-blood vessel wall imaging without contrast shows a hyperintense signal area inside the aneurysm due to treatment-induced thrombosis or slow flow. C and D, Subtraction of precontrast from postcontrast enhanced vessel wall images shows a thin rim of enhancement around the aneurysm wall and the flow diverter.

REPLY:

We thank Dr Corrêa and colleagues for their interest in providing feedback for our recent article, “Vessel Wall Enhancement in Unruptured Intracranial Aneurysms: An Indicator for Higher Risk of Rupture? High-Resolution MR Imaging and Correlated Histologic Findings.”¹ We described our findings in MR vessel wall imaging in unruptured middle cerebral artery aneurysms and correlated histologic features and proposed a possible association among aneurysm wall enhancement attributable to inflammatory cell invasion, wall degeneration, and higher risk of rupture.

Dr Corrêa and colleagues pointed out that mural enhancement might not be associated with a higher risk of progression and rupture in endovascularly treated aneurysms.

We agree that wall enhancement in intracranial vessels is not necessarily pathologic or associated with a poorer prognosis. Endovascular treatment of aneurysms with coiling or flow diversion substantially alters hemodynamic, morphologic, and subsequently histologic conditions in the aneurysm wall and the adjacent segments of the parent vessel. Mural enhancement in these patients might still be of diagnostic value, but the lack of long-term follow-up data addressing this issue makes it difficult, for the time being, to assess its relevance.

Moreover, mural enhancement occurs in intracranial vessels in proximity to the dural penetration and is believed to be attributable to the presence of the vasa vasorum.² Therefore, the significance of wall enhancement in unruptured aneurysms located in these vessel segments (eg, paraophthalmic internal carotid artery, posterior inferior cerebellar artery origin) ought to be critically and separately investigated.

Furthermore, among intracranial aneurysms, various entities have been described that possibly differ in pathogenesis, morpho-

logic features, progression rate, and clinical course.³⁻⁵ In our opinion, further investigation of distinct MR vessel wall imaging features in saccular-versus-fusiform, sidewall-versus-bifurcation, and small-versus-large aneurysms is in order.

REFERENCES

1. Larsen N, von der Brölie C, Trick D, et al. **Vessel wall enhancement in unruptured intracranial aneurysms: an indicator for higher risk of rupture? High-resolution MR imaging and correlated histologic findings.** *AJNR Am J Neuroradiol* 2018;39:1617–21 [CrossRef Medline](#)
2. Portanova A, Hakakian N, Mikulis DJ, et al. **Intracranial vasa vasorum: insights and implications for imaging.** *Radiology* 2013;267:667–79 [CrossRef Medline](#)
3. Baharoglu MI, Lauric A, Gao BL, et al. **Identification of a dichotomy in morphological predictors of rupture status between sidewall- and bifurcation-type intracranial aneurysms.** *J Neurosurg* 2012;116:871–81 [CrossRef Medline](#)
4. Wiebers DO, Whisnant JP, Huston J 3rd, et al. International Study of Unruptured Intracranial Aneurysms Investigators. **Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment.** *Lancet* 2003;362:103–10 [Medline](#)
5. Varble N, Tutino VM, Yu J, et al. **Shared and distinct rupture discriminants of small and large intracranial aneurysms.** *Stroke* 2018;49:856–64 [CrossRef Medline](#)

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The authors regret that in the article “In Vivo Imaging of Venous Side Cerebral Small-Vessel Disease in Older Adults: An MRI Method at 7T” (Shaaban CE, Aizenstein HJ, Jorgensen DR, et al. *AJNR Am J Neuroradiol* 2017;38:1923–28; <https://doi.org/10.3174/ajnr.A5327>), the legend for Fig 1 contained an error. The figure does not contain data used for the analyses. Instead, this is an illustration of the protocol used for tracing. The figure with the corrected legend is reproduced below.

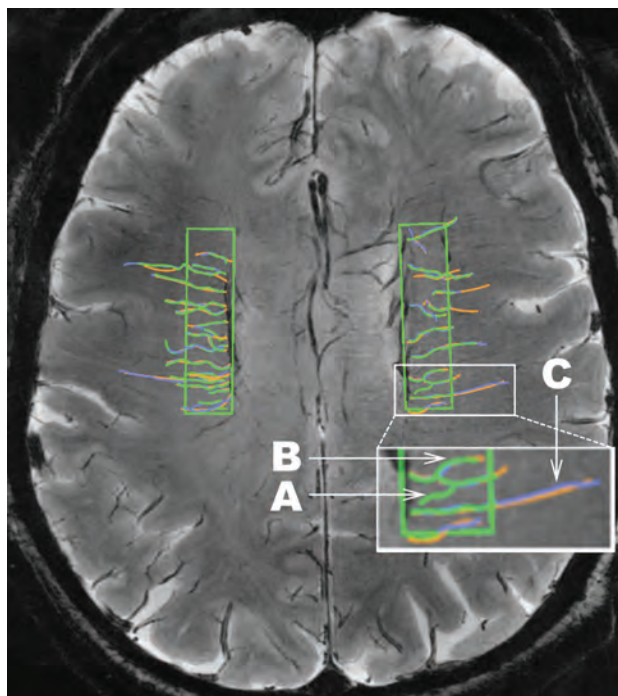


FIG 1. An illustration of the consensus venular tracing method used on SWI at 7T across ROIs in both hemispheres in the LIFE MRI study. Each rater traces the venules. A different color (green, purple, orange) is assigned to each rater, and the 3 sets of tracings are then overlaid. The inset in white is shown at larger magnification at the bottom of the figure to illustrate the following: A, Depiction of a venule that would not be included in the dataset because it was traced by only 1 of the 3 raters (green). B, An example of a tortuous venule. C, An example of a straight venule. Note that this illustration does not represent real data.

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