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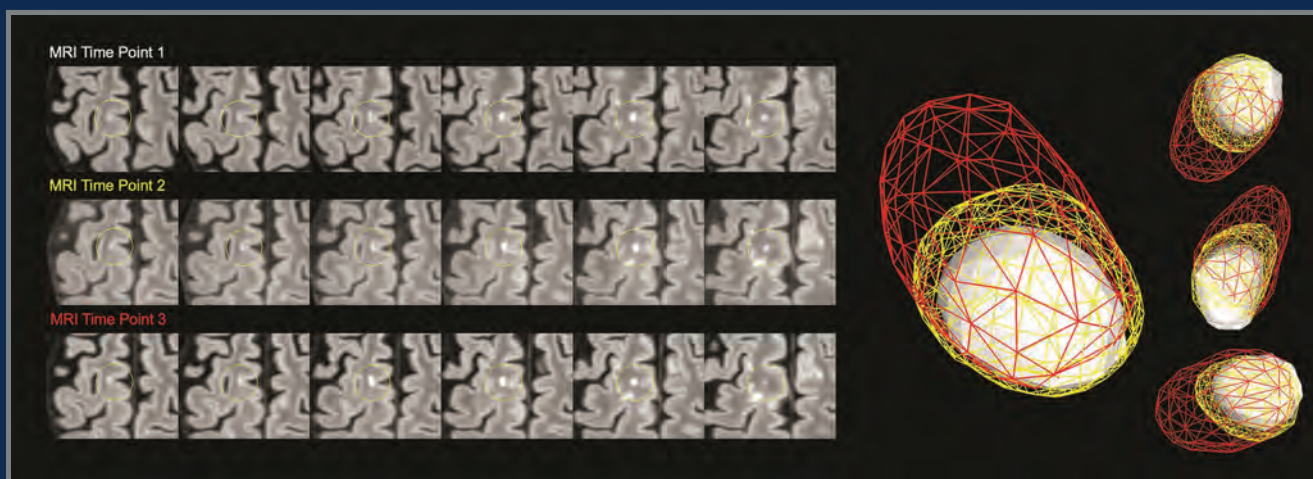
THE JOURNAL OF DIAGNOSTIC AND INTERVENTIONAL NEURORADIOLOGY

Gadolinium in patients with chronic kidney disease monitoring

Radiomics-based differentiation of glioblastoma and metastatic disease

IAC vascular loops and audiovestibular symptoms

β -Trace protein: Potential biomarker for CSF-venous fistulas



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VOLUME 46
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EDITORIAL

- 225 **The Generation Gap in Work Values Has Hit Medical Training**
John C. Benson

HEALTH POLICIES/
QUALITY IMPROVEMENT/
EVIDENCE-BASED
NEUROIMAGING

STATE OF PRACTICE

- ★ 227 **State of Practice: ASNR Statement on Gadolinium-Based Contrast Agent Use in Patients with Chronic Kidney Disease** *Kirk M. Welker, et al.*

HEALTH POLICIES/
QUALITY IMPROVEMENT/
EVIDENCE-BASED
NEUROIMAGING

REVIEW ARTICLES

- ☰ 231 **Cerebrovascular Anomalies in the Fetus** *Camilo Jaimes, et al.*

PEDIATRIC NEUROIMAGING

- ☰ 240 **Meningioma: Molecular Updates from the 2021 World Health Organization Classification of CNS Tumors and Imaging Correlates** *Neetu Soni, et al.*

BRAIN TUMOR IMAGING

GENERAL CONTENTS

- ☰ 251 **Quantification of Collateral Supply with Local-AIF Dynamic Susceptibility Contrast MRI Predicts Infarct Growth** *Mira M. Liu, et al.*

NEUROVASCULAR/
STROKE IMAGING

- ☞ 259 **Assessment of Attenuation in Pericarotid Fat among Patients with Carotid Plaque and Spontaneous Carotid Dissection** *Mohammed O. Alalfi, et al.*

NEUROVASCULAR/
STROKE IMAGING

- ☰ 265 **The Etiology of Intracranial Artery Stenosis in Autoimmune Rheumatic Diseases: An Observational High-Resolution MR Imaging Study** *Shun Li, et al.*

NEUROVASCULAR/
STROKE IMAGING

- ☰ 272 **Clinical Outcome of Pipeline Embolization Device with and without Coils to Treat Intracranial Aneurysm: A Systematic Review and Meta-Analysis** *Irfan Kesumayadi, et al.*

NEUROINTERVENTION

- ☰ 278 **Endovascular Thrombectomy versus Medical Management for Acute Basilar Artery Occlusion Stroke in the Elderly** *Huanwen Chen, et al.*

NEUROINTERVENTION

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	285	Image Quality Evaluation for Brain Soft Tissue in Neuroendovascular Treatment by Dose-Reduction Mode of Dual-Axis “Butterfly” Scan <i>Hisayuki Hosoo, et al.</i>	NEUROIMAGING PHYSICS/FUNCTIONAL NEUROIMAGING/ CT AND MRI TECHNOLOGY
		293 Imaging and Anesthesia Protocol Optimization in Sedated Clinical Resting-State fMRI <i>Elmira Hassanzadeh, et al.</i>	NEUROIMAGING PHYSICS/FUNCTIONAL NEUROIMAGING/ CT AND MRI TECHNOLOGY
	302	Advanced Distance-Resolved Evaluation of the Perienhancing Tumor Areas with FLAIR Hyperintensity Indicates Different ADC Profiles by MGMT Promoter Methylation Status in Glioblastoma <i>Gergely Bertalan, et al.</i>	BRAIN TUMOR IMAGING
	311	“Synthetic” DSC Perfusion MRI with Adjustable Acquisition Parameters in Brain Tumors Using Dynamic Spin-and-Gradient-Echo Echoplanar Imaging <i>Francesco Sanvito, et al.</i>	BRAIN TUMOR IMAGING
	321	Radiomics-Based Differentiation of Glioblastoma and Metastatic Disease: Impact of Different T1-Contrast-Enhanced Sequences on Radiomics Features and Model Performance <i>Girish Bathla, et al.</i>	BRAIN TUMOR IMAGING ARTIFICIAL INTELLIGENCE
	330	Predicting Post-Operative Side Effects in VIM MRgFUS Based on THalamus Optimized Multi Atlas Segmentation (THOMAS) on White-Matter-Nullled MRI: A Retrospective Study <i>Sonoko Oshima, et al.</i>	NEURODEGENERATIVE DISORDER IMAGING
	341	Diagnostic Performance of ASL-MRI and FDG-PET in Frontotemporal Dementia: A Systematic Review and Meta-Analysis <i>Richard Dagher, et al.</i>	NEURODEGENERATIVE DISORDER IMAGING
	349	The “Outline Sign”: Thin Hyperenhancing Perimeter as an MR Imaging Feature of Meningioma. A Useful Tool in the Temporal Bone Region for Differentiating Meningiomas from Schwannomas and Paragangliomas <i>Anil K. Vasireddi, et al.</i>	HEAD AND NECK IMAGING
	355	Comparison of Imaging Findings between Granulomatosis with Polyangiitis and Eosinophilic Granulomatosis with Polyangiitis on Sinus CT: Importance of High-Density Opacification of the Paranasal Sinuses <i>Inseon Ryoo, et al.</i>	HEAD AND NECK IMAGING
		362 Pre- and Postoperative Imaging of Cochlear Implantation in Cadaveric Specimens Using Low-Dose Photon-Counting Detector CT <i>Bjoern Spahn, et al.</i>	HEAD AND NECK IMAGING
		372 The Association of Vascular Loops within the Internal Auditory Meatus or Contacting the Vestibulo-Cochlear Nerve with Audiovestibular Symptoms: A Systematic Review and Meta-Analysis <i>Jake E. Cowen, et al.</i>	HEAD AND NECK IMAGING
	380	Quantitative Susceptibility Mapping with Source Separation in Normal Brain Development of Newborns <i>MinJung Jang, et al.</i>	PEDIATRIC NEUROIMAGING
	390	Dextromethorphan-Associated Neurotoxicity with Cerebellar Edema Syndrome in Young Children: Neuroimaging Features <i>Smily Sharma, et al.</i>	PEDIATRIC NEUROIMAGING
	395	Reversible Perfusion Changes during Acute Attacks in Glucose Transporter Type 1 Deficiency Syndrome: A Pediatric Case Series <i>Francesco Pacchiano, et al.</i>	PEDIATRIC NEUROIMAGING
		401 Safety and Technical Performance of Bilateral Decubitus CT Myelography Using Standard versus Increased Intrathecal Iodinated Contrast Volume <i>Diogo G.L. Edelmuth, et al.</i>	SPINE IMAGING AND SPINE IMAGE-GUIDED INTERVENTIONS
	408	Azygos Vein Stenosis in Frontotemporal Dementia Sagging Brain Syndrome <i>Wouter I. Schievink, et al.</i>	SPINE IMAGING AND SPINE IMAGE-GUIDED INTERVENTIONS
		416 β -Trace Protein as a Potential Biomarker for CSF-Venous Fistulas <i>Ian T. Mark, et al.</i>	SPINE IMAGING AND SPINE IMAGE-GUIDED INTERVENTIONS

-  421 **CSF-Venous Fistulas Arising Intraosseously within Bone Remodeled by Meningeal Diverticula** *Ajay A. Madhavan, et al.*
-  426 **Spontaneous Intracranial Hypotension Associated with Vascular Malformations** *Mark D. Mamlouk, et al.*
- 433 **Performance of the CT-Guided C1–C2 Facet (Lateral Atlantoaxial Joint) Injection** *Ryan D. Stockard, et al.*
- 434 **CT-Guided C2 Dorsal Root Ganglion Injection and Radiofrequency Ablation for Cervicogenic Headache** *J. Levi Chazen*
-  435 **Quantitative Susceptibility Mapping in Adults with Persistent Postconcussion Symptoms after Mild Traumatic Brain Injury: An Exploratory Study** *Tiffany K. Bell, et al.*
-   443 **Dynamic Expansion and Contraction of Multiple Sclerosis T2-Weighted Hyperintense Lesions Are Present below the Threshold of Visual Perception** *Darin T. Okuda, et al.*
- 451 **ERRATUM**
- LETTERS**
- 452 **Nidus of Brain AVMs: What If We Hadn't Understood Anything?** *Frédéric Clarençon, et al.*
- 454 **Letter to the Editor regarding “Automated Volumetric Software in Dementia: Help or Hindrance to the Neuroradiologist?”** *Dirk Smeets*
- 456 **Reply** *Jody Tanabe*

**SPINE IMAGING AND
SPINE IMAGE-GUIDED
INTERVENTIONS**

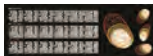
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**ULTRA-HIGH-FIELD
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As the ability to accurately evaluate longitudinal MRI data is essential to assess disease advancement, stability, or improvement, Okuda et al, retrospectively determined the dynamic changes of T2-weighted hyperintense lesions over 3 MRI time points. The 3D visual model illustrates the dynamic expansion of the multiple sclerosis demyelinating lesion between MRIs at different time points, which is not appreciated on the 2D axial MR images.

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The Generation Gap in Work Values Has Hit Medical Training

 John C. Benson

I serve as the director of Mayo Clinic's Resident Leadership Academy, a training program that develops foundational skills in our residents. As an educator and a midcareer physician, I am exposed to the concerns of both trainees and senior-level clinicians. So, I can confirm what many already suspect: There is a considerable divide in how different generations think of work and work-life balance. And its impact could be serious. Unless we help these groups understand each other's perspectives, we risk having this issue upend our training environment and future careers.

I know, I know. It is not just medicine that is affected. Across industries, there is a boisterous disagreement regarding how much, and how hard, people should work. The topic is predictably contentious: Employers gripe about lazy attitudes and entitlement, while young workers contend they are simply more attuned to the perils of burnout and place higher value on mental and physical wellness.

Why, then, does it feel so conspicuous in medicine? Partly, it is because of a string of educational reform policies that took place during the last decades. Medical schools and residency training programs, desperate to rein in trainee work hours and combat fatigue and medical errors, enacted a series of wellness initiatives. Grades were often eliminated. Resident work hours were restricted. And residency programs began directly engaging in mental health, offering class retreats, lectures, and - yes - yoga lessons as emotional outlets.

The senior physicians I have spoken to think these efforts, though commendable, were misguided. To them, the recent trend toward overly protective training environments led to decreased resident confidence and independence. Many also believe that these initiatives displaced, rather than solved, the pressures of medical education. Take the USMLE Step 1, for example. The examination, previously a primary mechanism by which residency programs evaluated medical students, recently became pass/fail. However, our trainees say this did little to diminish stress. Applicants interested in highly competitive residencies instead felt compelled to excel in other areas such as the USMLE Step 2, research, and letters of recommendation.

Most, however, are reluctant to publicly denounce antiburnout efforts. Those that have spoken out garnered significant attention. Dr. Amy Holthouser, a professor of pediatrics at the University of Louisville, went low-level viral for her comments in a *New England Journal of Medicine* podcast on the topic. In it, she expressed concern that attempts to improve trainee well-being led to a gradual creep in time off. Because incoming residents expected these allowances, any such changes had doubtful lasting effects on burnout rates. "Our main goal here is not to make [trainees] happy," she said, "[It] is to provide them with an education, mentorship, coaching, and guidance."¹

Let me be very clear: Burnout is real. It affects every level of medical professional, from students to late-career physicians. At its worst, burnout is unexpected, sudden, and has devastating consequences. I've seen it. Four years ago, a woman from my residency class died by suicide, which took an indescribably profound toll on her family, friends, and colleagues.² She was the colleague that never said no, and the system overworked her. It's less raw now, but it forever colored the way I view work and wellness.

For example, I believe workaholic clinicians are on inexorable paths toward occasional burnout. Physicians are not all built alike. However, the "gunners" keep their cups nearly full. They operate at 95% capacity, jammed with clinical efforts, research, education, and family commitments. Any person functioning at that intensity, regardless of their talent, dedication, or capability to manage stress, is perpetually at risk to tip past the breaking point. Even those who endure make substantial sacrifices to their physical and mental health and their relationships.

That behavior doesn't exactly set a healthy example. It also rings hollow to the younger generation. At each session of our leadership course, I invite a high-ranking speaker to share their "leadership journey" and engage in a Q&A session. Inevitably, the attendees steer the conversation toward work hours and finding harmony between their careers and homelife. Rarely do they get a satisfactory response. "It's doable," offered a medical school dean in a particularly stupefying exchange. "I just wake up early and swim laps in a nearby lake. And then I do pushups between meetings. I aim for 1000 each day."

However, while overworking is a threat, it is also irrefutable that medical training requires a tremendous amount of effort. Ask any medical student or resident, and they will tell you: there are no shortcuts. When I was a medical student, I remember studying until it felt like my brain hurt. My career is just as taxing; it seems impossible to learn enough. Even now, as a subspecialized neuroradiologist, I am constantly humbled by what I do not know.

So, residents, understand this: The luxuries offered to you did not exist 20, or even 10, years ago. Do not be surprised if there are limitations to the empathy you receive from your seniors. Most physicians will publicly, and sincerely, support initiatives to curb burnout. But those same people will share occasional jokes about your "wellness days" behind closed doors.

Boomers, it is the residents who think they will have the last laugh. Although you will soon look back at storied careers, your accomplishments and long CVs came at the expense of your personal well-being. Trainees are impressed, and sometimes in awe, of your achievements. But squeezing in pushups between meetings is no one's idea of wellness.

Somewhere between the outgoing gunners and incoming wellness seekers is that almost mystical word: balance. It's a fickle target, and it doesn't look the same for everyone. "I've given up on trying to achieve harmony in my daily life," a hospital CEO recently told our class. "I've come to accept that I need to find it over weeks and months."

Leaders and educators throughout medicine therefore have a Herculean task: to optimize physician wellness while maintaining

clinical excellence. To do so, they must navigate our generational divide, in which the same work week is viewed by some as a chronic grind and by others as a slide toward mediocrity. Ultimately, however, it is important to remember that we are all aiming for the same balance: feeling purpose in coming to work, and contentment in leaving it.

[Disclosure forms](#) provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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State of Practice: ASNR Statement on Gadolinium-Based Contrast Agent Use in Patients with Chronic Kidney Disease

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ABSTRACT

BACKGROUND: Beginning in 2006, neuroradiologists became increasingly aware of the risk of nephrogenic system fibrosis (NSF) when patients with chronic kidney disease (CKD) received gadolinium-based contrast agents (GBCAs) in conjunction with MRI scans. Radiology practices began withholding GBCAs from MRI patients with substantial CKD and instated a variety of safety measures to ensure that these individuals did not inadvertently receive GBCAs. As a result, the worldwide incidence of NSF was dramatically reduced. Since that time, a wealth of research on NSF and its etiology has found few unconfounded cases associated with those GBCAs categorized as group II agents by the American College of Radiology.

METHODS: In 2023 and 2024, members of the American Society of Neuroradiology (ASNR) Standards and Guidelines Committee reviewed new research evidence on GBCA safety and its relevance to current MRI contrast administration guidelines for patients with CKD. This focused on systematic reviews and meta-analyses conducted during the past 5 years. Upon consideration of this literature, recommendations for the administration of GBCAs to patients with CKD were formulated.

KEY MESSAGE: For neuroimaging applications, the ASNR recommends that group II GBCAs no longer be withheld in patients with CKD when these agents are medically indicated for diagnosis. Moreover, if group II GBCAs are exclusively used in an MRI practice, other safety measures, such as checking renal function or querying patients about CKD, can be discontinued.

ABBREVIATIONS: ACR = American College of Radiology; ASNR = American Society of Neuroradiology; CKD = chronic kidney disease; GBCA = gadolinium-based contrast agent; NSF = nephrogenic systemic fibrosis; eGFR = estimated glomerular filtration rate

The use of intravenous gadolinium-based contrast agents (GBCAs) is an important means of increasing diagnostic sensitivity and specificity in a wide variety of neurologic MRI applications.¹ Moreover, the administration of a GBCA bolus forms the basis for a variety of neurovascular examinations, such as dynamic susceptibility contrast perfusion imaging and gadolinium bolus MRA. Since their inception, GBCAs have demonstrated a favorable safety profile with very few adverse outcomes despite millions of gadolinium doses administered since the introduction of the first agent, gadopentetate dimeglumine (Magnevist), in 1988.² Nevertheless, in 2006, case reports and epidemiologic studies began

to implicate GBCA administration as a causative factor in the development of nephrogenic systemic fibrosis (NSF) in patients with compromised renal function.³ Given the serious and chronic nature of NSF, with reported mortality rates of up to 31%, various measures were undertaken by radiology practices across the world as a means of preventing new cases of NSF.⁴ These included questioning patients receiving GBCAs about any history of renal disease, acquiring laboratory measures of renal function such as estimated glomerular filtration rate (eGFR), and withholding GBCAs in those patients exhibiting historical or laboratory evidence of Class IV or V chronic kidney disease (CKD) or acute kidney injury.^{5,6}

Eventually, a mechanistic model of NSF emerged. GBCAs consist of elemental gadolinium bound within a chelate molecule that allows for its circulation and excretion.⁷ In patients with renal compromise, impaired urinary excretion leads to prolonged gadolinium circulation time within the blood. Over time, the chelate molecules can become unstable, releasing free gadolinium to deposit within a variety of bodily tissues.⁸ In rare circumstances, the deposition of unchelated gadolinium leads to NSF.⁹ It soon became clear that differing levels of chelate instability made some GBCAs more prone than others to cause NSF.^{7,10} In general, GBCAs with a linear chelate demonstrated more propensity to cause NSF in patients with CKD because their molecular

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Gadolinium-based contrast agents by ACR groups¹¹

ACR Group	Generic Name	Product Name(s)	Chemical Structure	3T Relaxivity
I	Gadopentetate dimeglumine	Magnevist (Bayer)	Linear/ionic	3.7
I	Gadodiamide	Omniscan (GE HealthCare)	Linear/nonionic	4
I	Gadoversetamide	Optimark (Guerbet)	Linear/nonionic	4.5
II	Gadobenate dimeglumine	Multihance (Bracco)	Linear/ionic	5.5
II	Gadoterate meglumine	Clariscan (GE HealthCare), Dotarem (Guerbet)	Macrocytic/ionic	3.5
II	Gadobutrol	Gadavist (Bayer), Gadovost (Bayer)	Macrocytic/nonionic	5
II	Gadoteridol	Prohance (Bracco)	Macrocytic/nonionic	3.7
II	Gadopiclenol	Elucirem (Guerbet), Vueway (Bracco)	Macrocytic/nonionic	11.6
II	Gadoxetate disodium	Eovist (Bayer), Primovist (Bayer)	Linear/ionic	6.2

structures bind elemental gadolinium less tightly than GBCAs with a macrocyclic chelate.⁷

ACR GBCA CATEGORIZATION

The varying risk for NSF among GBCAs prompted the American College of Radiology (ACR) to categorize GBCAs into 3 groups as outlined in the Table.¹¹ Group I GBCAs include the linear molecular agents gadopentetate dimeglumine (Magnevist), gadodiamide (Omniscan), and gadoversetamide (Optimark). These group I GBCAs carry the highest risk of NSF for renal compromised patients and are expressly contraindicated by the FDA for use in patients with an eGFR of less than 30 mL/min/1.73 m².¹² On the other hand, group II GBCAs, which include all the macrocyclic GBCAs, as well as the linear GBCAs gadobenate dimeglumine (Multihance) and gadoxetate disodium (Eovist/Primovist), are associated with very few unconfounded cases of NSF.^{13,14} In specific, there have been only 9 published case reports of unconfounded cases of NSF associated with group II GBCAs.¹⁵

ACR group III is reserved for GBCAs for “which data remains limited regarding NSF risk, but for which few, if any unconfounded cases of NSF have been reported.”¹¹ At the present time, there are no GBCAs assigned to group III. The agent gadoxetate disodium was reclassified from group III to group II in April 2024.¹¹ While there are no unconfounded cases of NSF resulting from gadoxetate disodium, data regarding the use of this agent in patients with stage IV or V CKD is limited. Only 106 cases of gadoxetate disodium administration to patients with stage IV or V CKD have been reported in the literature and none of these developed NSF.¹⁶ Of note, there are currently no neurologic applications for gadoxetate disodium. This GBCA is most often used for MR hepatobiliary imaging.¹⁷ Consequently, gadoxetate disodium is outside the scope of this statement.

It is important to understand that the risk stratification in the ACR-defined GBCA groups applies to patients with CKD and is not applicable to those with acute kidney injury. Although rare cases of NSF have been reported in patients with acute kidney injury, there are currently very little data available on the NSF risk associated with the various GBCAs in these patients.¹⁸

DECLINING NSF INCIDENCE

Once radiologists began withholding group I GBCAs from patients with renal disease as stipulated by various regulatory agencies including the FDA, Health Canada, and the European

Medicines Agency, the worldwide incidence of NSF dramatically dropped.^{19–21} Moreover, ever increasing amounts of research data have confirmed the safety of group II GBCAs, which demonstrate little risk for NSF even in patients with advanced CKD. Most of this research was subjected to a meta-analysis that was published by Woolen and colleagues in 2020.²² In this well-conducted meta-analysis that comprised 16 unique studies with 4931 patients, the risk of NSF in patients with stage IV or V CKD was found to be <0.07% if the risk even exists. Given that the benefit of GBCA administration likely outweighs the minuscule risk of acquiring NSF from a group II agent, there is growing consensus among both radiologists and nephrologists that withholding medically indicated group II GBCAs in patients with Stage IV or V CKD is unnecessary.²³ The most recent ACR Manual on Contrast Media states “the ACR Committee on Drugs and Contrast Media considers the risk of NSF among patients exposed to standard or lower than standard doses of group II GBCAs is sufficiently low or possibly nonexistent such that assessment of renal function with a questionnaire or laboratory testing is optional before intravenous administration.”¹¹

ASNR RECOMMENDATIONS

In this context, a subcommittee appointed by the American Society of Neuroradiology (ASNR) Standards and Guidelines Committee reviewed recent high-level evidence regarding the risk of NSF after administration of GBCAs in patients with CKD. The search terms “nephrogenic systemic fibrosis,” “gadolinium,” as well as “systemic review” or “meta-analysis” were employed in a PubMed search for manuscripts published during the past 5 years (2019 to 2024). Eight publications met these search criteria. Three publications that focused on the treatment of NSF, intra-arterial administration of gadolinium, and solely on the GBCA gadoxetate disodium were excluded as not being pertinent to the issue under consideration.^{16,24,25} After these exclusions, there were 4 remaining systematic reviews as well as the previously cited meta-analysis by Wollen and colleagues.^{13,15,18,22,26} After considering this literature, the Standards and Guidelines Committee, on behalf of the American Society of Neuroradiology, provides the following recommendations:

1. As mandated by the FDA, group I GBCAs should never be given to patients with a history of CKD.
2. In neuroimaging applications, group II GBCAs should not be withheld from patients with CKD over concern for NSF.

3. If there is a valid clinical indication for GBCA administration, group II GBCAs can be administered to patients with stage IV or V CKD without obtaining informed consent. As with all patients, GBCAs should only be administered when considered necessary by the supervising radiologist and should be given at the lowest dose needed for diagnosis.
4. If only group II GBCAs are employed in clinical practice, routinely questioning MRI patients about their history of renal disease or obtaining laboratory measures of renal function is unnecessary.
5. Recently, a newly approved high relaxivity GBCA was added to group II: gadopicholol (Elucirem/Vueway).²⁷ This agent is expected to have a favorable safety profile because of its macrocyclic chelate. While gadopicholol is probably safe in patients with CKD, this needs to be confirmed as the experience with this new contrast agent increases. Furthermore, this unknown risk needs to be assessed in the perspective that gadopicholol allows the same or higher image enhancement while administering only one-half the amount of gadolinium atoms compared with other contrast agents, which may have some advantages in terms of potential gadolinium retention, especially in patients who will receive multiple doses of gadolinium contrast agent over the course of time.^{28,29}
6. Although very few cases of NSF have been reported in the pediatric population as compared with adults with CKD, the above recommendations are applicable to pediatric patients with CKD.³⁰ As always, caution should be exercised in the administration of GBCAs to neonates and infants where the possibility of renal immaturity exists.

CONCLUSIONS

In summary, scientific research over the last decade has established the safety of group II GBCAs for use in patients with CKD. As long as group II GBCAs are employed, the risk of NSF as the result of a gadolinium-enhanced MRI scan is minuscule, if it even exists. Neuroradiologists should not withhold group II GBCAs in patients with CKD when contrast-enhanced MRI is clinically indicated for diagnosis. The potential benefit of a gadolinium-enhanced MRI scan greatly outweighs any risk of NSF when appropriate GBCAs are employed.

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Cerebrovascular Anomalies in the Fetus

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ABSTRACT

SUMMARY: Four distinct vascular anomalies can be seen to affect the brain on fetal imaging: vein of Galen malformations, nongalenic arteriovenous pial fistulas, dural sinus malformations, and intracranial venous malformations. These congenital disorders affect the arteries and veins of the developing brain and are rarely seen beyond the neonatal stage. The 4 fetal cerebrovascular anomalies are associated with quite disparate natural histories and prognoses. MRI plays a pivotal role in the evaluation of fetuses with these conditions because of its ability to definitively establish the diagnosis, to detect subtle parenchymal injuries, to delineate the course of abnormal vessels in detail and to some extent the nature of vascular flow, and to identify ischemic, thrombotic, and hemorrhagic complications. Recently, an investigational transuterine embolization procedure targeted at treating fetuses with vein of Galen malformations who are at high risk for neonatal decompensation has emerged as a promising alternative to expectant management and postnatal embolization, with imaging being used to identify suitable patients for the intervention and in preprocedural planning. This manuscript reviews the essential imaging and clinical features of these 4 fetal neurovascular anomalies and underscores the practical aspects related to counseling, prognosis, and the multidisciplinary management of these entities.

ABBREVIATIONS: b-SSFP = balanced steady-state free precession; DSM = dural sinus malformation; icVM = intracranial venous malformation; RASA1 = RAS P21 protein activator 1; SSFSE = single-shot fast spin-echo; VOGM = vein of Galen malformation

Historically, congenital cerebral vascular anomalies were diagnosed in symptomatic neonates postpartum.^{1,2} The improvements in fetal ultrasonography and MRI now allow for the detection and characterization of these anomalies prenatally. Despite the low incidence of these conditions in the general population, these disorders are collectively encountered with relative frequency in subspecialized maternal-fetal care centers and children's hospitals.^{3,4} To interpret these diagnostic studies accurately, radiologists must be familiar with the imaging characteristics, natural progression, and clinical trajectory of this distinctive group of disorders.

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In this manuscript, we review the key imaging and clinical features of 4 congenital cerebrovascular lesions: vein of Galen malformation (VOGM), nongalenic pial AVFs, dural sinus malformations (DSMs), and intracranial venous malformations (icVMs). We will emphasize the role of fetal MRI in the diagnosis and triage of these conditions, covering all aspects of image acquisition and interpretation. Furthermore, we will highlight the similarities and differences among these disorders and frame the discussion around practical implications pertinent to counseling and multidisciplinary management of the respective entities. Rarely, other vascular lesions that typically occur in late childhood and adulthood, such as cerebral cavernous malformations, have been reported in fetal life.⁵ These lesions will not be covered in detail in this manuscript, as their fetal onset constitutes an exception to their usual epidemiology, and their biology and appearance are distinct from the 4 unique lesions described above.

IMAGING

Most fetal cerebrovascular anomalies are diagnosed during the routine second-trimester fetal sonography.⁶ Fetal sonography not only allows for early detection of these malformations but also allows for the identification of vascular flow by utilizing color Doppler analysis.⁷⁻⁹ Invariably, a fetal MRI should be obtained in

MRI protocol for evaluation of fetal cerebrovascular anomalies

Sequence	Plane	TR/TE (msec)	In-Plane Voxel Dimension (mm)	Slice Thickness mm (Through-plane)	Acceleration Factor (iPat)
T2 SSFSE (maternal) ^a	Sag, Cor	1400/118	1×1	3–4	2
T2 SSFSE	Sag, Cor, Ax	1400/99	1×1	3–4	2
b-SSFP	Sag, Cor, Ax	4.25 /1.81	1×1	3–4	2
T1-weighted gradient-echo	Sag, Cor, Ax	3.64/1.35	1×1	2	2
Echo-planar T2* imaging	Sag, Cor, Ax	6670/81	1×1	2	—
DWI ^b	Ax, Cor	3000–4600/68	2×2	3–4	2

Note:—Parameters provided for a 3T Magnetom VIDA (Siemens) utilizing an 18-channel abdominal coil.

Ax indicates axial; Cor, coronal; Sag, sagittal.

^aMaternal acquisition utilizes a large field of view of approximately 400 × 400 mm to provide full coverage of the uterus.

^bDiffusion parameters include 6–12 directions, $b = 0 \text{ sec/mm}^2$ and $b = 700 \text{ seconds/mm}^2$.

cases where a neurovascular anomaly is suspected to confirm the diagnoses, characterize the anatomy, and evaluate for any parenchymal injuries.^{10,11}

MRI is the preferred imaging technique to evaluate fetuses suspected of having intracranial vascular lesions. Its high-quality soft tissue contrast offers insights into the brain parenchyma, and its multiplanar capabilities allow for the precise localization of abnormalities. Moreover, the large field of view images provide information about the entire fetus, which sheds light on possible systemic hemodynamic repercussions of the intracranial abnormalities. Fetal MRI is performed without sedation or intravenous contrast, and the images can be acquired by using either 1.5 or 3T magnets. In-depth knowledge of these vascular disease processes and their appearance on MRI allows the interpreting physician to assess fetal neuroanatomy and flow dynamics and comment on potential ischemic, hemorrhagic, or thrombotic complications.¹² The Table summarizes the fetal MRI protocol utilized at the authors' institution for the evaluation of these entities.

Neuroanatomic images are acquired with rapid MRI techniques. T2-weighted single-shot fast spin-echo (SSFSE) sequences use a long echo-train length to efficiently sample k -space and encode 1 slice per repetition time. Due to its spin-echo acquisition, flow within large vessels manifests as a signal void.^{12,13} Anatomic images are also acquired with a balanced steady-state free precession (b-SSFP) sequence. In this rapid gradient-echo technique, flowing blood appears hyperintense. This sequence has a high SNR, beneficial for delineating small structures and mitigating artifacts (eg, dielectric effect); however, tissue characterization is somewhat limited by its mixed T1/T2 contrast properties.^{12,13} These 2 sequences constitute the workhorse for the anatomic evaluation of normal and abnormal vascular structures, the parenchyma, and the CSF spaces.

DWI is a crucial component of fetal neurovascular protocols. Most centers acquire fetal DWI with b -values of $b = 0$ and $b = 700$ to preserve SNR. Institutions may opt to apply diffusion encoding gradients in 3–12 noncollinear directions, balancing acquisition speed and SNR. Diffusion-weighted MR imaging allows for the detection of acute ischemic injury and organized clots.^{14,15} T2*-weighted sequences rely on an echo-planar imaging acquisition with a long time-to-echo to accentuate transverse magnetization decay and are helpful for detecting blood products and venous congestion.¹⁶

A rapid gradient-echo T1-weighted sequence can cover the entire uterus in a single breath-hold. Evaluating the parenchyma for foci of T1 shortening can pinpoint areas of subacute injury

that may be unapparent on T2 SSFSE or b-SSFP. T1 hyperintense signal may also reveal subacute blood products within a clot.¹² Furthermore, due to the gradient-echo acquisition with a short repetition time, the sequence is sensitive to flow effects, aiding in the detection of fast-flow within vascular structures.⁴

More recently, Sampaio and colleagues¹⁷ have refined a 2D time-of-flight technique, another gradient-echo acquisition variant, to highlight flow-related signals within fetal vessels. The results of this preliminary study are promising, with consistent identification of the torcular herophili, vein of Galen, internal cerebral veins, basilar artery, and middle cerebral artery. However, due to the relatively long acquisition time, exceeding 3 minutes, the sequences had substantial artifacts in over 70% of cases.¹⁷ It is likely that with further developments in image acceleration techniques and with the extension of this work to 3T MRI, the results will be enhanced, thus enabling reliable identification of these and other major vascular structures.

FETAL CEREBROVASCULAR ANOMALIES

Vein of Galen Malformation

A VOGM, while constituting less than 1% of all intracranial vascular malformations, is the most commonly seen congenital brain vascular anomaly, occurring in approximately 1:58,100 deliveries¹⁸ and makes up nearly one-third of intracranial vascular anomalies in children.^{19,20} These malformations develop between the 6th and 11th weeks of gestation during cerebral angiogenesis.⁶ Recent genetic analysis has identified mutations in *RASA1*, Ephrin type-B receptor 4, activin A receptor like type 1, neurogenic locus notch homolog protein 1, integrin subunit beta 1, and protein tyrosine phosphatase non-receptor type 11 in VOGM probands, with endothelial cells localized spatiotemporally at the affected cellular locus.²¹ VOGMs result from pathologic fistulous connections between the choroidal arteries and the median prosencephalic vein, resulting in a high-flow arteriovenous lesion that induces arterialization of flow in the median prosencephalic vein with progressive dilation.^{3,10} Notably, the term “malformation of the vein of Galen” is a misnomer, as ontologically, the anomaly precedes the establishment of a mature vein of Galen, and the locus of the malformation is in the anterior aspect of the prosencephalic vein, which normally involutes entirely.⁶

Imaging. Despite their embryologic origin in early gestation, VOGMs are rarely detected before the second trimester's detailed anatomic survey and, occasionally, are identified even later.^{22,23} Sonographically, the malformation presents as a midline hypoechoic

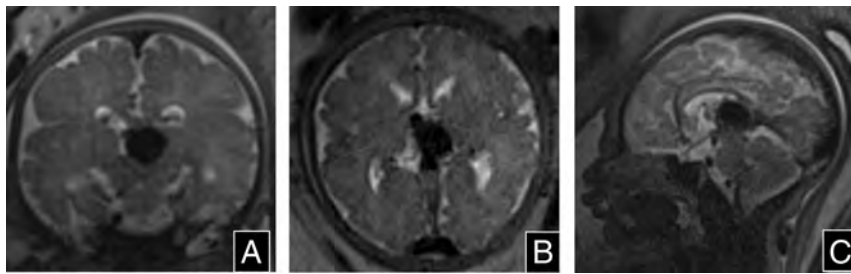


FIG 1. Vein of Galen malformation in a 35-week-old fetus. SSFSE in the (A) coronal, (B) axial, and (C) sagittal planes shows a varix in the quadrigeminal cistern corresponding to the dilated median prosencephalic vein. No parenchymal injury was identified.

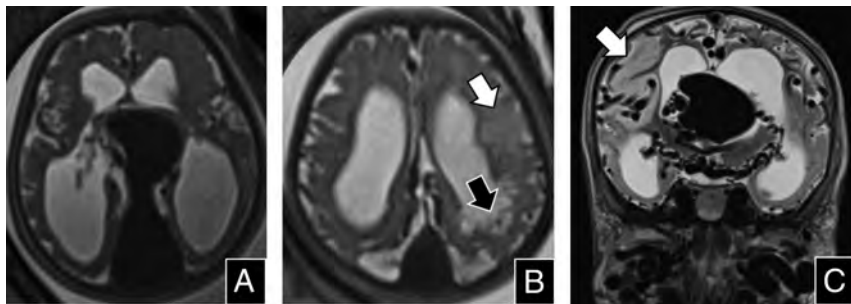


FIG 2. Vein of Galen malformation with parenchymal injuries in a 35-week-old fetus. A, Axial T2 SSFSE shows a dilated median prosencephalic varix, falcine sinus, and torcular, as well as ventriculomegaly. B, Axial T2 SSFSE shows areas of cystic degeneration (black arrow) and T2 hyperintensity in the left frontal lobe (white arrow), representing venous ischemia. C, Neonatal coronal T2 image demonstrates progression of parenchymal involvement, with new areas of ischemic injury in the right frontal lobe and insula (white arrow) associated with moderate ventriculomegaly.

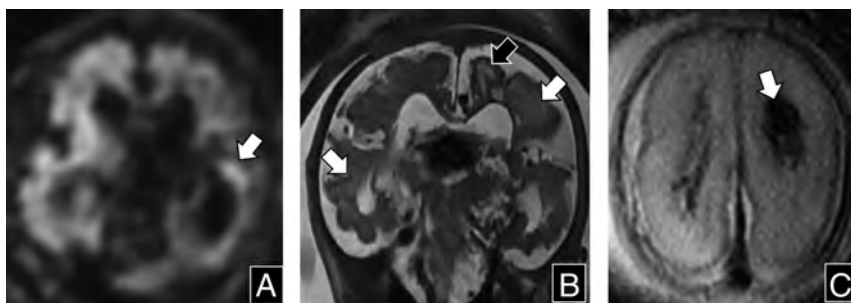


FIG 3. Parenchymal injuries in 2 fetuses with vein of Galen malformations. A, Axial DWI in a 31-week-old fetus shows restricted diffusion (white arrow) in the left temporal lobe. B, Coronal T2 SSFSE shows generalized volume loss, cystic change (black arrow), and T2 hyperintense signal (white arrows) related to encephalomalacia. C, Axial T2* echo-planar image in a different 24-week-old fetus shows hemorrhage in the left periventricular region.

lesion within the quadrigeminal cistern. Color Doppler imaging reveals rapid and turbulent flow within the varix and may, occasionally, identify the feeding arteries.⁹

On fetal MRI, the VOGM appears as a dilated varix located in the quadrigeminal cistern, just dorsal to the tectal plate (Fig 1). On T2-weighted SSFSE images, the varix presents as a large flow void, while on b-SSFP images, it exhibits as a hyperintense signal due to the flow within the lesion.²⁴ Occasionally, the high flow within the varix may appear as a hyperintense signal on T1-weighted gradient-echo images. Lasjaunias²⁵ classified VOGMs

based on the angioarchitecture of the arterial feeders into the choroidal type, characterized by numerous feeder vessels, and the mural type, which has a smaller number of large-caliber, fistulous feeders. This distinction can be apparent on T2-weighted SSFSE, leveraging the inherent contrast between the flow voids and the CSF, though most VOGMs do not neatly fit into this bifurcated paradigm, as they contain a complex inflow arterial network, within which 1 or 2 large pedicles are fistulous. The venous drainage of the varix is also distinctly outlined on imaging. The most common drainage pattern is via a persistent falcine sinus, but drainage via a straight sinus or a combination of the two is seen as well.²⁶

The fetal MRI examination also serves as a survey for nonvascular findings. Though uncommon, parenchymal injuries may occur because of progressive venous hypertension (Fig 2). DWI can reveal areas of decreased diffusivity in the deep white matter indicative of venous ischemia.²⁷ Additionally, zones of venous congestion and hemorrhage may become apparent as areas of low signal intensity on T2*-weighted sequences (Fig 3). As injury progresses, cystic encephalomalacia may develop. In the late subacute or chronic phases, injuries from these causes might present as nonspecific areas of T1 hyperintense or T2 hypointense signal. Mild ventriculomegaly is often observed in fetuses with VOGM, likely stemming from elevated venous pressure, which impedes CSF absorption into the venous system. If the ventriculomegaly is moderate to severe or asymmetrical, the possibility of ex vacuo dilation due to tissue loss should be contemplated.²⁷

Natural History. The landscape surrounding the counseling and management of fetuses with VOGMs is evolving rapidly because of the ability to confidently prognosticate clinical presentation based on fetal imaging as well as to the advent of a prenatal treatment option.³ Until recently, management in utero was largely expectant, as only postnatal endovascular procedures were available.^{28,29} Reviewing the natural history of VOGMs, including the outcomes of patients undergoing postnatal embolization, is helpful in understanding the drive toward new therapeutic avenues and the role of imaging.

The presence of a VOGM markedly alters fetal hemodynamics by creating a large arteriovenous shunt that precipitates a state

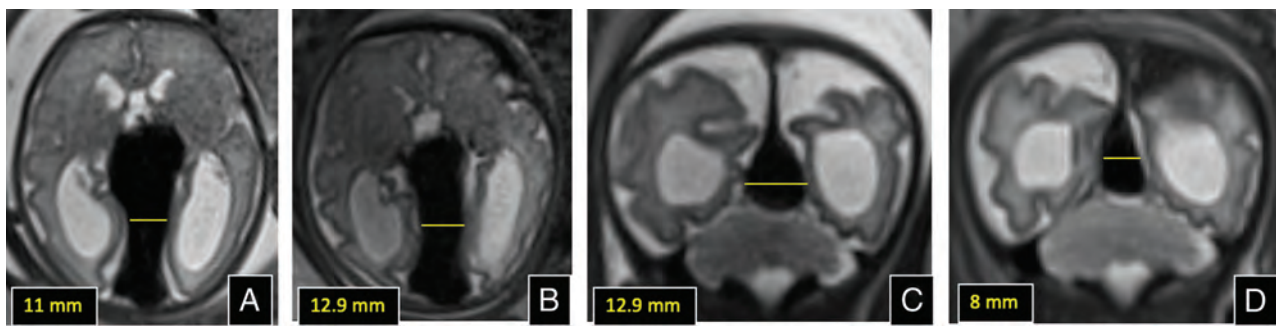


FIG 4. Measurement of the mediolateral width of the falcine sinus for consideration of fetal intervention and postintervention imaging. A, Axial T2 image at 32 weeks soon after the initial diagnosis of VOGM, with intact parenchyma and mild ventriculomegaly. B, Axial T2 image at 34 weeks, just before fetal embolization, shows interval growth in sinus width. C and D, Coronal T2 images prefetal embolization and 1-day post embolization respectively, showing diminution in width of the falcine sinus, indicative of diminution in lesional flow.

of high cardiac output with systemic repercussions.³⁰ Echocardiographic indicators of this hyperdynamic state include severe dilation of the superior vena cava, an increased cardiothoracic ratio, reversal of diastolic flow in the transverse aortic arch and sometimes the descending aorta, and right ventricular dysfunction.³¹ Fetal MRI may further illustrate high-output features such as cardiomegaly and subcutaneous tissue edema in the head, neck, and extremities.²⁴ Despite pronounced hemodynamic compromise, overt cardiac failure or cardiovascular collapse is rarely encountered prenatally, likely because of the low-resistance placental circulation's protective compensatory mechanisms.

Neuroprognostication for individuals prenatally diagnosed with VOGM is challenging.¹⁹ The rarity of this condition and variability in medical care, including the impact of pregnancy terminations and care redirection during the neonatal period, confound the reporting of long-term outcomes for fetuses newly diagnosed with VOGM. In a study spanning multiple institutions, which included 49 fetuses with VOGM, Paladini and colleagues³² reported a 37% survival rate free of neurologic complications within the overall cohort. This figure rose to 53% when excluding subjects who had undergone selective termination.³² More recently, a meta-analysis of all published fetal VOGM series from D'Amico et al³⁰ demonstrated a likelihood of 35.4% of survival past infancy free of neurologic impairment for all fetuses diagnosed with VOGM.

Patients can be more precisely categorized based on their neonatal presentation. Broadly, cases cluster into 3 distinct groups. A minority, ranging from 10%–18%, demonstrate extensive brain injuries on a neonatal brain MRI or progression of prenatally diagnosed brain injuries; these neonates are generally not considered candidates for embolization.^{32,33} A second group, comprising nearly 60% of cases, present with severe hemodynamic instability within the first 72 hours but have no substantive brain injuries. Termed “neonates at risk” by clinicians and researchers, these patients often derive benefit from prompt embolization. However, the prospects for survival with favorable neurologic outcomes are variable, ranging from 10% to 48%.^{29,33} A third group consists of neonates without brain injury and with minimal hemodynamic compromise. For these infants, embolization can be deferred until later in infancy, and they generally have a better neurologic prognosis. Known as the “infantile treatment

cohort” or “postneonatal treatment cohort,” these patients experience positive neurologic outcomes in 58%–77% of cases.^{3,29,33}

Imaging and Prenatal Risk Stratification. The previous review of clinical trajectories for neonates with VOGM underscores the vulnerability of the “neonates at risk” group, which represents the largest cohort of fetal diagnosed VOGM.³³ Although emergent postnatal embolization can be lifesaving for these neonates, it may not prevent neurologic disability.³⁰ Prenatal identification of these “at-risk” patients could open a critical window of opportunity to prevent circulatory collapse in the neonatal period and its neurologic sequelae. However, this pursuit necessitates reliable fetal biomarkers that differentiate these patients from fetuses with established brain injury,²⁷ who would not benefit from fetal intervention, and from those who are likely to have a mild neonatal course, allowing embolization to be safely deferred until infancy.

Jaimes and colleagues²⁷ investigated the significance of brain injury on fetal MRI. Their series showed that all forms of brain injury, including restricted diffusion, localized gliosis, volume loss, or venous patterns of injury, invariably progressed. This indicates that fetal MRI can reliably identify fetuses with end-organ injury to the brain who are unlikely to benefit from intervention. On the other hand, Arko and colleagues³⁴ sought to find a fetal biomarker predictive of neonatal cardiopulmonary decompensation. They found that the point of greatest constriction of the drainage pathway of the malformation, typically the falcine sinus, reliably forecasted the necessity for neonatal intervention, likely because of its function as a flow-limiting anatomic barrier. Specifically, a smaller mediolateral diameter or cross-sectional area of the falcine or straight sinus at its narrowest point correlated with a lower risk. Among these metrics, the mediolateral diameter is preferable for clinical use because of its ease of measurement. The risk of neonatal decompensation for subjects with a mediolateral diameter of 2 mm and 3 mm was 14% and 26%, respectively (Fig 4). In contrast, the risk for diameters of 9 mm and 10 mm was 93% and 96%, respectively.³⁴

Treatment (Fetal Embolization of VOGM). Over the past 2 decades, a considerable amount of evidence has accumulated demonstrating the clinical effectiveness of various fetal interventions and the technical proficiency required to implement fetal therapy programs both safely and effectively. Reflecting this advancement, a

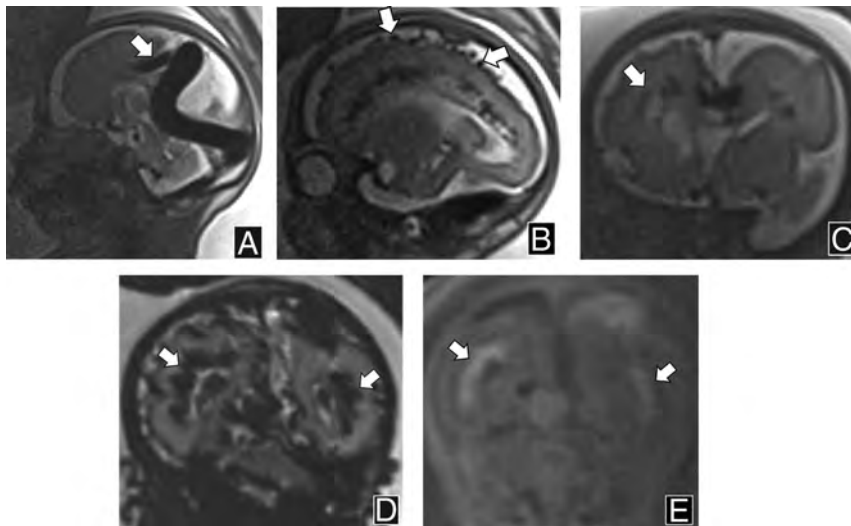


FIG 5. Pial arteriovenous fistula in a 32-week-old fetus. *A*, Sagittal T2 SSFSE shows a flow void in the frontal interhemispheric region (arrow) that drains into the deep venous system and eventually into the torcular. *B*, Sagittal T2 SSFSE through the right hemisphere shows the prominent pial vessels (white arrows), congestion of medullary veins, and developing periventricular cystic change. *C*, Coronal T2 SSFSE shows right greater than left parenchymal cystic changes (arrow), related to encephalomalacia and associated mild ventriculomegaly. *D*, Coronal T2* echo-planar image obtained 2 weeks later shows areas of blooming in the periventricular regions that correspond to areas of T1 shortening on (*E*) coronal T1 gradient-echo imaging (white arrows in *D* and *E*, respectively), related to venous congestion and subacute blood products.

multidisciplinary team at Boston Children's Hospital has launched a prospective clinical trial to evaluate the efficacy of prenatal embolization in fetuses diagnosed with VOGM who are at an elevated risk of neonatal decompensation.¹⁸ The criteria for participant inclusion and exclusion in the trial are detailed in the Online Supplemental Data.

The trial¹⁸ consists of a single embolization procedure performed via a percutaneous maternal approach with sonography guidance. Using catheters, wires, and coils identical to those used in postnatal embolizations, a team of maternal-fetal specialists, radiologists specialized in fetal imaging, and neurointerventionalists employ fetal sonography for real-time imaging and color Doppler to monitor blood flow. By relying on sonography guidance, the need for ionizing radiation is entirely circumvented. The procedure entails the transuterine insertion of an 18 G needle, guided transcranially through the occipital bone into the fetal torcular. Following this, a microcatheter and microwire are navigated to the prosencephalic varix, where embolization is performed with platinum detachable coils. The embolization aims for a packing attenuation of 15%–20%, as determined by fetal MRI measurements, to substantially reduce blood flow through the malformation while avoiding complete occlusion of the varix (Fig 4).

While the trial is still in its early stages,¹⁸ Orbach and colleagues³⁵ published a case report detailing the successful transuterine embolizations of a third-trimester fetus with a VOGM. The patient selected for the procedure was a 34-week fetus with a malformation that predicted a high risk of neonatal distress due to a falcine sinus width greater than 10 mm. Following fetal intervention, the cardiac output of the fetus decreased by 40%, and the

transverse diameter of the falcine sinus reduced from 13 to 8 mm on fetal imaging.³⁵ More notably, after birth the baby required no neonatal embolization and no cardiopulmonary support with intubation or medication; neurologic status has been normal (the patient is now 11 months old).

The postnatal management of VOGM is complex and beyond the scope of this review, which focuses on the fetal care of these patients. As mentioned above, hemodynamic stability in the first few days after birth dictates the need for early embolization. Meanwhile, sustained hemodynamic stability offers the advantageous option of delaying embolization until infancy, allowing the brain to mature and potentially improving outcomes. The manuscripts by Brinjikji et al²⁹ and Yan et al³⁶ cover these topics in detail.

Nongalenic Pial Fistulas

Less commonly, anomalous arteriovenous communications may occur between vessels located along the pial

surface of the brain. These pial AVFs are also referred to as nongalenic fistulas, emphasizing that they arise from an embryologic pathway different from VOGMs and, therefore, can occur in almost any intracranial location along the surface of the brain.³⁷

Imaging. Imaging reveals pial AVFs as dilated, tortuous vascular structures along the brain's surface. Frequently, a single enlarged draining vein is noted without an appreciable nidus.³⁸ Predictably, these vessels exhibit robust flow voids on SSFSE sequences, intermediate to high signals on b-SSFP imaging, and flow-related signals on gradient-echo T1-weighted images. A notable characteristic of pial AVFs is their off-midline position (Fig 5). When the shunt is situated over the hemispheric convexities, differentiation from a VOGM is straightforward. Nevertheless, pial AVFs may occasionally be found in the deep interhemispheric region or close to the midline in the choroidal fissure and be somewhat reminiscent of a VOGM.³⁹ The identification of asymmetrical or eccentric drainage veins that do not conform to the classic configuration of a median prosencephalic venous varix can serve to differentiate these 2 entities.

Natural History. The clinical course of pial AVFs diagnosed in utero is quite variable. Many of these present with signs of high-output cardiac failure prenatally, which may include cardiomegaly and hydrops.³⁹ Prenatal fetal MRI may reveal areas of brain injury, such as restricted diffusion, gliosis, or hemorrhage. Although based on limited observations, these injuries tend to be asymmetrical and localized to the territory involved in the fistula; this is in contrast to the more diffuse and symmetric pattern of brain injury observed in fetuses with VOGM.⁴⁰ In severe

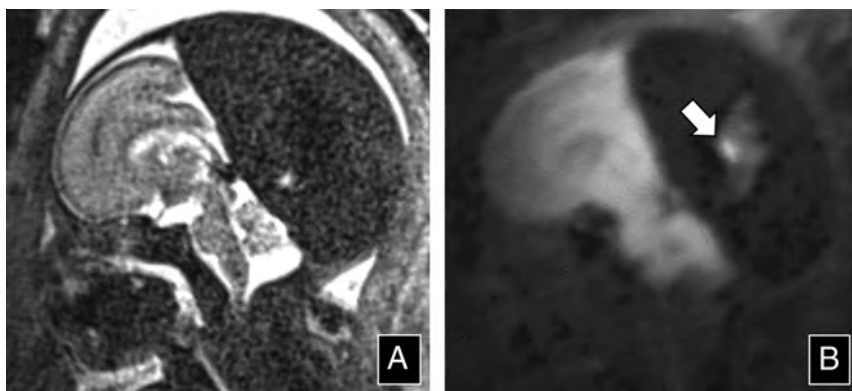


FIG 6. Dural sinus malformation in a 33-week-old fetus. *A*, Sagittal T2 SSFSE shows marked dilation of the posterior aspect of the superior sagittal sinus and torcular. *B*, Sagittal DWI confirms the presence of clot within the dilated sinus (arrow). The brain parenchyma appears normal.



FIG 7. Dural sinus malformation in a 32-week-old fetus who was referred with a diagnosis of ventriculomegaly. *A*, Fetal sonography revealed a dilated dural sinus with internal echogenicity representing clot (black arrow). The echogenicity of the parenchyma was also abnormal (white arrow), with cystic changes and volume loss associated with severe ventriculomegaly. *B*, Axial T2 SSFSE shows severe parenchymal injury with cystic encephalomalacia (white arrows), severe ex vacuo ventriculomegaly, and intermediate signal from clot within the distended torcular (black arrow). *C*, Axial T1 gradient-echo shows blood products within the torcular that demonstrate T1 hyperintensity (black arrow).

instances, brain injury may become extensive; however, a gradient of severity toward the fistula site is generally discernible. Similar to VOGM, the presence of prenatal brain injury is a dire indicator, suggesting a progressive cascade of ischemic injuries caused by venous hypertension. However, unlike for VOGM, in some cases of pial AVF, even extensive parenchymal loss adjacent to the AVF site may not be accompanied by clinical signs and symptoms, with patients demonstrating remarkable neuronal plasticity and functional remapping.³⁸

Treatment. Currently, there are no prenatal alternatives for the treatment of (nongalenic) pial AVFs. Their variable location across the brain does not lend itself well to the structured access pathway that has been devised for fetal embolization of VOGM. Pial AVFs have been associated with mutations in HHT genes and in *RASA1*⁴¹ and, invariably, these lesions require postnatal embolization, as they are high-flow shunting lesions that pose a high risk of growth and intracranial hemorrhage.⁴²

Dural Sinus Malformations

DSMs are rare intracranial congenital vascular anomalies; their precise incidence is unknown but estimated to be very low, with

less than 80 published cases in the literature before 2018.⁴³ This entity was first described in the neurointerventional literature as low-flow dural arteriovenous fistulas, presenting in neonates and infants with enlarged venous pools within the affected dural sinus, often at the torcular.^{4,43} With advancements in prenatal sonography and MRI, DSMs can now be identified before birth. A comprehensive understanding of the pathophysiology and prognosis of in utero-diagnosed DSMs is essential for appropriate counseling and management of these patients.

Imaging. Most DSMs are diagnosed during the mid-second trimester sonographic survey. Often, ultrasound can readily identify a hypoechoic and dilated venous structure at the location of the involved dural sinus.⁴⁴ Interrogation with color Doppler is crucial to confirm the vascular nature of the abnormality and to differentiate it from cystic abnormalities. An intraluminal clot may occasionally pose a diagnostic challenge, as the clot may show varying degrees of echogenicity, and demonstrating flow in a narrowed lumen can be difficult or impossible. MRI is invariably indicated in the setting of a suspected DSM to confirm the diagnosis and to assess the integrity of the brain parenchyma.⁴

Fetal MRI provides exquisite delineation of vascular and parenchymal anatomy. On T2-SSFSE images, the dilated dural sinus—often the torcular—appears as an enlarged tubular or saccular flow void (if patent) (Fig 6). On b-SSFP images, the DSM is relatively hyperintense due to the effects of flowing blood. The lumen of the dilated sinus and other intracranial venous structures must be carefully inspected for patency. A clot may appear as T1 hyperintense material with diffusion restriction within the DSM or other sinuses.⁴⁵ Signal alterations on T2 SSFSE (loss of flow void) or b-SSFP images, although more subtle, may also indicate thrombus. T2* sequences serve as valuable adjuncts to identify clots; however, findings should be corroborated on other sequences due to the inherently black-blood background (Fig 7). Finally, the T1 gradient-echo images (or a dedicated flow-sensitive sequences) should be carefully inspected for evidence of arterialized flow into the malformation, which appears to bear prognostic significance.⁴ The arteries most commonly involved in DSMs are branches of the middle meningeal artery, occipital artery, and posterior auricular artery.⁴

Natural History. It is imperative to recognize a discordance between the evolution and reported outcomes of DSMs diagnosed

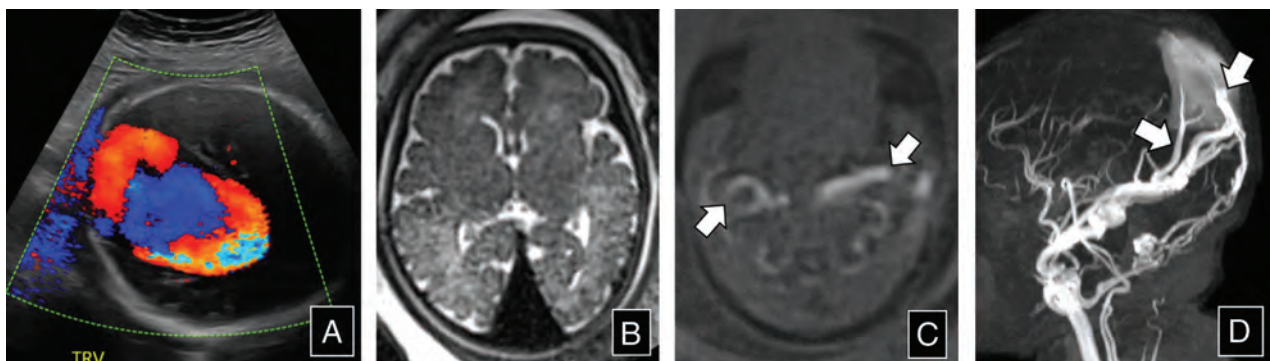


FIG 8. Dural sinus malformation in a 33-week-old fetus. A, Fetal sonography with color Doppler shows turbulent flow within a dilated torcular. B, Axial T2 SSFSE shows an enlarged flow void in the region of the torcular, without signs of clot. There were no sonographic changes in the brain parenchyma. C, Axial T1 gradient-echo shows flow-related signal within enlarged external carotid arteries bilaterally (arrows). D, 3D maximum intensity projection from the postnatal time-of-flight MRA shows arterialized flow within the dural sinus malformations and middle meningeal and occipital artery feeders (arrows).

prenatally and postnatally. Collective accounts by various investigators, including Yang et al^{4,43} and Merzoug et al,⁴⁶ indicate survival of fetuses affected by DSMs without significant neurologic sequelae in 83% and 88% of cases, respectively. These statistics contrast markedly with the classic neuroangiographic reports of DSMs diagnosed in neonates and infants, such as those detailed by Barbosa et al,⁴⁷ which presented a grim prognosis with severe neurologic disability or death in 46% of subjects. This discordance is likely due to a combination of ascertainment bias and improvement in management over the past 2 decades. Neonatal and infantile DSMs reported in the neuroangiography literature likely represented a sampling of noninvoluting malformations with unfavorable physiology, while spontaneously involuting fetal and asymptomatic neonatal DSMs likely remained undiagnosed.^{4,43}

Given the relatively low number of reported cases, describing the natural history of prenatally diagnosed DSMs remains challenging. Intraluminal thrombosis is observed almost invariably in fetal DSMs, probably due to the slow flow within the distended venous lake. In the systematic review published by Yang and colleagues,⁴³ 97% of the DSMs exhibited a spontaneous decrease in size, with a single fetus experiencing a transient increase followed by subsequent shrinkage. Although difficult to detect, arterialized flow was reported by Yang and colleagues⁴ in approximately one-third of cases (Fig 8). In their analysis, the presence of a clot and a shrinking DSM were identified as favorable prognostic factors, whereas parenchymal injury, ventriculomegaly, and the persistence of arterialized flow were associated with an adverse prognosis.^{4,43}

Treatment. Currently, there are no prenatal treatment options available for fetal DSMs, and given the prevailing notion that these entities have a favorable prognosis, such treatments are unlikely to be required. When a DSM is diagnosed in the early second trimester, it is prudent to obtain a follow-up in the third trimester to evaluate the trajectory of the DSM and the clot and to perform a query for arterialized flow. In all cases, a postnatal MRI should be obtained to further evaluate the anatomy and definitively exclude arterialized flow.

Intracranial Venous Malformations

An icVM is a recently identified entity that does not conform to a disease category recognized in the 2018 classification of the International Society for the Study of Vascular Anomalies (ISSVA) in 2018.⁴⁸ This framework recognizes brain arteriovenous malformations, arteriovenous fistulas, and cerebral cavernous malformations but does not recognize an intracranial entity homologous to venous malformations elsewhere in the body. Chen et al⁴⁹ documented the imaging characteristics of icVMs that constituted approximately 2% of the total cohort of patients with cerebrovascular anomalies reviewed in their tertiary academic referral center and that mirror those of well-known extracranial venous malformations.⁵⁰ Their research⁴⁹ includes a series of fetal and postnatal pediatric cases, describing these malformations as well-defined lobulated lesions in continuity with either the superficial or deep venous system of the brain. These differed from both the caput medusae configuration of developmental venous anomalies and from sinus pericranii lesions, as they do not span the cranial vault. In cases with postnatal presentations, the enhancement patterns on conventional angiography or postcontrast MRI matched those of other intracranial venous structures.⁴⁹

Imaging. On ultrasound, icVMs appear as well-circumscribed, extra-axial, lobulated lesions, frequently in a parafalcine or paramedian location, without arterialized flow on Doppler. Their appearance is nonspecific, and a final diagnosis is unattainable without additional imaging. On MRI, the lesions present as well-defined T2 hypointense structures, showing no indications of arteriovenous shunting, such as dilation of collecting veins or pulsatility (pulsation artifacts) (Fig 9). Chen and colleagues⁴⁹ identified 3 morphologic subtypes of icVMs: globoid, fusiform, and tubular. In their series, among the 3 cases diagnosed during fetal life, 2 were falcine, and 1 was globoid.

Natural History. The icVMs were associated with complex extracranial venous malformations in 79% of cases and with sinus pericranii in nearly 50% of cases. Consequently, fetal MRIs should be thoroughly evaluated for these potential associations. Even when such findings are not evident on prenatal imaging, postnatal MRI is advisable to fully delineate the anatomy and

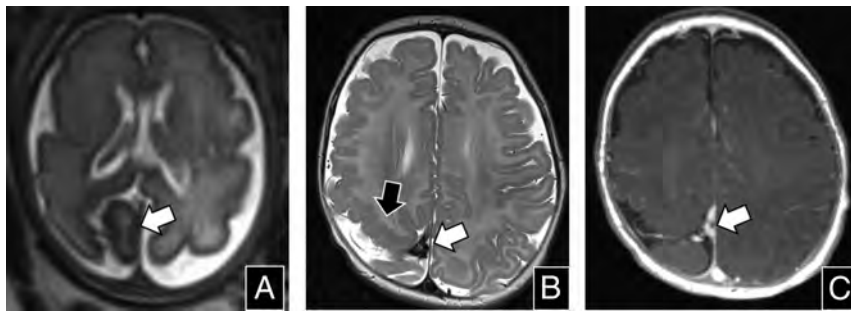


FIG 9. Intracranial VM in a 31-week-old fetus (white arrows in A to C). A, Axial T2 SSFSE shows a globoid soft tissue structure with internal signal heterogeneity located in the right posterior parafalcine region (arrow); the subjacent parietal parenchyma appears abnormally folded and hypointense. B, Axial T2 and (C) postcontrast axial MPRAGE demonstrate partial involution of the structure since the fetal examination (white arrows in B and C), with polymicrogyria adjacent to the lesion (black arrow in B). Persistent enhancement and a somewhat tubular and branching architecture are apparent on postcontrast imaging (C).

exclude associated anomalies. Although longitudinal follow-up data are scarce given the recent identification of these lesions, icVMs appear to remain stable over time and may be clinically silent.⁴⁹

Treatment. Because icVMs were only recently identified and the current evidence indicates that they are clinically silent in fetal life, there appears to be no reason to develop prenatal treatment approaches.

TAKE HOME POINTS

- In fetuses with VOGM, it is critical to recognize prognostic indicators. The presence of parenchymal injury carries a poor prognosis, as it often signifies the initiation of a venous ischemic cascade. The mediolateral (transverse) diameter of the falcine sinus should be estimated because larger dimensions predict a higher risk of neonatal hemodynamic collapse with the need for urgent embolization.
- A vascular lesion with arterial inflow, located anywhere other than the characteristic location of VOGMs, is indicative of a pial AVF. These malformations exhibit a variable prognostic range. Pial AVFs may lead to localized areas of parenchymal injury or high-output cardiac failure.
- A DSM should be considered in any fetus presenting with a dilated dural sinus, regardless of arterial inflow or the presence of a luminal clot. Most patients exhibit a favorable prognosis, independent of the size of the DSM. Shrinkage of the DSM during fetal life is reassuring. Conversely, the presence of arterialized flow may necessitate closer postnatal follow-up.
- A lobulated or “fleshy” lesion without arterial inflow should raise the possibility of an icVM, especially if parasagittal or parafalcine. As with most venous malformations in the body, the prognosis is excellent.

CONCLUSIONS

Fetal cerebrovascular anomalies represent a group of 4 conditions with diverse clinical outcomes and prognoses. Prenatal imaging, especially fetal MRI, is vital for the diagnosis and detailed

characterization of these lesions. This is increasingly important with the advent of prenatal therapeutic options for certain conditions, such as VOGM. Familiarity with the imaging features, natural history, and potential outcomes of these rare disorders is essential for the accurate interpretation of these complex studies.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Meningioma: Molecular Updates from the 2021 World Health Organization Classification of CNS Tumors and Imaging Correlates

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ABSTRACT

SUMMARY: Meningiomas, the most common primary intracranial neoplasms, account for more than one-third of primary CNS tumors. While traditionally viewed as benign, meningiomas can be associated with considerable morbidity, and specific meningioma subgroups display more aggressive behavior with higher recurrence rates. The risk stratification for recurrence has been primarily associated with the World Health Organization (WHO) histopathologic grade and extent of resection. However, a growing body of literature has highlighted the value of molecular characteristics in assessing recurrence risk. While maintaining the previous classification system, the 5th edition of the 2021 WHO Classification of Central Nervous System tumors (CNS5) book expands upon the molecular information in meningiomas to help guide management. The WHO CNS5 stratifies meningioma into 3 grades (1–3) based on histopathology criteria and molecular profile. The telomerase reverse transcriptase promoter mutations and cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*) deletions now signify a grade 3 meningioma with increased recurrence risk. Tumor location also correlates with underlying mutations. Cerebral convexity and most spinal meningiomas carry a 22q deletion and/or NF2 mutations, while skull base meningiomas have *AKT1*, *TRAF7*, *SMO*, and/or *PIK3CA* mutations. MRI is the primary imaging technique for diagnosing and treatment-planning of meningiomas, while DOTATATE PET imaging offers supplementary information beyond anatomic imaging. Herein, we review the evolving molecular landscape of meningiomas, emphasizing imaging/genetic biomarkers and treatment strategies relevant to neuroradiologists.

ABBREVIATIONS: *AKT1* = AKT serine/threonine kinase 1; *BAP1* = *BRCA1*-associated protein 1; *CDK4/6* = cyclin-dependent kinases 4 and 6; *CDKN2A/B* = cyclin-dependent kinase inhibitor 2A/B; CNS5 = Classification of Central Nervous System Tumors, fifth edition; KLF4 = Krüppel-like factor 4; mTOR = mammalian target of rapamycin; NF2 = neurofibromatosis type 2; *PIK3CA* = phosphatidylinositol-4,5-Bisphosphate 3-Kinase catalytic subunit alpha; *POLR2A* = RNA polymerase II subunit A; pTERT = telomerase reverse transcriptase promoter; *SMARCB1* = SWItch/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1; *SMO* = smoothened, frizzled class receptor; SM = spinal meningioma; SUVmax = maximum standard uptake value; TERT = telomerase reverse transcriptase; *TRAF7* = tumor necrosis factor receptor–associated factor 7; WHO = World Health Organization

Meningiomas are the most common primary intracranial extra-axial tumor, representing 37.6% of all intracranial tumors in adults. The annual age-adjusted rate is 8.58 cases per 100,000 in the United States.¹ Most (80.3%) meningiomas are located in the cerebral meninges, 4.2% in the spinal meninges, and approximately 14.7% lack a specified meningeal site.¹ Meningiomas are most frequently diagnosed between 40 and 70 years of age, with an age peak at around 65 years. Women are 2.3 times more likely to have benign (grade 1) meningiomas than

men.¹ Spinal meningiomas (SMs) account for 25%–46% of all primary spinal tumors.² The SM incidence ranges between 0.193 and 0.33 cases/100,000 persons.³ They have a strong female predilection (75%–90%), with the peak incidence after 6 decades.² The fifth edition of World Health Organization (WHO) Classification of Central Nervous System Tumors (CNS5 hereafter) incorporates molecular information to categorize meningiomas into 3 grades: benign (grade 1), atypical (grade 2), and anaplastic (or malignant, grade 3), applying atypical and anaplastic criteria to each subtype. CNS5 has recommended using an Arabic numeral grading system (1–3).^{4–6} Meningiomas originate from the arachnoid cells of the dura. They are generally benign, incidentally diagnosed, extra-axial dural-based enhancing masses at cerebral convexities, para-/suprasellar regions, tentorium, and occasionally intraventricular (Fig 1). Larger, symptomatic lesions present with mass effects, seizures, or increased intracranial pressure.^{7–10} SMs are commonly located in the thoracic (60–70%), followed by the cervical (20–30%) and lumbar region (5–10%).^{2,11,12} They present as gradual localized back

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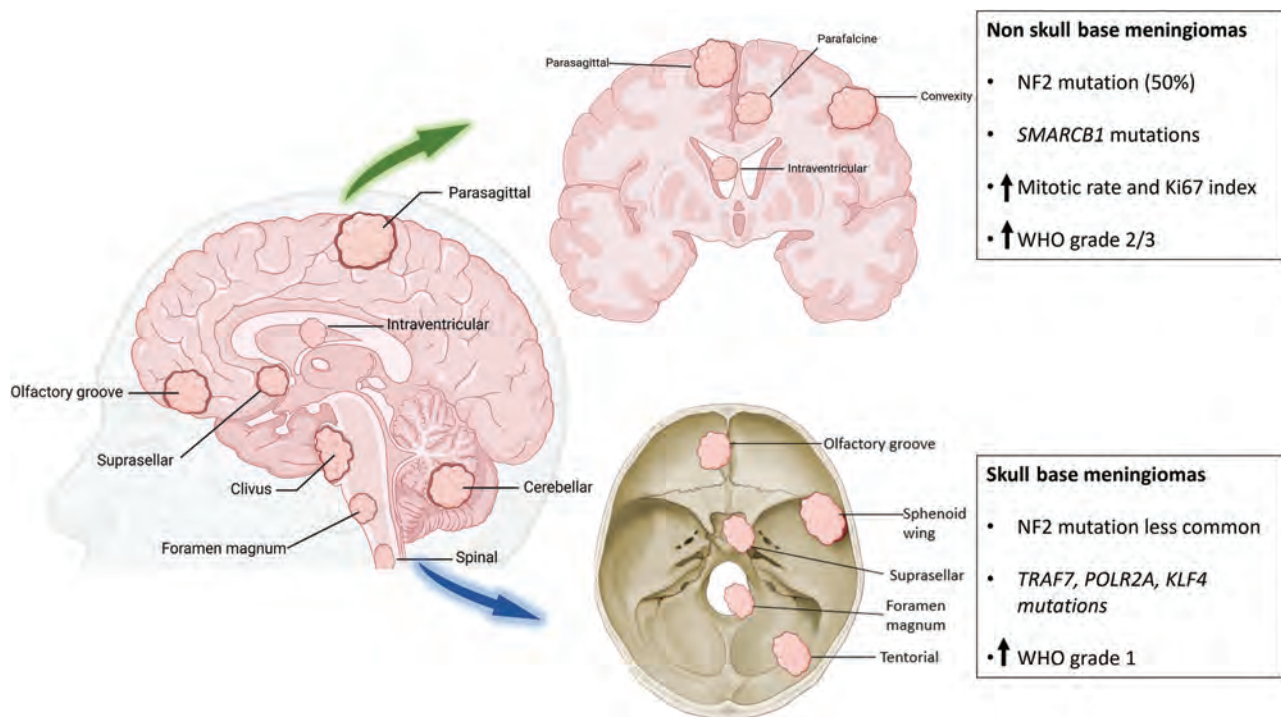


FIG 1. Illustration depicting the common location of meningiomas and associated genetic/cytogenetic alteration and grades. *NF2* and *SMARCB1* mutations are more frequently seen in convexity meningiomas. Grade 2 and 3 meningiomas are more common along the convexity than the skull base. *AKT1*, *KLF4*, *TRAF7*, and *POLR2A* genetic changes are more frequently seen in skull base meningiomas. Grade 1 is more common in the posterior fossa. Grade 2 (atypical) meningiomas are more frequently seen along the brain convexity and spine and can have a loss of a copy of chromosomes 1, 10, or 14.

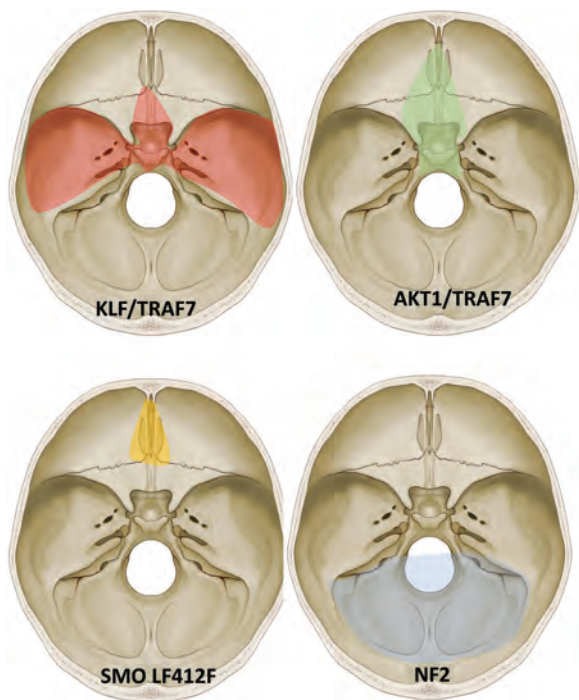


FIG 2. "Mutation map" of skull base meningiomas with a regional propensity of meningiomas dependent on specific mutations. Meningiomas arising from the sphenoid wing have *KLF4/TRA7* mutations, midline tumors have *AKT1/TRA7* mutations, and tumors originating from the olfactory groove tend to have *SMO* mutations. Meningiomas along the posterior skull base commonly have a loss of chromosome 22-loss (*NF2*). Adapted from Baranoski J. *Smardcb1-Mutant Intracranial Meningiomas: A Distinct Subtype of NF2-Mutant Tumors*, 2015. Yale Medicine Thesis Digital Library. 1947.

pain, sometimes radiating to the extremities. Cord or nerve root compression may lead to weakness, numbness, and tingling.¹¹

Meningiomas are associated with genetic syndromes, including most frequent Neurofibromatosis type 2 (NF2), and rare syndromes such as Gorlin, Li Fraumeni, NF1, and Von Hippel-Lindau. Mutations in the *SMARCB1*, *SWIth*/sucrose non-fermentable related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 (*SMARCB1*), *BRCA1*-associated protein 1 (*BAP1*), *SUFU*, *PTEN*, and *CREBBP* genes are linked to various syndromes that increase individual sensitivity to radiation.¹³ The tumor location correlates with mutation spectra, with 22q deletion and/or *NF2* mutations common in the convexity and SMs. Skull base meningiomas typically have *AKT* serine/threonine kinase 1 (*AKT1*), tumor necrosis factor receptor-associated factor 7 (*TRAF7*), smoothened, frizzled class receptor (*SMO*), and phosphatidylinositol-4,5-Bisphosphate 3-Kinase catalytic subunit alpha (*PIK3CA*) mutations (Fig 2).¹⁴ High-grade meningiomas predominantly originate from the convexity and non-skull base areas (Fig 3).^{15–20} Grade 1 meningiomas displace the brain and are easily separable, while higher grades are invasive, adhering to dural sinuses, skull, scalp, and skin.^{9,21} Extracranial metastases to the lung, pleura, bone, or liver are sporadic (0.67%) and are more common with grade 2 (2%) and 3 (9%) meningiomas.²² The incidence of WHO grade 1, 2, and 3 meningioma is 80.5%, 17.7%, and 1.7% respectively.¹

Management depends on tumor location, grade, and symptoms. Gross total resection is the primary treatment for most symptomatic and grade 1 meningiomas, and adjuvant radiation therapy is performed for grade 2 or 3.²³ Incomplete resection or aggressive histopathologies are associated with recurrence and

transformation into a higher grades.^{1,7,24} Benign meningiomas have excellent 10-year survival (83.7%), with better outcomes in the young. Malignant meningioma has a poor outcome (61.7% 10-year survival).¹ Recurrences are common in grades 2 (50%) and 3 (90%).⁷

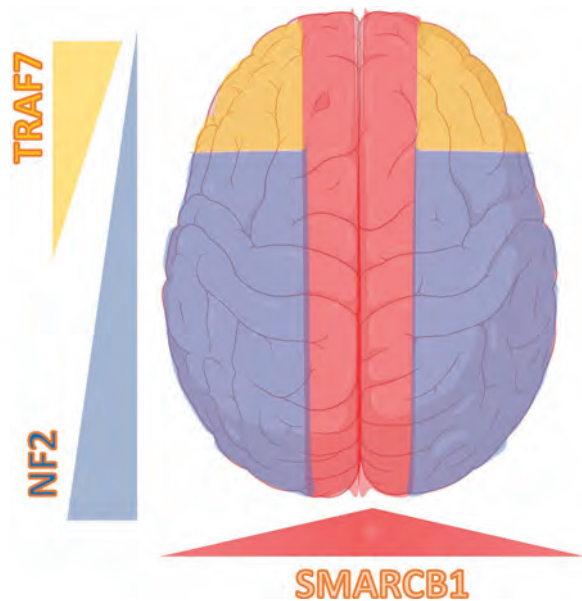


FIG 3. “Mutation map” of convexity meningiomas with the regional propensity of meningiomas dependent on a specific mutation. Meningiomas along the falx and midline parasagittal region tend to have the *SMARCB1* mutation. Meningiomas along the posterior cerebral convexity tend to have *NF2*/chromosomal 22 with higher chances of *TRAF7* mutation along the anterior cerebral convexity. Adapted from Baranoski J, *Smardcb1-Mutant Intracranial Meningiomas: A Distinct Subtype of Nf2-Mutant Tumors*, 2015. Yale Medicine Thesis Digital Library. 1947.

DISCUSSION

Updates in Recent WHO Guidelines

The CNS5 classification integrates molecular biomarkers for grading, which can supersede histologic features (Fig 4).²⁵ Grade 3 criteria are based on the telomerase reverse transcriptase promoter (pTERT) mutation and homozygous deletion of cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*) with a high mitotic rate ($\geq 20/10$ high power fields) and anaplastic histopathologic features (sarcoma/carcinoma/melanoma-like morphology) irrespective of histotype. Atypical or anaplastic meningiomas are defined across all histologic subtypes. Choroid and clear cell meningiomas are designated grade 2 due to a higher recurrence rate. Similarly, papillary and rhabdoid meningiomas can be grade 1, 2, or 3 and should not be graded on the basis of histology alone. CNS5 classification no longer uses other “atypical” features to designate grade 2 for other morphologic subtypes. The term “anaplastic” is replaced by grading based on molecular features that can categorize a tumor as grade 3, even without evident anaplastic histology characteristics.⁶ Rhabdoid and papillary variants may not meet CNS5 anaplastic grading without high-grade features, despite some studies cautioning against grading them similar to non-rhabdoid tumors due to potential aggressive behavior.²⁶ The introduction of genome-wide DNA methylation arrays has further refined classification.²⁷ A molecular-morphologic integrated score allocates points to the histologic grade, epigenetic methylation family, and specific copy-number variations. It is more accurate in the prognostic stratification of meningiomas.²⁸

Histopathological grading and its limitation

Meningiomas are characterized histopathologically by whorls of tumor cells, nuclear pseudo-inclusions, pseudo-syncytial growth, and concentric calcifications, called “psammoma bodies.”²⁹ Immunohistochemical markers, including epithelial membrane antigen, somatostatin receptor 2A (SSTR), progesterone (70–80%), and estrogen receptors (5–30%) aid in differentiating meningiomas from other dural-based lesions.³⁰ Supplementary Table 1 provides essential and desirable diagnostic criteria for meningioma. Under the WHO 2016 classification, meningiomas were graded (I–III) based on the mitotic index, histologic features (sheeting, hypercellularity, prominent nucleoli, and necrosis) and specific histotype. Meningothelial morphology is the most common histologic subtype and are usually grade 1. Presence of 4–19 mitotic figures per 10 high-power fields (HPF) is grade 2, whereas 20 or more mitotic figures is a criterion for grade 3. Histologic features like sheeting of tumor cells, spontaneous necrosis and brain invasion are findings of grade 2 lesion (Fig 5).²⁹ CNS5 outlines brain invasion criteria, necessitating tumors to breach the pia mater

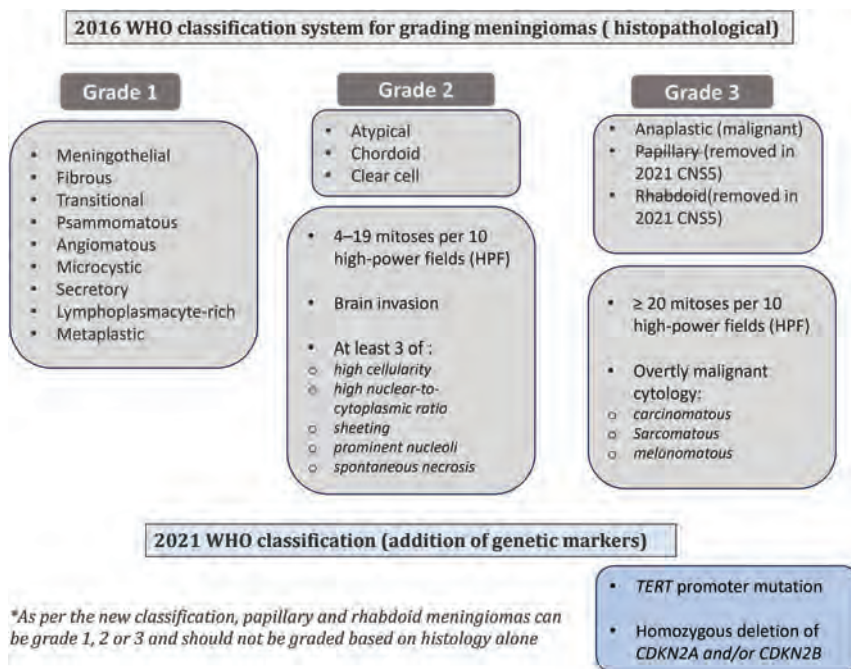


FIG 4. Chart illustration of the grading of meningiomas according to the 2016 WHO classification scheme and the changes made in the 2021 CNS5 classification, with the CNS5 addition of new molecular entities for grading and removal of a few grade 3 histologic subtypes.

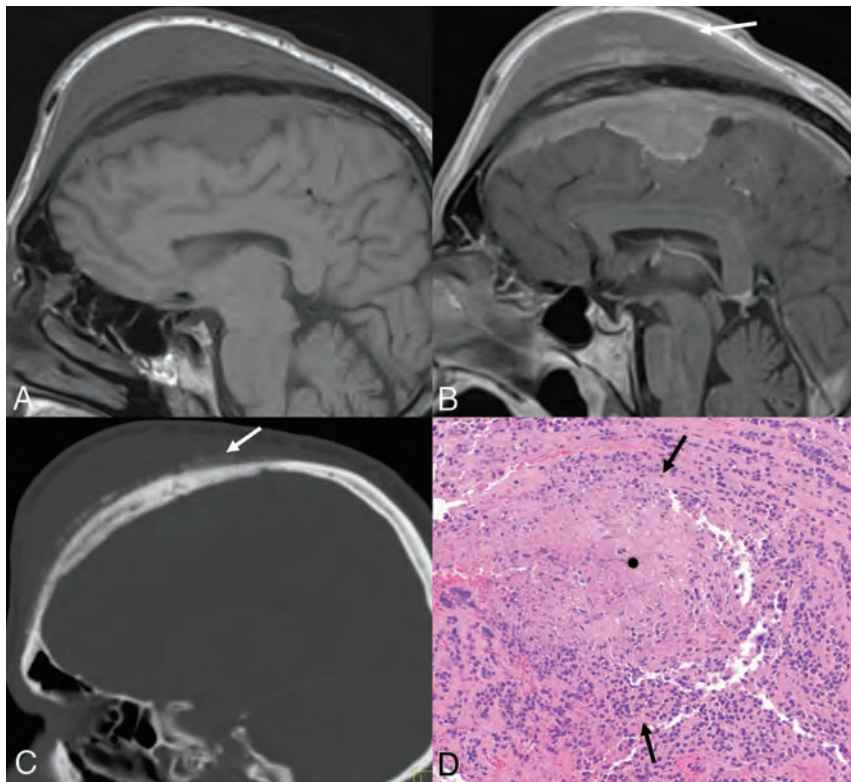


FIG 5. Transcalvarial frontal atypical, grade 2 meningioma in a 54-year-old man. Sagittal T1-weighted (A) and contrast-enhanced (B) images reveal a large frontal convexity meningioma with intraosseous components and transcalvarial extension into the scalp (B, arrow). Mild hyperostosis of the adjacent calvaria along with a “hair-on-end” periosteal reaction along the outer table is seen on CT (C, arrow). Tumor shows meningotheelial morphology, with, however, other features such as focal spontaneous necrosis (D, asterisk) and peripheral nests of tumor cells (D, arrows). A high Ki-67 rate in hot spot areas and areas of tumor that are devoid of progesterone receptors is also noted, supportive of the diagnosis of atypical meningioma (WHO grade 2). Mitotic count of 4 mitoses per 10 high-power fields is noted, on its own fulfilling the criteria for a diagnosis of an atypical meningioma.

rather than merely indent the brain or extend along perivascular spaces.⁶ Brain invasion is regarded as an unfavorable feature in CNS5; however, it is not uniformly accepted.³¹ Apart from mitotic figures (20 or more/10 HPF), presence of overtly malignant cytology, like sarcomatous or melanomatous, is an independent criteria for grade 3 meningiomas (Fig 6). WHO grading predicted recurrence risk, but consistent grading reproducibility remained challenging, with 87.2% interobserver agreement in a multicenter trial. Grade II tumors exhibit a higher inter-observer discrepancy (12.2%) compared to Grade I (7%) and Grade III (6.4%) tumors.³² Besides, some Grade II tumors behave similarly to grade I or III, leading to unexpected outcomes highlighting limitations of classical histological grading.^{4,33} Clinical and radiological features inadequately distinguish grade I from atypical grade 2 meningiomas. Atypical meningiomas progress rapidly, display aggressive imaging, and tend to recur early.³⁴ Differentiation between atypical and anaplastic meningioma is challenging due to the continuum of increasing anaplasia. Interobserver reproducibility is better for the mitotic count than for anaplasia.³⁵

Molecular and Genomic Characteristics in Meningiomas and Their Clinicopathologic Correlation

The clinicopathologic relevance of genetic alterations in meningiomas suggests certain alterations in specific subtypes and locations

(Table). Additionally, higher-grade meningiomas exhibit more frequent abnormalities.⁸ *NF2* alteration and/or 22 monosomy involves all grades and likely early tumor development events.³⁶ *NF2* alterations are prevalent in fibroblastic and transitional meningiomas (70%) and rare in meningotheelial, secretory, and microcystic subtypes.^{37,38} Sporadic *NF2* mutations are implicated in 40%–60% of meningiomas, while 50%–75% of those with germline mutations develop meningiomas.^{39,40} Many patients with *NF2* have multiple meningiomas in addition to vestibular schwannomas (Online Supplemental Data).⁴¹ Meningiomas in patients with *NF2* tend to have distinct clinical and genetic profiles compared with sporadic cases. Molecular research has identified additional meningioma mutations, including *SMARCE1* (clear cell subtype), *BAP1* (rhabdoid and papillary subtypes), Krüppel-like factor 4 (*KLF4*)/*TRAF7* mutations, pTERT mutation, *CDKN2A/B* deletion, *H3K27me3* loss, and methylome profiling.²⁵ pTERT alterations increase telomerase reverse transcriptase (*TERT*) expression and telomere length as a diagnostic marker for WHO grade 3 meningioma.^{27,42,43} pTERT mutations have higher malignant transformation, early recurrence, and worse survival than their wild-type counterparts (2.7 versus 10.8 years).⁴⁴ A meta-analysis

(59 pTERT-mutated and 618 pTERT wild-type meningiomas) observed poor survival in pTERT-mutated meningiomas (58 versus 160 months).⁴²

pTERT mutations may be acquired during lower-to-higher-grade progression. In a study of 40 patients, pTERT mutation was associated with higher recurrence (1.7; 95% CI, 0.65–4.44) and mortality ($\times 2.5$; 95% CI, 1.01–6.19) than pTERT wild-type (Fig 7).⁴³ The *CDKN2A/B* tumor-suppressor gene deletion indicates aggressive grade 3 tumors.^{45,46} In a study of 528 patient with meningiomas, 4.9% showed *CDKN2A/B* deletions in grades 2 (27%) and 3 (73%), with a median progression time of 8 months. *CDKN2A/B* deletions showed worse outcomes even without pTERT mutations.⁴⁶ The deletion of *CDKN2A/B* can be a crucial factor in upgrading the tumor from a histologic grade 1 to an anaplastic grade 3 (Fig 8).⁴⁷ Cyclin-dependent kinases 4 and 6 (*CDK4/6*) inhibitors, upstream regulators of crucial cell cycle pathways, could be a potential target for systemic treatments of high-grade meningiomas.⁴⁸ The *PBRM1* mutation is common in papillary meningiomas.⁴⁹ *BAP1* mutations are present in approximately 10% of rhabdoid meningiomas and have an aggressive clinical behavior.^{6,50}

Gene profiling is superior to routine histopathology in predicting recurrence risk. Four exclusive pathways drive meningioma

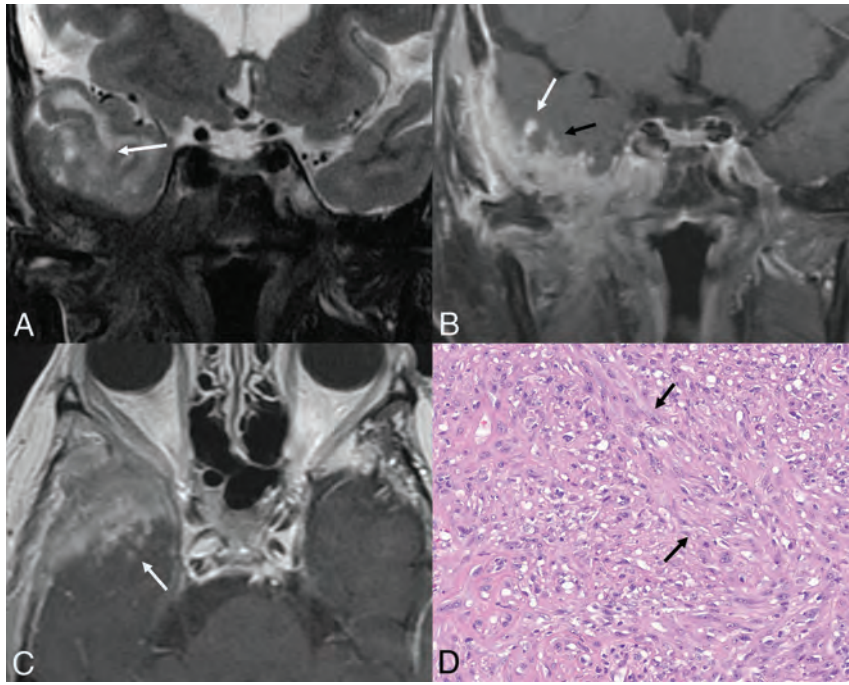


FIG 6. An anaplastic (malignant) grade 3 meningioma along the right middle cranial fossa floor. Coronal T2-weighted (A) and coronal and axial contrast-enhanced (B and C) images depict the meningioma with strongly suggestive imaging features of parenchymal invasion, including poor interface between the tumor and cortex (A, arrow) and nodules as foci of cortical enhancement (B and C, white arrows) along with linear leptomeningeal enhancement (B, black arrow). Histopathology shows frank anaplasia cells with numerous pleomorphic cells giving this tumor a sarcomatoid appearance (D, arrows) with a grade 3 classification. Mitotic count of 22 mitoses per 10 high-power fields was noted, on its own fulfilling the criteria for the diagnosis of an anaplastic meningioma.

development: heightened hedgehog signaling (*SMO*, *SUFU*, *PRKAR1A*), *TRAF7*, *KLF4*, and RNA polymerase II subunit A (*POLR2A*) mutations.^{18,51} In non-*NF2*-mutant meningiomas, *AKT1*, *PIK3CA*, *TRAF7*, *KLF4*, and *SMO* mutations are associated with classification and grading.^{15,16,18,19,52} *AKT1* and *SMO* mutations characterize meningothelial meningiomas.⁴⁵ *KLF4* and *TRAF7* alterations are linked to secretory meningiomas (Fig 9).⁵³ Foramen magnum meningiomas (4/7, 57%) often have *AKT1* mutations, making them suitable for targeted therapy.¹⁶ *SMO*-mutated olfactory groove meningiomas showed higher recurrence rates and larger tumor volumes in the anterior skull base than *AKT1*-mutated and wild-type meningiomas.^{17,40} Non-*NF2*-mutant meningiomas commonly present as benign, chromosomally stable, medial skull base tumors, contrasting with *NF2*-mutant tumors, which tend to be atypical, genomically unstable, and localized to the convexities.^{15,19} *PIK3CA*-mutant meningiomas showed limited chromosomal instability. Progesterone and cyproterone antiandrogen therapy showed higher *PIK3CA* mutation rates in skull base meningiomas.^{54,55} Meningiomas with *POLR2A* mutations are benign, exhibit distinct meningothelial histology, and tend to originate from the tuberculum sellae.⁵¹ Hedgehog tumors are typically midline, while non-*NF2* tumors occur at the anterior skull base. *KLF4*-mutant meningiomas display more peritumoral edema. *SMARCB1* meningiomas have a higher Ki-67 index.⁵⁶ Radiation-induced meningiomas are often aggressive. These tumors usually lack *NF2* mutations, and chromosome 1p loss plays an important role, followed by changes in 9p, 19q, and 22q locations.⁵⁷

H3K27 trimethylation inhibits tumorigenesis by regulating DNA repair and gene silencing.⁵⁸ Loss of *H3K27me3* trimethylation expression is rare (<5%).^{59,60} *H3K27me3* loss is prevalent in grade 3 (37%) compared with grade 2 (20%) meningiomas, correlating with rapid progression and poor prognosis.^{35,61} Global methylation profiling predicts recurrence risk independent of histopathologic grade, resection extent, and copy-number alterations.⁵⁹ Marastoni and Barresi⁶² proposed 3 classes to supplement WHO grading for prognostication. The first group lacks *NF2* alterations and chromosomal instability, with mutations in *AKT1*, *TRAF7*, or *KLF4* showing the best prognosis and response to cytotoxic drugs. The second group with intermediate prognosis has *NF2* alterations and mild chromosomal instability. The third group with poor outcomes exhibits *NF2* alterations, high chromosomal instability, and resistance to cytotoxic treatment, possibly with *pTERT* mutations and *CDKN2A/B* deletion.⁶² Low-grade meningiomas usually have isolated monosomy 22 or a balanced genome. In contrast, high-grade atypical and ana-

plastic meningiomas often have additional partial-arm chromosomal gains and losses, including loss of 1p, 6q, and 14q. Loss of 1p has been linked to higher rates of tumor recurrence and progression.^{27,63} The histologic subtypes of SMs are generally similar to cranial meningiomas. Genetic factors include *NF2*, *SMARCB1*, and *TRAF7* gene alterations. *NF2* homozygous deletion occurs in 80% of nonfamilial meningiomas and 100% of patients with *NF2*.²⁰ *NF2*-mutant tumors are noted in the thoracic spine, with female predominance. *AKT1*-mutant tumors, mainly meningothelial, are more common in the cervical spine. *SMARCB1* mutation is associated with multiple SMs and a clear-cell subtype.^{64,65} The Table summarizes commonly identified germline and somatic mutations in meningiomas by WHO grade, location, and clinical significance.

Imaging

On CT, meningiomas are sharply circumscribed homogeneous, iso- to hyperdense dural-based masses with homogeneous contrast enhancement, often with calcification and adjacent hyperostosis or osteolysis. Hyperostosis (25%–49%) is common with convexity (Fig 5) and sphenoid wing meningiomas.⁶⁶ MRI is the preferred imaging method, providing essential features like tumor size, location, invasion, and recurrence, potentially eliminating the need for biopsy.^{7,67} Meningiomas typically are isointense to gray matter, with a contrast-enhancing dural tail sign often seen in reactive fibrovascular tissue, not necessarily indicating dural involvement. Vasogenic edema may be seen

Commonly identified germline and somatic mutations in meningiomas with corresponding WHO grade, location, and clinical significance

Genetic Mutation Name	WHO Grade	Typical Location	Clinical Significance
<i>NF2</i>	1–3	Parafalcine, posterior fossa–falctentorial	Most common 70% of fibroblastic and transitional meningiomas Sporadic mutations present in 40%–60% of meningiomas 50%–75% of patients with germline mutations develop meningiomas Associated with larger, more aggressive course
<i>TRAF7</i>	1–3	Central and lateral skull base	2nd most common Secretory subtype High likelihood of hyperostosis Meningiomas tend to be benign, chromosome-stable
<i>TERT</i>	3	Any location	Commonly seen in higher grade, particularly grade 3 Associated with shorter time to progression, shorter overall survival, and higher recurrence
<i>CDKN2A/B</i>	3	Any location	Mutations associated with shorter time to recurrence Classification criteria for WHO grade 3 meningiomas
<i>SMO/SUFU</i>	1	Olfactory groove meningiomas, anterior skull base	Higher recurrence rates among olfactory groove meningiomas Larger tumor volume among anterior skull base meningiomas Linked to development of isolated familial and multiple meningiomas
<i>KLF4</i>	1	Central and lateral skull base	Secretory subtype Larger peritumoral brain edema Results in up-regulation of HIF-1 α pathway May respond to <i>mTOR</i> inhibition
<i>POLR2A</i> <i>AKT1</i>	1	Parasellar/tuberculum sellae Anterior and middle skull base, posterior fossa	Found almost exclusively in WHO grade 1 meningiomas (meningothelial) Meningothelial Mutations occur with higher frequency among skull base meningiomas Associated with shorter time to recurrence
<i>PIK3CA</i>	1–3	Anterior and middle skull base	Low recurrence risk Progesterone and cyproterone antiandrogen therapy show higher <i>PIK3CA</i> mutation rates in skull base meningiomas
<i>Hedgehog</i> <i>SMARCB1</i> <i>SMARCE1</i>	1–3	Midline anterior skull base Parafalcine and lateral skull base	Low-grade and less aggressive Clear cell type <i>SMARCB1</i> has been linked to multiple meningiomas <i>SMARCE1</i> mutations linked with familial multiple spinal meningiomas Higher recurrence risk, faster growth
<i>BAP1</i> <i>PBRM1</i>	3		Rhabdoid and papillary subtypes Aggressive clinical behavior (consistent with CNS5 WHO grade 3)

Note:— HIF-1 α indicates hypoxia-inducible factor 1.

both with and without brain invasion. Prominent peritumoral edema is seen in secretory (Fig 9), angiomatous/microcystic, lymphoplasmacytic-rich, and high-grade meningiomas.^{56,68} Perfusion imaging generally reveals high relative CBF and relative CBV using the dynamic susceptibility contrast technique.⁶⁹ On MRS, high alanine and low NAA levels are seen.⁷⁰ The primary imaging differential includes primary brain tumors, inflammation, infections, and metastasis.^{70,71} A large study (1000 cases) found that only 2% of resected dural masses were nonmeningiomas.⁷² In a series by Nagai Yamaki et al,⁷³ approximately 7.2% (25/348) of cases were meningioma mimics, including hemangiopericytoma/solitary fibrous tumor (48%), lymphoma (12%), and schwannoma. The authors highlighted 5 imaging red flags that can alert radiologists to consider meningioma mimics: 1) bone erosion (22.2%), 2) the dural displacement sign (36%), 3) marked T2 hypointensity (32%), 4) marked T2 hyperintensity (12%), and 5) absence of a dural tail (48%).⁷³

Quantitative and qualitative MRI features can offer insights into tumor grades and clinical outcomes.^{74,75} A systematic review of 35 studies by Spille et al⁶⁷ noted that irregular tumor shape, non-skull base location, heterogeneous enhancement, and tumor-brain interface disruptions were associated with grade 2

and 3 histology. Tumor and edema size usually correlates with recurrence, while heterogeneous contrast enhancement, cyst formation, T2-weighted intensity, and tumor capsule enhancement lack predictive value. A blurry brain/tumor surface with disruption of the peritumoral CSF cleft is supportive, however not definitive, of brain invasion (Fig 6).⁷⁶ High-grade tumors show necrosis, hemorrhage, heterogeneity, nonspherical shape, and larger volumes. Radiomic (quantitative) and semantic (qualitative) classifiers demonstrated significant grade predictability (Area under curve semantic = 0.76 and Area under curve radiomic = 0.78).⁷⁴ Similarly, clinical and radiologic features, such as symptoms, brain edema, shorter doubling time, and older age, predict high-grade meningiomas.⁷⁷ Preoperative ADC values differentiate low-grade and high-grade meningiomas. In a meta-analysis of 25 studies with 1552 meningiomas (1102 low-grades, 450 high-grades), high-grade tumors had lower ADC values (0.79 versus 0.92). The ADC threshold achieved 69% sensitivity, 82% specificity, and an AUC of 0.84 for grade differentiation.⁷⁸ Tumor volume is the primary predictor of higher-grade meningioma. Tumor necrosis and location along the falx or convexity may also independently predict higher-grade meningiomas.⁷⁹ A combination of MR DTI parameters (Apparent

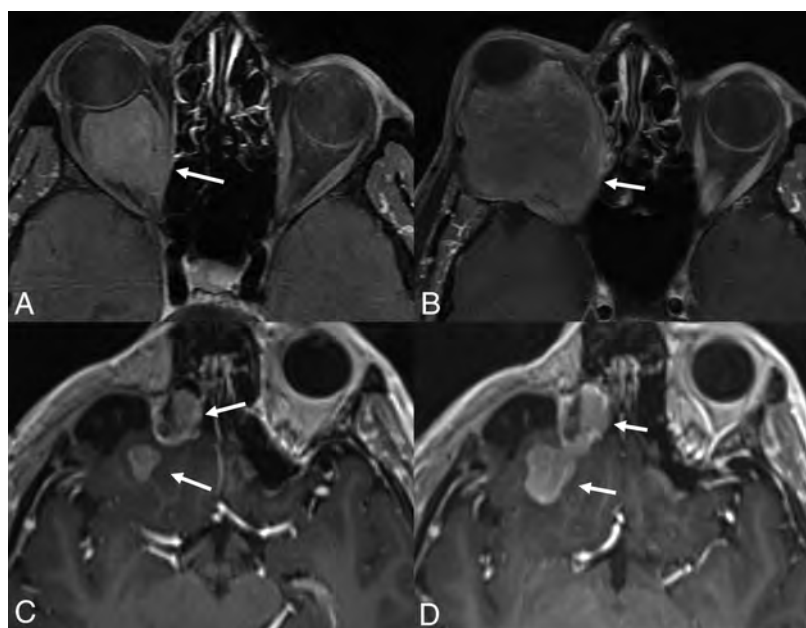


FIG 7. Right intraorbital CNS WHO grade 3 meningioma with activation of the *TERT* promoter. A meningioma is initially classified as grade 2 (atypical) based on histopathologic features; however, it was upgraded to grade 3 on the basis of detection of *TERT* activation on chromosomal microarray. Preoperative contrast-enhanced MRI at presentation (A) and at 6 months' follow-up (B) reveals rapid enlargement of the intraorbital meningioma (arrows). The patient had multiple postoperative recurrences during the next 18 months. Preoperative contrast-enhanced MRI (C and D) performed at 3-month intervals shows rapid enlargement of recurrent enhancing tumor along the orbital roof (C and D, arrows).

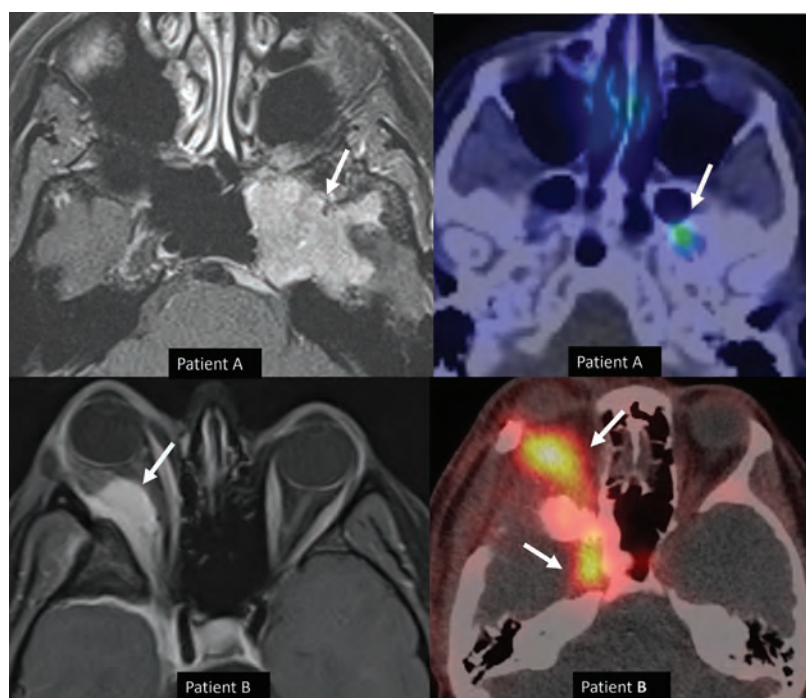


FIG 8. Histologic grade 1 skull base meningiomas in 2 different patients (patients A and B) with upgrading to grade 3 (anaplastic) in patient B based on *CDKN2* deletion. Axial (A) contrast-enhanced MRI in patient A reveals a left middle cranial fossa meningioma (arrow) with no recurrence and minimal residual activity on the 1-year postresection follow-up DOTATATE scan (B, arrow). A right sphenoid wing meningioma with intraorbital extension is seen on axial contrast-enhanced MRI (C, arrow) in patient B. Tumor recurrence was noted at the 1-year postresection follow-up DOTATATE scan (D, arrows), consistent with high-grade morphology. Despite histologic grade 1, the meningioma was upgraded to grade 3 (anaplastic) on the basis of identification of a *CDKN2* deletion.

diffusion coefficient minimum, fractional anisotropy, axial diffusivity, and radial diffusivity) accurately differentiates high-grade from low-grade meningiomas with 96.2% accuracy.⁸⁰ On MRS, higher-grade tumors have high lipid and lactate peaks. However, they do not reliably differentiate typical and atypical meningiomas.⁸¹

FDG-PET/CT predicts recurrence. Lesions with minimal tracer uptake suggest favorable surgical outcomes, while hypermetabolism indicates atypical or recurrent meningiomas.⁸² Gallium 68 (⁶⁸Ga) DOTATATE PET/CT can help differentiate meningioma mimics, detect recurrence, plan radiation therapy, and monitor posttreatment effects (Figs 8 and 10).^{83–86} Sommerauer et al⁸⁷ found a strong correlation between the maximum standard uptake value (SUVmax) and the tumor growth rate for grade 1 and 2 meningiomas. In contrast, grade 3 meningiomas showed lower SUVmax without a correlation with the tumor growth rate. Afshar-Oromieh et al⁸⁸ observed ⁶⁸Ga-DOTATOC uptake in all meningiomas (190), missing 10%, mainly along petroclival and falx cerebri. ⁶⁸Ga DOTATATE PET/CT shows higher sensitivity (98.5% versus 53.7%) and specificity (86.7% versus 93.3%) for osseous involvement compared with MRI with transosseous meningiomas having larger volume (12.8 versus 3.3 mL; $P < .001$) and being more avid (SUVmax, 14.2 versus 7.6; $P = .011$).⁸⁹

Somatostatin receptor PET for residual tumor assessment surpasses intraoperative estimation via Simpson grading or MRI. In a post hoc analysis by Teske et al⁹⁰ involving 46 patients with 49 grade 1 meningiomas, progression occurred in 14% of patients. ⁶⁸Ga DOTATATE-positive PET (SUVmax > 2.3) was linked with progression ($P = .015$) and poor progression-free survival ($P = .029$), whereas MRI was not. All 20 patients with negative findings on PET remained recurrence-free. ⁶⁸Ga-DOTATATE PET/MRI shows promise for planning and assessing focal radiation treatment for atypical and anaplastic meningiomas. A significant post-radiation therapy decrease in DOTATATE avidity (somatostatin receptor 2 expression) correlates with progression-free survival, highlighting its potential in evaluating

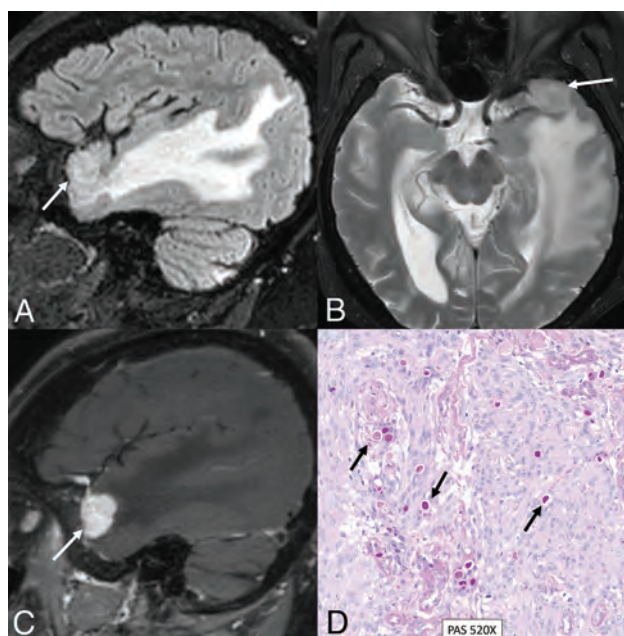


FIG 9. Secretory meningioma with a *TRAF7* mutation in a 71-year-old woman. Sagittal FLAIR (A), axial T2-weighted (B), and sagittal contrast-enhanced (C) images reveal a small meningioma along the left greater wing of the sphenoid bone (arrows). Extensive parenchymal edema is noted in the right temporal lobe, disproportionate to the size of the meningioma. Histopathology revealed a secretory histologic subtype, with clusters of eosinophilic globules highlighted by pseudopsammoma bodies (D, arrows) with low mitotic activity (<1 mitosis in 10 high-power fields) and no atypical features, supporting a CNS WHO grade 1 designation. Next-generation sequencing studies demonstrated a pathogenic variant in *TRAF7* (c.1136-1G>A).

radiation therapy response.⁸⁴ Incorporating ⁶⁸Ga DOTATATE PET into future trials could aid the clinician's decision-making and enhance patient outcomes.⁸⁵ The Online Supplemental Data detail 15 meningioma subtypes, covering histology, molecular characteristics, key imaging features, and clinical significance.

Prognosis and Treatment Strategies for Meningioma

Integrating histologic grading with genetic and epigenetic profiles provides a more accurate prognostic stratification, but it is not widely used in clinical practice.⁹¹ The extent of resection is a significant clinical predictor of recurrence and overall survival. The location, invasion, attachment to critical intracranial structures, and availability of expert neurosurgical services influence resection.⁹² Preoperative embolization of meningiomas reduces major surgical complications and improves follow-up.⁹³ Advances in radiation therapy and image guidance allowed the safer delivery of higher doses without compromising treatment tolerance to unacceptable levels.⁹¹ High-grade meningiomas receiving adjuvant radiation therapy showed a higher overall recurrence rate than the stereotactic radiosurgery group (38% versus 25%, $P = .01$).⁹⁴ Stereotactic radiosurgery effectively controls cerebellopontine angle meningiomas with minimal complications. Gendreau et al⁹⁵ (meta-analysis of 6 studies, 406 patients) found 95.6% tumor control with low cranial nerve deficits. In SMs, complete surgical resection is the preferred treatment with low recurrence (1.3%–6.4%). Radiation therapy is used

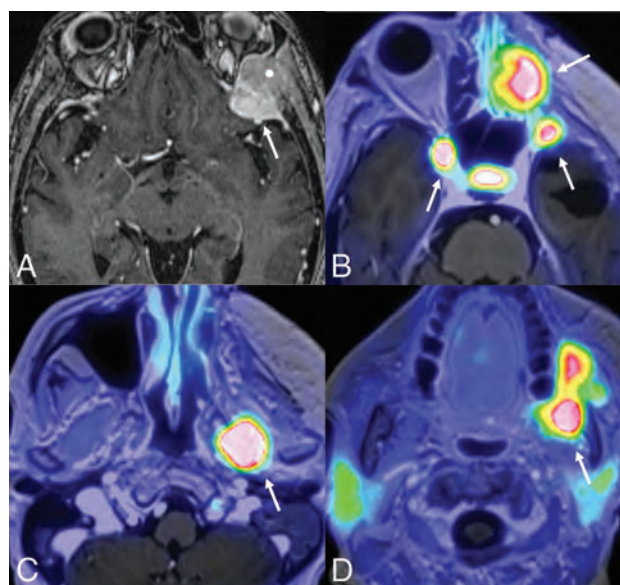


FIG 10. Rapid multifocal recurrence of *CDKN2A/B*-deleted CNS WHO grade 3 meningioma along the left sphenoid wing. The meningioma was initially classified as grade 2 (atypical) on the basis of histopathologic features; however, it was upgraded to grade 3 on the basis of detection of a homozygous deletion of *CDKN2A/B* on next-generation sequencing. Contrast-enhanced axial MRI depicts the left sphenoid wing meningioma (A, arrow) with intraosseous extension (asterisk). Rapid multifocal recurrence is noted on PET (DOTATATE) MRI (B–D, arrows) within a few months postresection.

after subtotal resection and for grade 2 and 3 SMs.^{11,12} Patients with SMs have better 10-year survival than those with their benign (95.6% versus 83.2%) and malignant (73.4% versus 55.7%) cerebral counterparts.¹

Meningioma recurrence has limited treatment options, with increasing neurologic worsening in patients undergoing first, second, and third surgeries. Repeat surgery should be considered when assessing the benefit-to-risk ratio.⁹⁶ Despite advances in genomic and DNA methylation classification, treatment progress is slower.²³ Somatostatin analogs, despite initial promise in recurrent and unresectable cases, in subsequent trials did not corroborate the benefits.⁹⁷ In Phase II trials, peptide receptor radionuclide therapy (with ⁹⁰Y- and ¹⁷⁷Lu-DOTATOC) has demonstrated disease stabilization in progressive meningiomas.⁹⁸ Systemic treatments, including antiangiogenic treatments and mammalian target of rapamycin (mTOR) inhibitors, have limited utility and are used for recurrent or progressive meningiomas.⁹⁹ NF2 inactivation and mTOR overexpression focused on mTOR inhibitors (everolimus, combined with octreotide)¹⁰⁰ or bevacizumab.¹⁰¹ PRRT has extended the 6-month PFS for grades 1 (89.7%) and 2 (57.1%) meningiomas.¹⁰² Limited treatment options and variable success rates have prompted several ongoing trials. These trials evaluate the possible therapeutic effects of immunotherapy, small molecule inhibitors, radionuclide therapy, and electrical field therapy for recurrent meningiomas (Online Supplemental Data). Management should be tailored individually, considering genetic changes that may favor systemic therapies. New WHO CNS5 grading and classification systems potentially influence management and outcomes like recurrence rates,

albeit limited by the cost and availability of technologies such as DNA methylation and next-generation sequencing.

CONCLUSIONS

Most meningioma molecular biomarkers need further evaluation in prospective clinical trials. Their inclusion in the meningioma diagnosis and management may guide future targeted therapies. Adding *CDKN2A/B* and *pTERT* mutations in CNS5 classification is a step forward, particularly for grade 3 meningiomas. However, imaging biomarkers, including functional imaging like PET/CT, are still in their infancy in predicting tumor grades and histopathologic subtypes. CNS5 classification with multimodality imaging may improve the prediction of the clinical course of meningiomas. This has yet to yield meaningful therapeutic advancements. Ongoing effort aims to translate molecular knowledge into clinical management.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Quantification of Collateral Supply with Local-AIF Dynamic Susceptibility Contrast MRI Predicts Infarct Growth

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ABSTRACT

BACKGROUND AND PURPOSE: In ischemic stroke, leptomeningeal collaterals can provide delayed and dispersed compensatory blood flow to tissue-at-risk despite an occlusion and can impact treatment response and infarct growth. The purpose of this work is to test the hypothesis that the inclusion of this delayed and dispersed flow with an appropriately calculated local arterial input function (local-AIF) is needed to quantify the degree of collateral blood supply in tissue distal to an occlusion.

MATERIALS AND METHODS: Seven experiments were conducted in a preclinical middle cerebral artery occlusion model. Dynamic susceptibility contrast MRI was imaged and postprocessed to yield quantitative cerebral blood flow (qCBF) maps with both a traditionally chosen single arterial input function applied globally to the whole brain (ie, “global-AIF”) and a delay and dispersion corrected AIF (ie, “local-AIF”) that is sensitive to retrograde flow. Leptomeningeal collateral arterial recruitment was quantified with a pial collateral score from x-ray angiograms, and infarct growth was calculated from serially acquired diffusion-weighted MRI scans.

RESULTS: The degree of collateralization at x-ray correlated more strongly with local-AIF qCBF in the ischemic penumbra ($R^2 = 0.81$) than with traditional global-AIF qCBF ($R^2 = 0.05$). Local-AIF qCBF was negatively correlated with infarct growth (slower infarct progression with higher perfusion, $R^2 = 0.79$) more strongly than global-AIF qCBF ($R^2 = 0.02$).

CONCLUSIONS: In acute stroke, qCBF calculated with a local-AIF is more accurate for assessing tissue status and collateral supply than traditionally chosen global-AIFs. These findings support the use of a local-AIF that corrects for delayed and dispersed retrograde flow in determining quantitative tissue perfusion with collateral supply in occlusive disease.

ABBREVIATIONS: AIF = arterial input function; Gd = gadolinium; IVIM = intravoxel incoherent motion; MCAO = middle cerebral artery occlusion; MD = mean diffusivity; PCS = pial collateral score; qCBF = quantitative cerebral blood flow; rCBF = relative cerebral blood flow; Tmax = time-to-maximum

In acute ischemic stroke, where a major blood vessel feeding the brain becomes occluded, it is well-known that the development of compensatory blood flow through the leptomeningeal collateral arterial network (collateral supply) can maintain blood to tissue-at-risk and slow the growth of an infarction of tissue. Minimizing “door-to-needle time” between hospital arrival and treatment currently drives ischemic stroke triage/treatment protocols regardless of an individual’s collateral supply. However,

neuroprotection/bridge therapies, which enhance collateral supply for “drip-and-ship” cases before transfer for specialized intervention, and “wake-up strokes”¹ with unknown time of onset, may benefit from accurate quantification of collateral supply.² Further, the patient-to-patient variability of collateral supply contributes to unwanted variability of perfusion-diffusion mismatch, a measure used to predict positive outcomes in patients undergoing thrombectomy.³ Previous studies have observed a slowing of infarct growth with flow augmentation therapies^{4,5} and that the benefit of flow augmentation may be reduced in a setting of robust collateralization.^{6,7} Accurate quantification of collateral supply may identify if blood supply is sufficient to maintain viability, determine if blood supply can be therapeutically enhanced to serve as a “bridge” to thrombectomy and provide a more accurate prediction of infarct growth.

Collateral supply can be estimated by x-ray digital subtraction angiography, single-photon emission CT perfusion, CT perfusion, and MR perfusion¹ via prolonged time-to-maximum (Tmax)⁸ from DSC. However, difficulties measuring perfusion as absolute

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SUMMARY

PREVIOUS LITERATURE: In acute ischemic stroke, the development of compensatory blood flow through the leptomeningeal collateral arterial network can maintain blood to tissue-at-risk and slow the growth of an infarction of tissue. Further, success of flow augmentation to serve as a bridge to thrombectomy may be dependent on leptomeningeal collateralization. Difficulties in measuring blood flow in acute ischemic stroke with a traditional single global-AIF DSC include overestimation of perfusion deficits and failure to include delayed and dispersed compensatory blood flow.

KEY FINDINGS: Local-AIF DSC that incorporated delayed and dispersed flow improved correlation of penumbral perfusion against collateral supply at x-ray and against infarct growth compared with global-AIF DSC. Local-AIF is an important correction in DSC of acute stroke to include compensatory collateral perfusion distal to an occlusion, even for relative perfusion.

KNOWLEDGE ADVANCEMENT: These findings support the use of a local-AIF rather than a single global-AIF to 1) calculate quantitative cerebral blood flow in tissue-at-risk, 2) reduce false hypoperfusion in DSC of large vessel occlusions, and 3) quantify the blood supplied to a compromised perfusion bed through the leptomeningeal arteries.

CBF with traditional DSC include highly variable compensatory vasodilation of CBV⁹ and deconvolution of a traditionally chosen single global arterial input function (global-AIF), overestimating perfusion deficits.¹⁰ While using global-AIF assumes a more uniform input function for ease of computation, the use of a more complex local-AIF allows one to correct for the delay and dispersion of the contrast bolus in every voxel when calculating CBF, thereby providing a more accurate map of CBF.

This study investigates if quantitative cerebral blood flow (qCBF), calculated by using a local-AIF, may reflect compensatory blood supply to tissue at risk of infarction more accurately than traditional DSC deconvolution analysis (global-AIF). Using a standard MRI acquisition sequence in a preclinical animal model of ischemic stroke, we postprocessed DSC with both 1) a traditional global-AIF,¹¹ and 2) an automatically generated voxel-wise “local-AIF” that corrects for delay and dispersion of the contrast bolus within every voxel. We hypothesized that quantification of perfusion calculated with an appropriate local-AIF would correlate with the degree of collateral supply to a perfusion bed distal to an occlusion and better predict infarct growth.

MATERIALS AND METHODS

Experimental Protocol

All experiments were conducted by using a preclinical canine model of ischemic stroke.^{5,9,12-14} The 2-day experimental protocol was approved by the University of Chicago Institutional Animal Care and Use Committee and reported in compliance with ARRIVE guidelines. In this study, a series of 7 purpose-bred adult canines (mean age = 4.1 ± 2.9 years; mean weight = 25.8 ± 3.7 kg; 6 female, 1 male) underwent permanent endovascular middle cerebral artery occlusion (MCAO) via embolic occlusion coils at the M1 segment proximal to the bifurcation (Online Supplemental Data). Subjects underwent x-ray arteriography, MRI DSC perfusion, and serial quantification of infarct volume by DTI and were euthanized either the same evening or the following day.

Pial Collateral Score via X-Ray Arteriography

Collateral supply was quantified 30 minutes post-MCAO by assessing x-ray arteriographic images (OEC9800; GE Healthcare) with a pial collateral score (PCS).¹³⁻¹⁵ PCS is an ordinal score from 1–11

developed for this preclinical model from a score of 1–5 for humans.¹⁵ The scores were evaluated blinded to MRI qCBF by a neurointerventional radiologist with over 20 years of experience with human angiography and over 15 years with angiography in this canine model. Scoring was based on the delay and extent of retrograde filling of arterial branches distal to the occluded artery, with 1 being minimal/no collateralization and 11 being retrograde reconstitution of the collateral network up to the occlusion (Online Supplemental Data). Subjects with PCS ≤ 8 were considered “poor,” and PCS ≥ 9 considered “good” collateral supply, determined by a previous study showing “poor” collaterals with core infarct growing rapidly by assessment at the 2-hour time point and “good” collaterals still having a large volume of tissue-at-risk.¹⁴

MR Acquisition

All MRI scans were performed on a 3T MRI scanner (Ingenia Philips) with canines in a head-first, prone position by using a 15-channel receive-only coil. DSC perfusion images were acquired 2.5 hours after occlusion (2D gradient-echo, T2*-weighted EPI, FOV = 160 × 160 mm/matrix = 176 × 176, 5 slices/6 mm thick, TR/TE = 500/30 ms, 120 phases, total scan time = 60s). Rapid, 15-second T1 maps were acquired by using a 2D inversion recovery look-locker scan with a single-shot EPI readout (slice thickness = 6 mm, FOV = 160 × 160 mm/matrix = 176 × 176) for the T1-bookend method. Gadolinium (Gd)-based contrast agent (Multihance, Bracco) was injected in the forepaw, followed by a saline flush (Gd: 3 mL at 2 mL/s, saline: 20 mL at 2 mL/s).

DTIs were acquired at 30-minute intervals to calculate mean diffusivity (MD) post-MCAO for measuring infarct volume growth over time. A stack of 50 2D DTI was prescribed to cover the entire head (slice thickness = 2 mm, FOV = 128 × 128 mm/matrix = 128 × 128, TR/TE = 2993/83 ms, flip angle = 90°, b-values = 0, 800 seconds/mm², 32 directions). MD, rather than ADC, maps were used as DTI was acquired to study separate aspects of this model beyond the scope of the current study; for the purposes of detecting infarct in this study, the sequences are treated as equivalent.

Traditional Global-AIF DSC Postprocessing

For traditional DSC, the single global-AIF was chosen automatically based on a simultaneous assessment of early arrival time, narrow

bolus, and large area under the concentration curve.¹⁶ qCBF was calculated by using the T1-bookend method¹⁷ where T1 (in ms) changes in the parenchyma and blood pool are input to a 2-compartment model^{18–20} that yields qCBF (in mL/100 g/min) including intra- to extravascular water exchange.¹⁹ This T1-bookend method has undergone extensive validation,^{9,10,21} is fully automated to minimize user bias,²⁰ and is available for use.^{22,23} Deconvolving the voxelwise parenchymal tissue curves against the global-AIF yields mean transit time values for the calculation of qCBF by using the central volume principle,

$$qCBF(\text{mL}/100\text{g}/\text{min}) = \frac{qCBV(\text{mL}/100\text{g})}{MTT(\text{min})}$$

In the remainder of this manuscript, we refer to these values as “global-AIF qCBF” with Tmax calculated as the time at which the residue function reaches its maximum after deconvolution with the global-AIF.²⁴

Local-AIF DSC Postprocessing

In a setting of vascular occlusion, the traditional global-AIF as a global estimate of the contrast bolus shape as it enters the brain has been shown to overestimate the degree of hypoperfusion in vascular beds fed via collateral supply.¹¹ To address this shortcoming, a local-AIF was automatically generated for every voxel within the deconvolution analysis of DSC perfusion to yield a map of qCBF in mL/100 g/min. This local-AIF was calculated by using a previously reported technique,¹⁰

$$\text{Local-AIF}(t) = \text{Global-AIF}(t) \otimes \frac{\alpha}{(\Delta t + 1)} e^{-\frac{\beta t}{\Delta t}}$$

which includes correction for delayed arrival time (Δt) and bolus dispersion ($\otimes e^{-\frac{\beta t}{\Delta t}}$) before arrival in the vascular bed from comparison between global-AIF and venous outflow (Online Supplemental Data). The local-AIF is patient-dependent, has been previously validated^{9,10,21} in humans, and is available for use.^{22,23} A prior study supports the local-AIF accounting for both antegrade flow through a tight flow-limiting stenosis, cross-filling through the circle of Willis communication, and retrograde blood supply through collateral vascular networks when calculating perfusion.¹⁰

Territories of Interest

Three physiologically relevant territories were operationally defined: 1) diffusion-positive core (core infarct), 2) hypoperfused yet viable (tissue-at-risk) in the ipsilateral MCA territory, and 3) contralateral normal hemisphere MCA territory. All territories were defined as being within the MCA territory across 3 consecutive 6-mm coronal slices starting at and posterior to the M1 segment. The core infarct and tissue-at-risk territories were selected by thresholding MD from DTI and Tmax calculated from global-AIF DSC.

Core infarct was defined, as previously reported,^{12,13} as MD < 5.7e⁻⁴ mm²/s⁶, converted to binary infarction maps, and used to calculate infarct volumes. Infarction maps taken 2.5 hours post-MCAO were co-registered to DSC (Matlab 2021b, MathWorks) for analysis of the perfusion deficit within and around the core infarct.

Tissue-at-risk (ie, the ischemic penumbra) was defined as having prolonged Tmax relative to the global-AIF (Tmax > 1.0 second) but not yet infarcted (ie, MD > 5.7e⁻⁴ mm²/s). Tmax^{25,26} thresholds for “hypoperfusion” established in larger human brains may not be appropriate in canines. Therefore, this study’s threshold of Tmax > 1.0 second encompassed all tissue potentially at risk with delayed arrival. These global-AIF Tmax maps, minus the binary infarction maps, were applied to both global-AIF qCBF and local-AIF qCBF maps as binary masks to measure qCBF in tissue-at-risk. Contralateral MCA territory was selected on the same 3 slices based on visible anatomic cues. Perfusion beds in the ipsilateral hemisphere that were not “at-risk” or core infarct were not evaluated in the analysis.

Statistical Analyses

Wilcoxon signed rank test, boxplots, and scatterplots (linear regression and Bland-Altman) were used to compare tissue qCBF as calculated with a global-AIF and local-AIF. Local-AIF qCBF, global-AIF qCBF, and the difference between the 2 ($\Delta qCBF = \text{local-AIF qCBF} - \text{global-AIF qCBF}$) were correlated against reference standard x-ray angiographic PCS with linear regression and Spearman rank. To examine how relative CBF (rCBF) would be impacted by AIF selection, rCBF was calculated as the ratio qCBF in tissue-at-risk to contralateral middle cerebral artery territory. As robust collateral supply would maintain homeostasis and slow infarct growth, local-AIF qCBF and global-AIF qCBF distal to the occlusion were correlated against infarct growth via linear regression. Local-AIF and global-AIF qCBF were calculated in mL/100 g/min within territories of interest (infarcted, tissue-at-risk, contralateral) and compared via Wilcoxon signed rank test. Wilcoxon rank sum was used to compare local-AIF and global-AIF qCBF in tissue-at-risk for cases with poor collaterals against cases with good collaterals. To investigate potential influence of AIF selection, the difference in quantitative CBV ($\Delta qCBV = \text{local-AIF CBV} - \text{global-AIF CBV}$) was compared as a function of collateral score.

The bootstrap Z-test was used to estimate effect size for power calculation. All statistical analysis was performed in R (Rstudio 3.6.1, Posit PBC, 2019) and Python 3.11.4 (Anaconda, 2024), with statistical significance determined at the $P = .05$ level.

RESULTS

Access to all results, raw images, and tabulated data are available upon request to the corresponding author. Eighty-three percent of the parent study experiments were “successful” and performed to completion, ie, physiologic parameters maintained as planned and no complications such as procedural-related vessel perforation; the success rate improved over time and reached 100% success for the most recent 9 consecutive experiments of the parent study (this current study analyzed only successful controls of the parent study). Representative parametric qCBF maps of a left MCAO were calculated with a global-AIF and a local-AIF for subjects with (Fig 1A, -B) poor collateral supply (PCS = 8) and (Fig 1C, -D) good collateral supply (PCS = 11). The observed differences in qCBF between Fig 1A, -B, as well as between Fig 1C, -D, result exclusively in postprocessing from the choice of AIF (global versus local); identical DSC images and territory ROIs were used for Fig 1A–B and for Fig 1C–D. The corresponding 1-hour infarct

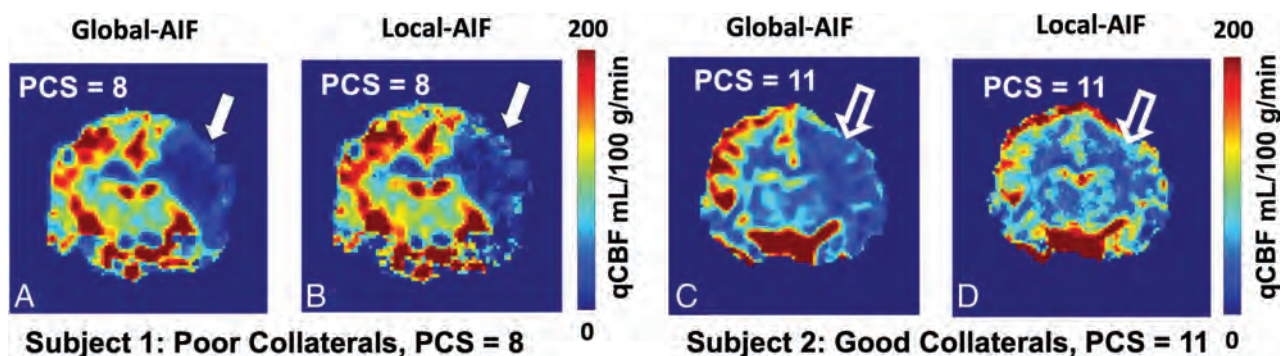


FIG 1. Coronal projection parametric qCBF maps in mL/100 g/min. A, Poorly collateralized subject (PCS = 8), by using a single global-AIF. B, The same subject/images postprocessed by using voxelwise local-AIF. Note the severe hypoperfusion (deep blue, denoted by arrow) in the poor collateral supply case, which persists when using a local-AIF. C, A subject with robust collateralization (PCS = 11) shown with a global-AIF used to calculate qCBF and (D) the same subject/images by using local-AIF to calculate qCBF. Note the markedly higher perfusion values (hollow, white arrow) attributable to the use of a delay and dispersed local-AIF.

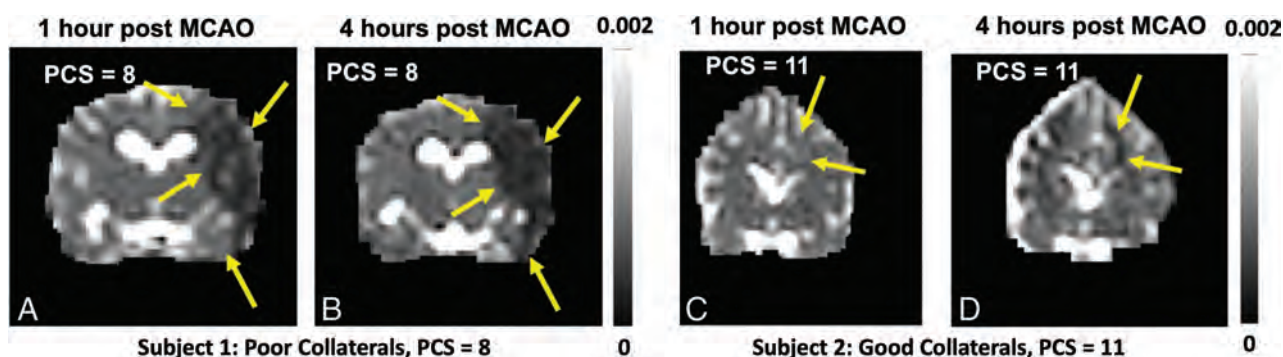


FIG 2. Coronal projection parametric mean diffusivity images acquired 1 and 4 hours after coil deployment in the left MCA. These are corresponding diffusion-weighted images from the experiments displayed in Fig 1 with (A and B) poor collateral supply and (C and D) good collateral supply. Note that robust collateralization results in significantly slower growing and smaller infarction (yellow arrows).

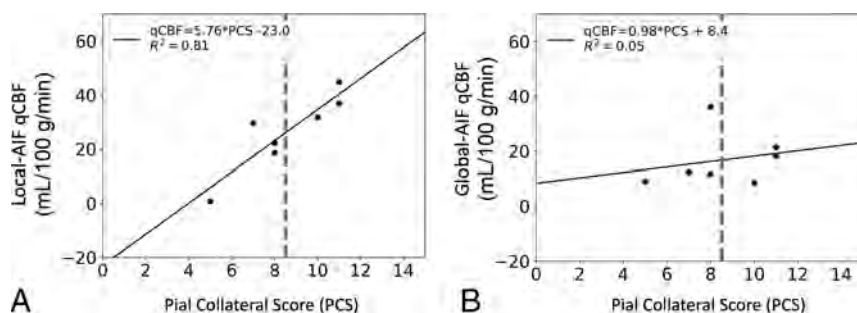


FIG 3. Scatterplots of tissue qCBF in mL/100 g/min versus pial collateral score within the operationally defined ischemic penumbra reconstructed with (A) a local-AIF and (B) a traditional global-AIF. Note: qCBF values are quantitative; values above ~18 mL/100 g/min have sufficient flow to slow infarct growth.

and 4-hour infarct of the 2 cases in Fig 1 are shown in Fig 2 as MD images. Visual inspection of Fig 1 demonstrates that the presence of robust collateral supply (PCS = 11) effectively mitigates the formation and growth of an infarct (Fig 2, yellow arrows).

Collateral Supply

Local-AIF qCBF values in the tissue-at-risk were more strongly correlated (Fig 3A, $R^2 = 0.81$) with PCS than traditional global-

AIF DSC (Fig 3B, $R^2 = 0.05$). This was also true for Spearman rank correlation (local-AIF statistic = 0.87, $P = .01$; global-AIF statistic = 0.34, $P = .45$). The difference between local-AIF and global-AIF qCBF ($\Delta qCBF = CBF_{LOCAL-AIF} - CBF_{GLOBAL-AIF}$) was moderately positively correlated with PCS ($R^2 = 0.49$).

Infarct Growth

qCBF calculated by using the local-AIF algorithm in the tissue-at-risk was strongly negatively correlated with infarct growth (higher local CBF = slower infarct growth; Fig 4A, $R^2 = 0.79$). In comparison, qCBF values calculated by using a global-AIF were consistently lower than local-AIF values and did not correlate well with infarct growth (Fig 4B, $R^2 = 0.02$).

Comparison in Territories of Interest

A comparison between traditional global-AIF and delay and dispersion corrected local-AIF qCBF in mL/100 g/min is shown as boxplots in Fig 5. Median qCBF of the core infarct (Fig 5A,

MD < 5.7 × 10⁻⁴ mm²/s), tissue-at-risk (Fig 5B, MD > 5.7 × 10⁻⁴ mm²/s and Tmax > 1.0 second), and the contralateral hemisphere MCA (Fig 5C) are included. In the infarcted core, both global- and local-AIF showed qCBF values below the threshold for cell death from a study in primates (gray band < 18 mL/100 g/min provided for context to the quantitative value this study calculated).²⁷ In the tissue-at-risk, the CBF of “good” collaterals (PCS ≥ 9, n = 4) and “poor” collaterals (PCS ≤ 8, n = 3) is presented separately and color-coded to highlight the sensitivity of the local-AIF to collateral supply (Fig 5B).

A statistical comparison with Wilcoxon signed rank test is shown in the Table. Median qCBF in mL/100 g/min from local-AIF and global-AIF were not statistically significantly different in the core infarct. In the tissue-at-risk, local-AIF and global-AIF were not significantly different for poor collaterals. However, for

good collaterals, local-AIF was higher than global-AIF qCBF by +26.0 mL/100 g/min (P = .06), raising the average qCBF above the ischemic threshold. Further, the local-AIF qCBF was an average +25.9 mL/100 g/min higher for subjects with good collaterals compared with local-AIF of poor collaterals (rank sum statistic = -2.2, P = .03), while global-AIF qCBF of good and poor collaterals were not significantly different (Fig 5B).

Relative CBF

In the contralateral hemisphere, the local-AIF qCBF was lower for good collaterals by -92.5 mL/100 g/min (rank sum statistic = 1.9, P = .05). In other words, local-AIF showed higher qCBF in tissue-at-risk and lower contralateral qCBF for subjects with robust collateral supply while global-AIF showed lower qCBF in the tissue-at-risk and higher contralateral qCBF. As such, *relative* rCBF = tissue-at-risk/contralateral perfusion with a local-AIF correlated to collateral score (R² = 0.62, Spearman rank statistic = 0.76, P = .04) while global-AIF rCBF did not (R² = 0.04, Spearman rank statistic = 0.38, P = .40). The influence of local-AIF on qCBV was not significant.

Statistical Power

Regarding power analysis for sample size, difference in the slopes for prediction of infarct growth by using local-AIF (Fig 4A) or global-AIF (Fig 4B) qCBF did not demonstrate statistical

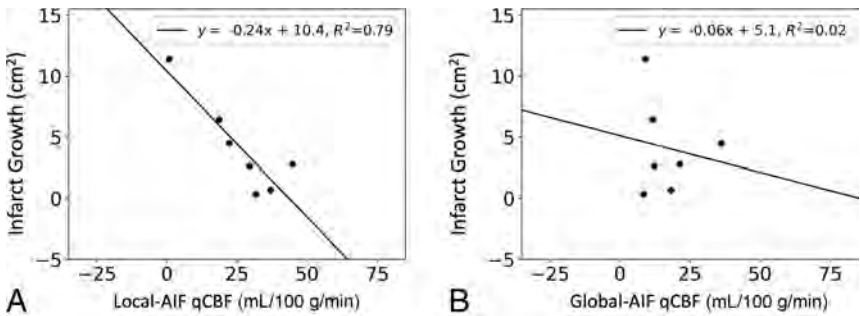


FIG 4. In the ischemic penumbra (MD > 5.7 × 10⁻⁴ mm²/s, Tmax > 1.0) (A) qCBF calculated by using a local-AIF more strongly correlates with slower infarct growth whereas (B) qCBF from a traditionally chosen global-AIF is less predictive of infarct growth in the acute phase of an ischemic stroke.

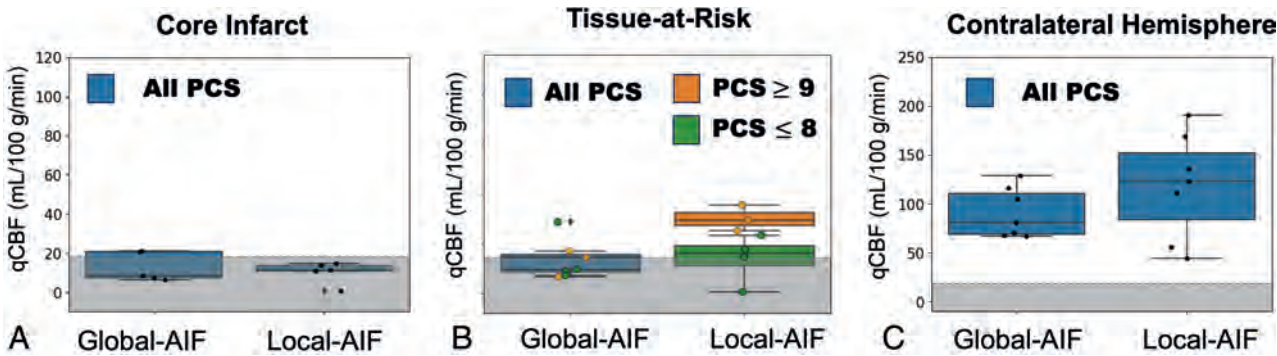


FIG 5. Boxplots of CBF in (A) the core of an infarct, (B) the penumbral tissue-at-risk, and (C) the contralateral, unaffected hemisphere. Local-AIF qCBF in tissue-at-risk is separated into good collaterals (PCS > 8) and poor collaterals (PCS < 8) by color and with scatterplots colored according to score. Contralateral qCBF is in a different range due to systemic compensatory mechanisms to include all data. The gray band represents qCBF values below 18 mL/100 g/min, the ischemic threshold for neuronal death in primates.

Differences between local-AIF and global-AIF DSC (Δ qCBF = local-AIF qCBF - global-AIF qCBF) in the 3 territories of interest, with all collateral scores dichotomized into good and poor^a

Δ qCBF Dichotomized by Collateral Score			
Mean Difference (mL/100 g/min) [Wilcoxon signed rank statistic, P value]			
	Core Infarct	Tissue-at-Risk	Contralateral Hemisphere
All PCS	+2.26 [11.0, P = .68]	+14.3 [5.0, P = .07]*	-30.06 [16.0, P = .84]
Good PCS > 8	+10.78 [0.0, P = .125]	+25.96 [0.0, P = .06]*	-89.2 [2.0, P = .19]
Poor PCS < 8	-9.08 [1.0, P = .50]	-5.07 [1.0, P = .50]	+68.60 [1.0, P = .50]

^aThe underestimation of CBF values by using a single global-AIF compared with a voxelwise local-AIF (Δ qCBF) is greater when collateral supply is robust but not significant in a setting of poor collateral supply; this is especially prevalent in tissue-at-risk. Statistical significance at the P = .10 level is denoted with *.

significance by the bootstrap Z-test ($Z = -0.49$, $P = .62$). However, R^2 values were significantly different ($Z = 2.03$, $P = .04$). In terms of power, the study was underpowered for both end points due to the sample size, with a minimum requirement of 41 subjects for ideal 80% power of both slope and R^2 . However, the trend of improved slope and correlation with a local-AIF remains (Fig 4).

DISCUSSION

This study found that a voxelwise “local-AIF” that incorporates delay and dispersion of the bolus reflects the existence of compensatory collateral supply distal to an occlusion and predicts infarct growth better than a traditional single global-AIF in DSC MRI. This suggests that a traditional global-AIF without delay and dispersion correction does not include collateral supply and, therefore, may result in a less accurate determination of hypoperfusion when robust leptomeningeal collateralization exists. These findings support the use of a local-AIF to 1) calculate qCBF by using the previously reported “T1 bookend method,”^{9,17-21} 2) image CBF supplied through the leptomeningeal arteries, and 3) more accurately predict infarct growth in acute ischemic stroke.

When contrast agent is injected intravenously, it travels through the heart and lungs and finally to the circle of Willis before perfusing the brain. In DSC MRI, the shape of the contrast bolus upon entering the brain represents a global-AIF. However, when there is an occlusion of a major artery, blood will have to travel around the occlusion to reach the infarcted hemisphere through the leptomeningeal collateral arterial network. The delay and the dispersion as blood travels through this collateral network can be corrected for with a local-AIF. The local-AIF presented in this work incorporates a term to account for the late arrival and the additional blunting of the bolus as it is propagated through the brain through the collateral network (Online Supplemental Data). The amount of delayed and dispersed blood that this local-AIF corrects for was hypothesized to be directly related to the extent of collateralization of a subject.

Quantification of local qCBF distal to an occlusion by using a local-AIF demonstrated a strong correlation with the collateralization (ie, PCS). Further, local-AIF qCBF in the tissue-at-risk that would benefit most from robust collateral supply was reported above the threshold of 18 mL/100 g/min for subjects with good collaterals. Meanwhile, in the core infarct, as well as in tissue-at-risk for subjects with minimal collateral supply, local-AIF showed no change in the degree of hypoperfusion. In other words, mathematically, the local-AIF qCBF is the same as the global-AIF qCBF when there is no delayed and dispersed arrival of the bolus through the collateral network ($Local-AIF_{lim \Delta t \rightarrow 0} = Global-AIF$). This supports the automatic local-AIF deconvolution analysis being applicable to all cases, irrespective of collateral supply, delayed antegrade flow, or circle of Willis cross-filling.

Global-AIF qCBF demonstrated poor correlation to collateral supply and no difference between good and poor collaterals, suggesting global-AIF qCBF does not reflect the presence of collateral blood that is supplied, delayed, and dispersed through the leptomeningeal network. The absolute difference between the global-AIF qCBF and the local-AIF qCBF ($\Delta qCBF$) correlated

with PCS, further supporting local-AIF, including the degree of collateral supply (versus slow antegrade stenotic flow) in an ischemic stroke. As both global-AIF and local-AIF use identical input images and regions of interest, the difference was only due to the use of a voxelwise delay and dispersion-corrected local-AIF. The effect of the local-AIF was observed in relative perfusion as well. Local-AIF is an important correction in DSC of acute stroke to include compensatory collateral perfusion distal to an occlusion, even if the intent is for relative perfusion.

A previous study of a perfusion collateral index by Nael et al²⁸ demonstrated that good collaterals showed smaller volumes of severe hypoperfusion (arterial delay >6 seconds) and larger volumes of moderate hypoperfusion (arterial delay = 2–6 seconds). While severe hypoperfusion with larger arterial delay represents tissue that is not receiving delayed compensatory flow, the moderate arterial delay may represent the delayed and dispersed flow through the collateral network. The current study supports quantifying this collateral supply as qCBF by correction of delay and dispersion with a local-AIF. Further, collaterals from the posterior cerebral artery and anterior cerebral artery territory may have differing timing in the superior and inferior division territories of the occluded MCA; this itself may affect the transit time and lead to qCBF requiring a local-AIF to measure accurately.

Prior studies have reported a correlation between infarct growth from both PCS and arrival time by DSC.¹⁴ The current study provides a mechanistic validation for prior studies by indicating that subjects with higher local-AIF qCBF, which includes contribution from collateral supply and corrected arrival time, observed slower infarct growth. The local-AIF will improve the prediction of infarction compared with global-AIF as it can more accurately represent the perfusion in the tissue-at-risk, even if the perfusion is being supplied, delayed, and dispersed through the collateral network. Robust collateralization may have a longer window of treatment, particularly if collateral supply can be therapeutically enhanced, than an ischemic stroke case without robust collateral supply, which must be treated immediately. As such, local-AIF qCBF may be a predictor of infarct growth and provide insight into novel stroke therapeutic treatments.⁷

Tmax, by definition, identifies the presence of delayed bolus arrival as prolonged Tmax and depicts a malignant pattern used in acute stroke triage to identify patients who would benefit from immediate intervention.¹ The goal of this study was to quantify the leptomeningeal supply that mitigates infarct growth. The results suggest that Tmax can identify the *location* of delayed bolus arrival as tissue-at-risk and that a local-AIF can then *quantify* the local flow (ie, degree of collateral supply) from the collateral network in that tissue-at-risk.

A previous study by Federau et al²⁹ has reported “local perfusion fraction” in acute stroke by using noncontrast intravoxel incoherent motion (IVIM), with excitation and readout in the same plane, as a measure of collateral blood supply that traditional global-AIF DSC cannot capture. This current study demonstrated that traditional global-AIF can be improved by correcting for the delay and dispersion to return the local perfusion. The correlation of local-AIF qCBF to x-ray DSA PCS supported the ability of DSC to quantify “local” collateral supply in mL/100 g/min. In addition, as the influence of a local-AIF on qCBV was not significant, the increased

correlation with a local-AIF was predominately due to the mean transit time component rather than the blood volume component. Since qCBF (in mL/100 g/min) from a combination of the qCBV (with a T1 bookend) and local mean transit time (with a local-AIF) correlated with collateral supply and infarct growth, studies of local IVIM perfusion fraction²⁹ in acute stroke may benefit from an inclusion of mean transit time to quantify collateral supply.³⁰

This work was not without limitations. The use of a complex preclinical animal model limited the number of experiments that were run and vascular territories that were studied. We present a retrospective reanalysis of an animal model that was designed to study flow augmentation in MCAO and was not powered for study of more subtle local- versus global-AIF qCBF differences between groups. This MCAO model and use of contrast afforded a limited number of perfusion measurements; a method that allows dynamic assessment of perfusion over the course of infarct development could be beneficial.^{29,30} Coregistration and resampling were required for mapping of core infarct and tissue-at-risk, enabling imperfect coregistration of perfusion and diffusion images; images were analyzed region-by-region, rather than voxel-by-voxel. Translation of conclusions derived from animal-based models is a potential limitation; however, an MCAO model reduces error in evaluating methods for CBF calculation by allowing for a more accurate assessment of occlusion time and comparison of subjects at multiple time points under similar physiologic conditions, which is not possible in humans. The finite number of subjects used in this study limits statistical interpretation and significance. Additional studies are planned and underway in humans to examine translation from a canine model to humans. While the time of reconstruction of local-AIF qCBF maps is not prohibitive and could be incorporated into existing analysis at the scan console, “time-to-needle” constraints remain for clinical use of MRI in acute stroke; the automatic voxelwise local-AIF may have more clinical value as an adaptation in CT perfusion deconvolution.

CONCLUSIONS

When there is an occlusion of a major artery, the delay and dispersion as blood and contrast travel around the occlusion via the collateral network can be corrected to capture collateral supply with a local-AIF. By using a local-AIF to calculate qCBF, the collateral supply was quantified, correlated with PCS, and predicted infarct growth. These findings support the use of a local-AIF rather than a single global-AIF to 1) calculate qCBF in tissue-at-risk, 2) reduce false hypoperfusion in DSC of large vessel occlusions, and 3) quantify the blood supplied to a compromised perfusion bed through the leptomeningeal arteries. This quantitative local-AIF qCBF may be of benefit to studies of novel stroke therapeutics that would be influenced by collateral supply and for translation to clinical CT perfusion.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Assessment of Attenuation in Pericarotid Fat among Patients with Carotid Plaque and Spontaneous Carotid Dissection

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ABSTRACT

BACKGROUND AND PURPOSE: Changes in perivascular fat density (PFD) and its association with inflammation have been topics of interest in both atherosclerotic and nonatherosclerotic vasculopathies. The objective of this study was to assess the PFD in patients with spontaneous internal carotid artery dissection (SICAD) or carotid atherosclerotic plaque, with and without intraplaque hemorrhage (IPH).

MATERIALS AND METHODS: A cross-sectional retrospective bicentric analysis of 130 patients (30 with SICAD and 100 with carotid atherosclerotic plaque) who underwent CT angiography was performed. Among the subjects with atherosclerotic plaque, 36 showed the presence of IPH. PFD analysis was performed by 2 radiologists who placed 2 ROIs to identify the perivascular fat tissue attenuation. The Mann-Whitney *U* test was conducted to evaluate the difference between patient cohorts.

RESULTS: Carotid arteries with SICAD and IPH demonstrated an average PFD of -68.97 HU (95% CI, -72.11 to -65.82 HU) and -69.97 HU (95% CI, -73.00 to -66.95 HU), respectively, in comparison with patients without IPH, who showed an average PFD -77.11 HU (95% CI, -78.78 to -75.44 HU) ($P < .001$ for both). Conversely, no significant differences were found between patients with SICAD and those with carotid plaque with IPH ($P = .324$).

CONCLUSIONS: The average PFDs in patients with SICAD and carotid atherosclerosis plaque with IPH were similar and higher than those in patients with carotid plaque without IPH. This finding suggests a shared pathologic inflammatory mechanism in these 2 conditions. Studies comparing pathologic specimens directly with radiologic images may be needed to confirm this indirect hypothesis.

ABBREVIATIONS: ICC = intraclass correlation coefficient; IPH = intraplaque hemorrhage; PFD = perivascular fat density; SICAD = spontaneous internal carotid artery dissection

The assessment of attenuation in pericarotid fat among patients with carotid atherosclerotic plaque and spontaneous carotid dissection has become an increasingly relevant topic in vascular medicine and neuroradiology. This interest is increased by emerging evidence linking perivascular fat density (PFD) with the presence and characteristics of atherosclerotic plaques,¹⁻⁴ which are critical in the pathogenesis of cerebrovascular events.¹

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The research in this area, bridging the gap between advanced imaging techniques and clinical outcomes, offers valuable insight into the noninvasive identification and assessment of high-risk vascular conditions. Recent studies have shown a correlation among perivascular fat inflammation, carotid plaque vulnerability, and cerebrovascular events. Similarly, another study showed a significant correlation between PFD and contrast plaque enhancement on CTA, a marker of vulnerable carotid plaque.² These findings, derived from a retrospective analysis of 100 patients, indicate that higher PFD is associated with plaque instability, particularly in symptomatic patients. Baradaran et al¹ explored the association between carotid artery PFD and cerebrovascular ischemic events. Through a meticulous analysis of CTA examinations in patients with ICA stenosis, their work underlined the role of increased PFD as a surrogate marker for perivascular inflammation, particularly in those with stroke or TIA.

Additionally, growing evidence also demonstrated a role for pericarotid fat in nonatherosclerosis carotid diseases. Cheng et al⁵ explored changes in PFD in a cohort of patients with spontaneous

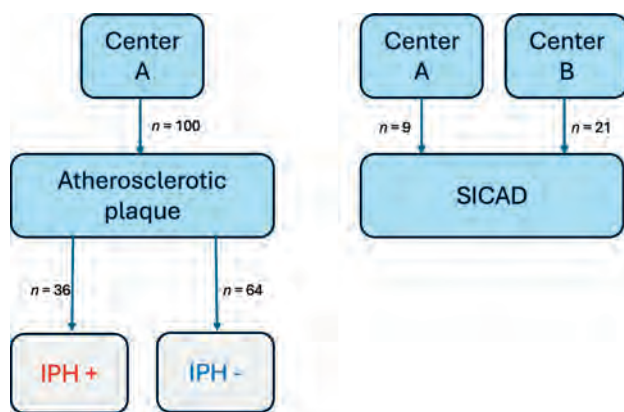


FIG 1. Flow chart of the SICAD and atherosclerotic patient recruitment.

internal carotid artery dissection (SICAD), demonstrating higher PFD values in patients with carotid artery dissection compared with those without it. Including patients with dissection allows us to investigate whether similar pathophysiologic mechanisms involving inflammation and PFD changes are at play in both atherosclerotic and nonatherosclerotic carotid conditions. Understanding these mechanisms could offer new insight into the management and risk stratification of patients with diverse carotid pathologies.

Among the features of vulnerability, intraplaque hemorrhage (IPH) is considered one of the most severe and could represent a subcategory of features of vulnerability related to the local inflammation that could alter the PFD.^{6–8} Therefore, the purpose of this study was to investigate the association between PFD values in patients with SICAD and carotid atherosclerosis with and without IPH.

MATERIALS AND METHODS

Study Design and Patient Population

This study was an observational cross-sectional cohort study conducted in 2 centers (AOU Cagliari and AO Brotzu). Institutional review board approval was obtained, and informed consent waived because of its retrospective nature. This study was conducted in accordance with STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for cross-sectional studies.

The cohort of patients with carotid atherosclerotic disease comprised consecutive adult subjects who underwent CTA for suspected atherosclerotic disease of the carotid arteries from May 2019 to March 2020 (Fig 1). Patients with acute ischemic stroke secondary to ipsilateral carotid disease were included, whereas patients with alternative stroke etiologies were excluded. Exclusion criteria were the following: subjects younger than 18 years of age; CTAs performed for reasons other than suspected atherosclerotic disease (ie, dissection); and other etiologies for ischemic stroke such as evidence of a cardiac embolic source (fibrillation, endocarditis), evidence of embolism from the thoracic aorta, and evidence of vertebrobasilar artery disease. Moreover, those with the presence of known pathologies of the arterial wall (collagenopathies such as Marfan syndrome

and inflammatory conditions) and patients with a history of major neck surgeries and radiation therapy to the neck were also excluded.

The presence of IPH using CTA was calculated using the model suggested by Saba et al⁹ (threshold of <25 HU).

Patients with SICAD were those who had evidence of acute carotid dissection on imaging (CTA with MRI confirmation) in the absence of any traumatic events (both minor and major trauma) in their medical history. The exclusion criteria were subjects younger than 18 years of age and the presence of known pathologies of the arterial wall (collagenopathies such as Marfan syndrome and inflammatory conditions). Patients with history of major neck surgeries, radiation therapy to the neck, and active bloodstream infections like endocarditis were also excluded. Patients with a concomitant atherosclerotic process (considered as a plaque determining a degree of stenosis of >50%) ipsilateral to the SICAD were excluded. These cases were selected from April 2015 to October 2022 in 2 different centers (Azienda Ospedaliero Universitaria, di Cagliari, Cagliari, Italy, and ARNAS Brotzu Hospital, Cagliari, Italy). A patient was considered symptomatic when he or she had a TIA or stroke. In this study, we considered 3 months the time window to be included in the symptomatic group.

CTA Technique

CTA of the carotid arteries was performed with multiple scanner technologies according to a standardized protocol. None of the patients who underwent CTA of the carotid arteries had a medical history of cardiac output failure or contraindications to iodinated contrast media. The patients were positioned supine with their heads inclined backwards to avoid dental artifacts. Scanning coverage extended from the aortic arch to the carotid siphon, proceeding in a caudocranial direction. Scans were obtained both pre- and post-contrast administration. For the angiographic phase, a preheated contrast medium was used, injecting 40–60 mL at a rate of 4–5 mL/s. To determine the optimal scan timing, we used a bolus-tracking technique. Dynamic monitoring scanning commenced 6 seconds after the start of the IV contrast injection. Inside the ROI, the trigger threshold was set at +80 HU over the baseline. There was a 1-second interval between each monitoring scan acquisition. On reaching the threshold, patients were instructed to hold their breath. After a 4-second interval, scanning in the caudocranial direction began. CT technical parameters included the following: matrix, 512 × 512; field of view, 14–19 cm; 180–250 mAs; 120 kV. A convolution filter algorithm was applied. Interactive window/level settings were usually set at W 850:L 300, progressing to very wide settings in the case of attenuated hyper dense calcifications.¹⁰

Carotid Plaque Analysis

Hounsfield unit measurements were performed by 2 radiologists in consensus. The data sets were assessed in a circular or elliptical ROI ($\geq 1 \text{ mm}^2$) in the predominant area of the plaque to measure the Hounsfield units.¹¹ Areas showing contamination by contrast material or calcifications and regions of beam-hardening were excluded. In cases in which 50% of the plaque contained calcium components, we considered the plaque calcified.

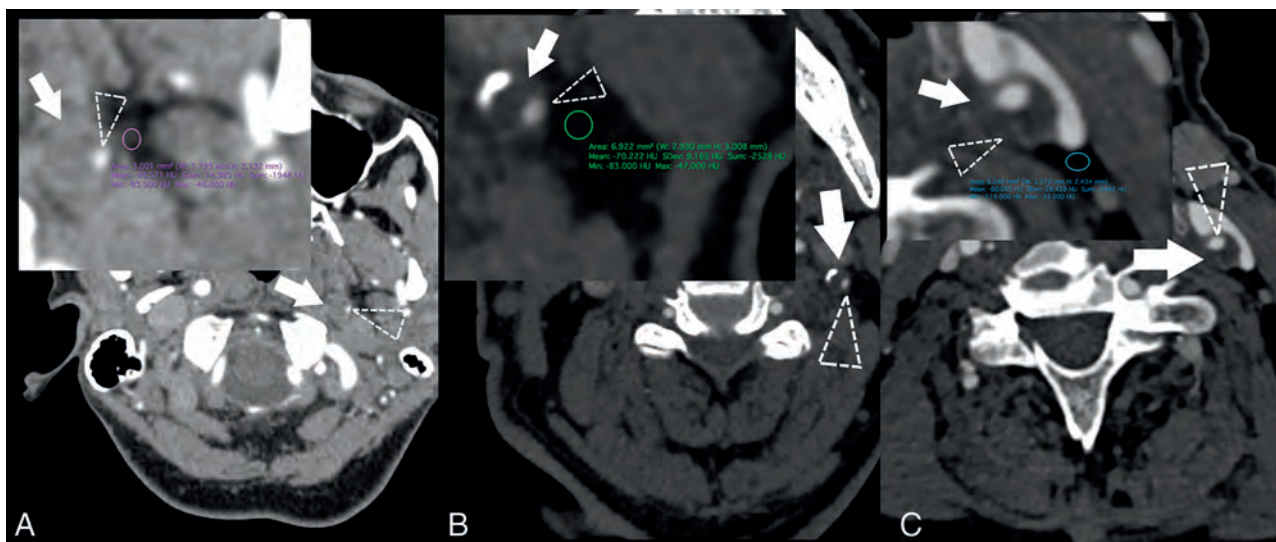


FIG 2. Examples of pericarotid fat measurement in a subject with SICAD (A), showing a value of 69 HU, with an atherosclerotic plaque with IPH (B), where a value of 70 HU can be observed, and with an atherosclerotic plaque without IPH (C), where a value of 80 HU can be observed.

Table 1: Baseline characteristics

	Total Population (n = 130)	SICAD Population (n = 30)	Carotid Plaque Population (n = 100)	P Value
Age (mean)	67 (SD, 12.8)	60.3 (SD, 8.42)	68.98 (SD, 13.24)	.001
Sex (male)	100 (76.9%)	24 (80%)	76 (76%)	.834
Hypertension	36 (27.7%)	9 (30%)	27 (27%)	.928
Coronary artery disease	56 (43.1%)	12 (40%)	44 (44%)	.858
Smoking status	46 (35.4%)	13 (43.3%)	33 (33%)	.411
Diabetes	16 (12.3%)	2 (6.7%)	14 (14%)	.449
Dyslipidemia	89 (68.5%)	20 (66.7%)	69 (69%)	.986

Analysis of Perivascular Fat Attenuation

Two radiologists, in consensus, conducted the PFD analysis using a previously validated method.^{1,2} To identify the fat tissue area, the 2 radiologists chose the ROIs, and each ROI measured at least 2.5 mm² and was placed on the perivascular fat seen on the same axial slice that showed the highest degree of ICA stenosis as defined by the North American Symptomatic Carotid Endarterectomy Trial (NASCET; <https://pubmed.ncbi.nlm.nih.gov/2057968/>) (Fig 2). Postcontrast scans were used for the analysis. The values obtained from these 2 ROIs were then averaged.

Statistical Analysis

The suitability of each group of continuous variables for normal distribution was assessed with the Kolmogorov-Smirnov Z-test. We represented continuous data as mean (SD), while binary variables were presented as count and percentage. To determine the relationship in patients between PFD and carotid plaque (with and without IPH), we computed Pearson ρ product moment correlation coefficients. To compare these ρ correlation values, we used the Fisher r-to-z transformation. Additionally, the Mann-Whitney U test was conducted to evaluate the differences between groups. The intraclass correlation coefficient (ICC) was calculated for the PFD analysis in 40 patients (20 with SICAD and 20 with atherosclerotic plaques). Statistical significance was considered for P values < .05, and all correlation analyses were based on a 2-tailed significance level. For all statistical calculations, R software (www.r-project.org) was used.

RESULTS

Baseline Characteristics

Of a cohort of 130 patients, 30 patients had SICAD (Center A contributed 9 cases of SICAD and Center B contributed 21 cases of SICAD), while 100 patients (all subjects from the center A) had carotid atherosclerotic plaque. Thirty-six patients of 100 (36%) showed IPH. Baseline demographic characteristics are summarized in Table 1. In patients with SICAD, the median time interval between symptoms and events was 18 hours (range, 3 hours to 6 days), whereas in non-SICAD symptomatic patients, the median time between symptoms and events was 31 hours (range, 3 hours to 18 days), with a statistically significant difference ($P < .001$).

Perivascular Fat Attenuation in Carotid Artery Dissection versus Carotid Plaque

In patients with carotid atherosclerotic plaque (both with and without IPH, $n = 100$), the average PFD was -74.54 HU (95% CI, -76.18 to -72.9 HU), while the average PFD in patients with SICAD was -68.97 HU (95% CI, -72.11 to -65.82 HU) ($P < .001$). Figure 3 illustrates the difference in PFD between patient groups with SICAD and carotid plaque.

In the patient group with carotid atherosclerotic plaque ($n = 100$), 36 patients demonstrated the presence of IPH and had a mean PFD value of -69.97 HU (95% CI, -73.00 to -66.95 HU). Patients without IPH ($n = 64$) had a more negative PFD value of -77.11 HU (95% CI, -78.78 to -75.44 HU) ($P < .001$).

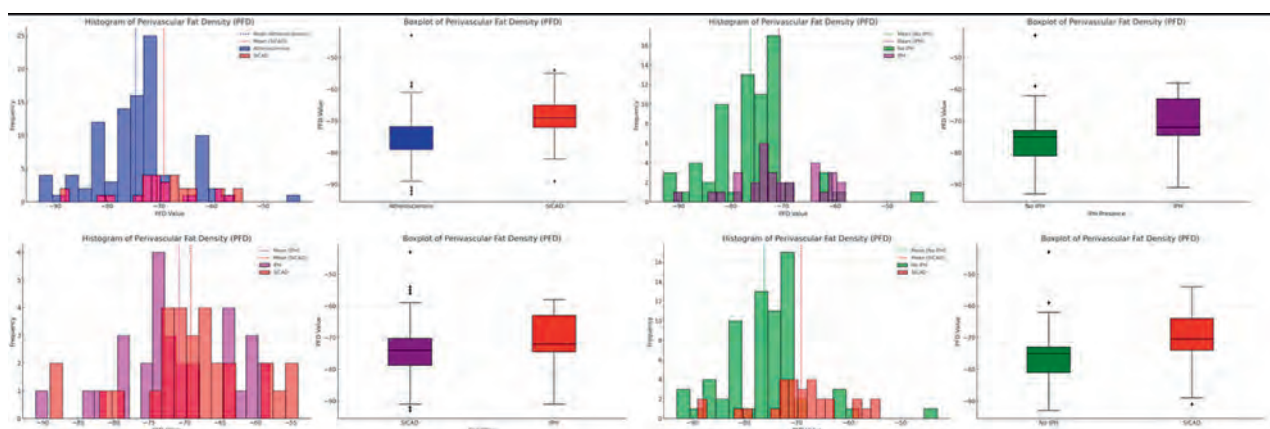


FIG 3. Histograms and boxplots illustrating the difference of PFD value in patients with atherosclerosis and SICAD. Patients with atherosclerosis with no IPH had lower PFD values than those with IPH and SICAD. Patients with SICAD and IPH had relatively close values.

Table 2: Mann-Whitney U Test

Patient Group	Statistical Value	P Value
Plaque with IPH vs without IPH	567.5	<.001
Plaque with IPH vs SICAD	463	.324
Carotid plaque vs SICAD	806.5	<.001
Carotid plaque without IPH vs SICAD	1576.5	<.001

Table 3: PFD values of carotid plaque versus SICAD

Patient Group	Mean PFD Value	Range (HU)
Carotid plaque	−74.54 (SD, 8.286)	−93 to −43
Uncomplicated by IPH	−77.11 (SD, 6.698)	−93 to −59
Complicated by IPH	−69.97 (SD, 8.939)	−91 to −43
SICAD	−97 (SD, 8.418)	−89 to −54

A plot demonstrating the relationship of PFD in patients with uncomplicated carotid plaque versus patients with carotid plaque complicated by IPH is shown in Fig 3.

Finally, further analysis showed that the PFD value of patients with IPH was very similar (average value of −69.97 HU [95% CI, −73.00 to −66.95 HU]) compared with the PFD value of patients with SICAD (average value of −68.97 HU [95% CI, −72.11 to −65.82 HU]) ($P = .324$). Figure 3 shows the PFD values for SICAD and carotid plaque with IPH.

Mann-Whitney analysis demonstrated a statistically significant difference in PFD according to the disease in question as shown in Table 2.

Table 3 summarizes the PFD values depending on the different groups. The ICC analysis performed in the sample of 40 cases showed a value of 0.893, which can be considered good reliability.

DISCUSSION

This study hypothesizes that changes in PFD are associated with inflammatory processes in both atherosclerotic and nonatherosclerotic carotid diseases, specifically SICAD and carotid atherosclerotic plaque with IPH. The central premise is that increased PFD is an indicator of inflammation that may contribute to the pathogenesis and progression of these 2 conditions, potentially serving as a noninvasive marker for identifying high-risk vascular conditions.

In our cohort study of 130 patients, the mean PFD value in the patient group with SICAD was higher than that in patients with carotid atherosclerotic plaque without IPH ($P < .001$), while it was nearly equivalent to that in the group with IPH ($P = .324$). These findings suggest the presence of a higher level of inflammation in the perivascular fat of both patients with SICAD and carotid plaque with IPH.

The value of PFD and its association with vascular pathology is an increasing topic of interest, and its value has been demonstrated in different organs such as pericarotid and periaortic attenuation.¹²⁻¹⁴ It is well-demonstrated in the literature that there is a complex and bidirectional crosstalk between the vascular wall and the surrounding perivascular adipose tissue.¹⁵ Therefore, it is plausible for perivascular fat attenuation to serve as a surrogate marker of inflammation.

The etiology of SICAD is complex and not completely understood, but it is hypothesized that several factors interplay, including genetic predisposition and environmental triggers such as infection.^{16,17} The hypothesis is that underlying constitutional weakness of the vessel wall in patients with SICAD is genetically determined and that environmental factors such as acute infection could trigger it.¹⁸ The likely common denominator between these complex etiologies could be the role of inflammation.^{5,19}

In a retrospective analysis of 29 patients, 18 with SICAD, Naggara et al²⁰ demonstrated the association between inflammation and SICAD by showing the presence of periarterial edema using cervical high-resolution MR imaging and elevated acute phase reactants such as the erythrocyte sedimentation rate and C-reactive protein. However, serum inflammatory markers were unable to pinpoint the specific location of vascular inflammation.^{21,22}

Other authors have reinforced the role of imaging to detect inflammation-induced changes in perivascular carotid fat tissue in patients with carotid and coronary dissection.^{5,23} In a study by Pfefferkorn et al,²⁴ increased [¹⁸F] FDG accumulation on PET/CT and perivascular contrast enhancement on high-resolution MRI, respectively, were found in patients with SICAD, suggesting vessel wall inflammation in patients experiencing an acute carotid dissection. The attenuation alteration in the periarterial fat is demonstrated in the coronary arteries, where the variation of

attenuation in the fat is considered an indirect parameter of coronary plaque inflammation.²⁵

Our findings are in line with these hypotheses suggesting a strong correlation between SICAD and inflammation as demonstrated by the presence of a more positive PFD compared with patients with uncomplicated carotid plaque ($P < .001$) and also consistent with the findings of Cheng et al.⁵ Given the cross-sectional nature of our study, we can show only an association, and further studies are needed to establish a potential causation between the inflammation and SICAD. If there is any causation, its directionality (inflammatory state leading to an instability in the blood vessel, thus a dissection versus blood vessel rupture and intramural hematoma causing perivascular inflammation) will also be crucial to determine.

Similarly, inflammation is recognized as a significant contributor to atherosclerotic plaque formation and progression, and pericarotid fat contributes to promoting atherosclerosis through its bidirectional cross-talk between the vascular wall.^{1,2}

IPH is a well-known biomarker of plaque vulnerability.²⁶⁻²⁹ The available body of literature discussing the relationship between IPH and PFD is scarce^{3,4} but, nevertheless, supports the idea of the presence of high PFD in patients with IPH. Our findings support this claim by demonstrating a more positive PFD value compared with patients with uncomplicated carotid plaque ($P < .001$) and are concordant with those of Yu et al.,⁴ who found that PFD was significantly associated with high-risk American Heart Association lesion type VI plaque characterization and IPH.

A key point of this article was identifying plaque with IPH to assess the characteristics of the pericarotid fat. It is widely demonstrated that MRI is the imaging-based criterion standard for IPH identification, but some recent evidence has shown that CT also offers good performance. In particular, the threshold of 25 HU for identifying plaque with IPH was chosen on the basis of the publication by Saba et al.⁹ The authors found that using 25 HU, the receiver operating characteristic analysis showed a sensitivity of 93.22% and a specificity of 92.73%.

Our findings of altered PFD in patients with both SICAD and IPH could suggest an overlap between the inflammatory pathways of these entities. In vulnerable plaques, the interconnected pathways between the vessel wall and pericarotid fat release inflammatory cytokines, resulting in heightened vascular oxidation and inflammation. Consequently, this process increases microvascular permeability, potentially contributing to the subsequent rupture of intraplaque neovessels.⁴ Most interesting, similar mechanisms have been proposed in arterial dissection.^{5,30-32} Arterial dissection is characterized by an intramural hematoma and/or a dissected intimal layer, with a complex and multifaceted pathogenesis, potentially involving vasa vasorum and vascular smooth-muscle cell proliferation.^{33,34} In this scenario, dysfunctional perivascular fat can promote endothelial dysfunction, vascular smooth-muscle cell proliferation, and vasa vasorum proliferation and rupture,³⁵ consequently leading to arterial dissection.³⁴

Clinically, recognizing a link between IPH and SICAD could enhance our understanding of the inflammatory mechanisms underlying carotid artery diseases. By establishing a link between

PFD and vascular inflammation, we could improve risk stratification for patients with SICAD and carotid atherosclerosis. Additionally, these insights might lead to the development of targeted interventions to stabilize vulnerable plaques and prevent adverse cerebrovascular events, thereby reducing the burden of stroke and other complications related to carotid artery diseases. Lifestyle modifications, aggressive risk factor control, and anti-inflammatory medications may emerge as key interventions to stabilize vulnerable arterial walls and reduce plaque instability across these conditions. Currently, there is no proven therapy to prevent SICAD.

Furthermore, when comparing the repeatability and complexity of the other imaging methods, MRI vessel wall imaging is highly accurate and provides detailed visualization of the pericarotid fat due to the assessment of the signal intensities, yet it can be time-consuming and expensive. In contrast, ultrasound is more accessible and cost-effective, offering real-time assessments, but interpretation may be more operator-dependent and less repeatable across different settings.

We acknowledge several limitations in our study. First, due to the retrospective nature of our study and the small patient cohorts, our findings need validation in a larger prospective analysis. SICAD represents a very challenging subgroup, highly dependent on an accurate medical history, which can be suboptimal in a retrospective approach. Second, the use of different CT scanners in a relatively long timeframe could have introduced a technologic bias related to the energy level (milliampere-seconds and care dose systems with amperage modulation) used that may have an impact on the Hounsfield unit attenuation values. The third point is related to the method of attenuation measurements on CT, by which confounding factors and inaccuracies may affect the results, in particular, the variability in ROI placement, the involved segment possibly being much longer than 1 slice, and patients with a small amount of pericarotid fat. The fourth point is related to the absence of assessment of intracranial stenosis, presenting a potential confounding factor. A further point is related to IPH detection with CTA, which can present some bias due to the Hounsfield unit overlap between blood and lipid/fibrous tissue. The last point concerns the 3-month time window used to consider patients as symptomatic: This is a long interval and could have introduced potential bias in terms of variation in the degree of inflammation in the pericarotid fat.

CONCLUSIONS

In patients with SICAD and IPH, changes in perivascular carotid fat tissue are found, suggesting a common pathologic inflammation pathway in these 2 entities. Further studies may be needed to confirm this indirect hypothesis by comparing pathologic and radiologic data.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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The Etiology of Intracranial Artery Stenosis in Autoimmune Rheumatic Diseases: An Observational High-Resolution MR Imaging Study

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ABSTRACT

BACKGROUND AND PURPOSE: Autoimmune rheumatic diseases (AIRD) can cause intracranial artery stenosis (ICAS) and lead to stroke. This study aimed to characterize patients with ICAS associated with AIRD.

MATERIALS AND METHODS: Using data from a high-resolution MR imaging database, we retrospectively reviewed patients with AIRD with ICAS. Stratification into vasculitis, atherosclerosis, and mixed atherovascularitis subtypes was based on imaging findings, followed by a comparative analysis of clinical characteristics and outcomes across these subgroups.

RESULTS: Among 139 patients (mean, 45.1 [SD, 17.3] years; 64.7% women), 56 (40.3%) were identified with vasculitis; 57 (41.0%), with atherosclerosis; and 26 (18.7%), with mixed atherovascularitis. The average interval from AIRD onset to high-resolution MRI was 5 years. Patients with vasculitis presented at a younger age of AIRD onset (mean, 34.5 [SD, 19.4] years), nearly 10 years earlier than other groups ($P = .010$), with a higher artery occlusion incidence (44.6% versus 21.1% and 26.9%, $P = .021$). Patients with atherosclerosis showed the highest cardiovascular risk factor prevalence (73.7% versus 48.2% and 61.5%, $P = .021$) but fewer intracranial artery wall enhancement instances (63.2% versus 100% in others, $P < .001$). The mixed atherovascularitis group, predominantly men (69.2% versus 30.4% and 24.6%, $P < .001$), exhibited the most arterial involvement (5 arteries per person versus 3 and 2, $P = .001$). Over an average 21-month follow-up, 23 (17.0%) patients experienced stroke events and 8 (5.9%) died, with the mixed atherovascularitis group facing the highest risk of stroke events (32.0%) and the highest mortality (12.0%).

CONCLUSIONS: Intracranial arteries are injured and lead to heterogeneous disease courses when exposed to AIRD and cardiovascular risk factors. While atherosclerosis acceleration is common, vasculitis may further contribute to the early development of occlusion and multiple artery involvement. Varied intracranial arteriopathies may result in different outcomes.

ABBREVIATIONS: AIRD = autoimmune rheumatic diseases; HRMRI = high-resolution MRI; ICAS = intracranial artery stenosis

Autoimmune rheumatic diseases (AIRD) are characterized as immune dysregulation, primarily affecting joints and muscles, and causing damage to host tissue and organs.¹ This category encompasses diseases including systemic vasculitis, systemic lupus erythematosus, primary antiphospholipid syndrome, rheumatoid arthritis, Sjogren syndrome, and so forth.¹ AIRD are known to increase the risk of cardiovascular and

cerebrovascular events, particularly among young individuals.² The underlying mechanism is primarily attributed to the arterial diseases, which are among the most common complications of AIRD.^{3,4} Previous studies have indicated that AIRD accelerate the risk of premature coronary artery diseases and carotid artery diseases, mostly premature atherosclerosis or vasculitis.^{3,4} Intracranial artery stenosis (ICAS) may also occur in patients with AIRD at a young age.^{5,6} However, the underlying pathophysiology remains insufficiently studied, in part due to the difficulties in establishing an etiologic diagnosis through conventional lumen imaging. Whether it involves intracranial

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SUMMARY

PREVIOUS LITERATURE: AIRD can cause ICAS and lead to stroke, yet the etiology of this ICAS has not been systematically reported in the previous literature.

KEY FINDINGS: A novel subtype characterized by the coexistence of atherosclerosis and vasculitis was identified and named mixed atherovasculitis, which not only encompasses the characteristics of both arteriosclerosis (older) and vasculitis (more intracranial artery wall enhancement) but also presents unique features (male dominance, multiple arterial involvement), potentially resulting in the worse outcomes.

KNOWLEDGE ADVANCEMENT: The results emphasize that intracranial arteries are injured and lead to heterogeneous disease when exposed to AIRD and cardiovascular risk factors. While atherosclerosis acceleration is common, vasculitis may further contribute to early development of occlusion and multiple artery involvement.

vasculitis or atherosclerosis, ICAS may manifest as segmental artery narrowing and poststenotic dilation on MRA, CTA, or DSA.⁷ The uncertain etiology greatly complicates clinical decision-making and leads to confused treatment.

In the last decade, high-resolution MR imaging (HRMRI) has emerged as a noninvasive technique for visualizing intracranial artery wall structure.⁸ Previous studies have suggested that HRMRI is instrumental in identifying intracranial artery diseases, including atherosclerosis, dissection, Moyamoya disease, vasculitis, and reversible cerebral vasoconstriction syndrome.⁹ In this study, our objectives were to elucidate intracranial artery diseases associated with patients with AIRD using HRMRI and compare the differences in the clinical characteristics and outcomes across the etiology subgroups. This article follows the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

MATERIALS AND METHODS

This was a retrospective analysis of data from the HRMRI database spanning January 2015 to September 2023 at Peking Union Medical College Hospital. Ethics approval for this study was granted by the local ethics committee (K24C1320).

Patient Selection

Patients were included if they fulfilled the following criteria; 1) had ICAS on MRA (including the C6/C7 segment of the ICA, the M1/M2 segment of the MCA, the A1 segment of the anterior cerebral artery, the V4 segment of the vertebral artery, the basilar artery, and the P1 segment of the posterior cerebral artery; and 2) had a diagnosis of AIRD, confirmed by experienced rheumatologists according to American College of Rheumatology/European League Against Rheumatism classification criteria.^{10–15} Patients with poor-quality images were excluded. Exclusion criteria also encompassed patients diagnosed with primary CNS vasculitis, Moyamoya disease, and reversible cerebral vasoconstriction syndrome, which were attributed to the high heterogeneity of etiologies in addition to AIRD.^{7,16,17}

Imaging Protocol

All MRIs were obtained on two 3T systems (Cube, GE Healthcare; and sampling perfection with application-optimized contrasts by using different flip angle evolutions [SPACE], Siemens), following

the standardized protocol.^{18,19} The protocol included conventional 3D TOF-MRA, DWI, ADC, 3D T1-weighted head-neck joint HRMRI, and 2D T2-weighted vessel wall imaging of the MCA. Contrast enhancement was applied selectively to 3D T1WI (Cube system) following gadolinium administration (0.01 mmol/Kg of gadopentetate dimeglumine). The imaging parameters are listed in the Online Supplemental Data.

Imaging Definition

Image analysis was performed on each stenotic artery, and individuals were categorized into 3 subtypes (Fig 1): 1) atherosclerosis, characterized by eccentric vessel wall thickening in the orthogonal plane, with the maximal wall thickness exceeding twice the thinnest wall thickness on visual inspection;¹⁸ 2) vasculitis, characterized by concentric stenosis in the orthogonal plane, potentially accompanied by concentric enhancement following gadolinium administration;²⁰ and 3) mixed atherovasculitis, representing the coexistence of atherosclerosis and vasculitis within a single patient, manifested across different arteries or within distinct segments of a single artery. Concentric enhancement was interpreted as circular when uniform or circumferential thickening occurred, whereas eccentric enhancement was identified in the absence of 360° circumferential thickening or when the thickest portion exceed twice the thinnest wall thickness in cases showing circumferential enhancement.²¹ The degree of artery stenosis was evaluated according to the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) criteria.²² On completion of vascular imaging follow-up, the imaging data were re-examined to ascertain changes in the stenotic artery etiology and the degree of stenosis.²³ All images were independently evaluated using the Osirix software (Version 14.0.1; <http://www.osirix-viewer.com>) by 2 readers (S.L. and M.L., with 8 and 20 years of experience, respectively). Should a disagreement arise, a third reader (W.X., with 20 years of experience) was consulted to make a final decision.

Clinical Characteristics and Outcomes

Clinical characteristics, including age at HRMRI examination, AIRD-onset age, stroke-onset age, sex, and traditional cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, and smoking) were collected. Given the delayed diagnosis of AIRD, the age of the earliest symptoms associated with AIRD was defined as the

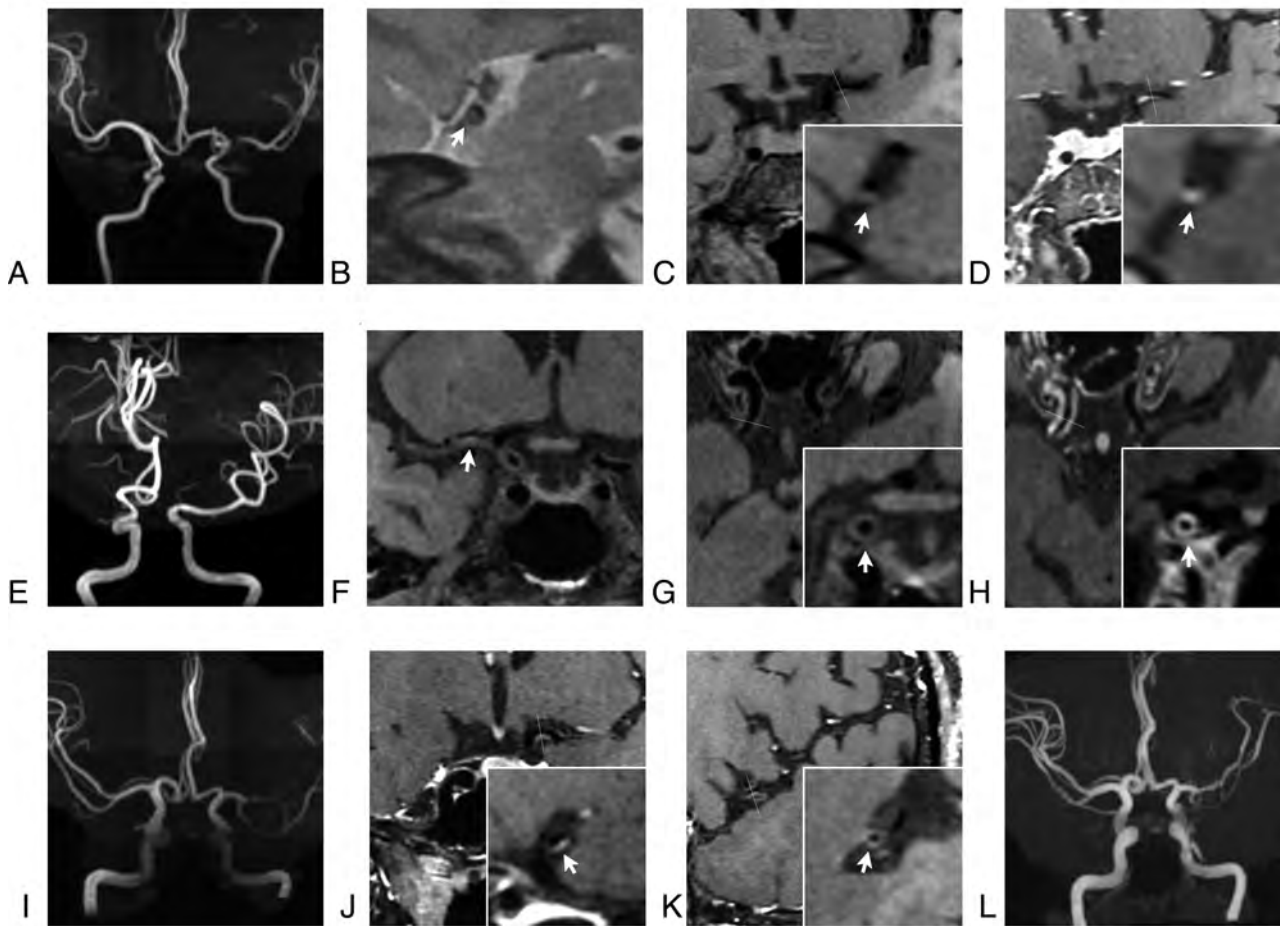


FIG 1. Three representative cases of ICAS associated with AIRD, as revealed by HRMRI. *A–D*, Intracranial atherosclerosis. MRA shows the left MCA stenosis associated with systemic lupus erythematosus (*A*). HRMRI reveals an eccentric wall thickening of the left MCA in the coronal and sagittal planes (*B* and *C*, white arrow), accompanied by eccentric enhancement in the coronal and sagittal planes (*D*, white arrow), suggesting an atherosclerosis etiology. *E–H*, Intracranial vasculitis. MRA shows right ICA stenosis and right MCA occlusion associated with systematic vasculitis (*E*). HRMRI shows right MCA thrombus in the coronal plane (*F*, white arrow), a concentric wall thickening (*G*, white arrow), and concentric enhancement of the right ICA C6 segment (*H*, white arrow) in the axial and coronal planes, suggesting a vasculitis etiology. *I–L*, Mixed atherovasculitis. MRA shows the left MCA stenosis associated with primary antiphospholipid syndrome (*I*). HRMRI shows an eccentric wall thickening and eccentric enhancement of the left MCA M1 segment in the coronal and sagittal planes (*J*, white arrow), accompanied by a concentric wall thickening and concentric enhancement of the left MCA M2 segment (*K*, white arrow), suggesting a mixed atherovasculitis etiology. The follow-up MRA shows regression of arterial stenosis after immunosuppressive and antithrombotic therapy (*L*).

AIRD-onset age.¹ If stroke was the initial manifestation of AIRD, especially in patients with primary antiphospholipid syndrome, the age at stroke was consequently defined as the AIRD-onset age.²⁴

Patients were monitored through clinical visits or telephone interviews at 3, 6, and 12 months and annually after the HRMRI examination. Administration of medications during the follow-up period (including glucocorticoid, immune-suppressant, biologic agents, and drugs for stroke prevention) and clinical outcomes (defined as any new stroke events, including ischemic stroke and hemorrhage, and death) were recorded.

Statistical Analysis

Patients were grouped according to the varied artery disease subtypes and AIRD subgroups, respectively. Continuous variables were reported as mean (SD) or median (interquartile range), depending on their distribution. Categorical variables were presented as numbers and percentages. Cox regression was conducted to estimate the

cumulative stroke event-free rate. A value of $P < .05$ indicated a statistically significant difference. All statistical analyses were conducted using SPSS 26.0 software (IBM).

RESULTS

A total of 196 patients with AIRD underwent HRMRI examinations, of whom 156 with AIRD presented with ICAS. After excluding 10 patients with primary CNS vasculitis, 6 with Moyamoya disease, and 1 patient with Sjogren syndrome who developed reversible cerebral vasoconstriction syndrome after intrathecal drug injection, the data of 139 patients with AIRD with ICAS were ultimately analyzed (Fig 2). Among them, 51 were diagnosed with systemic vasculitis (25 with large-vessel vasculitis; 18 with medium-small vessel vasculitis; and 8 with Behcet disease); 34 with systemic lupus erythematosus; 32 with primary antiphospholipid syndrome; 9 with rheumatoid

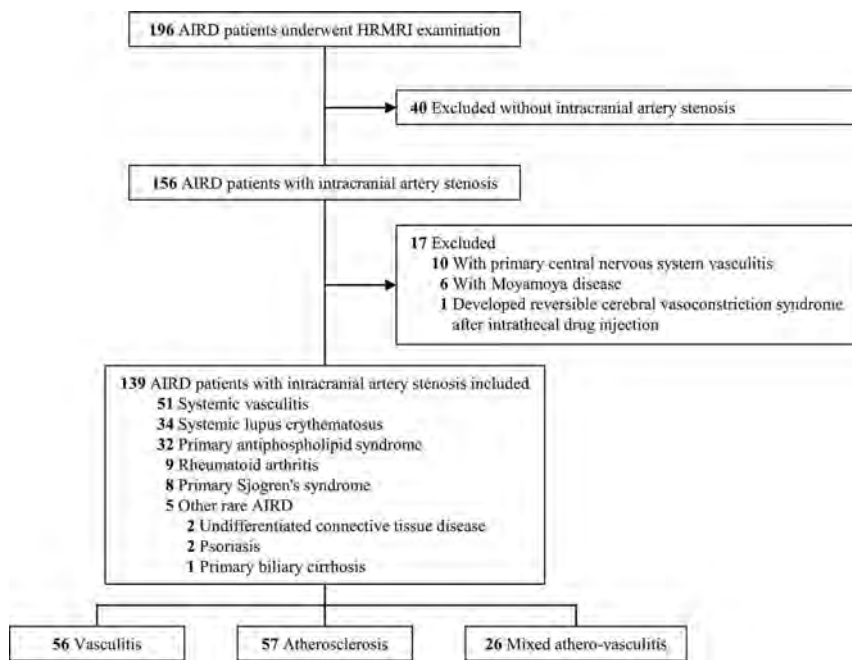


FIG 2. Flow chart.

arthritis; 8 with primary Sjogren syndrome; and 5 with other rare AIRD [2 with psoriasis, 2 with undifferentiated connective tissue disease, and 1 with primary biliary cirrhosis]. Eighty-nine patients underwent contrast-enhanced imaging.

Clinical Characteristics

As shown in the Online Supplemental Data, the mean age at HRMRI examination was 45.1 years, the mean age of AIRD onset was 39.9 years, and 90 (64.7%) were women. One hundred ten (79.1%) patients had a history of stroke, including 2 patients with both ischemic stroke and hemorrhage, and 93 cases (66.9%) were attributed to symptomatic ICAS. Forty-four (31.7%) patients had intracranial artery occlusion. There were 56 (40.3%) patients diagnosed with intracranial vasculitis; 57 (41.0%), with atherosclerosis; and 26 (18.7%), with mixed atherovascularitis.

As shown in the Online Supplemental Data, patients with vasculitis experienced an AIRD onset (34.5 versus 42.9 and 45.0 years old, $P = .010$) and stroke onset (36.8 versus 45.5 and 47.3 years old, $P = .019$) nearly ten years earlier than patients with atherosclerosis and those with mixed atherovascularitis, and were more likely to have artery occlusion (44.6% versus 21.1% and 26.9%, $P = .021$). Patients with atherosclerosis demonstrated the highest cardiovascular risk factor exposure (73.7% versus 48.2% in the vasculitis group and 61.5% in the mixed atherovascularitis group, $P = .021$) and the lowest incidence of intracranial artery wall enhancement (63.2% versus 100.0% in others, $P < .001$). Patients with mixed atherovascularitis were more likely to be men (69.2% versus 30.4% in the vasculitis group and 24.6% in the atherosclerosis group, $P < .001$), smokers (34.6% versus 10.7% in the vasculitis group and 14.0% in the atherosclerosis group, $P = .040$), and exhibit the greatest artery involvement (mean, 5 arteries/person versus 3 in the vasculitis group and 2 in the atherosclerosis group, $P < .001$).

When analyzing the AIRD subgroups, patients with systemic vasculitis were more likely to have intracranial vasculitis than intracranial atherosclerosis (49.0% versus 25.5%), while patients with primary antiphospholipid syndrome were on the contrary (21.9% versus 53.1%). In patients with systemic lupus erythematosus, both intracranial vasculitis (52.9%) and atherosclerosis (41.2%) were observed frequently.

Treatment and Clinical Outcomes

A total of 135 patients completed follow-up, with a median of 21 (range, 12–51) months. Among them, 73 (54.1%) patients were administered glucocorticoids, 83 (61.5%) received immune suppressants, and 10 (7.4%) were treated with biologic agents. For stroke prevention, 96 (71.1%) were prescribed antithrombotic drugs and 93 (68.9%) were prescribed lipid-lowering agents. As shown in the Online Supplemental

Data, maintenance therapy with glucocorticoids was more common among patients with vasculitis (72.2%), while fewer patients with AIRD (46.4%) with intracranial atherosclerosis received immune-suppressant therapy. Forty-four patients completed the vascular imaging follow-up, with a median of 20 (range, 12–40) months, including 20 HRMRI follow-ups. No subtype changes among vasculitis, atherosclerosis, and mixed atherovascularitis were observed. Most patients remained stable, while 9 (20.5%) patients had artery stenosis regression and 5 (11.4%) had artery stenosis progression.

During the follow-up period, 23 (17.0%) patients experienced stroke events, including 21 ischemic strokes and 2 intracranial hemorrhages, all of whom had a history of stroke. Eight (5.9%) patients died, of whom 7 had a history of stroke and 4 experienced ischemic stroke events during follow-up. Regarding the causes of death, 6 deaths were attributed to infection and the other 2 remained unknown. Patients with mixed atherovascularitis had the highest incidence of stroke events (32.0%), while patients with intracranial atherosclerosis had the lowest (10.7%). After adjusting for age and sex, there were no significant differences concerning stroke events during follow-up among etiology subtypes, with the exception of a higher incidence of stroke events in patients with mixed atherovascularitis than patients with atherosclerosis (HR, 3.146; 95% CI, 1.033–9.585, $P = .044$, Fig 3). Patients with mixed atherovascularitis had the highest mortality (12.0%).

DISCUSSION

We conducted a systematic investigation into the clinical characteristics and outcomes of 3 imaging-defined etiologies of ICAS associated with AIRD, including atherosclerosis, vasculitis, and mixed atherovascularitis. Patients with vasculitis experienced the earliest AIRD onset but were more likely to have artery occlusion.

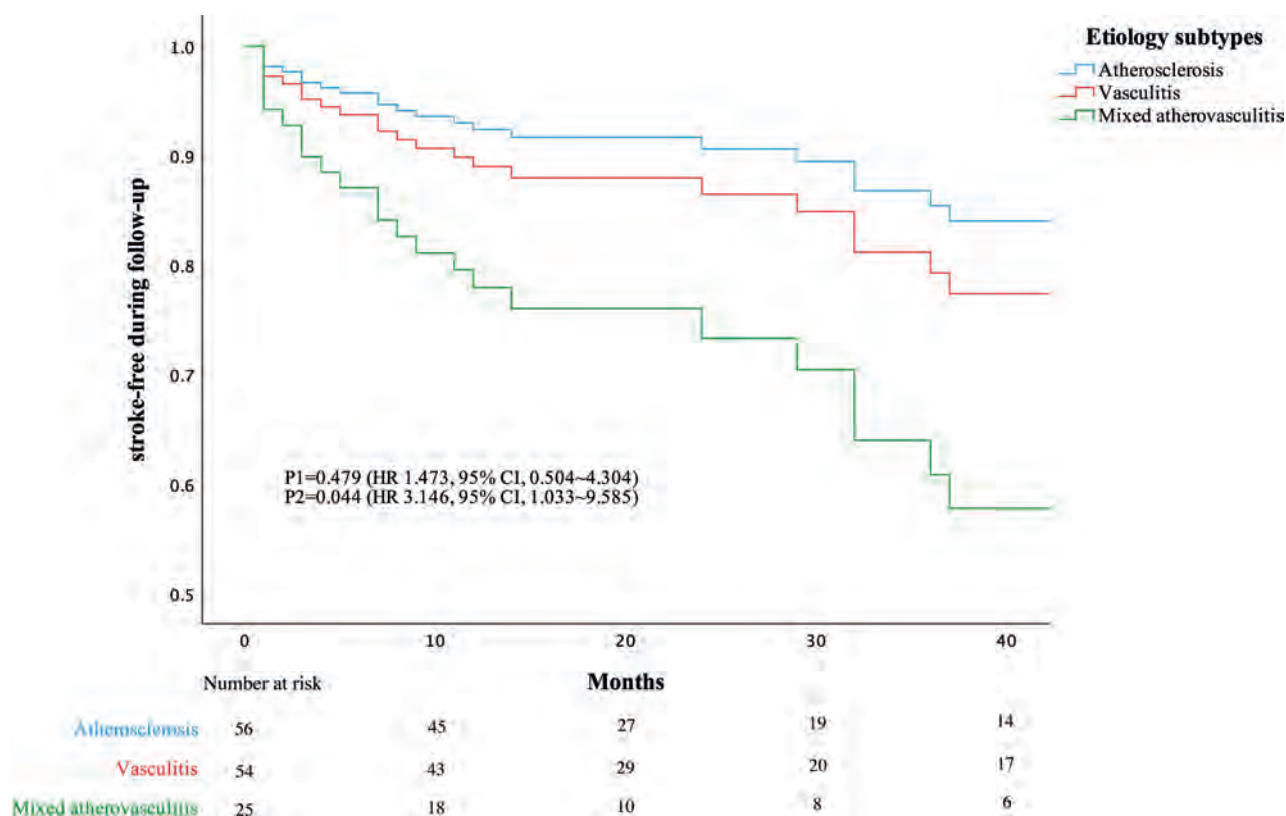


FIG 3. Cox regression of the stroke-free rate during follow-up among etiology subtypes. P1 indicates vasculitis versus atherosclerosis; P2, mixed atheroarteritis versus atherosclerosis.

Patients with atherosclerosis exhibited the highest cardiovascular risk factor exposure and showed less intracranial artery wall enhancement. Patients with mixed atheroarteritis constituted the only subtype with male preponderance and exhibited the most artery involvement. During follow-up, patients with mixed atheroarteritis experienced the highest stroke event risk and the highest mortality.

In previous studies, ICAS was reported in patients with AIRD with or without stroke.^{5,6} The detailed clinical characteristics and etiology, however, have been largely elusive. In our study cohort, the mean age at HRMRI examination was 45.1 years, merely 5 years subsequent to the initial symptoms of AIRD, suggesting that intracranial vascular damage could occur in early life and the early stage of the disease. It may be also partly due to the high percentage (61.2%) of patients exposed to coexistent cardiovascular risk factors, which accelerates vascular damage in AIRD. Should intracranial vasculitis be the predominant etiology, it is posited that inflammation encompassing all arterial layers could induce wall edema, endothelium hyperplasia, and thrombosis formation. These factors collectively exert synergistic effects, exacerbating stenosis severity and precipitating early arterial occlusion.²⁵ It was anticipated that patients with atherosclerosis were older and exhibited a higher proportion of cardiovascular risk factor exposure than those with vasculitis.²⁶ Nevertheless, the mean age of 49.3 years and a high percentage of stroke history (80.7%) suggested that these individuals may have premature atherosclerosis, making them more susceptible to stroke than the

general population.²⁷ The novel finding was that nearly one-fifth of our patients exhibited mixed atheroarteritis. Their age was similar to that in patients with atherosclerosis, yet they demonstrated intracranial artery wall enhancement (100%) on HRMRI comparable with that in the patients with vasculitis, indicating an overlap of atherosclerosis and vasculitis. Although previous studies reported that vasculitis may turn into atherosclerosis with time,²⁸ this outcome was not supported by our follow-up imaging data. The characteristics of male dominance and multiple artery involvement imply that mixed atheroarteritis may have unique underlying mechanisms.

Atherosclerosis was observed more frequently in patients with primary antiphospholipid syndrome but less frequently in patients with systemic vasculitis, potentially due to the different pathophysiology of the 2 diseases. Endothelial dysfunction, mediated by autoantibodies, is recognized as the initial factor in primary antiphospholipid syndrome. This, combined with the coaction of cardiovascular risk factors, promotes the macrophage uptake of oxidized low-density lipoprotein and deposition under the intima, gradually developing into atherosclerosis plaque,²⁹ while systemic vasculitis is characterized as artery inflammation and is attributed to the immune complexes, mainly situated in the media and adventitia.³⁰ That explanation may elucidate why intracranial atherosclerosis was more prevalent in antiphospholipid syndrome. In systemic lupus erythematosus, the deposition of immune complexes may lead to vasculitis, while concurrent endothelial injury may result in atherosclerosis, particularly when

combined with secondary antiphospholipid syndrome.^{29,31} As a result, both vasculitis and atherosclerosis were common in patients with systemic lupus erythematosus.

Nearly four-fifths of our patients had a history of stroke. During a median follow-up of 21 months, 17.0% of patients experienced stroke events and 5.9% died. Compared with the results in other studies of young individuals with stroke, the incidence of stroke was much higher than that in the Italian Project on Stroke in Young Adults study (3.2% at 1 year, 10.9% at 5 years)³² and mirrored the findings of the Follow-Up of Transient ischemic attack and stroke patients and Unelucidated Risk factor Evaluation (FUTURE) study (19.6%), with a longer follow-up of 9.1 years.³³ The results indicated that patients with AIRD with ICAS were at high risk of stroke and death, despite undergoing immune-suppressive and stroke-prevention therapies. Timely initiation of more precise management is imperative. Patients with mixed atherovascularitis exhibited the highest stroke-recurrence risk and the highest mortality, suggesting that they required more aggressive management.

Our study has limitations. First, this was a retrospective analysis. Selection bias may exist because patients with asymptomatic ICAS were less likely to be enrolled; future prospective studies are warranted to confirm our findings. Second, due to the infeasibility of the intracranial large-artery tissue, the imaging-defined etiology lacks the criterion standard confirmation of pathologic diagnosis, though evidence has been provided by several imaging postmortem studies.^{34,35} Combining serum or CSF biomarkers with HRMRI may further improve the diagnostic accuracy and monitoring of disease activity in ICAS associated with AIRD.

CONCLUSIONS

Our study suggests that the intracranial arteries are injured and lead to heterogeneous disease when exposed to AIRD and cardiovascular risk factors. While atherosclerosis acceleration is common, vasculitis may further contribute to the early development of occlusion and multiple artery involvement. Varied intracranial arteriopathies may result in different outcomes.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Clinical Outcome of Pipeline Embolization Device with and without Coils to Treat Intracranial Aneurysm: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: The use of a Pipeline Embolization Device (PED) in combination with coils (PEDC) to treat intracranial aneurysms remains unclear as to whether it offers significant benefits for the patients because the results have varied.

PURPOSE: This study aimed to investigate the clinical outcome of the PEDC compared with the PED in treating intracranial aneurysms.

DATA SOURCES: We systematically searched the articles from PubMed, Web of Science, and the Cochrane Library databases published before January 25, 2024.

STUDY SELECTION: We selected studies comparing the PEDC versus the PED to treat intracranial aneurysms. Patients treated with the PEDC but using dense coiling were excluded from the study.

DATA ANALYSIS: The clinical outcomes observed in this meta-analysis were intraprocedural complications, postoperative complications (stenosis, stroke, hemorrhage, mortality), favorable outcome (mRS ≤ 2), complete occlusion rate, and retreatment rate. A forest plot was used to analyze pooled OR of clinical outcomes.

DATA SYNTHESIS: A total of 3001 subjects from 9 observational studies were included. The PEDC was mainly used to treat larger aneurysms. The PEDC has a significantly higher complete occlusion rate at 6 months (OR = 2.66; 95% CI, 1.26–115.59; $P = .01$), a lower retreatment rate (OR = 0.18; 95% CI, 0.05–0.07; $P = .010$), higher stroke-related complications (OR = 1.66, 95% CI, 1.16–2.37; $P = .005$), and higher hemorrhage-related complications (OR = 1.98; 95% CI, 1.22–13.21; $P = .005$). There was no significant difference in intraprocedural complications, stenosis-related complications, mortality, favorable outcomes, and complete occlusion at the end of the study.

LIMITATIONS: No randomized controlled trials have been performed comparing the PEDC and PED. Considering that all the included studies were observational, the patients' baseline characteristics were not completely balanced.

CONCLUSIONS: This meta-analysis study showed that the PEDC in large intracranial aneurysms induces a faster complete occlusion rate at 6 months and a lower retreatment rate. However, it increases the risk of stroke-related postoperative complications, and the faster complete aneurysm occlusion rate found in this study did not correlate with a reduction in long-term aneurysm or distal artery ruptures. Thus, this study suggests the need to find a better strategy to improve long-term hemorrhage-related complications in large intracranial aneurysms.

ABBREVIATIONS: FDDs = flow-diverter devices; NOS = Newcastle-Ottawa Scale; PEDC = Pipeline Embolization Device in combination with coils

Flow-diverter devices (FDDs) are novel constructive techniques in neuroendovascular surgery to treat intracranial aneurysms.¹ FDDs have gained popularity for their safety and efficacy in treating

“uncoilable” large and wide-neck intracranial aneurysms.^{2–4} FDDs could improve intracranial aneurysms by reconstructing the parent vessel, redirecting blood flow, and altering hemodynamic blood flow within the aneurysm dome. These mechanisms result in better aneurysm neck reconstructions and complete occlusion compared with traditional endovascular surgery.^{5–7} However, FDDs do not provide direct dome protection, show limited efficacy in arterial bifurcation, and could potentially prolapse in large aneurysm sacs, unlike coil embolization.^{8,9} There are several types of FDDs known today, ie, the Pipeline Embolization Devices (PED; Medtronic),

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Silk (Balt Extrusion), Flow Re-direction Endoluminal Devices (MicroVention), p64 Flow Modulation Devices (phenox), Surpass flow diverters (Stryker Neurovascular), and novel flow-diverting devices (Tubridge; MicroPort Medical Company).^{1,10} The FDD that is most commonly studied and used in practice is the PED.¹¹⁻¹³

The PED is designed as a stand-alone device for intracranial aneurysm surgery, but some practitioners often combine it with coils. Some practitioners believe that adjunctive coils in PEDs offer direct protection in an aneurysm dome, thus inducing a higher occlusion and a lower retreatment rate than the PED alone,¹⁴⁻¹⁸ while others believe it induces a higher complication rate.¹⁹⁻²¹ Studies have reported the safety and effectiveness of the PED alone versus the PED with coils (PEDC), but the results have varied across studies. The PEDC evaluated here was placed with loose coiling because dense coiling has been shown to significantly increase perioperative complications compared with loose coiling.^{16,19} To date, it remains unclear whether the PED in combination with loose coiling offers significant benefits for the patients.¹⁴⁻²³ Here, we performed a systematic review and meta-analysis to evaluate the clinical outcome of the PED with loose coiling compared with the PED for treating intracranial aneurysms.

MATERIALS AND METHODS

Search Strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. We systematically searched the articles from PubMed, Web of Science, and the Cochrane Library databases for observational studies and randomized controlled trials comparing the PEDC versus the PED to treat intracranial aneurysm published before January 25, 2024. We used Endnote 20 reference manager (<https://libguides.nie.edu.sg/c.php?g=942031&p=6820754>) to retrieve the articles from PubMed and the Web of Science. The articles were retrieved using the keywords in the Title, Abstract, and Keyword sections with “and/or” for the following terms: pipeline, flow-diverter, flow diversion, coil, embolization, assisted, and combination. Separately, the articles from the Cochrane Library databases were retrieved independent of the Web site and imported to the Endnote 20 reference manager. We removed all the retrieved articles that were duplicates. Then, 2 researchers systematically screened the remaining articles using the Title and Abstract according to the inclusion and exclusion criteria.

Inclusion and Exclusion Criteria

The inclusion criteria for this study were the following: 1) patients with intracranial aneurysms (unruptured and ruptured), 2) the treatment choices being the PEDC in comparison with the PED alone, 3) data for 2 groups provided in the literature, and 4) a randomized controlled trial or observational study (case-control and cohort study). Meanwhile, the exclusion criteria included the following: 1) studies with similar registry or overlapping data, 2) case series on either the PEDC or PED-only with <10 patients, 3) patients treated with the PEDC but using dense coiling, ie, complete occlusion of aneurysm (Class I-II Raymond-Roy Classification System) because it showed a higher complication rate,^{16,19} 4) literature that did not compare the EDC and PED,

and 5) case reports, review articles, news and editorials, and conference abstracts.

Two researchers extracted the data from selected articles, and any disagreements were discussed with an independent senior neurosurgeon at our hospital. We extracted primary information from the selected articles, including the first author's name, year, study design, sample size, total aneurysms, age, sex, aneurysm size, location, shape, and rupture. The primary outcome and analyzed data included the following: 1) intraprocedural complications (due to its rare incidence, we accumulated all complications into 1 variable); 2) postoperative complications such as stenosis, consisting of in-stent stenosis and parent artery stenosis; 3) stroke, consisting of TIA and ischemic stroke, 4) hemorrhage, consisting of a ruptured aneurysm and distal artery rupture; 5) mortality at the latest follow up; and 6) the mentioned postoperative complications above accumulated into overall postoperative complications; 7) favorable outcome, with (mR) ≤ 2 at the latest follow-up, 8) complete occlusion rate in the latest follow-up, 9) 6 months' follow-up, and 10) retreatment rate. Using the Newcastle-Ottawa Scale (NOS), we assessed the risk of bias in all eligible articles, considering that all the included studies are either case-control or cohort studies. Studies were graded on a scale of 0–9, with 0–2 representing poor quality, 3–5 representing fair quality, and 6–9 representing good quality.²⁴

Statistical Analysis

We used the “meta” package within the R Foundation for Statistical Computing Platform (Version 4.2.1 (<http://www.r-project.org/>)) to conduct statistical analyses. Heterogeneity among studies was assessed using the Cochran Q test, while the I^2 statistic investigated its magnitude. Pooled outcomes and their respective 95% CIs were calculated using the Mantel-Haenszel test with either a random-effects (if $I^2 > 50\%$) or a fixed-effects model (if $I^2 < 50\%$). We used funnel plots and the Egger test to assess publication bias. A P value $< .05$ was considered significant. Sensitivity analysis was performed by excluding studies with an NOS of <6 and with zero events, to ensure the robustness of the pooled results in our study.

RESULTS

Study Selection and Quality Assessment

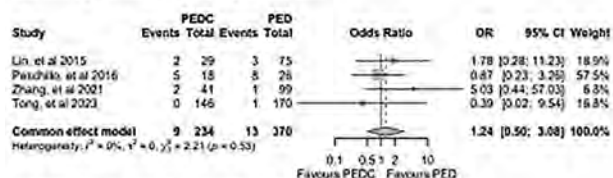
A total of 1470 articles were identified from the database search. Among them, 402 duplicates were removed and 1040 studies were excluded through an initial screening. This meta-analysis included 9 studies after a full-text assessment of the eligibility of the remaining 28 articles. The flow chart of the literature search, reasons for literature exclusion, and the results of the study selection are available in the Online Supplemental Data.

All 9 studies were observational, consisting of 4 case-control studies and 5 cohort studies. Eight of the 9 studies had a good quality assessment, with an NOS score of >6 (Online Supplemental Data).

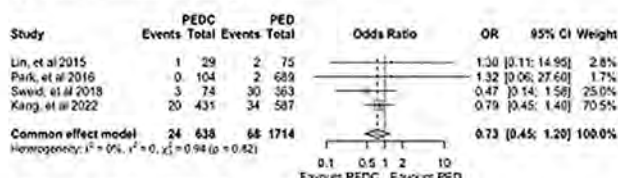
Patient Characteristics

A total of approximately 3001 subjects with 3269 aneurysms were included. Among these, 949 underwent PEDC treatment, while

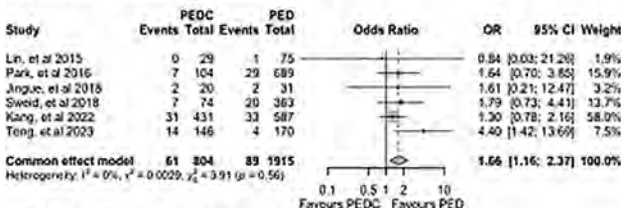
a) Intraprocedural complications



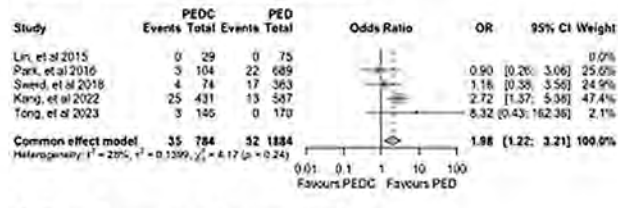
b) Stenosis-related complications



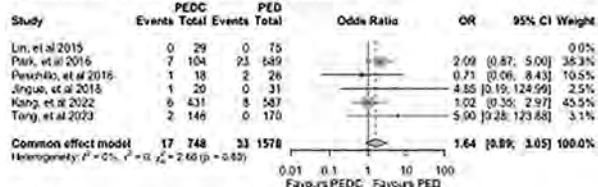
c) Stroke-related complications



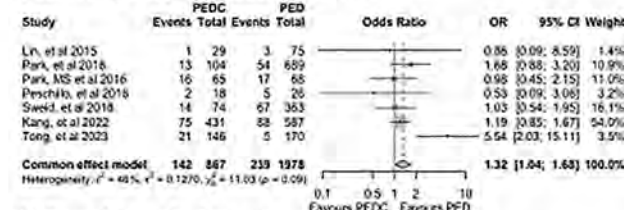
d) hemorrhage-related complications



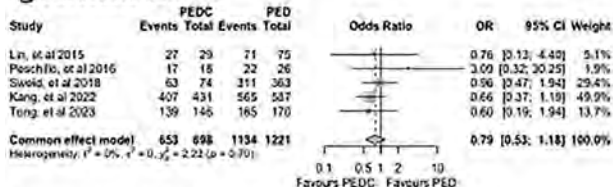
e) Mortality-related complications



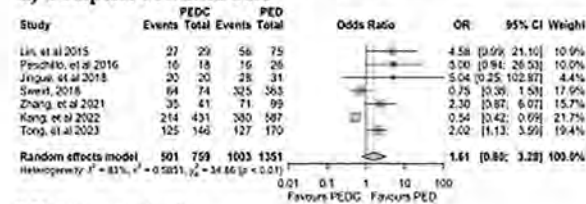
f) Overall postoperative complications



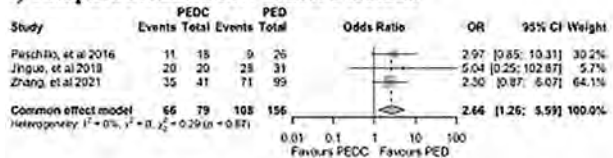
g) Favorable outcome



h) Complete occlusion rate



i) Complete occlusion rate at first 6 months



j) Retreatment rate

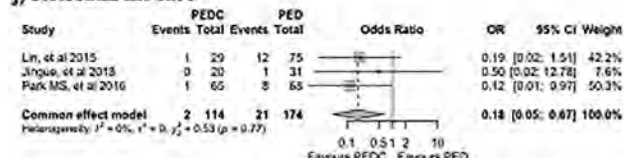


FIGURE Forest plot and meta-analysis of intraprocedural (A), stenosis-related (B), stroke-related (C), hemorrhage-related (D), mortality-related (E), overall postoperative complications (F), favorable outcome (G), complete occlusion rate (H), complete occlusion rate at first 6 months (I), and retreatment rate (J).

2320 underwent PED-only treatment. The mean age for both groups was older than 50 years, predominantly women, and most cases were ICA aneurysms with a saccular type. In all 9 studies, the PEDC was mainly used to treat larger aneurysms compared with the PED. The detailed patient characteristics are provided in the Online Supplemental Data.

Outcome of PEDC versus PED

Four studies reported intraprocedural complications, with no significant difference in incidence between the PEDC and PED groups (3.85% versus 3.51%) (OR = 1.24; 95% CI, 0.50–13.08; $P = .643$) (Fig 1A).

We evaluated postoperative complications that were stenosis-related, stroke-related, hemorrhage-related, and mortality-related. Stenosis-related complications were reported in 4 studies and were not significantly different between the PEDC- and PED-treated patients (3.76% versus 3.97%) (OR = 0.73; 95% CI, 0.45–1.20; $P =$

.217) (Fig 1B). Stroke-related complications were reported in 6 studies and were significantly lower in the PED compared with the PEDC-treated patients (4.65% versus 7.59%) (OR = 1.66; 95% CI, 1.16–2.37; $P = .005$) (Fig 1C). Hemorrhage-related complications were reported in 5 studies and were significantly lower in the PED-compared with the PEDC-treated patients (2.76% versus 4.4%) (OR = 1.98; 95% CI, 1.22–3.21; $P = .005$) (Fig 1D). Mortality-related complications were reported in 6 studies and were not significantly different between the PEDC and PED-treated patients (2.27% versus 2.09%) (OR = 1.64; 95% CI, 0.89–3.05; $P = .114$) (Fig 1E). Overall, the incidence of postoperative complications was higher in the PEDC- than in the PED-treated patients (16.3% versus 12.1%), with a statistically significant difference between the 2 groups (OR = 1.32; 95% CI, 1.04–1.68; $P = .022$) (Fig 1F).

Five studies evaluated treatment outcomes on follow-up using the mRS scoring system. The incidence of favorable outcome

(mRS ≤ 2) was not significantly different between the PEDC- and PED-treated patients (93.6% versus 92.8%) (OR = 0.79; 95% CI, 0.53–11.18; $P = .246$) (Fig 1G). The complete occlusion rate at the end of the study was reported in 7 studies and was not significantly different between the PEDC- and PED-treated patients (66% versus 74.3%) (OR = 1.61; 95% CI, 0.80–13.28; $P = .185$) (Fig 1H). However, 3 studies reported a significantly higher complete occlusion rate at 6 months' follow-up, which was significantly higher in the PEDC- compared with the PED-treated patients (83.5% versus 69.2%) (OR = 2.66; 95% CI, 1.26–15.59; $P = .01$) (Fig 1I). The retreatment rate was reported in 3 studies and was significantly lower in the PEDC- compared with the PED-treated patients (1.75% versus 12.1%) (OR = 0.18; 95% CI, 0.05–10.07; $P = .010$) (Fig 1J).

Publication Bias and Sensitivity Analysis

Because all the included studies were observational, there is a potential of publication bias in each study. Thus, publication bias was assessed using funnel plots and the Egger test. The funnel plots were mostly symmetric with no significant publication bias ($P > .05$), except for the complete occlusion rate at the end of the study ($P = .02$) (Online Supplemental Data). The results of the sensitivity analysis were mostly consistent with the pooled analysis (Online Supplemental Data), except for overall postoperative complications after excluding the study by Park et al, 2016.

DISCUSSION

Here, we systematically reviewed and performed a meta-analysis on 9 observational studies comparing the PEDC and PED to treat intracranial aneurysms to determine whether the PEDC offers a significant benefit for the patients.^{14–22} The PEDC-treated patients in these studies had larger aneurysms compared with those treated with the PED, indicating the practitioners' preferences for using the PEDC for complex and difficult aneurysms as well as potentially explaining the significantly higher postoperative complications found in the PEDC-treated patients. Despite this discrepancy in aneurysm size between the 2 groups, no significant difference was found in terms of intraprocedural complications, stenosis-related complications, mortality, mRS-measured outcome, and complete occlusion rate at the end of the study. PEDC-treated patients even showed faster occlusion (< 6 months) and a lower retreatment rate. However, PEDC-treated patients also showed a higher incidence of postoperative stroke, indicating that this technique increases the risk of stroke complications.^{16,19,21} They also experienced more aneurysms and distal artery ruptures, as inferred from the higher incidence of hemorrhage-related postoperative complications compared with PED-treated patients.

The use of coils together with the PED is expected to mitigate delayed aneurysm rupture,²⁵ because 4% of these ruptures were associated with the use of the PED alone, resulting in 80% unfavorable clinical outcomes or even mortality.^{26–28} Delayed aneurysm rupture shows a peak incidence within the first month, and coil placement offers a direct occlusion strategy to mitigate this rupture after PED placement.²⁹ However, mitigation of delayed aneurysm rupture could not be confirmed in our study because PEDC-treated patients had significantly higher hemorrhage-related postoperative complications compared with PED-treated

patients. It remains unclear in our study whether hemorrhage-related postoperative complications are partly attributed to the larger aneurysm size or the plausible lack of PEDC effectiveness in mitigating delayed aneurysm rupture. A large intracranial aneurysm is generally defined in clinical practice by its diameter size of 10–25 mm and is known to have a higher rupture rate.³⁰ Previous studies showed that although PEDC-treated patients had a larger aneurysm size, there was no significant difference in delayed aneurysm and distal artery rupture within the first month compared with the PED-treated patients.^{15,19}

Unfortunately, in our study, we could not perform matching based on aneurysm size and the interval of aneurysm rupture because individual patient data were not reported in the included studies. Our meta-analysis also showed that PEDC-treated patients had significantly higher stroke-related postoperative complications, and previous studies have also reported that the PEDC could prolong surgery time, resulting in higher rates of ischemic stroke or postoperative neurologic morbidity.^{16,19,21} Other factors, such as operator skills and postoperative maintenance with anticoagulants, could also contribute to patient outcomes but were unfortunately not reported in the included studies. These factors could explain why PEDC-treated patients showed higher postoperative complications than those treated with the PED in this study.

Despite having larger aneurysms, PEDC-treated participants showed no significant difference in intraprocedural complications, mortality, and favorable outcomes. There was also no difference in the complete occlusion rate at the end of the study. This outcome, however, is likely influenced by the high heterogeneity in the follow-up time used to measure this variable: Two studies were followed up to ± 6 months,^{14,20} another 2 up to ± 8 months,^{15,19} and 3 up to 1 year.^{16,17,22} This heterogeneity could also explain why publication bias was found only in this variable and not in the others. Five of 7 studies included in the meta-analysis of this variable showed a higher complete occlusion rate. We performed additional analysis on 3 studies reporting a follow-up period of 6 months and confirmed that the PEDC does have a faster complete occlusion rate compared with the PED.^{14,17,20} This finding is further supported by another study documenting that the occlusion in the PED-treated patients mostly occurs more than a year.³¹ In addition to a faster complete occlusion rate, PEDC-treated patients also showed a lower retreatment rate compared with those treated with the PED.

The PEDC evaluated here is placed with loose coiling as indicated by nonimmediate complete occlusion on angiography follow-up. Insurance often does not cover the PEDC, and the cost of dense coiling is significantly higher than that of loose coiling.¹⁶ Studies have reported that the PEDC with dense coiling results in a mass compression effect and causes longer surgery times, leading to higher perioperative complications compared with loose coiling.^{16,19} This finding highlights the importance of the volume embolization ratio of coils used in the PEDC—that is, 3 studies have shown that a volume embolization ratio of $\leq 15\%$ in the PEDC has been reported to improve occlusion outcomes, prevent nerve compression, induce aneurysm shrinkage, and reduce the risk of aneurysm rupture.^{25,32,33} Besides the volume embolization ratio, the use of multiple PEDs to cover the

aneurysm neck should also be considered when comparing the PEDC and PED in a future study.

Altogether, our meta-analysis showed that the PEDC induces faster complete occlusion and a lower retreatment rate in large intracranial aneurysms. However, it also increases the risk of postoperative stroke-related complications and may not be an effective strategy to prevent hemorrhage-related postoperative complications in large intracranial aneurysms. Previous studies have proposed that the PEDC is favorable in complex aneurysms, such as large or giant, wide-neck, blister, and morphologically irregular ones.^{33,34} Coiling subsequently followed by the PED has also been shown to be beneficial for ruptured intracranial aneurysms, in which coils are initially placed during the acute phase, followed by subsequent deployment of the PED postrecovery.^{35,36} These data highlight a synergistic effect between coils and the PED; ie, Coiling provides direct occlusion within the aneurysm dome and prevents PED prolapse, while the PED prevents coil migration into the parent vessel and induces hemodynamic disturbances within the aneurysm dome.^{15,37-39} Moreover, other FDDs have garnered interest for use in combination with coils, such as Flow-Redirection Endoluminal Device (FRED; MicroVention) and Tubridge, which further highlight more potential approaches in treating large intracranial aneurysms.^{40,41}

CONCLUSIONS

This meta-analysis showed that the PEDC in large intracranial aneurysms induces a faster complete occlusion rate at 6 months and a lower retreatment rate. However, it increases the risk of stroke-related postoperative complications and may not be an effective strategy to prevent hemorrhage-related postoperative complications. Further study with comparable patients' baseline characteristics, including aneurysm size, is needed to confirm the effectiveness of coiling in preventing hemorrhage-related postoperative complications. Nevertheless, the faster complete aneurysm occlusion rate found in this study did not correlate with a reduction in long-term aneurysm or distal artery ruptures. This study suggests the need to find a better strategy to improve long-term hemorrhage-related complications in large intracranial aneurysms.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Endovascular Thrombectomy versus Medical Management for Acute Basilar Artery Occlusion Stroke in the Elderly

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ABSTRACT

BACKGROUND AND PURPOSE: The efficacy and safety of endovascular thrombectomy (EVT) for elderly patients with basilar artery occlusion (BAO) stroke is unclear. The purpose of this study is to investigate the safety and efficacy of EVT for elderly BAO stroke patients.

MATERIALS AND METHODS: This was an explorative retrospective analysis of the 2016–21 National Inpatient Sample in the United States. Elderly patients with BAO stroke (80 years of age or older) with an NIHSS score of at least 5 were included. Primary outcome was discharge home. Secondary outcomes included in-hospital mortality and intracranial hemorrhage (ICH). Outcomes were compared between patients treated with EVT and those treated with medical management (MM) alone. Propensity score matching (PSM) was performed to control confounders. Subgroup analyses were conducted for patients who did and did not receive IV thrombolysis (IVT).

RESULTS: We identified 2520 elderly patients with BAO stroke; 830 received EVT and 1690 received MM alone. After PSM, 1115 patients and 715 patients remained in the MM and EVT groups, respectively. Compared with PSM controls, EVT was not significantly associated with different rates of home discharge (17.5% versus 12.2%; OR, 1.36 [95% CI, 0.76–2.44], $P = .30$) or in-hospital mortality (31.5% versus 32.9%; OR, 1.00 [95% CI, 0.63–1.60], $P = .99$), but it was significantly associated with higher rates of ICH (18.2% versus 7.3%; OR, 2.69 [95% CI, 1.41–5.15], $P = .003$). Among patients who did not receive IVT, EVT was significantly associated with higher rates of home discharge (21.5% versus 11.5%; OR, 1.93 [95% CI, 1.02–3.66], $P = .044$), whereas EVT was not significantly associated with a different rate of home discharge among those treated with IVT (5.6% versus 15.0%; OR, 0.28 [95% CI, 0.05–1.46], $P = .13$). Interaction analysis revealed that IVT was a negative modulator of the positive association of EVTs with home discharge (interaction $P = .031$).

CONCLUSIONS: EVT was not significantly associated with more favorable hospitalization outcomes for elderly patients with BAO stroke, and it was significantly associated with an increased risk of ICH. EVT may be an effective treatment for patients who did not receive IVT.

ABBREVIATIONS: BAO = basilar artery occlusion; EVT = endovascular thrombectomy; ICH = intracranial hemorrhage; IVT = intravenous thrombolysis; LVO = large-vessel occlusion; MM = medical management; NIS = National Inpatient Sample; PSM = propensity score matching; RR = regression rate ratio

Endovascular thrombectomy (EVT) is an effective treatment for acute ischemic stroke due to intracranial large-vessel occlusion (LVO);^{1,2} however, its benefit over medical management (MM)

for elderly patients with stroke is less clear.^{3,4} Elderly patients are an important and unique subgroup of patients with stroke. A higher comorbidity burden, baseline cognitive deficits, leukoarteriosclerosis, and reduced neuroplasticity have all been suggested to contribute to the overall lower likelihood of good neurologic outcomes despite successful stroke reperfusion treatment.^{3,5,6} Despite these obstacles, currently available clinical data suggest that EVT is still likely beneficial for elderly patients with stroke with anterior circulation LVOs, and current guidelines do not recommend restricting anterior circulation EVT treatment based on age alone.^{7,8}

While EVT may be effective for elderly patients with stroke with anterior circulation LVO, whether this outcome is true for basilar artery occlusion (BAO) stroke is largely unknown. Historically, patient selection for BAO-EVT has been challenging. Early trials in 2020 and 2021 (Acute Basilar Artery Occlusion: Endovascular Interventions vs Standard Medical Treatment (BEST))⁹

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SUMMARY

PREVIOUS LITERATURE: While recent randomized controlled trials showed that EVT for acute BAO stroke may be safe and effective in carefully selected patients, there remains a dearth of clinical data on the risks and benefits of BAO-EVT for the elderly stroke population.

KEY FINDINGS: In this nationwide study of 2520 elderly patients with BAO stroke, we found that EVT was not significantly associated with more favorable short-term hospitalization outcomes compared with MM. The efficacy of EVT appeared to be significantly modulated by IVT treatment, and EVT was associated with significantly improved outcomes for patients who did not receive IVT.

KNOWLEDGE ADVANCEMENT: These findings highlight important nuances in patient selection for BAO-EVT in the elderly population and identify IVT treatment as a significant modulator.

and Basilar Artery International Cooperation Study (BASICS),¹⁰ respectively) failed to demonstrate the efficacy of BAO-EVT, likely contributing to the use of more stringent clinical and radiographic inclusion/exclusion criteria for the later positive Endovascular Treatment for Acute Basilar-Artery Occlusion (ATTENTION)¹¹ and Basilar Artery Occlusion Chinese Endovascular (BAOCHE)¹² trials in 2023. With more stringent patient selection, the elderly population was under-represented in the positive 2023 trials. In the ATTENTION trial,¹¹ only 37 participants (of a total of 340) were 80 years of age or older, and EVT was not associated with significantly higher odds of good neurologic outcomes in this subgroup. In the BAOCHE trial,¹² patients older than 80 years of age were excluded. Thus, there is currently no high-level clinical evidence of the effectiveness of BAO-EVT among the elderly.

In this study, we performed an explorative analysis of a nationwide database of elderly patients (80 years of age or older) hospitalized for acute BAO stroke to investigate the comparative efficacy and safety of EVT and MM.

MATERIALS AND METHODS

Study Design

This was a retrospective study of the 2021 National Inpatient Sample (NIS) database.¹³ The NIS, which is part of the Health Care Cost and Utilization Project, is a database of stratified discharge information in the United States, representing 20% of all hospitalizations. The NIS contains no patient identifiers; thus, this analysis was exempt from informed consent or institutional review board approval under the Health Insurance Portability and Accountability Act. This study complies with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline for retrospective cohort studies (Online Supplemental Data).

Patient Population

Elderly patients with BAO stroke were identified using the International Classifications of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. Patients with concomitant stroke in the anterior circulation were excluded. Finally, patients with minor stroke symptoms (NIHSS score of ≤ 5) were excluded. All ICD-10 codes used in this study are detailed in the Online Supplemental Data. The main study exposure of interest was endovascular thrombectomy, angioplasty, or stent placement, which were identified using ICD-10-Procedural Coding System

(ICD-10-PCS) codes (Online Supplemental Data). Patients were separated into the EVT and the non-EVT (MM) arms.

Study End Points

The primary end point of this study was discharged home with or without services. While routine discharge home without services is a more commonly used end point for NIS studies and was the primary end point of the BARONIS study,¹⁴ elderly patients may have baseline disability and may already be using home services before the stroke. Thus, routine discharge home with self-care was included as a secondary end point. Other secondary end points include in-hospital mortality and any intracranial hemorrhage (ICH) identified by ICD-10-CM codes (Online Supplemental Data).

Other Variables of Interest

Patient age and sex were recorded. Stroke characteristics such as NIHSS intravenous thrombolysis (IVT) treatment and stroke etiology (embolic, thrombotic, or unspecified) and additional sites of vascular occlusion (vertebral, cerebellar, and/or posterior cerebral arteries) were captured using ICD-10-CM codes. Comorbidities such as atrial fibrillation, hypertension, hyperlipidemia, smoking, diabetes, and dementia were also captured with ICD-10-CM codes, as was the chronic use of antithrombotic medicines. The Elixhauser comorbidity index was calculated for each patient to estimate the overall medical comorbidity burden, and hospital length of stay information was also collected for each patient.

Statistical Methods

The total number of patients was calculated using discharge-level weights. Patient characteristics were presented as mean (SD) or percentage (No.), and differences between treatment arms were assessed using the standardized mean difference, in which values > 0.10 indicate substantial differentiation. The primary statistical model of this study was propensity score matching (PSM), in which a multivariable regression model accounting for all covariables captured in this study was used to calculate propensity scores, and 1-to-2 nearest neighbor matching with a maximum distance of 0.05 was performed to match patients with EVT with similar patients with MM. To compare differences in study outcomes between treatment groups, we generated ORs and 95% CIs between the PSM cohorts. Comparisons between the unmatched cohorts were also reported, and multivariable logistic or Poisson

Table 1: Patient characteristics^a

Characteristic	Total (n = 2520)	Unmatched			PSM		
		MM (n = 1690)	EVT (n = 830)	SMD	MM (n = 1115)	EVT (n = 715)	SMD
Age (mean) (yr)	85.6 (3.5)	85.8 (3.4)	85.2 (3.5)	0.172	85.4 (3.4)	85.4 (3.5)	0.039
Female sex	59.9% (1510)	61.5% (1040)	56.6% (470)	0.099	56.1% (625)	55.9% (400)	0.014
Stroke etiology							
Embolism	23.2% (585)	24.9% (420)	19.9% (165)	0.125	21.5% (240)	23.1% (165)	0.079
Thrombosis	39.1% (985)	32.2% (545)	53.0% (440)	0.416	42.2% (470)	47.6% (340)	0.007
Unspecified	37.7% (950)	42.9% (725)	27.1% (225)	0.355	36.3% (405)	29.4% (210)	0.063
Additional sites of vascular occlusion							
Vertebral artery	8.7% (220)	9.5% (160)	7.2% (60)	0.086	8.5% (95)	7.0% (50)	0.041
Cerebellar artery	5.8% (145)	5.0% (85)	7.2% (60)	0.085	6.3% (70)	7.7% (55)	0.054
Posterior cerebral artery	8.1% (205)	7.7% (130)	9.0% (75)	0.047	8.1% (90)	7.7% (55)	0.024
Stroke risk factors							
Atrial fibrillation/flutter	42.1% (1060)	40.8% (690)	44.6% (370)	0.075	45.7% (510)	44.8% (320)	0.028
Hypertension	88.5% (2230)	87.9% (1485)	89.8% (745)	0.062	90.1% (1005)	88.8% (635)	0.035
Hyperlipidemia	57.3% (1445)	55.0% (930)	62.0% (515)	0.145	60.5% (675)	59.4% (425)	0.050
Diabetes	27.8% (700)	26.9% (455)	29.5% (245)	0.057	27.8% (310)	30.1% (215)	0.023
Smoking	20.0% (505)	22.2% (375)	15.7% (130)	0.180	22.4% (250)	18.2% (130)	0.077
Dementia	19.8% (500)	24.9% (420)	9.6% (80)	0.516	10.3% (115)	11.2% (80)	0.083
Baseline antithrombotic medications							
Anticoagulant	13.9% (350)	14.2% (240)	13.3% (110)	0.028	14.3% (160)	14.0% (100)	0.031
Antiplatelet	26.4% (665)	27.5% (465)	24.1% (200)	0.080	25.6% (285)	25.2% (180)	0.000
Elixhauser comorbidity index (mean)	15.4 (8.4)	14.9 (8.3)	16.6 (8.5)	0.198	15.6 (8.3)	16.1 (8.1)	0.042
NIHSS (mean)	17.9 (9.5)	17.2 (9.5)	19.2 (9.5)	0.208	18.4 (9.7)	19.4 (9.5)	0.042
IVT	21.6% (545)	20.7% (350)	23.5% (195)	0.066	20.6% (230)	25.2% (180)	0.099

^a Data are mean (SD) or % (n) unless otherwise indicated; SMD indicates standard mean difference.

regression models for the unmatched cohorts accounting for all captured variables in this study were used for sensitivity analyses. Secondary analyses that were decided a priori include assessments of the impact of ICH on outcomes as well as EVT outcomes stratified by IVT administration. In the secondary analyses, the interaction terms of IVT and EVT were introduced to identify the presence of significant effect modulation. Additional sensitivity analyses considering only patients who did not receive angioplasty or stent placement were also conducted. *P* values <.05 were deemed statistically significant. All statistical analyses were performed using R, Version 3.6.2. (<http://www.r-project.org/>).

RESULTS

Patient Characteristics

We identified 2520 patients hospitalized for acute BAO stroke: Eight hundred thirty received EVT; and 1690, MM alone. Among patients with EVT, 105 (12.7%) received endovascular angioplasty or stent placement. Differences in patient characteristics in the 2 treatment cohorts are presented in Table 1. Compared with MM, patients with EVT had higher rates of hyperlipidemia (62.0% versus 55.0%), lower rates of smoking (15.7% versus 22.2%), and lower rates of dementia (9.6% versus 24.9%). Furthermore, patients with EVT had more severe stroke symptoms compared with those with MM (mean NIHSS scores, 19.2 versus 17.2). Next, we performed 1-to-2 PSM for age, sex, etiology, additional sites of occlusion, hypertension, hyperlipidemia, diabetes, atrial fibrillation, smoking, dementia, antithrombotic medication use, the Elixhauser comorbidity index, NIHSS scores, and IVT treatment, yielding 1115 and 715 patients in the MM and EVT groups, respectively. Overall, matching performed well, and patient characteristics were similar between the 2 groups as evidenced by low standardized mean differences (all, <0.10; Table 1).

Overall EVT Outcomes

In the total unmatched cohorts, EVT, compared with MM, was not significantly associated with different rates of home discharge (18.7% versus 14.8%; OR, 1.32 [95% CI, 0.81–2.20], *P* = .27; Table 2) or in-hospital mortality (31.6% versus 27.8%; OR, 1.25 [95% CI, 0.83–1.89], *P* = .28; Table 2), though it was significantly associated with higher rates of ICH (17.5% versus 5.9%; OR, 3.37 [95% CI, 1.83–6.18], *P* < .001; Table 2). These findings persisted when comparing the PSM cohorts, in which EVT was not significantly associated with different rates of home discharge (17.5% versus 12.2%; OR, 1.36 [95% CI, 0.76–2.44], *P* = .30; Table 2 and the Figure) or in-hospital mortality (31.5% versus 32.9%; OR, 1.00 [95% CI, 0.63–1.60], *P* = .99; Table 2 and the Figure) with significantly higher rates of ICH (18.2% versus 7.3%; OR, 2.69 [95% CI, 1.41–5.15], *P* = .003; Table 2 and the Figure). Further sensitivity analyses with multivariable logistic regression of the total cohorts again revealed similar findings (Table 2).

Of note, EVT was significantly associated with higher rates of routine discharge home to self-care; however, the proportion of patients achieving this outcome was low in both the EVT and MM arms (7.2% and 2.7% respectively, *P* = .021; Table 2). This significant difference persisted after PSM and multivariable logistic regression analyses (Table 2).

In terms of hospital length of stay, the median was 4 days (interquartile range, 2–8) for the MM group, which was similar to a median of 5 days (interquartile range, 3–8) in the EVT group in both unadjusted and PSM analyses (Poisson regression rate ratio [RR], 1.05 [95% CI, 0.89–1.23], *P* = .59; and RR, 1.03 [95% CI, 0.86 to 1.23], *P* = .73, respectively). With multivariable Poisson regression analysis, EVT remained not statistically associated with different lengths of stay compared with MM (RR, 0.99 [95% CI, 0.83–1.17], *P* = .90).

Table 2: Study outcomes^a

	MM	EVT	OR for EVT [95% CI]	P Value
Unmatched cohort				
Home discharge	14.8% (250/1690)	18.7% (155/830)	1.32 [0.81–2.20]	.27
Routine discharge	2.7% (45/1690)	7.2% (60/830)	2.85 [1.17–6.92]	.021
In-hospital mortality	27.8% (470/1690)	31.6% (270/830)	1.25 [0.83–1.89]	.28
ICH	5.9% (100/1690)	17.5% (145/830)	3.37 [1.83–6.18]	<.001
PSM cohorts				
Home discharge	12.2% (135/1115)	17.5% (125/715)	1.36 [0.76–2.44]	.30
Routine discharge	1.7% (20/1115)	6.3% (45/715)	3.68 [1.10–12.3]	.034
In-hospital mortality	32.9% (365/1115)	31.5% (225/715)	1.00 [0.63–1.60]	.99
ICH	7.3% (81/1115)	18.2% (130/715)	2.69 [1.41–5.15]	.003
Multivariable logistic regression				
Home discharge	—	—	1.53 [0.88–2.68]	.13
Routine discharge	—	—	3.16 [1.28–7.79]	.013
In-hospital mortality	—	—	1.04 [0.64–1.69]	.86
ICH	—	—	3.43 [1.68–6.98]	<.001

Note:—The en dash indicates no statistic possible given the statistical methods. There are no percentage (*n*/*N*) available to report for logistic regression models.

^a Data are mean (SD) or % (*n*) unless otherwise indicated.

Table 3: Rates of home discharge stratified by IVT use^a

	MM	EVT	OR [95% CI]	P Value	Interaction P Value
Unmatched cohorts					
Received IVT	18.6% (65/350)	7.7% (15/195)	0.37 [0.10–1.40]	.14	.033
No IVT	13.8% (185/1340)	22.0% (140/635)	1.77 [1.03–3.04]	.040	
PSM cohorts					
Received IVT	15.0% (35/235)	5.6% (10/180)	0.28 [0.05–1.46]	.13	.031
No IVT	11.5% (100/880)	21.5% (115/535)	1.93 [1.02–3.66]	.044	
Multivariable logistic regression					
Received IVT	—	—	0.38 [0.07–1.93]	.24	.059
No IVT	—	—	2.10 [1.12–3.91]	.020	

Note:—The en dash indicates no statistic possible given the statistical methods. There are no percentage (*n*/*N*) available to report for logistic regression models.

^a Data are mean (SD) or % (*n*) unless otherwise indicated.

Because angioplasty and stent placement may be associated with increased rates of ICH due to early initiation of postprocedural antithrombotic medications, we performed a sensitivity analysis to confirm the association of EVT with elevated rates of ICH among patients who did not undergo angioplasty or stent placement. Here, EVT remained statistically significantly associated with higher odds of ICH in unmatched (OR, 3.64 [95% CI, 1.96–6.76], *P* < .001), PSM (OR, 2.91 [95% CI, 1.50–5.63], *P* = .002), and multivariable logistic regression analyses (OR, 3.56 [95% CI, 1.76–7.26], *P* < .001).

Impact of ICH on Outcomes

Among the 245 patients who experienced ICH, only 15 (6.1%) were discharged home and 115 (46.9%) died during the hospitalization. In comparison, among the 2275 patients who did not experience ICH, 390 (17.1%) were discharged home and 625 (27.5%) died (*P* = .047 and .004 compared with ICH subgroup, respectively). After multivariable adjustment for all captured variables, ICH remained strongly associated with lower odds of home discharge (OR, 0.29 [95% CI, 0.07–1.14], *P* = .077) and significantly associated with higher odds of in-hospital mortality (OR, 2.12 [95% CI, 1.09–4.11], *P* = .026).

EVT Outcomes Stratified by IVT Treatment

Next, we investigated whether EVT may have different efficacy and safety outcomes among patients who were and were not

treated with IVT. Among IVT-treated patients, EVT was associated with numerically lower but statistically similar rates of home discharge (7.7% versus 18.6%; OR, 0.37 [95% CI, 0.10–1.40], *P* = .14; Table 3). Among non-IVT-treated patients, EVT was significantly associated with higher rates of home discharge (22.0% versus 13.8%; OR, 1.77 [95% CI, 1.03–3.04], *P* = .040; Table 3). Further interaction analysis revealed that IVT treatment was a significant negative modulator of the efficacy of EVT in terms of rates of home discharge (interaction *P* = .033; Table 3). Analyses of the PSM cohorts yielded similar results (interaction *P* = .031; Table 3 and the Figure), as did further sensitivity analyses with multivariable logistics regression models (interaction *P* = .059; Table 3). IVT did not significantly modulate the association of EVT with rates of in-hospital mortality due to ICH (interaction *P* > .05 for outcomes both in PSM and multivariable logistic regression analyses).

Finally, because angioplasty and stent placement may be associated with higher rates of hemorrhage (by way of postprocedure antithrombotic use) and poor outcomes, we performed a sensitivity analysis excluding patients who underwent these procedures. Here, IVT continued to significantly suppress the association of EVT with home discharge in unadjusted, PSM, and multivariable logistic regression analyses for patients who did not undergo angioplasty or stent placement (interaction *P* = .028, .049, and .029, respectively).

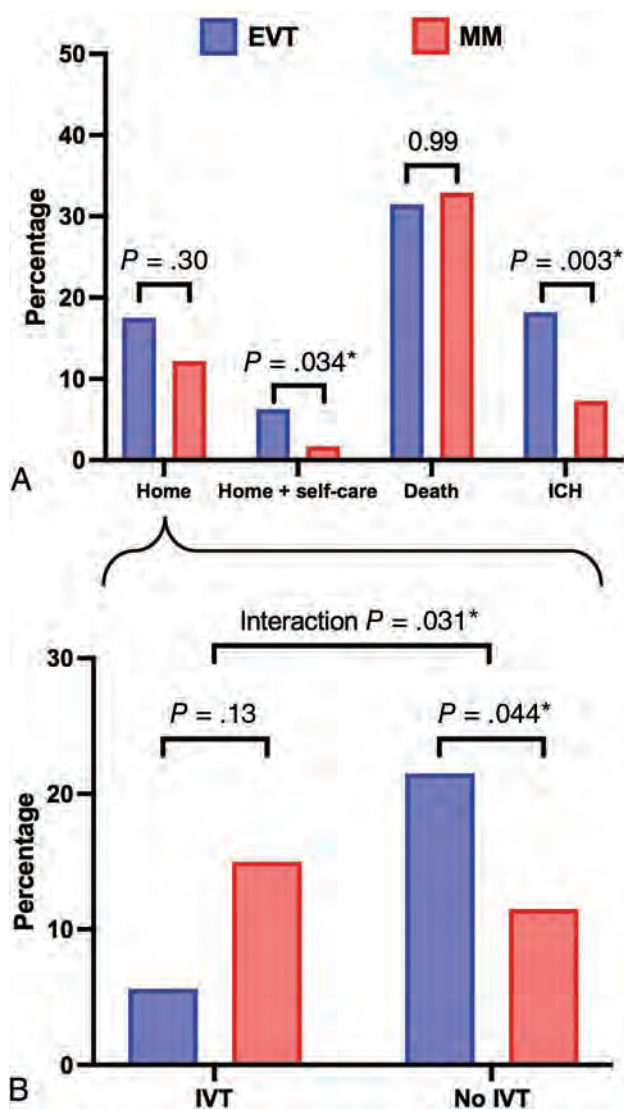


FIGURE. Hospitalization outcomes for elderly patients with BAO stroke treated with EVT versus MM alone after 2-to-1 PSM for age, sex, stroke etiology, additional sites of vascular occlusion, stroke risk factors, antithrombotic medication use, comorbidity, NIHSS score, and IVT use. *A*, Rates of home discharge, home discharge with self-care, in-hospital mortality, and ICH. *B*, Rates of home discharge of stratified by IVT administration.

DISCUSSION

In this retrospective explorative analysis of a national database of hospital admissions in the US, we found that EVT for acute BAO stroke was not significantly associated with more favorable short-term outcomes compared with MM alone, while it was associated with significantly higher rates of hemorrhage. Subgroup analyses revealed that while EVT may be superior to MM without IVT, its short-term efficacy is significantly diminished for patients treated with IVT. These findings highlight the need for careful risk-benefit assessments of EVT for elderly patients with BAO stroke, particularly regarding hemorrhagic risk and concurrent IVT treatment.

The elderly population represents a significant portion of patients with stroke worldwide, and optimal management of acute stroke for the elderly has been an area of clinical uncertainty.³ Older age is a well-known risk factor for EVT futility,

possibly due to poor collateral circulation and penumbra sustenance, leading to faster infarct growth and higher rates hemorrhagic transformation.^{3,6,15} Baseline cognitive deficits, leukoaraiosis, and brain atrophy may also impede poststroke recovery.⁵

Currently available clinical data suggest that EVT is beneficial for anterior circulation LVOs among elderly patients;^{16,17} however, the efficacy and safety of EVT for elderly patients with BAO stroke is largely unknown. Unlike EVT in the anterior circulation, BAO-EVT has been consistently associated with a higher risk of symptomatic ICH in randomized trials,¹⁸ perhaps due to anatomic features of the posterior fossa and the higher risk of symptomatic mass effect. This heightened hemorrhagic risk may be particularly problematic for elderly patients, because older age itself is an independent risk factor for hemorrhagic transformation.^{19,20} In the current study, we observed a significantly higher risk of ICH among elderly patients with BAO stroke treated with EVT compared with those treated with MM alone. This finding, in addition to our secondary findings showing that ICH was significantly associated with worse hospitalization outcomes, emphasizes the need for careful patient selection for BAO-EVT among the elderly population, specifically regarding ICH risk. Radiographic markers of early ischemic changes on CT such as posterior occlusion, stroke risk factors, antithrombotic medication use, comorbidity, NIHSS score, and IVT use. *A*, Rates of home discharge, home discharge with self-care, in-hospital mortality, and ICH. *B*, Rates of home discharge of stratified by IVT administration.

(which is prevalent among elderly patients) and artifacts in the posterior fossa may be challenging.²² Future studies should consider investigating whether adjunctive use of CT perfusion metrics,²³ collateral status,²⁴ or MRI²⁵ may be helpful to further optimize hemorrhagic risk stratification for elderly patients with BAO stroke.²⁶

While our primary analysis did not reveal a significant short-term benefit of EVT for elderly patients with BAO stroke measured by the rate of discharge home, our subgroup analyses revealed that EVT may be associated with significantly higher odds of home discharge compared with MM among patients who were not treated with IVT. Current guidelines recommend administering IVT for all eligible patients with stroke regardless of EVT candidacy;^{7,8} however, combined IVT and EVT have not been formally trialed in the BAO stroke population. Observational data have suggested that IVT before BAO-EVT

may be associated with more favorable outcomes compared with EVT alone;²⁷ however, whether this suggestion is true for elderly patients is unclear. Underlying deficits in the coagulation pathway may be associated with less favorable EVT outcomes, and they may accentuate the detrimental effects of hemorrhagic transformation.²⁸ An analysis of the NIS in the United States suggested that IVT before EVT may yield a diminished benefit for elderly patients with anterior circulation LVO stroke, possibly due to higher hemorrhagic risk.²⁹ This phenomenon, in addition to an inherently higher risk of symptomatic hemorrhage associated with BAO-EVT,¹⁸ may have culminated in the net-negative modulatory effect of IVT on the efficacy of EVT in the current study. Another possible explanation of the negative impact of IVT on the efficacy of EVT for BAO strokes is that IVT may compete with the efficacy of EVT. In a recent observational cohort study, Rätty et al³⁰ suggested that IVT alone may be a potent treatment for BAO stroke that compared favorably with the efficacy of EVT. BAO stroke treated with IVT may also be associated with higher rates of pre-EVT recanalization.³¹ Thus, for elderly patients with BAO stroke, prior IVT treatment may not only increase hemorrhagic risk but also erode the net benefit of EVT via its own clinical efficacy. Future studies are needed to further explore the interplay between EVT and IVT for elderly patients with BAO stroke.

Our study has several limitations. First, the NIS only provides hospitalization outcome; therefore, only short-term outcomes were assessable. Moreover, while discharge home is a favorable outcome, it is not a direct measure of neurologic function. Thus, findings reported in this study should be interpreted with caution, and future investigations are needed to assess longer-term neurologic outcomes for elderly patients with BAO-EVT. Second, the NIS does not report detailed information regarding the location of the BAO, which may be an important factor for treatment decisions and prediction of clinical outcomes. Third, information regarding clinical (eg, treatment time windows, time elapsed from thrombolysis to EVT, Glasgow Coma Scale, and so forth) and radiographic biomarkers (eg, posterior circulation ASPECTS, MRI findings, and so forth) is not available, and these factors may have confounded our findings. Third, patients with anterior circulation insufficiency may be heavily dependent on a vascular source from the posterior circulation to supply the cerebral hemispheres, which can be seen in conditions such as Moyamoya disease.³² BAO stroke may be particularly devastating for these patients, and we were unable to fully assess this confounder because this information is not provided in the NIS. However, given that our analysis accounts for the NIHSS score and thus the variability of symptom severity among the study cohort, our results are likely robust to confounding from anterior circulation insufficiency. Fourth, uncaptured neurologic and non-neurologic baseline disability among the elderly population may have influenced EVT treatment decisions and introduced treatment bias.³³ EVT providers may also take more conservative measures for elderly patients in terms of pursuing additional distal occlusions (eg, posterior cerebral artery³⁴), the number of EVT attempts, and final angiographic goal, which may culminate in overall reduced EVT efficacy.^{35,36}

Fifth, the NIS does not report more granular outcomes such as embolism to new territories and angiographic outcomes. Furthermore, while the presence of ICH can be identified using the NIS,^{29,34,37} information on clinical or radiographic grading of hemorrhagic complications (eg, symptomatic versus asymptomatic, hematoma versus hemorrhagic infarction, and so forth) is not available. Future prospective studies that capture these variables are needed to fully elucidate the efficacy and safety of EVT for elderly patients with BAO stroke. Finally, this study ended at 2021, which was before recent advances in EVT devices and techniques as well as the publication of the 2023 landmark trials demonstrating the safety and efficacy of BAO-EVT.^{11,12} Future investigations are needed to confirm our findings in more contemporary clinical settings.

CONCLUSIONS

In this explorative nationwide analysis of elderly patients with BAO stroke in real-world practice, we found that EVT was not significantly associated with higher rates of favorable short-term hospitalization outcomes measured by discharge home, while it was associated with an increased risk of ICH. Subgroup analyses revealed that EVT may be beneficial for patients who were not treated with IVT and that IVT may exert a negative modulatory effect on the efficacy of EVT.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Image Quality Evaluation for Brain Soft Tissue in Neuroendovascular Treatment by Dose-Reduction Mode of Dual-Axis “Butterfly” Scan

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ABSTRACT

BACKGROUND AND PURPOSE: Flat panel conebeam CT (CBCT) is essential for detecting hemorrhagic complications during neuroendovascular treatments. Despite its superior image quality and trajectory over conventional CBCT (circular scan), the dual-axis butterfly scan has a slightly higher radiation dose relative to conventional CBCT. This study evaluates the image quality in dose-reduction mode to uncover the appropriate radiation dose for the butterfly scan.

MATERIALS AND METHODS: We prospectively included patients who were scheduled for neuroendovascular treatment and underwent conventional CBCT and the dose-reduction mode of the butterfly scan. Two reduced radiation dose modes were used for the butterfly scan: medium-dose butterfly scan (70% of the original dose, 45 mGy) or low-dose butterfly scan (50% of the original dose, 30 mGy). The enrolled patients were assigned alternately to undergo either the medium- or low-dose butterfly scan. We evaluated and compared artifacts, contrast, and discrimination of the corticomedullary junction between conventional CBCT and one of the dose-reduction modes of the butterfly scan, with a 5-point scale scoring system.

RESULTS: Twenty patients were enrolled in each of the medium- and low-dose groups, totaling 40 patients. Compared with conventional CBCT, the medium-dose butterfly group exhibited reduced artifacts, enhanced contrast, and corticomedullary junction discrimination (except in the occipital lobe). While the low-dose butterfly group exhibited markedly reduced artifacts and improved contrast (except in the occipital lobe), a significant improvement in corticomedullary junction discrimination was not observed.

CONCLUSIONS: Even with dose reduction, the specialized trajectory of the butterfly scan enables artifact reduction, contrast improvement, and enhanced corticomedullary junction discrimination. However, the impact of the reduced dose was more noticeable, particularly in the occipital region where susceptibility to bone interference resulted in decreased contrast and compromised corticomedullary junction discrimination.

ABBREVIATIONS: angio-suite = angiography suite; CBCT = conebeam CT; CTDI = CT dose index

The early detection of hemorrhagic complications in neuroendovascular therapy is crucial for subsequent appropriate interventions.¹ To check and detect these complications through CT imaging, recent angiography suite (angio-suite) devices use C-arm conebeam CT (CBCT) technology. This technology enables the 3D reconstruction of CT-like images from C-arm rotational imaging.² This feature enables the acquisition of CT-like images

without the need to move the patient during the procedure, enabling the swift identification of hemorrhagic complications.

In conventional CBCT, the rotation of the C-arm is controlled by a single-axis motor, capturing x-ray images with pulse irradiation along the rotational trajectory, specifically focusing on the vertical cross-section of a patient. The 3D reconstruction is then performed. However, due to the limitation of a 240° rotation range, artifacts caused by high x-ray absorption in bony structures degrade image quality, making it inferior to standard CT. The C-arm rotation is controlled by a single-axis motor to collect x-ray images using a rotational trajectory confined to the vertical plane. The rotation spans 240° from right anterior oblique (RAO) 120° to left anterior oblique (LAO) 120° without irradiation from the occipital side, making it prone to artifacts attributable to the bone structure. This effect is particularly pronounced in the posterior cranial fossa surrounded by bones, thereby impeding the detection of small amounts of bleeding.

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SUMMARY

PREVIOUS LITERATURE: A newly developed CBCT protocol with a novel trajectory (dual-axis butterfly scan) controls C-arm rotation using a dual-axis motor. Our previous comparative analysis of image quality between conventional and dual-axis butterfly CBCT revealed reduced artifacts, enhanced contrast between the brain parenchyma and CSF, and improved corticomedullary junction discrimination for the latter procedure. However, a previously used dual-axis butterfly scan required a slightly higher radiation dose (65 mGy) than conventional CBCT (45 mGy).

KEY FINDINGS: Compared with conventional CBCT, medium-dose butterfly CBCT (45 mGy) reduced artifacts and improved contrast and corticomedullary junction evaluation, as observed for the normal dose. Low-dose butterfly CBCT (30 mGy) also achieved reduced artifacts and improved contrast, but similar or worse corticomedullary junction discrimination was observed.

KNOWLEDGE ADVANCEMENT: CBCT with angiographic devices can be used to quickly detect hemorrhage and diagnose acute infarction. Butterfly scans, especially at high (65 mGy) and medium (45 mGy) doses, provide reduced artifacts and better contrast. The low-dose mode (30 mGy) is preferred for pediatric cases to limit radiation exposure.

A newly developed CBCT with a novel trajectory (dual-axis butterfly scan) controls C-arm rotation with a dual-axis motor.³ This introduced a new rotation trajectory, capturing cross-sectional information not only in the vertical plane but also from oblique angles, resembling a pendulum motion. The dual-axis butterfly scan follows a dual-axis trajectory and features a propeller-like rotation for cardiac imaging that spans LAO 65° to RAO 176°, coupled with a pendulum-like tilting motion ranging from 15° cranially to 15° caudally (Fig 1). X-ray images from pulse irradiation in each direction are collected, allowing 3D image reconstruction. The multidirectional image information enables the correction of artifacts caused by high x-ray absorption, promising enhanced image quality through artifact reduction. Our previous comparative analysis of image quality between conventional CBCT and dual-axis butterfly CBCT revealed reduced artifacts, particularly in the posterior cranial fossa, enhanced contrast between the brain parenchyma and CSF, and

improved corticomedullary junction discrimination, leading to enhanced image quality.⁴

However, the dual-axis butterfly scan used in the previous study had a slightly higher radiation dose compared with conventional CBCT (conventional CBCT irradiation exposure: 45 mGy; dual-axis butterfly scan; 65 mGy). In this study, addressing the concern of radiation exposure, 2 dose-reduction modes were developed for the new dual-axis butterfly CBCT system. In comparison with the normal dual-axis butterfly CBCT dose of 65 mGy set as 100%, these modes include a medium-dose mode with a 70% reduction in dose and a low-dose mode with a 50% reduction. These dose-reduction modes are anticipated to be applicable especially for patients requiring lower invasiveness, such as pregnant women and children.⁵ Adjusting the trajectory did not affect the dose, and it is possible to create different dose levels for the same acquisition type. The dose (CT dose index [CTDI]) is a design choice of the x-ray protocols, and it depends on the frame

rate, scan length, tube current, exposure time, voltage, and prefilter setting. The voltage and prefilter setting were not changed in any of the protocols. The frame rate was increased from 30 to 60 frames per second to lower the scan time. Finally, the CTDI was measured on a CTDI phantom; then, the tube current (milliamperere) and exposure time (millisecond) were increased or decreased until the measured CTDI matched the requirements (30, 45, and 65 mGy for low, medium, and normal doses, respectively).

This study aimed to compare and assess the image quality of medium- and low-dose dual-axis butterfly scans against conventional CBCT and to examine the appropriate clinical use for each dose.

MATERIALS AND METHODS

Study Participants

Between July 2022 and January 2023, we enrolled patients who had undergone

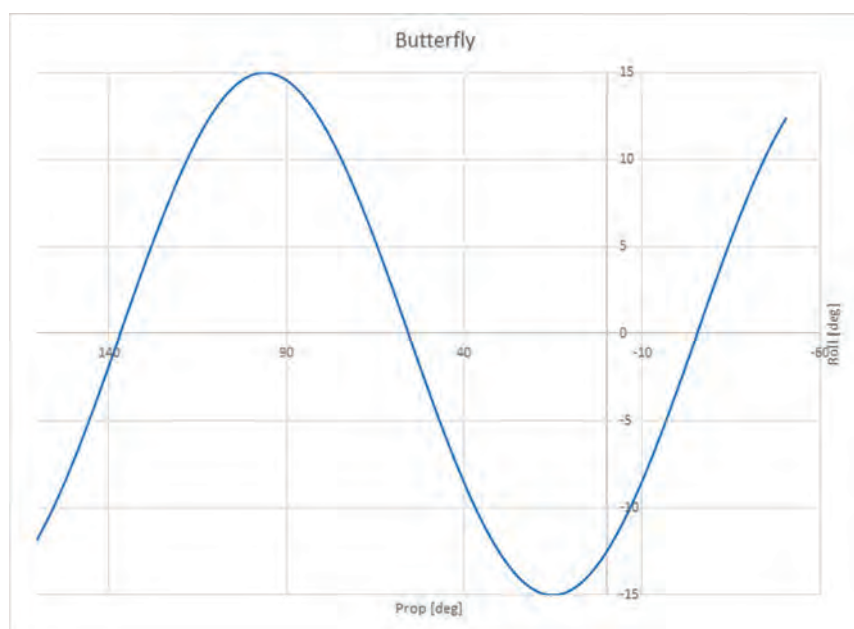


FIG 1. Schematic of the trajectory of the butterfly scan. Prop indicates propeller; deg, degree.

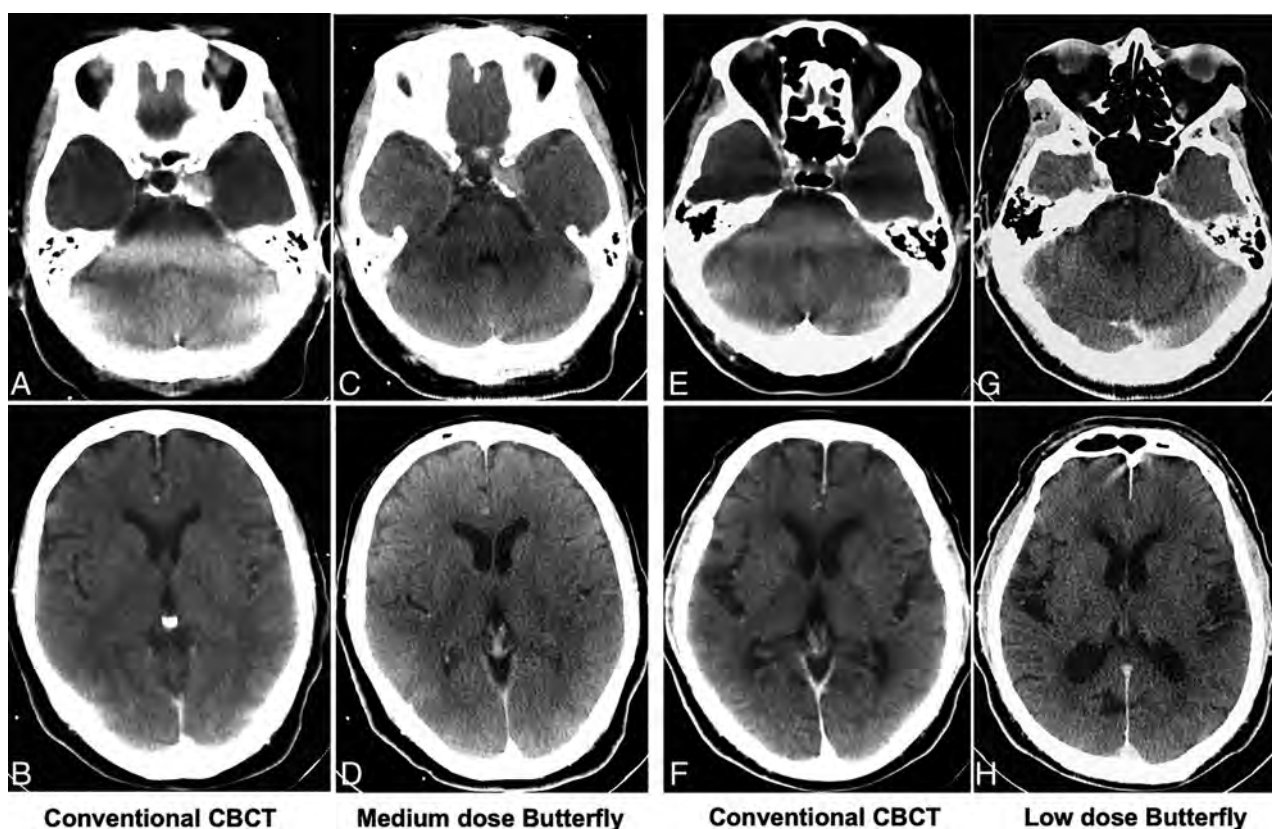


FIG 2. Illustrative case of each medium-dose group and low-dose group. *A–D*, Imaging from the same patient in the medium-dose group, with *A* and *B* being a conventional CBCT and *C* and *D* being a medium-dose butterfly scan. *E–H*, Imaging from the same patient in the low-dose group. *E* and *F*, Conventional CBCT. *G* and *H*, Low-dose butterfly scan.

scheduled neuroendovascular treatment and CBCT as a postoperative assessment. Informed consent was obtained from all patients or their surrogates. Participants agreed to undergo both conventional CBCT and a reduced-dose-mode butterfly scan. Exclusion criteria were patients experiencing challenges with head immobilization during imaging, individuals with acute ischemic stroke, and women who were pregnant or capable of becoming pregnant. Approval for this study protocol was granted by our institutional review board and registered on the Japan Registry of Clinical Trials (jRCTs032220133).

Angio-Suite Equipment and Imaging Protocol

A biplane angiography system (AzurionB20/15; Philips Healthcare) was used for C-arm-based conebeam CT. The frontal C-arm features a cesium iodide-amorphous silicon flat panel detector, measuring 30×40 cm and comprising 2586×1904 pixels. The detector was 4×4 , binned and resized to 512^2 , providing a pixel size of 0.741 mm. The x-ray tube voltage was adjusted to 120 kV with a focal spot of 0.7 mm. Additionally, a copper filter, sized at 0.4 mm, was used.

This study compared 2 acquisition protocols following neuroendovascular treatment. The first protocol used the commercially available XperCT HD protocol (conventional CBCT; Philips Healthcare), featuring a circular trajectory lasting 20.8 seconds with 30 frames per second (620 images for 3D reconstruction) (45 mGy). The second protocol involved an investigational device for optimized conebeam CT with a dual-axis butterfly trajectory

lasting 8 seconds, with an acquisition of 60 frames per second (480 images for 3D reconstruction). The radiation dose was 65 mGy in the high-quality mode of a butterfly scan, which was investigated in a previous study.⁴ As mentioned earlier, the current study used 2 modes with reduced radiation doses: a medium dose (70% of the original dose, ~45 mGy, termed medium-dose butterfly scan) and a low dose (50% of the original dose, ~30 mGy, termed low-dose butterfly scan). The enrolled patients were assigned alternately to receive either dose.

After the treatment, CBCT imaging was performed using conventional CBCT and one of the reduced-radiation butterfly scans, which was assigned before treatment. The obtained images were processed using a workstation (Interventional Workstation; Philips Healthcare), applying metal artifact reduction, and were evaluated in axial sections (Fig 2). The image slice thickness was set to 5 mm for investigation. The size of the reconstructable field of view was slightly smaller at the neck, which is typically not relevant.

Regarding the 3D reconstruction algorithm, the algorithm used in this study followed a previously reported method.⁶ Briefly, 3D reconstruction for both protocols was achieved using the Schomberg method,⁷ with an additional 2-pass bone beam-hardening correction applied, as is common in CT reconstruction.^{8,9} The new protocols use both optimized acquisition settings and reconstruction improvements to analyze and reconstruct imaging data collected from an oblique direction, whereas the conventional protocols do not use the reconstruction improvements. Butterfly CBCT thus uses a more advanced algorithm with

reduced artifacts. At a CTDI of 45 mGy, both the butterfly scan (medium dose) and conventional CBCT have an effective dose of 1.6 mSv.³

The evaluation method and criteria were conducted as previously reported for the butterfly scan.⁴ In both the medium- and low-dose butterfly groups, the image quality of the conventional CBCT was compared with that of the respective butterfly scans.

Image Artifact Evaluation

The primary outcome involved assessing artifacts in both the supra- and infratentorium areas. Images obtained from 2 different imaging methods from the same patient were individually evaluated for image quality by 3 evaluators: a certified neurosurgeon (H.H.), stroke neurologist (M.H.), and neuroradiologist (T.M.). Each evaluator provided a subjective assessment. We used a 5-point subjective rating scale (1, little or no artifacts; 2, some artifacts seen but not interfering with the diagnosis; 3, artifacts seen in a wide range but not interfering with the diagnosis; 4, diagnosable areas remained but interfered with the diagnosis; and 5, no diagnosable areas). The average score of the 3 investigators was calculated. During the evaluation, the identity of each image was blinded to avoid bias.

Brain Contrast Evaluation

We also conducted similar evaluations for the contrast between brain parenchyma structures and CSF spaces. For each of the medulla oblongata, pons, midbrain, basal ganglia, frontal lobe, temporal lobe, and occipital lobe, 3 evaluators independently rated the contrast on a 5-point scale (1, sufficient contrast for diagnosis; 2, insufficient contrast in some areas; 3, insufficient contrast in large areas but not impairing diagnosis; 4, areas of contrast remaining but impairing diagnosis; and 5, poor contrast throughout, not diagnostic at all). The average score of the 3 investigators was calculated.

Corticomedullary Junction Evaluation

Corticomedullary junction discrimination was evaluated. The evaluation method was the same as the aforementioned brain contrast evaluation. We assessed the following areas: basal ganglia,

frontal lobe (precentral), temporal lobe (temporal tip), and occipital lobe (superior medial to the calcarine sulcus).

Statistical Analysis

For each evaluation criterion, the average scores from the 3 evaluators for each subject were statistically compared between the 2 imaging methods. We used the Wilcoxon signed-rank test for comparison of paired variates. The data were shown as median (25th to 75th percentile). A *P* value of < .05 was defined as significant. The Cronbach α was calculated for each imaging method and each item to assess interrater agreement. SPSS Version 29 (IBM) was used for statistical analysis.

RESULTS

During the study period, 20 patients (40 paired images) were registered in the medium-dose butterfly group; and 20 patients (40 paired images), in the low-dose butterfly group. The Table summarizes the patient characteristics and the details of the neurointervention treatments in each group. The Cronbach α for each imaging method and evaluation item was as follows: artifacts, 0.889 for conventional CBCT and 0.921 for the butterfly scan; contrast, 0.895 for conventional CBCT and 0.859 for the butterfly scan; and corticomedullary junction, 0.814 for conventional CBCT and 0.769 for the butterfly scan.

Results of the Medium-Dose Butterfly Group

Figure 2A–D shows 1 case of representative images of both conventional CBCT and the medium-dose butterfly scan in the medium-dose group (Fig 2A, –B, conventional CBCT; Fig 2C, –D, medium-dose butterfly scan).

In artifact evaluation, medium-dose butterfly scans showed a significant reduction in artifacts in both supra- and infratentorium areas compared with conventional CBCT. The scores for each area were as follows: conventional CBCT versus medium-dose butterfly scan; supratentorium, 2.67 versus 1.50, *P* < .001; infratentorium, 3.67 versus 2.33, *P* < .001 (Fig 3A).

In contrast evaluation, the medium-dose butterfly scan showed significantly better contrast than the conventional CBCT in all the areas examined. The scores for each area were as

follows: conventional CBCT versus medium-dose butterfly scan: medulla oblongata, 4.00 versus 2.33, *P* < .001; pons, 4.00 versus 2.00, *P* < .001; midbrain, 2.83 versus 1.67, *P* < .001; basal ganglia, 1.33 versus 1.00, *P* < .001; frontal lobe, 1.67 versus 1.00, *P* < .001; temporal lobe, 2.33 versus 1.67, *P* < .001; occipital lobe, 2.33 versus 1.67, *P* = .001 (Fig 4A).

In corticomedullary junction discrimination, medium-dose butterfly scans exhibited superiority in the basal ganglia, frontal lobe, and temporal lobe, though no significant difference in the occipital lobe was observed. The scores for each area were as follows: conventional CBCT versus medium-dose butterfly scan: basal ganglia,

Summary of patient characteristics and details of treatment in the medium- and low-dose butterfly groups

	Medium Dose (n = 20)	Low Dose (n = 20)
Age (mean) (yr)	60.4 (SD, 15.5)	62.0 (SD, 15.7)
Sex (No.) (%)		
Male	12 (60.0)	12 (60.0)
Female	8 (40.0)	8 (40.0)
Treatment details (No.) (%)		
Embolization or FD for aneurysm	11 (55.0)	9 (45.0)
Tumor embolization	2 (10.0)	2 (10.0)
Embolization for DAVF	3 (15.0)	1 (5.0)
CAS	2 (10.0)	4 (20.0)
PTAS	1 (5.0)	2 (10.0)
Embolization for AVM	1 (5.0)	2 (10.0)
Anesthesia (No.) (%)		
General anesthesia	17 (85.0)	16 (80.0)
Local anesthesia	3 (15.0)	4 (20.0)

Note:—DAVF indicates dural arteriovenous fistula; CAS, carotid artery stenting; PTAS = percutaneous transluminal angioplasty and stenting; FD, flow diverter.

1.83 versus 1.67, $P = .035$; frontal lobe, 1.67 versus 1.33, $P < .001$; temporal lobe, 2.83 versus 2.33, $P < .001$; occipital lobe, 3.00 versus 2.33, $P = .085$ (Fig 5A).

Results of the Low-Dose Butterfly Group

Figure 2E–H shows 1 case of representative images of both conventional CBCT and low-dose butterfly scans in the low-dose group (Fig 2E, -F, conventional CBCT; Fig 2G, -H, low-dose butterfly).

In artifact evaluation, low-dose butterfly scans showed significant reductions in artifacts in both supra- and infratentorial areas compared with conventional CBCT. The scores for each area were as follows: conventional CBCT versus low-dose butterfly scan: supratentorium, 2.33 versus 1.00, $P < .001$; infratentorium, 3.67 versus 2.00, $P < .001$ (Fig 3B).

In contrast evaluation, low-dose butterfly scans showed significantly better contrast than conventional CBCT in all the areas examined except for the occipital lobe. The scores for each area were as follows: conventional CBCT versus low-dose butterfly scan: medulla oblongata, 4.00 versus 3.17, $P = .001$; pons, 3.83 versus 2.33, $P < .001$; midbrain, 2.33 versus 1.67, $P < .001$; basal ganglia, 1.33 versus 1.00, $P < .001$; frontal lobe, 1.67 versus 1.00, $P = .001$; temporal lobe, 2.00 versus 1.33, $P < .001$; occipital lobe, 2.00 versus 1.67, $P = .218$ (Fig 4B).

In corticomedullary junction discrimination, no significant difference was observed between the 2 imaging methods in the basal ganglia, frontal lobe, or temporal lobe. In the occipital lobe, the low-dose butterfly scan showed a deterioration compared with conventional CBCT: conventional CBCT versus low-dose butterfly scan: basal ganglia, 1.67 versus 2.00, $P = .212$; frontal lobe, 2.50 versus 2.33, $P = .093$; temporal lobe, 1.67 versus 1.83, $P = .565$; occipital lobe, 2.50 versus 2.67, $P = .010$ (Fig 5B).

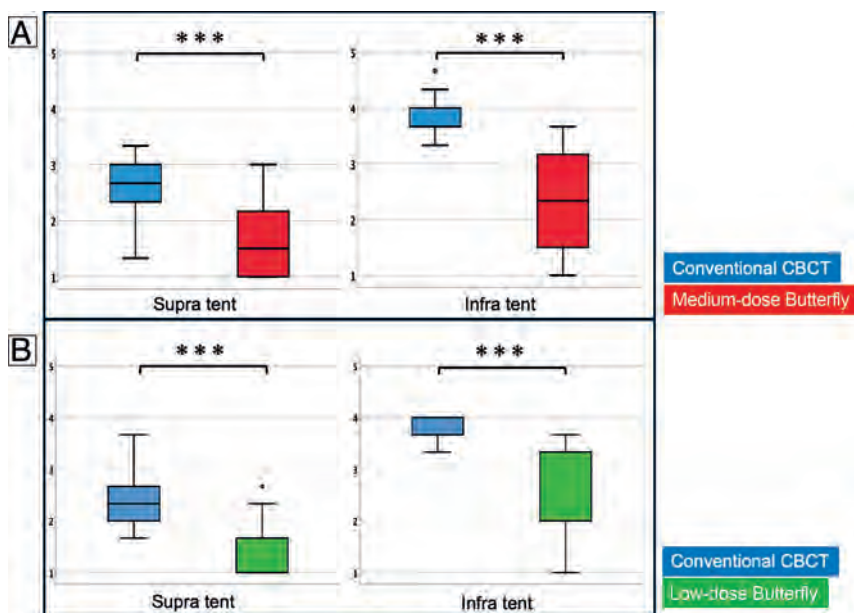


FIG 3. Results of artifact evaluations. *A*, The results of the medium-dose group. *B*, The results of the low-dose group: ***, $P < .001$; **, $P < .01$; *, $P < .05$. Supra tent indicates supratentorial; Infra tent, infratentorial.

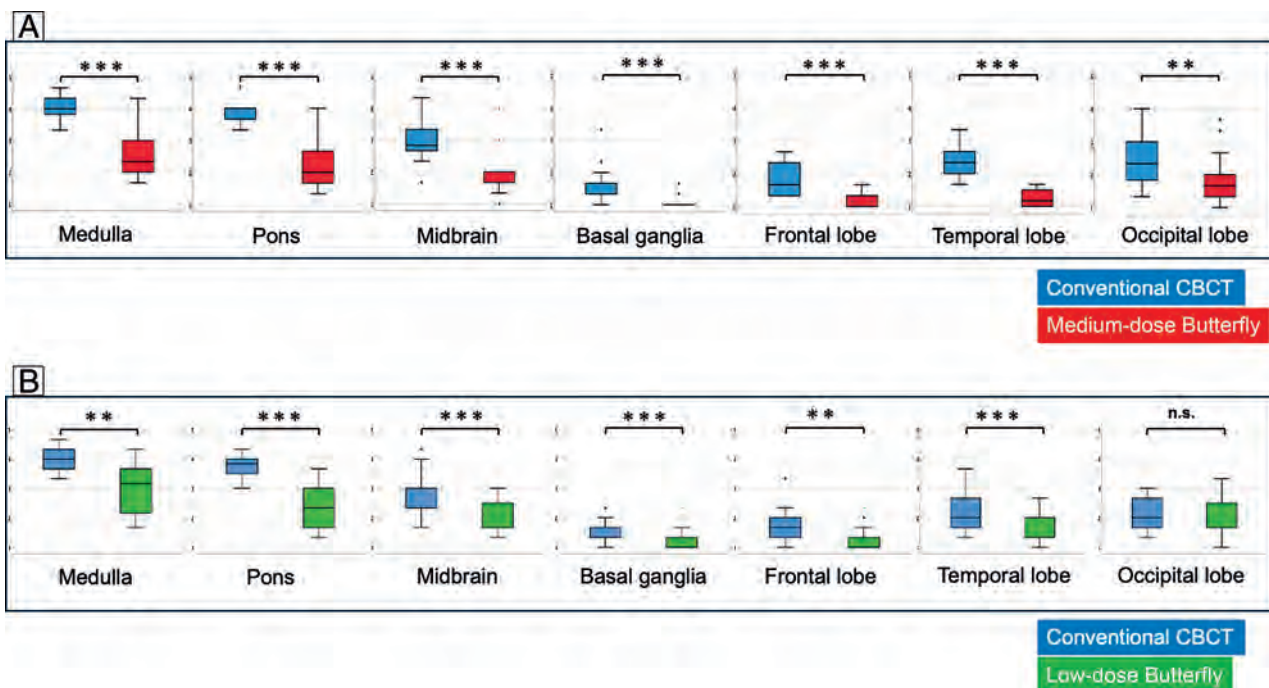


FIG 4. Results of contrast evaluations. *A*, The results of the medium-dose group. *B*, The results of the low-dose group: ***, $P < .001$; **, $P < .01$; *, $P < .05$; n.s., not significant.

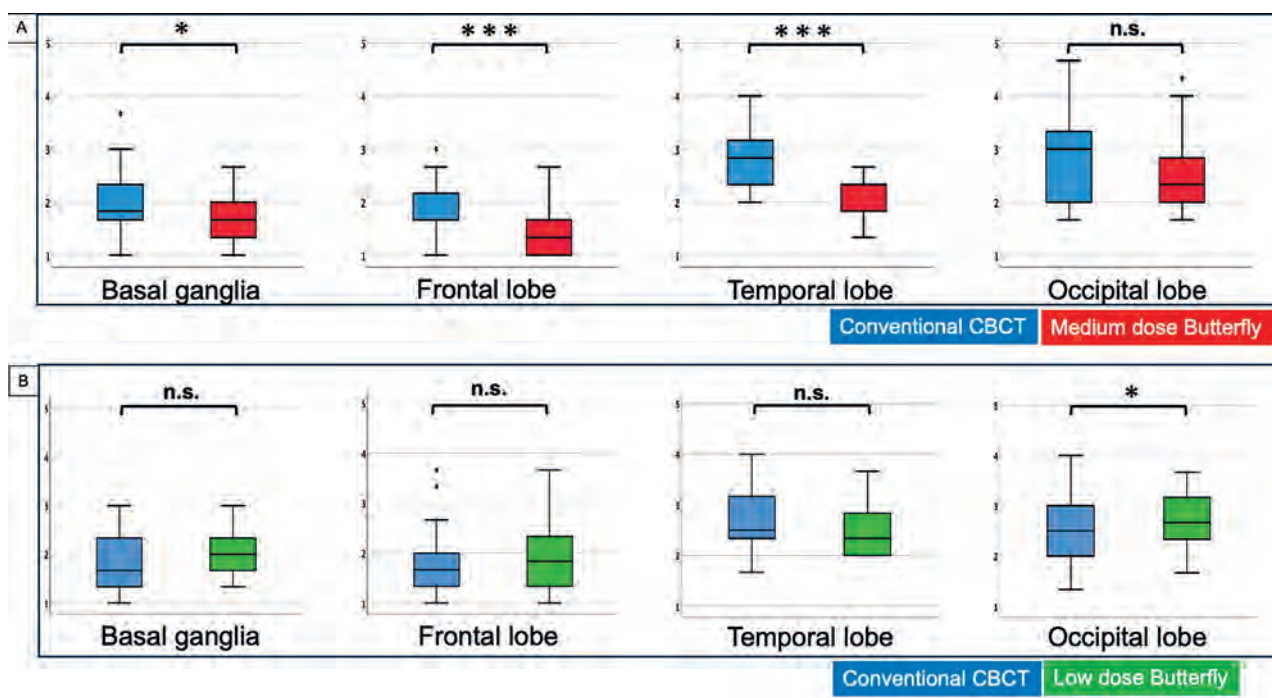


FIG 5. Results of corticomedullary junction discrimination. *A*, The results of the medium-dose group. *B*, The results of the low-dose group: ***, $P < .001$; **, $P < .01$; *, $P < .05$; n.s., not significant.

DISCUSSION

Compared with conventional CBCT, the medium-dose butterfly scan (45 mGy), similar to the previously investigated normal dose of high-quality mode (65 mGy), exhibited reduced artifacts and improved contrast evaluation and corticomedullary junction discrimination, though no significant advantage was observed in corticomedullary junction discrimination in the occipital lobe. As the dose decreased to low-dose butterfly scan (30 mGy), the superiority in reducing artifacts and improving contrast, except in the occipital lobe, compared with conventional CBCT, was maintained. However, in terms of corticomedullary junction discrimination, it was either equivalent in all regions examined or inferior in the occipital lobe.

In a dual-axis butterfly scan, both horizontal movements and pendulum-like vertical movements are involved, resulting in reduced artifacts because bone beam-hardening and conebeam effects are mitigated, leading to reduced artifacts and improved contrast and corticomedullary junction discrimination. Despite the fewer acquired images and shorter imaging time exhibited by dual-axis butterfly scans relative to conventional CBCT, image quality improves due to this unique imaging trajectory.^{3,4,6} However, when the dose decreases to around 50%, though the artifact-reduction effect of the unique trajectory is maintained, superiority in brain parenchymal image quality may diminish. This result is particularly evident in areas susceptible to bone influence. The deteriorating image quality of the occipital lobe may be attributed, in part, to reconstruction using images acquired from inclined angles not irradiated in the conventional circular rotation in the butterfly scan. Specifically, data obtained from x-ray irradiation along a line connecting the mandible to the occipital lobe tend to have higher bone density and lower x-ray penetration,

resulting in insufficient contrast during reconstruction. Although the low-dose butterfly scan yielded improvement in infratentorium artifacts compared with conventional CBCT, reducing the dose may also lower the effectiveness of artifact reduction.

The medium-dose butterfly scan and conventional CBCT in this study had approximately the same radiation dose, but the former had superior image quality in almost all aspects, implying that the new trajectory of the butterfly scan has a direct effect on reducing artifacts and improving contrast.

CBCT performed with angiographic devices offers the advantage of promptly detecting hemorrhagic complications during or after procedures. In addition, we expect it may also have potential utility in diagnosing acute-phase cerebral infarction. Patients suspected of having acute ischemic stroke usually undergo CT imaging for diagnosis first. Early ischemic changes are recognized by the blurring of the gray-white matter interface, allowing estimation of the ischemic core from this area.¹⁰ CT findings are important not only in excluding hemorrhagic stroke but also in determining the treatment strategy for large-vessel occlusion. In cases of large-vessel occlusion, early reperfusion therapy is desirable for a more favorable outcome. In recent years, the concept of the Direct to Angio-Suite Protocol has emerged, in which routine CT is bypassed and patients are directly transported to the angio-suite. The time metrics of direct transport to angiography suites has been reported in several observational studies and single-center randomized controlled trials.^{11–14} Requena et al¹⁴ conducted a randomized controlled trial and reported that the use of this strategy increased the odds of patients undergoing endovascular treatment, decreased hospital workflow, and improved clinical outcome compared with the conventional workflow. They used flat panel CBCT for diagnosis. Subsequently, a diagnostic angiogram

was obtained to confirm the presence of a large-vessel occlusion. A meta-analysis integrating these studies also suggested that directly transporting patients to angiography suites could lead to faster treatment and reperfusion, potentially resulting in improved long-term functional outcomes.¹⁵ To ensure the quality of this treatment workflow, the image quality of CBCT is crucial. A butterfly scan, which improves corticomedullary junction discrimination, can detect early signs of ischemia while effectively differentiating hemorrhagic stroke. Furthermore, given the frequent agitation and inability of patients to remain still, the butterfly scan, which has a shorter duration (8 seconds) compared with conventional CBCT (20.8 seconds), is anticipated to offer substantial benefits. Considering the dose for the butterfly scan, the high-quality mode (65 mGy) is recommended for the detailed detection of early ischemic changes.

Conversely, for evaluating hemorrhagic complications post-conventional neuroendovascular treatment, doses at or above the medium-dose mode (45 mGy) are likely sufficient for effective detection. The low-dose mode (30 mGy) has decreased ability in identifying corticomedullary junction discrimination, yet artifact reduction and contrast remain superior to those of conventional CBCT. In cases of pediatric cerebral arteriovenous shunt diseases, such as vein of Galen aneurysmal malformation, dural sinus malformation, and arteriovenous malformation, in which repeated treatments are often necessary,^{16,17} consideration should be given to using the low-dose mode to mitigate potential future effects of radiation exposure.

Compared with conventional CBCT, the butterfly scan also involves movement in the vertical direction; thus, consideration is needed to avoid interference with surrounding equipment such as anesthesia machines. However, patient positioning can be performed in the same manner.⁴

In recent years, reports have described the imaging trajectories in CBCT using flat panel detectors with other types of angiography suites that incorporate vertical movement, similar to the imaging protocol used in this study. Although the angle of vertical movement differs, with ours being 15° cranially and caudally and that in other reports being 10° in both directions, the addition of vertical movement contributes to improved image quality.^{18,19} It is expected that further improvements in image quality can be achieved by adjusting the angle and range of movement of the flat panel.

This study has certain limitations. It was based on a small number of cases within a single institution and a limited time period. It was anticipated beforehand that reducing the dose versus the full dose could result in lower image quality. Therefore, we aimed to verify through comparisons with conventional CBCT whether the improvement in image quality of the new trajectory of the butterfly scan could be ensured with a lower dose. The reduction in dose suggested a decrease in contrast and discrimination of the corticomedullary junction; however, the comparison was made only between the butterfly scan and conventional CBCT. Although the reduction in dose maintained the artifact reduction effect compared with conventional CBCT, the specific changes resulting from dose reduction of butterfly scans require further investigation. Furthermore, this study and previous research did not compare the image quality between the dual-axis butterfly scan and conventional CT. Future studies should address this omission by evaluating the extent to which the dual-

axis butterfly scan improves image quality compared with conventional CT.

CONCLUSIONS

In the dose-reduction mode of the butterfly scan, reducing the dose to 70% of the original dose still resulted in satisfactory artifact reduction, contrast enhancement, and corticomedullary junction discrimination. However, at a 50% dose reduction, while artifact reduction and contrast improvement were still attainable, the images became more susceptible to interference from bone. Improved corticomedullary junction discrimination was then lost. Even with a reduction in dose, the specialized trajectory of the butterfly scan enables artifact reduction, improvement in contrast, and enhancement of corticomedullary junction discrimination. However, the impact of the reduced dose was more noticeable, particularly in the occipital region where susceptibility to bone interference results in decreased contrast and compromised corticomedullary junction discrimination. Overall, setting the dose to at least 45 mGy is recommended to maintain optimal imaging quality.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Imaging and Anesthesia Protocol Optimization in Sedated Clinical Resting-State fMRI

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ABSTRACT

BACKGROUND AND PURPOSE: The quality of resting-state fMRI (rs-fMRI) under anesthesia is variable and there are no guidelines on optimal image acquisition or anesthesia protocol. We aim to identify the factors that may lead to compromised clinical rs-fMRI under anesthesia.

MATERIALS AND METHODS: In this cross-sectional study, we analyzed clinical rs-fMRI data acquired under anesthesia from 2009–2023 at Massachusetts General Hospital. Independent component analysis–driven resting-state networks (RSNs) of each patient were evaluated qualitatively and quantitatively and grouped as robust or weak. Overall networks were evaluated by using the qualitative method, and motor and language networks were evaluated by using the quantitative method. RSN robustness was analyzed in 4 outcome categories: overall, combined motor-language, individual motor, and language networks. Predictor variables included rs-fMRI acquisition parameters, anesthesia medications, underlying brain structural abnormalities, age, and sex. Logistic regression was used to examine the effect of the study variables on RSN robustness.

RESULTS: Sixty-nine patients were identified. With qualitative assessment, 40 had robust and 29 had weak overall RSN. Quantitatively, 45 patients had robust, while 24 had weak motor-language networks. Among all the predictor variables, only sevoflurane significantly contributed to the outcomes, with sevoflurane administration reducing the odds of having robust RSN in overall (OR = 0.2, 95% CI = 0.05–0.79, $P = .02$), motor-language (OR = 0.18, 95% CI = 0.04–0.80, $P = .02$), and individual motor (OR = 0.1, 95% CI = 0.02–0.64, $P = .02$) categories. Individual language network robustness was not associated with the tested predictor variables.

CONCLUSIONS: Sevoflurane anesthesia may compromise the visibility of fMRI RSN, particularly impacting motor networks. This finding suggests that the type of anesthesia is a critical factor in rs-fMRI quality. We did not observe the association of the MR acquisition technique or underlying structural abnormality with the RSN robustness.

ABBREVIATIONS: BOLD = blood oxygen level–dependent; rs-fMRI = resting-state fMRI; RSN = resting-state network

Noninvasive functional brain mapping in young children and cognitively impaired patients is challenging with

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standard awake task-based fMRI, which requires patient cooperation, and effort. Resting-state fMRI (rs-fMRI) is task-free and can address this challenge by revealing multiple functional brain networks without a need for direct patient participation.^{1,2} However, rs-fMRI under anesthesia, which is often required for this patient population, is technically challenging and is prone to failure.³ The use of rs-fMRI is expanding in clinical settings, currently complementing task-based fMRI and invasive methods such as direct electrical cortical stimulation. The development of new reliable analytical methods, combined with the unique insights rs-fMRI provides about functional anatomy, makes this technique promising as a stand-alone clinical tool in the future, particularly for patients who cannot undergo traditional methods.^{4–6} Optimizing rs-fMRI is essential for noninvasive personalized treatment planning in neurologic disorders in this patient population. In this study we aim to identify the factors that may lead to compromised clinical rs-fMRI under anesthesia.

SUMMARY

PREVIOUS LITERATURE: Limited literature is available on the effect of accelerated resting-state fMRI and other imaging parameters on the quality of rs-fMRI in a clinical setting where visibility of surgically relevant networks is crucial. Most of the prior work has used nonaccelerated techniques. Vast literature on rs-fMRI under anesthesia has focused on functional connectivity metrics to arrive at neuronal correlates of anesthesia, rather than clinical metrics that can be used for individual patients. The literature on the optimal anesthesia protocol for rs-fMRI is mixed with conflicting findings.

KEY FINDINGS: Sixty-nine clinical rs-fMRI examinations under anesthesia were evaluated retrospectively for network activation robustness. Among all the tested variables, including accelerated and nonaccelerated MR techniques, scan length, structural abnormalities, and multiple anesthesia medications, only sevoflurane was associated with weak networks.

KNOWLEDGE ADVANCEMENT: Sevoflurane may compromise the visibility of MRI resting-state networks under anesthesia, mainly the motor network, without affecting the language network.

Blood oxygenation level-dependent (BOLD) imaging is the main technique used for rs-fMRI.⁷ Synchronous fluctuation of the BOLD signal in distant parts of the brain at rest form functionally connected resting-state networks (RSNs).² BOLD signal is an indirect marker of neuronal activity and depends on a phenomenon called neurovascular coupling where neuronal activity leads to increased blood flow.⁸ Decreased intrinsic neuronal activity or neurovascular uncoupling may degrade fMRI ability to reveal RSN. Cerebral blood flow is decreased under anesthesia as is the intrinsic signaling of certain parts of the brain depending on the anesthetic,^{9,10} which may lead to neurovascular uncoupling or drop of BOLD signal below detection levels.

Functional MR sequences under anesthesia need to be tailored to capture this suppressed signal. Accelerated rs-fMRI is a desired technique for its fast acquisition, high temporal resolution, and low motion artifact. The trade-off is a low SNR in each BOLD volume compared with nonaccelerated fMRI. In awake imaging, moderately accelerated rs-fMRI can detect resting BOLD signal fluctuation.¹¹ However, under anesthesia, a low SNR from acceleration may outweigh the benefits. In sedated animal studies accelerated rs-fMRI has been used,¹² but in humans, the key studies did not use accelerated rs-fMRI.¹³⁻¹⁷ We hypothesize that acceleration may compromise rs-fMRI under anesthesia in humans.

The literature on neurovascular coupling in sedated humans is limited¹⁸ and the optimal anesthetic regimen to produce visible networks in rs-fMRI is unknown. Animal studies favor a combination of medetomidine and isoflurane anesthetic agents for rs-fMRI.¹⁹ In humans, the commonly studied anesthetics (sevoflurane and propofol) decrease connectivity of thalamocortical and frontoparietal networks.^{10,20,21} Nonetheless successful utilization of these agents has been reported in pilot clinical studies.^{13,14,20-25} Given our institutional experience, we hypothesized that propofol compromises the RSN further than other agents.

To test our hypotheses, we evaluated the impact of different MR acquisition parameters and anesthesia medications on the quality of clinical rs-fMRI under anesthesia in individual patients.

MATERIALS AND METHODS

Study Design

We conducted this retrospective, cross-sectional study by using human subject data with institutional review board approval

(#2021A019008). Informed consent was waived with institutional review board approval.

Setting. The research was carried out in a tertiary adult and pediatric care hospital, utilizing the hospital's extensive database of rs-fMRI, acquired as part of institutional battery of functional MR sequences.

Participants

Consecutive patients of all age groups and all pathologies who underwent rs-fMRI under anesthesia at Massachusetts General Hospital from 2009–2023 were included in the study. The patients were excluded if the sedation was not done for image acquisition purposes, as in sedated or comatose intensive care unit patients. Patients who did not have a structural MRI performed during the same session as the rs-fMRI were excluded. Patients with hematoma that would interfere with the image analysis were excluded. The functional imaging was requested by the referring provider in each of the subjects.

Variables. Outcome variables are rs-fMRI network quality (robust versus weak) as defined in the following sections. Predictor variables, also detailed in the following sections, include fMRI acquisition parameters (multiband versus regular, scan length, and number of BOLD volumes), anesthesia medications (propofol, sevoflurane, N₂O, and other), underlying structural abnormalities, age, and sex.

Data Sources/Measurement. *Anesthesia.* The decision to administer anesthesia during MRI acquisition was made clinically and not influenced by this study. The type of anesthesia was chosen by the anesthesiologist and individualized for each patient. One or more medications were used for each patient without a particular pattern. Frequently used medications for our study group (sevoflurane, propofol, and N₂O) were each considered as a predictor variable. Less frequently used medications (eg, fentanyl and dexmedetomidine) constituted the "other medication" variable. The primary investigator retrieved the data directly from the anesthesia event documented at electronic medical record by the anesthesiologist.

MRI Acquisition. All scans were performed on a Siemens (Prisma fit or TrioTim) 3T MRI scanner. Anatomic images were

obtained by using MPRAGE 3D T1-weighted sequences (TE: 2.3 ms, TR: 2300 ms, flip angle: 8, voxel size: $1 \times 1 \times 1 \text{ mm}^3$). Resting-state BOLD fMRI was obtained by using a 2D echo-planar imaging either with acceleration (TE: 36 ms, TR: 1250 ms, flip angle: 60, axial pixel size: $2 \times 2 \text{ mm}^2$, slice thickness 2 mm, multiband factor: 5), or without acceleration (TE: 30 ms, TR: 3000 ms, flip angle: 90, axial pixel size: $2 \times 2 \text{ mm}^2$, slice thickness 3 mm). All the scans from the TrioTim scanner were without acceleration. The rs-fMRI scan lengths ranged between 5–10 minutes in 1 or multiple runs, and total BOLD volumes ranged between 90–550 per subject. Given all our subjects were under anesthesia, there was no control on eyes open or eyes closed during rs-fMRI acquisition. rs-fMRI sequences were acquired before contrast administration. No passive task-based fMRI was performed during the scans.

We documented the presence of acceleration technique for fMRI (multiband versus regular), scan length, and number of BOLD volumes as the 3 MR-related predictor variables.

Image Analysis. Preprocessing was performed by using fMRIPrep²⁶ at participant level. Initially, raw data underwent motion correction by using a rigid body transformation to realign the time-series. Brain extraction (skull-stripping) was performed by using the MNI152NLin2009cAsym template. Slice timing correction was not performed. Data were then spatially normalized to the MNI152NLin2009cAsym template at 2-mm resolution, the native T1-weighted anatomic space, the native FreeSurfer anatomic space, and the FreeSurfer average surface space (fsaverage6). Noise reduction was applied by using CompCor to mitigate physiologic noise, and confound regression included motion parameters, global signals, and Anatomic CompCor components. Spatial smoothing was not applied at this stage and was performed during independent component analysis. ICA by using FSL MELODIC (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC>) software²⁷ was used for functional connectivity analysis and network delineation. Mixture modeling on Z-transformed independent component maps was performed for multiple comparison correction. Assessment of RSN robustness was performed by using qualitative and quantitative methods.

Qualitatively, a neuroradiologist (E.H., with 2–3 years of subspecialty experience) grouped each patient's surgically relevant RSN into overall robust or overall weak. At the time of grouping, the neuroradiologist (E.H.) was blind to the study variables including anesthesia medication. Similar to clinical practice, patient-specific visual thresholding was used to reveal meaningful RSN activation maps. Language, sensorimotor, visual, and auditory RSN were considered surgically relevant, while default mode, salient, attention, and executive function networks were considered not relevant. An overall robust RSN was defined as large cortical activations within boundaries of 2 or more surgically relevant networks. An overall weak RSN was defined as absent, small or <2 surgically relevant network activations.

For the quantitative analysis, the preprocessed data underwent further analysis with an in-house Matlab (MathWorks) script built on established techniques detailed previously with modification.⁴ Briefly, a template matching process with Discriminability Index-based Component Identification score analyzed the ICA components and created a motor and a language

map for each patient in their native brain space. A visual quality assurance step was performed by a neuropsychologist (A.A., with 3–5 years of functional brain mapping and analysis) to ensure the selected maps were accurate. In cases of algorithm failure, for example if a noise component was selected as the functional map, the algorithm was adjusted to select the next best map. Next, for each of the language and motor maps, we computed a separate Dice coefficient to quantify the extent of overlap between the map and the corresponding template. The combined motor-language network quality for each patient was considered “robust” if Dice coefficients for both motor and language maps were above 0.5, otherwise “weak.” Similarly for individual analysis of motor and language networks, robustness was defined as Dice coefficient above 0.5. The decision to use Dice coefficient cutoff of 0.5 was based on our review of the data in this sample and general guidelines that consider the coefficient of 0.5 as fair overlap. On retrospective evaluation, this cutoff appropriately identified the cases in our study population with no meaningful RSN.

The following rs-fMRI network robustness outcome variables were documented: overall (qualitative), motor-language (quantitative), motor (quantitative), and language (quantitative).

Motion Parameters. The mean framewise displacement at the individual patient level was recorded from fMRIPrep derivatives and used for analysis. Framewise displacement was calculated as the sum of the absolute values of the differentiated realignment estimates, including both translational (x, y, z) and rotational (pitch, roll, yaw) movements.

Bias. Analysis bias was addressed by the addition of quantitative steps. Qualitative analysis bias was decreased by blinding the interpreting neuroradiologist to the study variables at the time of grouping the RSN.

Statistical Analysis. Logistic regression was used to determine the association of study variables (MRI parameters, anesthesia medication, age, sex, and presence of structural abnormality) with robustness of RSN in 4 defined categories (overall, motor-language, motor, and language). Variance inflation factor was used to quantify the level of multicollinearity among the variables. We intended to keep all the predictor variables in the final regression model. However, we removed BOLD volume variable given its collinearity with accelerated MRI variable. In addition, we performed polynomial regression for continuous variables where we did not observe the effect of higher orders, thus confirming the linear assumption for our model, precluding the need for sensitivity analysis. ORs were calculated to measure the strength of these associations, with P values < .05 considered statistically significant. Missing data were excluded from the analysis and are reported as count and percentage. Comparison of mean motion parameter between groups was done by using independent sample t test. R software (R Version 4.0.1, <http://www.r-project.org>) and SPSS (Version 28.0, IBM) was used for analysis (M.H. and Z.L.). The sample size was determined based on the availability of eligible patients within the study period. Post hoc power analysis was done by using type I error rate (α) = .05, and sample size of 69. The null hypothesis was set to sevoflurane OR = 1 (no effect) in each outcome category. Alternative

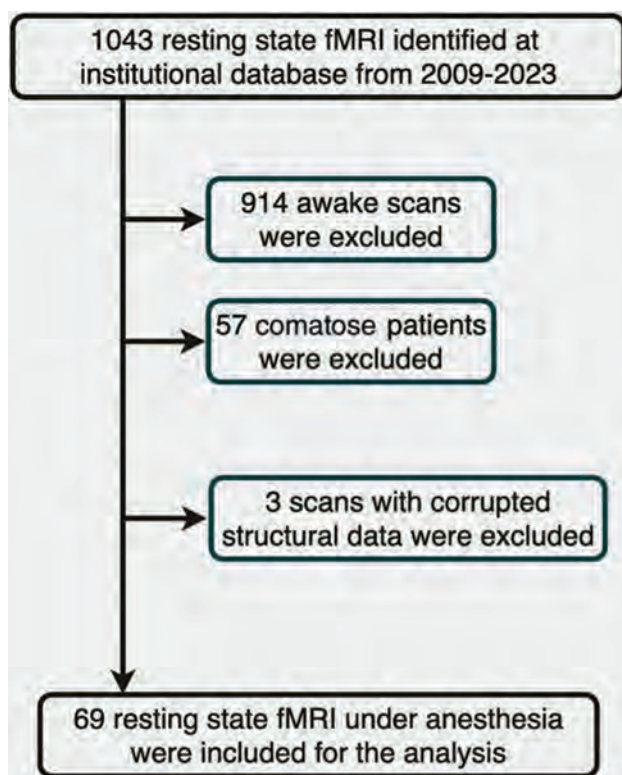


FIG 1. Flow diagram of patient selection.

hypotheses were set to the observed sevoflurane ORs in our data in each outcome category (ie, overall RSN OR = 0.2, motor-language OR = 0.18, and individual motor OR = 0.1, as seen in the following Results section). The analysis was performed on G*Power software (Version 3.1.9.7).

RESULTS

Participants and Descriptive Data

A total of 69 scans from 69 patients (mean age = 6.9 ± 4.3 , 39 boys) were included in the study (Fig 1). Detailed demographic information, imaging protocols and anesthesia types are shown in Table 1. Most (59%) of the rs-fMRIs were performed without acceleration. Anesthesia medications included propofol (84%), sevoflurane, N₂O, and other (fentanyl, dexmedetomidine). Approximately 43% of the structural examinations were normal. The structural abnormalities seen on the remainder included, but were not limited to, nonspecific white matter lesions, tumor, encephalomalacia, hemorrhage, abnormalities of gyration and sulcation (eg, polymicrogyria), and mesial temporal sclerosis. Indication for the examination was primarily epilepsy/seizure (51% of the cases) but also included traumatic brain injury, developmental delay, stroke, and headache.

Outcome Data

With qualitative assessment, 40 patients (58%) had overall robust RSN and 29 (42%) had weak networks. With quantitative assessment, 45 patients (65%) had robust combined motor-language networks while 24 (35%) had weak networks. With individual assessment of motor and language, 57 patients (83%) had robust language network and 52 patients (75%) had robust motor

Table 1: Demographics, clinical, and imaging characteristics of study population

Variables	n = 69
Age (yr)	
Mean (SD)	6.9 (4.26)
Range	1–17
Sex	
Girl	30 (43%)
Indication for the examination	
Seizure	35 (51%)
Tumor	7 (10%)
Other	27 (39%)
rs-fMRI with multiband	28 (41%)
fMRI scan length (minute)	
Mean (SD)	7.7 (2.01)
Range	4.5–10.4
Number of BOLD volumes	
Mean (SD)	271.3 (167.8)
Range	90–550
Frame-wise displacement (mm)	
Mean (SD)	0.05 (0.04)
Range	0.02–0.2
MRI with structural abnormality	39 (57%)
Anesthesia with propofol	58 (84%)
Anesthesia with sevoflurane	34 (49%)
Anesthesia with N ₂ O	12 (17%)
Anesthesia with other agents	15 (22%)

network. Examples of robust and weak RSN in our study population are shown in Figs 2 and 3.

Main Results

Among all the tested variables, only sevoflurane was significantly associated with the quality of RSN; with sevoflurane use reducing the odds of having robust overall RSN (OR = 0.2, $P = .02$), combined motor-language networks (OR = 0.18, $P = .02$), and individual motor network (OR = 0.1, $P = .02$) as detailed in Tables 2, 3, and 4. None of the tested variables were associated with weak individual language network (Table 5).

Other Analysis

Negligible motion was observed in all of the 69 examinations (Table 1). No significant difference was noted between the mean framewise displacement parameter between the patients who received sevoflurane (mean = 0.05 ± 0.03) compared with the group who did not (mean = 0.06 ± 0.04) ($P = .35$). In a post hoc power analysis, our sample size achieved a power of 80% and above to detect statistically significant results.

DISCUSSION

This study evaluated the factors that might have a role in the quality of clinical rs-fMRI under anesthesia and found that sevoflurane anesthetic is associated with weak overall RSNs and motor network individually. Our result did not show association of other factors, including image acquisition parameters (multiband acceleration or scan length) or other anesthetics (propofol or N₂O) with network robustness. Of note, language network robustness was not associated with any of the tested variables.

We used clinically relevant outcome measures and individual patient-level analysis, enhancing clinical translation compared with previous literature that mainly used functional connectivity

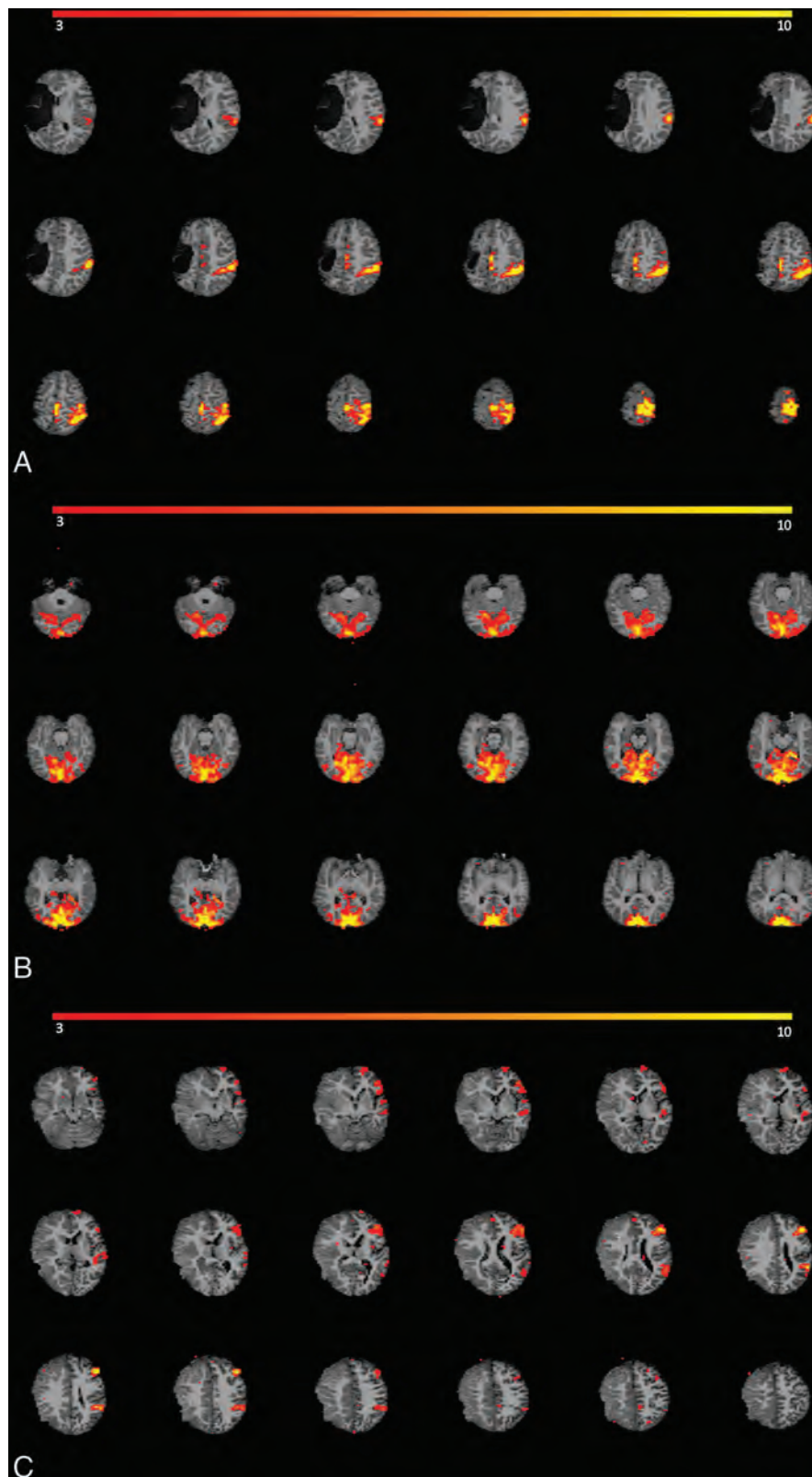


FIG 2. Examples of robust RSNs in our study population. Network activations are depicted in red-yellow spectrum. *A*, Robust motor network activation is seen (both visually and quantitatively) in an 8-year-old boy with epilepsy who underwent a 10.4-minute rs-fMRI with acceleration under propofol anesthesia. Structural images showed chronic right MCA infarction. *B*, Robust visual network activation is seen in a 9-year-old boy with epilepsy who underwent a 7.25-minute rs-fMRI without acceleration under propofol anesthesia. No structural abnormality was detected. *C*, Robust language network activation is seen (both visually and quantitatively) in a 5-year-old girl with seizure who underwent a 6.75-minute rs-fMRI without acceleration under propofol, sevoflurane, and fentanyl anesthesia. Subacute infarction in the right MCA territory was seen on structural images.

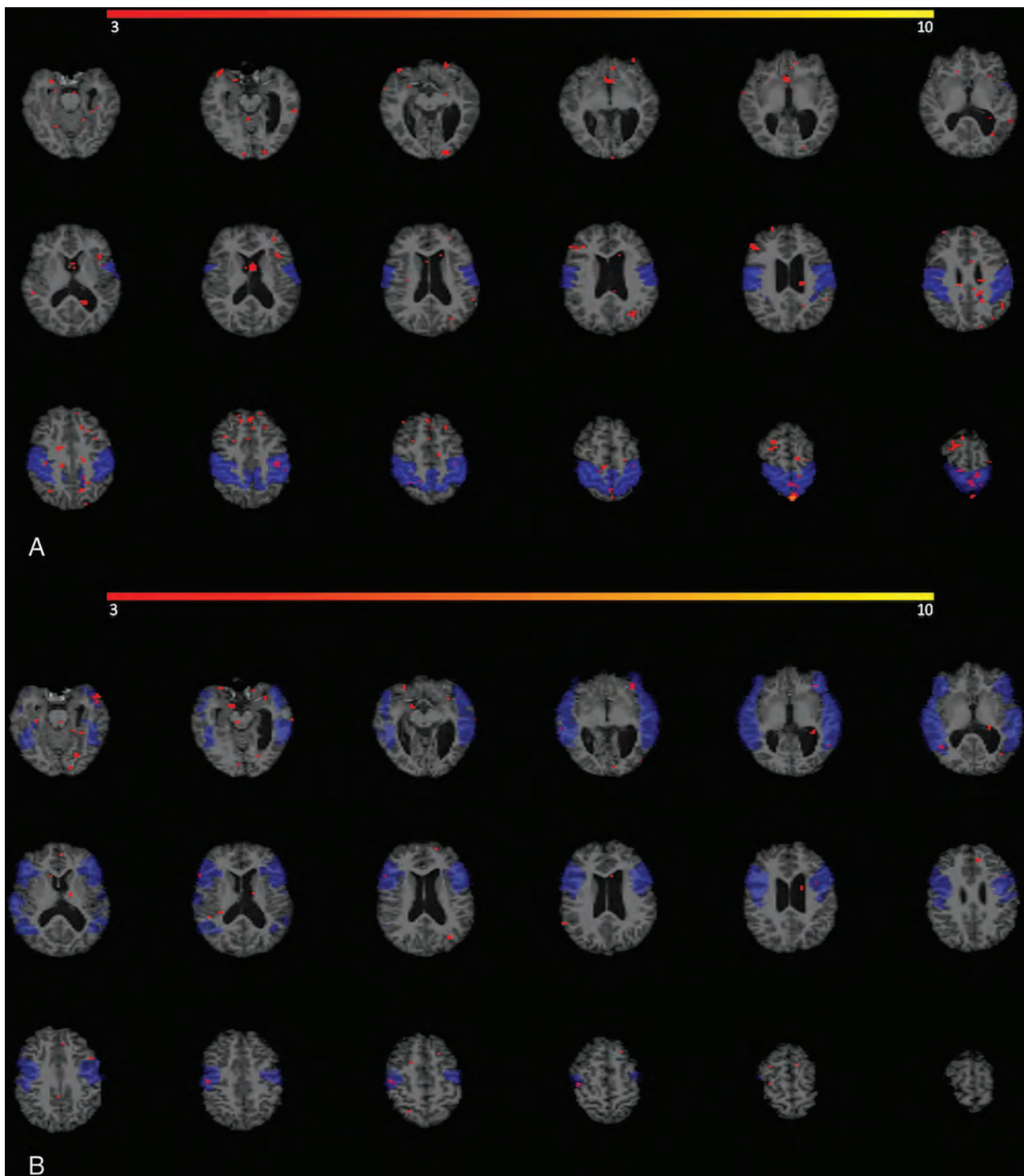


FIG 3. Example of weak RSNs in a 9-year-old boy with seizure who underwent 7-minute rs-fMRI under propofol, sevoflurane, and N₂O anesthesia. Structural images showed mesial temporal sclerosis, and chronic left germinal matrix hemorrhage. No meaningful activation (depicted in red) is seen in motor network (A) or language network (B) boundaries, shown as blue template masks.

metrics.^{14,20} These metrics, while essential in advancing knowledge about neuronal correlate of anesthesia, are less useful for individual patients. We bridged this gap with various measures. First, akin to task-based fMRI, we applied visual inspection of statistical maps, integrating knowledge about eloquent cortical regions associated with the evaluated functions. Second, we focused on motor and language networks, which are paramount

in presurgical planning. More importantly, we used individual-level analysis, crucial for personalized treatment plans, diverging from the common practice of group-level analysis.¹³

Our research enhances the understanding of RSN under anesthesia by examining imaging parameters alongside the widely studied anesthesia regimen. Prior studies focused on the effect of various anesthetics on resting-state connectivity, and most used

Table 2: ORs and CIs from multivariable logistic regression analysis of predictive factors in robust rs-fMRI overall networks with qualitative assessment

Variable	OR (Exp (B))	95% CI for Exp (B)	P Value
rs-fMRI with multiband	2.37	0.44–12.65	.31
Anesthesia with propofol	1.41	0.27–7.29	.68
Anesthesia with sevoflurane	0.20	0.05–0.79	.02 ^a
Anesthesia with N ₂ O	0.80	0.16–4.11	.79
Anesthesia with other agents	1.42	0.32–6.42	.65
Abnormality on structural MRI	1.02	0.34–3.09	.97
Sex = boy	0.97	0.32–2.91	.96
Age	0.93	0.81–1.06	.27
Scan length in minutes	1.06	0.73–1.53	.76

^a Indicates statistical significance at the .05 level.**Table 3: ORs and CIs from multivariable logistic regression analysis of predictive factors in robust rs-fMRI motor-language networks with quantitative assessment**

Variable	OR (Exp (B))	95% CI for Exp (B)	P Value
rs-fMRI with multiband	1.11	0.21–5.97	.90
Anesthesia with propofol	2.51	0.44–14.32	.30
Anesthesia with sevoflurane	0.18	0.04–0.80	.02 ^a
Anesthesia with N ₂ O	0.41	0.08–2.13	.29
Anesthesia with other agents	2.15	0.40–11.52	.37
Abnormality on structural MRI	1.57	0.47–5.26	.46
Sex = boy	1.96	0.55–6.92	.29
Age	0.93	0.81–1.07	.31
Scan length in minutes	1.15	0.79–1.67	.47

^a Indicates statistical significance at the .05 level.**Table 4: ORs and CIs from multivariable logistic regression analysis of predictive factors in robust rs-fMRI motor network with quantitative assessment**

Variable	OR (Exp (B))	95% CI for Exp (B)	P Value
rs-fMRI with multiband	3.29	0.41–26.63	.26
Anesthesia with propofol	5.39	0.84–34.75	.08
Anesthesia with sevoflurane	0.10	0.02–0.64	.02 ^a
Anesthesia with N ₂ O	1.04	0.16–6.54	.97
Anesthesia with other agents	1.72	0.26–11.14	.57
Abnormality on structural MRI	1.54	0.38–6.23	.55
Sex = boy	2.83	0.63–12.70	.17
Age	0.94	0.81–1.10	.47
Scan length in minutes	1.06	0.68–1.65	.81

^a Indicates statistical significance at the .05 level.**Table 5: ORs and CIs from multivariable logistic regression analysis of predictive factors in robust rs-fMRI language network with quantitative assessment**

Variable	OR (Exp (B))	95% CI for Exp (B)	P Value
rs-fMRI with multiband	0.97	0.13–7.49	.98
Anesthesia with propofol	0.41	0.05–3.40	.41
Anesthesia with sevoflurane	0.34	0.06–2.01	.23
Anesthesia with N ₂ O	0.22	0.03–1.35	.10
Anesthesia with other agents	1.68	0.26–11.03	.59
Abnormality on structural MRI	0.91	0.21–3.98	.89
Sex = boy	1.72	0.38–7.69	.48
Age	1.00	0.85–1.19	.97
Scan length in minute	1.41	0.91–2.20	.13

single imaging technique uniformly for all subjects in the studies. Most of the prior literature has used no accelerated rs-fMRI. However, a large sample study of healthy volunteers was reported to use accelerated rs-fMRI.²⁸ Contrary to our hypothesis, decreased SNR in each BOLD volume of an accelerated scan did not compromise rs-fMRI, consistent with awake rs-fMRI

literature.^{11,29} We observed no quality compromise with short scans, analyzing scans as short as 5 minutes without acceleration and 6 minutes with acceleration. The previous studies in awake subjects have shown that increasing scan length improves reliability of rs-fMRI.^{30,31} A recent study with anesthetized subjects further revealed that optimal scan length under anesthesia is shorter compared with awake scan because the rs-fMRI metrics show less variability under anesthesia compared with awake scan.¹⁷ It is important to note that these studies assessed the connectivity metrics and signal driven measures rather than visibility of RSN that we have evaluated in current study. Therefore, it is possible that the clinical question of visualizing RSN can be answered with shorter scans than in prior research if the scan is performed under anesthesia. These findings have potential implications for reducing scan length under anesthesia.

Sevoflurane is associated with decreased RSN robustness likely due to its established role in decreasing connectivity of frontoparietal and thalamocortical networks.^{14,15} Suppression of motor network has also been reported. Peltier et al³² evaluated motor network activation by using rs-fMRI in 6 volunteers and observed that, compared with awake state, functional connectivity maps were smaller under sevoflurane anesthesia. In a retrospective study of passive task-based fMRI in 100 patients, no significant effect of anesthetic choice was seen in language activation, consistent with our finding.³ The differential effect of sevoflurane on motor networks, as opposed to language networks, may arise from susceptibility of the frontal lobe, which houses the motor network, to anesthesia as opposed to resilience of the temporal lobe, which houses most of the language network. This phenomenon is well documented in the literature, including a recent work in pediatric

patients with epilepsy who underwent sedated fMRI with passive tasks, where frontal language activation under sedation was weak, whereas temporal activation was more robust.^{33,34} We believe the gravity of motor network compromise in our data resulted in compromised combined motor-language networks as the language network was not compromised. Successful use

of halogenated anesthetics has been reported in clinical settings. In a feasibility study and by using group level analysis, Warren et al¹³ identified default-mode, sensorimotor, and frontoparietal networks in 11 patients with epilepsy who underwent rs-fMRI with low-dose isoflurane combined with remifentanyl anesthesia. In another study of 13 adults who received sevoflurane for rs-fMRI, most RSNs were reported detectable.²³

It is unclear however why a similar effect was not seen with propofol, which also decreases the connectivity of frontoparietal and thalamocortical networks in a large body of literature.^{15,35,36} One potential explanation is the additional motion induced by administration of inhalation agents, such as sevoflurane and N₂O, compared with intravenous medications such as propofol. We used motion regression in a preprocessing step and the residual motion parameters were negligible in our entire study population and did not differ between the group who received inhalation agents and the group who did not. Furthermore, the fact that the effect is only seen with sevoflurane and not N₂O decreases the possibility of motion influencing the result.

Sevoflurane dosage is a critical factor affecting RSN connectivity, with higher doses leading to greater reduction in connectivity. For instance, doubling the sevoflurane dose from 1%–2% resulted in a 20% additional reduction in functional connectivity map sizes.³² While we lack precise records of sevoflurane concentration during rs-fMRI acquisition, we posit that our subjects did not receive high doses. This is based on literature indicating lower order sensory networks, like the auditory network, are maintained only up to moderate sevoflurane levels, consistent with our findings of preserved temporal activation.^{34,37} Additionally, varied anesthesiologists' preferences and absence of an institutional dosage consensus suggest low likelihood of systematic administration of high doses. Our methodology accounts for potential synergistic effects by creating individual variables for commonly used anesthetics (sevoflurane, propofol, and N₂O) with the caveat that only additive effects were evaluated.

Our findings should be interpreted within the study's design and limitations, including its retrospective nature and specific patient population. The sample size was limited to 69 available subjects, but post hoc power analyses demonstrated sufficient power. The largest study with comparable design consisted of 13 subjects.¹³ Studies with comparable size only evaluated the resting-state functional connectivity metrics under a single uniform anesthesia regimen and image protocol.²⁸ Other previous large studies evaluated passive task-based fMRI rather than rs-fMRI.^{3,38} Our study is limited by its retrospective nature, where the blood levels or mean alveolar concentration of anesthetics were not recorded and only multiband factor 5 was used. The latter may be a minor limitation in the clinic where common acceleration factors range between 2–5. Given the diverse pathology in our population, it was not feasible to group the structural abnormalities into distinct variables. The type and extent of structural abnormalities, along with treatments and medications, especially antiepileptic drugs, could influence the quality of rs-fMRI and were not controlled for in our analysis. Future studies should stratify participants by abnormality type and severity and conduct controlled studies to isolate treatment and medication effects. Potential image quality improvements from

removing sevoflurane should also be explored. Future studies should include sensitivity analysis to identify a generalizable and optimal Dice coefficient cutoff for grouping the rs-fMRI data.

CONCLUSIONS

We did not observe any effect of acceleration or duration of fMRI on the quality of RSNs. With the goal of reducing scan time under anesthesia, future studies should further evaluate sufficiency of our fastest scan parameters (6 minutes with acceleration or 5 minutes without acceleration) in demonstrating clinically relevant RSNs. We observed association of sevoflurane with weaker RSNs. This association was particularly observed in the motor network but not in the language network and underscores the need for meticulous selection of anesthetic agents in fMRI protocols. Specifically, until future prospective studies can confirm our findings, it might be prudent to avoid sevoflurane if motor network mapping is required. Future studies should evaluate the effect of various dosages of sevoflurane.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Advanced Distance-Resolved Evaluation of the Perienhancing Tumor Areas with FLAIR Hyperintensity Indicates Different ADC Profiles by *MGMT* Promoter Methylation Status in Glioblastoma

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ABSTRACT

BACKGROUND AND PURPOSE: Whether differences in the O⁶-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status of glioblastoma (GBM) are reflected in MRI markers remains largely unknown. In this work, we analyze the ADC in the perienhancing infiltration zone of GBM according to the corresponding *MGMT* status by using a novel distance-resolved 3D evaluation.

MATERIALS AND METHODS: One hundred one patients with *IDH* wild-type GBM were retrospectively analyzed. GBM was segmented in 3D with deep learning. Tissue with FLAIR hyperintensity around the contrast-enhanced tumor was divided into concentric distance-resolved subvolumes. Mean ADC was calculated for the 3D tumor core and for the distance-resolved volumes around the core. Differences in group mean ADC between patients with *MGMT* promoter methylated (m*MGMT*, *n* = 43) and *MGMT* promoter unmethylated (u*MGMT*, *n* = 58) GBM was analyzed with Wilcoxon signed rank test.

RESULTS: For both m*MGMT* and u*MGMT* GBM, mean ADC values around the tumor core significantly increased as a function of distance from the core toward the periphery of the perienhancing FLAIR hyperintensity (approximately 10% increase within 5 voxels with *P* < 0.01). While group mean ADC in the tumor core was not significantly different, the distance-resolved ADC profile around the core was approximately 10% higher in m*MGMT* than in u*MGMT* GBM (*P* < 10^{−8} at 5 voxel distance from the tumor core).

CONCLUSIONS: Distance-resolved volumetric ADC analysis around the tumor core reveals tissue signatures of GBM imperceptible to the human eye on conventional MRI. The different ADC profiles around the core suggest epigenetically influenced differences in perienhancing tissue characteristics between m*MGMT* and u*MGMT* GBM.

ABBREVIATIONS: AUC = area under the curve; GBM = glioblastoma; *IDH* = isocitrate dehydrogenase; *MGMT* = O⁶-methylguanine-DNA methyltransferase; m*MGMT* = *MGMT* methylated glioblastoma; PE = perienhancing FLAIR hyperintensity; PIZ = perienhancing infiltration zone; ROC = receiver operating characteristic; SD = standard deviation; T1c = postcontrast T1-weighted image; TC = T1 contrast-enhanced tumor; TC_{total} = tumor core including contrast-enhanced tumor and corresponding necrotic part; u*MGMT* = *MGMT* unmethylated glioblastoma

Glioblastoma (GBM) is the most common brain tumor in adults, with a median overall survival of only 15 months despite multimodal therapy.¹ The molecular characteristics of the tumor and the surgical component of the therapy are critical for the patient's response to radiation therapy and chemotherapy. Silencing of the O⁶-methylguanine-DNA methyltransferase (*MGMT*) gene by promoter methylation increases the efficacy of temozolomide and has become an important biomarker to

predict tumor resistance or sensitivity to chemotherapy.^{2–6} *MGMT* promoter methylation status of GBM correlates with longer progression-free survival and overall survival.^{2–6} In addition, pseudoprogression after radiation and chemotherapy is more common in tumors with *MGMT* promoter methylation, which should be considered when interpreting treatment response on follow-up MRI.⁷

Currently, the determination of the *MGMT* promoter methylation status requires tissue sampling, which is obtained through surgical tumor resection or biopsy. In general, the resection, which is commonly the first step of the treatment, is conducted without any molecular information about the tumor, including no information about the *MGMT* promoter methylation status. In addition, *MGMT* promoter methylation status in recurrent GBM may change during treatment.^{8,9} Therefore, efforts have been made to predict *MGMT* methylation status from MRI to complement histopathologic analysis. However, whether differences in

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SUMMARY

PREVIOUS LITERATURE: *MGMT* promoter methylation status of GBM correlates with longer progression-free survival and overall survival. Therefore, efforts have been made to predict *MGMT* methylation status from MRI to complement histopathologic analysis. However, whether differences in *MGMT* promoter methylation are reflected in MRI markers remains largely unknown. To date, preoperative characterization of the perienhancing infiltration zone in GBM remains challenging, and little is known about its imaging characteristics. In addition, it was significantly less studied than the visible tumor core due to the lack of image analysis methods for volumetric 3D evaluation.

KEY FINDINGS: ADC values around the contrast-enhanced tumor significantly increase as a function of distance from the tumor core toward the periphery of the perienhancing FLAIR hyperintensity. The distance-resolved ADC profile around the tumor core was significantly different between *MGMT* methylated and unmethylated GBM.

KNOWLEDGE ADVANCEMENT: We provide new insights into the evaluation of perienhancing zone in GBM by introducing a novel volumetric and distance-resolved approach. We show that *MGMT* methylation status in the perienhancing zone is associated with different distance-resolved ADC signatures and that *MGMT* status estimation seems to be feasible with MRI.

MGMT promoter methylation are reflected in MRI markers remains largely unknown.

In general, GBM shows infiltrative growth and tumor cell migration from the inside out.¹⁰⁻¹⁴ It is characterized by the presence of a biologically highly complex diffuse perienhancing infiltration zone (PIZ) around the T1 contrast-enhanced tumor (TC) and the absence of clear tumor boundaries. The PIZ represents the main site of progression and its cellular composition is thought to influence aggressiveness, invasion, and recurrences significantly.¹⁵⁻¹⁷ More than 80% of GBM cases are characterized by local progression, in which tumor recurrence appears within 2–3 cm of the resection margin.^{18,19} Although not enhancing on postcontrast T1-weighted images (T1c), the tissue in the immediate vicinity around the edge of the TC with hyperintensity on FLAIR images is a mixture of PIZ and pure edema as the infiltrating cells' spread exceeds the TC and infiltrates into the surrounding tissue.^{15,20} It has been shown that tumor cell attenuation and alteration of the extracellular matrix due to tumor infiltration is higher in the proximity of TC than at a greater distance from it.^{15,20} These aspects suggest that the distance to the TC may be an important determinant of tissue composition and tumor cell attenuation of the PIZ. Therefore, there is an increasing need to characterize volumetric MRI markers around the TC as a function of distance from it.

Quantitative MRI, such as the ADC, is more sensitive to changes in tissue composition on the cellular level than conventional MRI.²¹ Constriction of the extracellular space by swelling or increased cellularity affects the ADC values, which are influenced by tumor cell attenuation, necrosis, and vasogenic edema.²¹⁻²⁶ In GBM, TC has regional low ADC values due to its relative high cellularity that decreases the available extracellular space for water movement, while the relative high ADC in perienhancing FLAIR hyperintensity reflects the increased fluidity in the tissue caused by vasogenic edema.^{22,27,28} ADC values before treatment were associated with the overall survival of patients with GBM,^{24,29-34} while the usefulness of ADC for predicting *MGMT* promoter methylation status has shown conflicting results.³⁵⁻⁴¹ Several studies found a correlation between ADC values and *MGMT* promoter methylation status,^{35,38-41} while others did not measure any correlation.^{36,37}

Only a small number of studies analyzed ADC or other quantitative MRI markers in the PIZ of GBM,^{39,42,43} as most published studies concentrated on the TC. The contradictory results from the literature suggest that the possible ADC differences between *MGMT* promoter methylated (m*MGMT*) and *MGMT* promoter unmethylated (u*MGMT*) GBM, if they exist at all, are extremely small. According to our interpretation, the visible tumor core (contrast-enhanced tumor and corresponding necrotic part) is less important in this context than the perienhancing zone. The tumor core is commonly removed by surgery and is an unsalvageable area with abnormally disturbed ADC due to the combination of an extremely high tumor cell attenuation and corresponding necrosis. Therefore, we hypothesized that the perienhancing zone, which is a biologically active area in terms of tumor growth^{14,15} and is not completely dominated by the tumor, is a better candidate. In addition, we hypothesized that dividing the perienhancing zone into relatively small subvolumes by using a relatively large distance resolution would increase the sensitivity of the analysis.

The overall aim of this paper is 2-fold: 1) introduce a methodology for 3D distance-resolved analysis of the PIZ in GBM and 2) investigate the ADC characteristics of the PIZ. To this end, we divided the perienhancing FLAIR hyperintensity into concentric distance-resolved subvolumes around the TC (in an onion-skin manner) and investigated the distance-resolved ADC profile of the FLAIR hyperintensity in 2 GBM groups with different *MGMT* characteristics (methylated versus unmethylated GBM).

MATERIALS AND METHODS

Patients

A retrospective analysis of 201 patients treated within our institution between 2018 and 2022 was performed. Main inclusion criteria were: 1) known *MGMT* methylation status determined according to Bady et al;⁴⁴ 2) availability of T1, T1 postcontrast (T1c), T2, and FLAIR preoperative MRI and corresponding DWI with ADC measured with the same 3T scanner; 3) visually apparent T1-contrast-enhanced tumor (TC) on T1c; and 4) larger than 1000 mm³ volume for TC and perienhancing FLAIR hyperintensity as measured with our image analysis pipeline

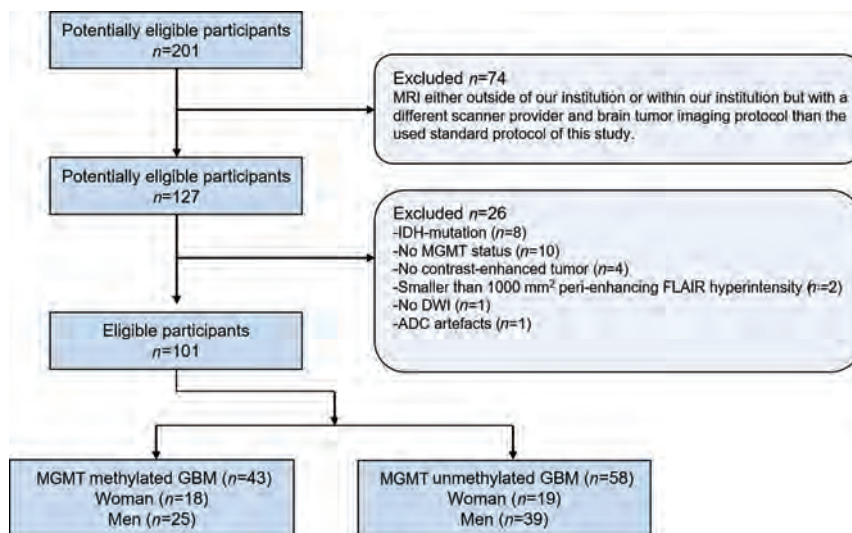


FIG 1. Patient-selection protocol and criteria for inclusion and exclusion.

(see Imaging). WHO grade 4 *IDH*-mutant astrocytomas were also excluded, as they respond significantly better to therapy than *IDH* wild-type GBMs. Seventy-four patients had preoperative MRI either outside of our institution or were measured within our institution with a different scanner provider (GE Healthcare and Phillips) and brain tumor imaging protocol than the Siemens protocol used for this study and were also excluded. Figure 1 shows the patient-selection protocol and criteria for inclusion and exclusion. All tumors were newly diagnosed, imaging was performed before resection, and none of these patients received any treatment before imaging (no radiation therapy, no chemotherapy, no treatment-related drugs). Histopathologic reports were available for all patients, and the diagnosis of GBM without *IDH* mutation was confirmed after surgery. *IDH1/2* mutation status was analyzed by the next-generation sequencing-based Oncomine Comprehensive Assay v3, DNA-part (Oncomine Comprehensive Assay v3M, thermofisher.com). The study protocol (ethical application number 2022-00041) conforms to the ethical guidelines of the Declaration of Helsinki. The study was conducted according to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines.⁴⁵

Imaging

Representative T1, T1c, FLAIR, T2, and ADC images of our clinical protocol obtained in patients with mMGMT and uMGMT are shown in the Online Supplemental Data. MRI was performed on a 3T (Skyra; Siemens) scanner by using a 32-channel head coil (Siemens). The clinical protocol consisted of precontrast native 3D T1, transversal 2D T2, transversal 2D ADC, 3D FLAIR, and 3D T1c after contrast agent administration. ADC was measured with a 2D spin-echo echo-planar imaging sequence by using segmented *k*-space readout (RESOLVE, Siemens): FOV of 220 × 220 mm, number of slices 34, image size 190 × 190 voxels, voxel size of 1.2 × 1.2 mm with 3 mm slice thickness, 2 b-values (0 with TE = 71 ms and 1000 with TE = 117 ms), TR = 7220 ms, GRAPPA acceleration factor of 2 with 5 readout segments. Total measurement time

was 4:29 minutes. Quantitative ADC maps based on the measured b-values were generated automatically by the scanner.

Image Processing and Statistical Analysis

Postprocessing and statistical analysis were done with Python 3.16 (Python Software Foundation) and Matlab 2022 (MathWorks). All images were resampled to a uniform 256 × 256 × 220 matrix size with 1 mm isotropic resolution and coregistered to each other by using dipy (dipy.org).⁴⁶

Online Supplemental Data show representative segmentation of GBM in 1 patient. GBM was segmented into TC, necrotic tumor (NT), tumor core (TC_{total} = TC + NT), and perienhancing

FLAIR hyperintensity (PE, including the entire volume around the TC_{total} with FLAIR hyperintensity) by a semiautomatic approach. A standard U-Net model⁴⁷ was trained on the BraTS 2022 data set⁴⁸ containing MRI of 1140 presegmented patients with high-grade gliomas. Images were resampled to the same matrix size with 1-mm isotropic resolution as our clinical images. The model was trained in a slice-wise fashion in 2D by using 4 contrasts for each slice position: T1, T2, FLAIR, and T1c. GBM was automatically segmented by this model and, if necessary, manually corrected in 3D Slicer.⁴⁹ Automatic tumor segmentation was evaluated and corrected by consensus between N. H. and G.B. Each 2D transversal slice of the GBM volume was segmented to obtain a complete 3D segmentation of the entire GBM volume.

For perienhancing tissue analysis, the subvolume of PE up to a distance of 5 voxels around the TC_{total}, which was the nonenhancing component of the perienhancing FLAIR hyperintensity with radiologic changes due to edema and possible tumor infiltration, was considered in this study. Figure 2 illustrates the generated subvolumes of PE around the TC_{total}, which can be interpreted as the hypothetical edges of the PIZ in PE. The PE volume up to a distance of 5 voxels was divided into 5 1-voxel wide subvolumes (from PIZ₁ to PIZ₅ with 1 voxel increment) by using the VTK toolkit in Python (pypi.org/project/vtk/).⁵⁰ The total PIZ volume (PIZ_{total}) was the union of the distance-resolved subvolumes (PIZ_{total} = PIZ₁ ∪ PIZ₂ ∪ PIZ₃ ∪ PIZ₄ ∪ PIZ₅).

Mean ADC for the generated segments were computed for each patient separately by using: 1) each voxel in the segment; 2) voxels with 20th percentile of lowest ADC values (ADC_{low}) representing tissue with high cellularity; and 3) voxels with 20th percentile of highest ADC values (ADC_{high}) representing tissue with increased fluidity. Group mean ADC (based on 43 mMGMT and 58 uMGMT patient-resolved mean values) for TC_{total}, TC, PIZ_{total}, and distance-resolved PIZ volumes were compared between mMGMT and uMGMT tumors. Correlation between distance and mean ADC around the TC was analyzed by Spearman rank correlation coefficient. Significance analysis was done by the 2-sided

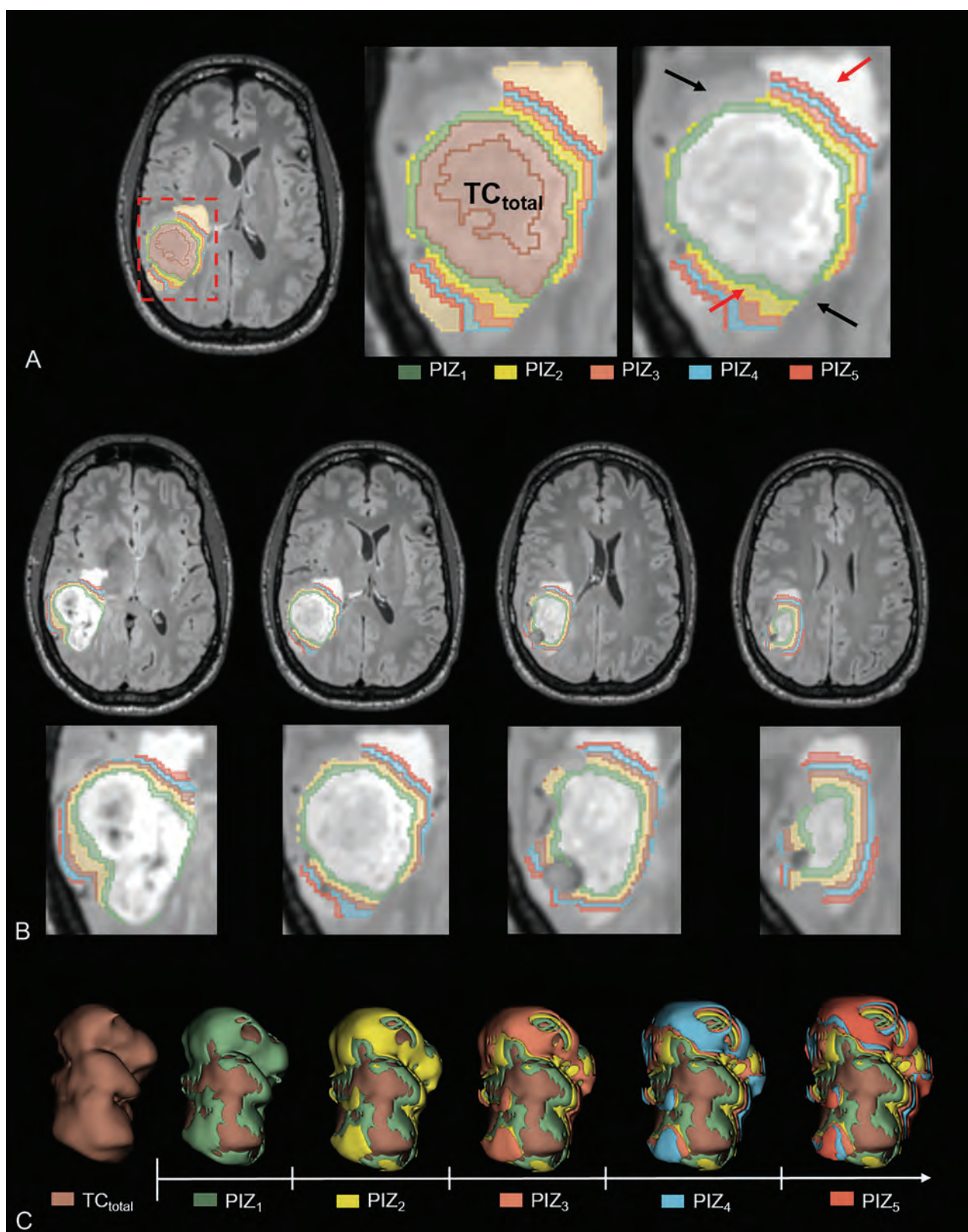


FIG 2. Generated subvolumes of perienhancing infiltration zone (PIZ) in perienhancing FLAIR hyperintensity around the tumor core in 2D (A and B) and in 3D (C). Black arrows (A) show perienhancing tissue without radiologic signs of tumor infiltration. Red arrows (A) show the PE in which the PIZ subvolumes were generated. Dark areas on FLAIR containing fluid with relatively high ADC values, such as the ventricles or brain folds, were not included in the PE and, therefore, excluded from the PIZ analysis. B, The same tumor as in (A) for different slice positions, is visualized in 3D in (C). The distance between the margin of the tumor core and PIZ₁, PIZ₂, PIZ₃, PIZ₄, and PIZ₅ is 1, 2, 3, 4, and 5 voxels with 1-mm isotropic resolution, respectively.

Wilcoxon-Mann-Whitney-test. For P values less than .05, differences were considered as significant.

The receiver operating characteristic (ROC) curves and corresponding area under the curve (AUC) were determined 1) by using a single ADC threshold based on PIZ_{total} and 2) by using an ADC threshold for each distance-resolved PIZ subvolume separately and majority voting. The threshold values were determined as group mean ADC value of mMGMT in the 3D segment minus 50% of the standard deviation (SD): threshold = mean(ADC_{mMGMT}) - (SD $\times$ 0.5). Tumors with mean ADC below the threshold were classified as uMGMT. Using the 5 PIZ subvolumes, MGMT status was determined by using majority voting. For example, if in PIZ_1 , PIZ_2 , and PIZ_3 ADC was below the corresponding threshold (3 votes for uMGMT) and in PIZ_4 and PIZ_5 above the corresponding threshold (2 votes for mMGMT), the tumor was classified as uMGMT.

RESULTS

Figure 3 shows representative mMGMT and uMGMT cases and corresponding distance-resolved ADC. There were no significant differences in group mean ADC values in the TC and TC_{total} between mMGMT and uMGMT tumors. In contrast, group mean ADC in PIZ_{total} (including all 5 subvolumes) was approximately 9% higher in mMGMT than in uMGMT GBMs (1431 ± 205 versus $1313 \pm 179 \times 10^{-6} \text{ mm}^2/\text{s}$, with $P = .04$, Fig 4B, Table).

For both mMGMT and uMGMT GBMs, group mean ADC increased as a function of distance from TC_{total} toward the periphery of the perienhancing FLAIR hyperintensity (Fig 4C, Table). Between PIZ_1 and PIZ_5 , we measured a 12.4% (1298 ± 153 versus $1459 \pm 131 \times 10^{-6} \text{ mm}^2/\text{s}$, $P < 10^{-5}$) and 9.5% (1189 ± 124 versus $1302 \pm 145 \times 10^{-6} \text{ mm}^2/\text{s}$, $P < 10^{-5}$) increase for mMGMT and uMGMT, respectively.

In the closest neighboring PIZ subvolume around the TC_{total} (PIZ_1), we measured 9.1% (1298 ± 153 versus $1189 \pm 124 \times 10^{-6} \text{ mm}^2/\text{s}$, $P < 10^{-4}$) higher ADC in mMGMT than in uMGMT (Fig 4C, Table). This difference between mMGMT and uMGMT and the degree of its statistical significance was at 5 voxel distance from the periphery of TC_{total} even higher. We measured 12.1% (1459 ± 131 versus $1302 \pm 145 \times 10^{-6} \text{ mm}^2/\text{s}$, $P < 10^{-8}$) higher ADC in PIZ_5 of mMGMT than uMGMT (Fig 4C, Table).

Similarly to ADC, for both mMGMT and uMGMT GBMs, group mean ADC_{low} increased as a function of distance from TC_{total} toward the periphery of the FLAIR hyperintensity (Table, Online Supplemental Data). Between PIZ_1 and PIZ_5 , we measured a 14.1% (888 ± 118 versus $1013 \pm 87 \times 10^{-6} \text{ mm}^2/\text{s}$, $P < 10^{-5}$) and 7.6% (837 ± 99 versus $901 \pm 92 \times 10^{-6} \text{ mm}^2/\text{s}$, $P < 10^{-5}$) ADC_{low} increase for mMGMT and uMGMT, respectively. Similarly to ADC, this distance-resolved ADC_{low} increase around the TC_{total} was significantly different for the 2 subgroups. From PIZ_2 , we measured significantly higher ADC_{low} values in mMGMT than in uMGMT tumors, as illustrated in the Online Supplemental Data. The evaluation of ADC_{high}, which shows a similar trend to ADC and ADC_{low}, can be found in the Online Supplemental Data.

Figure 5 shows the ROC analysis. The classification based on a single threshold value of ADC = $1328.5 \times 10^{-6} \text{ mm}^2/\text{s}$ determined for PIZ_{total} (Table) yielded an AUC of 0.59 with a

sensitivity of 62% and a specificity of 55%. In contrast, by using the distance-resolved group mean ADC values and majority voting of the 5 PIZ subvolumes, we calculated an AUC of 0.75 with a sensitivity of 70% and a specificity of 80% (ADC threshold value was 1221.5, 1295, 1351.5, 1384.5, and $1393.5 \times 10^{-6} \text{ mm}^2/\text{s}$ for PIZ_1 , PIZ_2 , PIZ_3 , PIZ_4 and PIZ_5 , respectively, Table).

The mean group volume of the 3D segments did not differ significantly between mMGMT and uMGMT tumors (Fig 4A). Patient age or sex did not correlate with the measured volume sizes or ADC values (results not shown). Measured values are tabulated in Table and shown with boxplots in Fig 4 and the Online Supplemental Data.

DISCUSSION

We report a 3D volumetric and distance-resolved evaluation of preoperative ADC in the PIZ of GBM. This novel method reveals marked differences in the subvolumes of PE around the TC. We measured a significant increase of group mean ADC as a function of distance from TC toward the periphery of the FLAIR hyperintensity, a probable indication of tissue alteration due to tumor infiltration. Interestingly, while group mean ADC of TC_{total} showed no differences between mMGMT and uMGMT, the distance-resolved 3D analysis revealed a significant difference in the ADC profile around the TC_{total}, a probable indication of differences in tissue composition in this area.

In contrast to the tumor core (TC_{total}), which contains mainly solid tumor tissue and necrosis, which are mostly removed by surgery, the PE is a mixture of brain parenchyma and infiltrating tumor cells and represents the main site of tumor progression.^{15-17,20} Therefore, the PE is an area of interest for GBM treatment as the differentiation between pure edema and the PIZ is crucial to define resection margins and target volumes for radiation therapy. However, to date, preoperative characterization of the PIZ in GBM remains challenging. In this study, a 5-voxel wide adjacent volume of PE around the TC was the focus (Figs 2 and 3), as this tissue is directly affected by infiltrative growth, with radiologic changes due to invasion and edema, and is the main target for both radiation therapy and possible recurrence.

We found a significant ADC increase from the neighboring to the peripheral PIZ regions in both groups (Fig 4C and Online Supplemental Data) that was imperceptible to the human eye in the images. Auer et al⁴² and Blystad et al⁴³ analyzed the PE in 2D with quantitative T1 and T2 relaxometry. They found a gradient of relaxation values from TC_{total} toward the PE periphery that was also not visually apparent on the images. PE is mainly caused by tumor infiltration that involves vascularization, micronecrosis, angiogenesis, cell proliferation, and apoptosis, effects that are higher in the proximity of TC_{total} than at greater distance from it.^{15,20} The increase of ADC from PIZ_1 toward PIZ_5 might be accountable for changes in extracellular matrix composition due to invasive growth as GBM always shows an infiltrative growth and tumor cell migration from the inside out.^{15,20}

Several studies have quantitatively investigated the correlation between ADC and MGMT status and overall survival rate, with varying results. Romano et al⁴⁰ used the lowest 15th percentile of ADC values within the TC and reported significantly higher

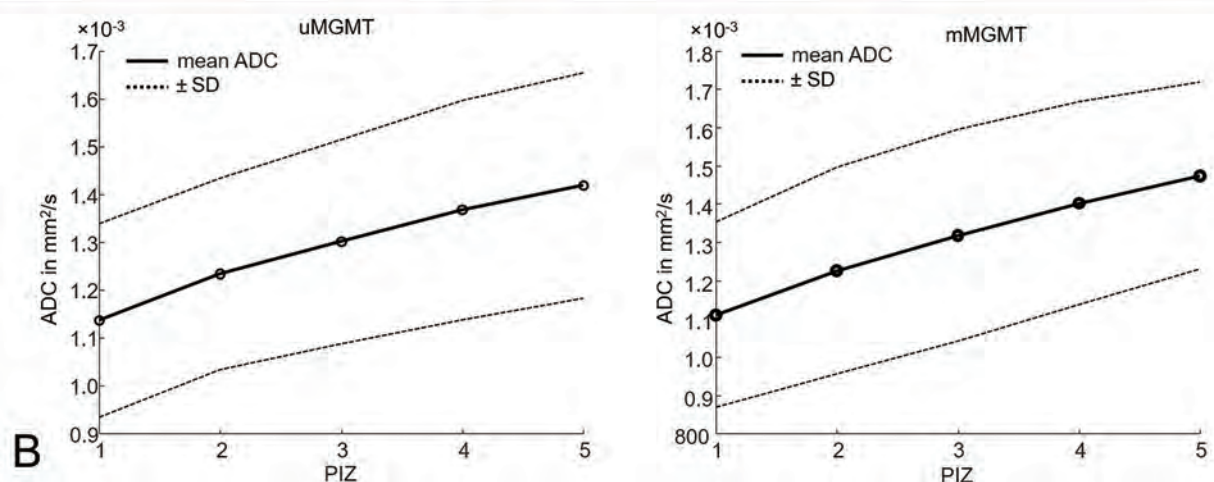
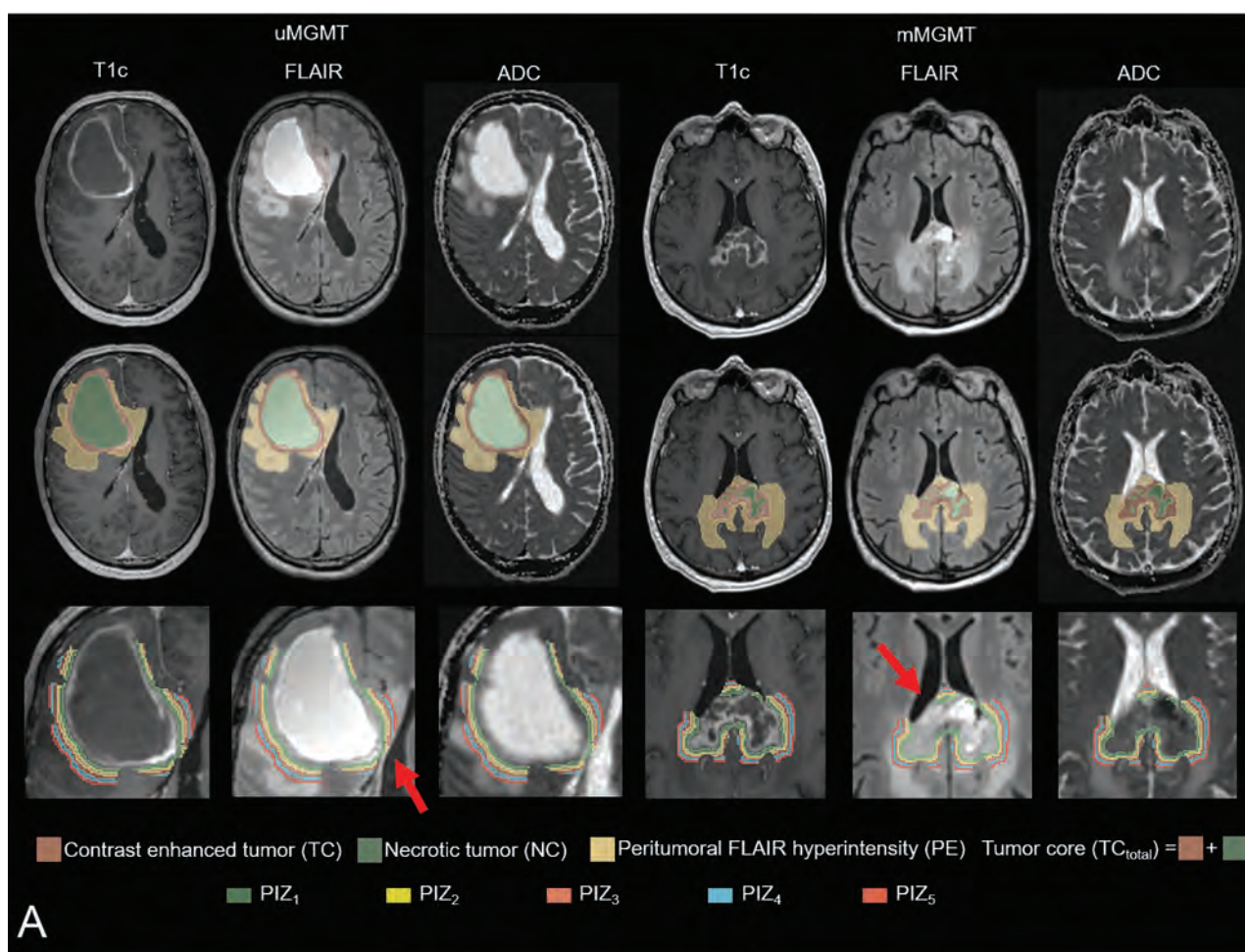


FIG 3. Representative mMGMT and uMGMT cases. **A**, Tumor segmentation and the corresponding distance-resolved subvolumes of the perienhancing FLAIR hyperintensity. Dark areas on FLAIR containing fluid with relatively high ADC values, such as the ventricles or brain folds, were not included in the PE and, therefore, excluded from the PIZ analysis, as indicated by the red arrows. **B**, The corresponding distance-resolved ADC evaluation around the tumor core (mean $\pm$ SD).

minimum ADC values in mMGMT than in uMGMT tumors. Similarly, Moon et al²³ reported that ADC was significantly higher in the TC of mMGMT. In contrast, Pope et al³⁰ reported lower ADC in TC of mMGMT than in uMGMT. Ladenhauf et al³⁹ found significantly lower group mean ADC in the PIZ of mMGMT than in uMGMT, while these colleagues did not

measure any difference in TC_{total} . We hypothesize that the reason for the conflicting results is at least partly due to the single slice evaluation used in 2D that can significantly influence the analysis as GBM is characterized by heterogeneous tumor tissue.

Using volumetric 3D evaluation, we did not measure any significant difference between mMGMT and uMGMT tumors for

the TC_{total} or TC volume regardless of whether we used ADC, ADC_{low}, or ADC_{high} (Fig 4B, Online Supplemental Data). This finding is in agreement with Ladenhauf et al³⁹ and indicates that ADC tissue structure of the tumor core is not significantly different between the 2 GBM subgroups, resulting in similar mean ADC values. In contrast, ADC in PIZ of mMGMT was significantly higher than in the uMGMT subgroup (Fig 4B, Online Supplemental Data), indicating that the underlying tissue structure may differ between these 2 groups. This assumption is further supported by our distance-resolved analysis, which further highlights the difference between the PIZ of mMGMT and uMGMT. The approximately 12% difference in distance-resolved ADC increase in the PIZ between mMGMT and uMGMT tumors (Fig 4C, Online Supplemental Data) strongly suggests the presence of differences in tissue characteristics. We speculate that the measured ADC difference is due to differences in tumor cell attenuation and/or extracellular matrix degradation through tumor infiltration. In the only other publication focusing on the PIZ and ADC differentiation of MGMT, Ladenhauf et al found significantly lower ADC in mMGMT GBM³⁹ by using 2D analysis. Furthermore, based purely on visual analysis, Ellingson et al⁵¹ found more pronounced PE in uMGMT compared with mMGMT. Our findings, at least in the PIZ, suggest the opposite, ie, less edema-component and higher cellularity in uMGMT compared with mMGMT.

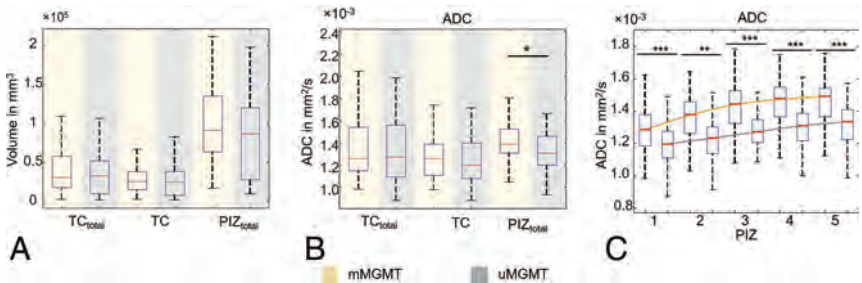


FIG 4. Volumetric analysis of mMGMT and uMGMT GBM. A, Volume of the total tumor core (TC_{total}), T1-contrast-enhanced tumor (TC), and perienhancing infiltration zone containing all 5 distance-resolved PIZ segments (PIZ_{total}) was not significantly different between mMGMT and uMGMT. B, Group mean ADC in TC_{total} and TC show no statistically significant differences between mMGMT and uMGMT while group mean ADC in the PIZ_{total} was significantly higher in mMGMT than in uMGMT. C, Distance-resolved volumetric ADC analysis around the tumor core. For both mMGMT and uMGMT, ADC increased significantly as a function of distance from the neighboring zone of TC_{total} (PIZ₁) toward the zone at 5 voxel distance from it (PIZ₅). Spearman ρ for correlation analysis between ADC and distance from the tumor core is everywhere under 10^{-10} . $P < .05$, $P < .005$, and $P < .00001$ of Wilcoxon rank sum test is indicated by *, **, and ***, respectively. Error bars show the standard deviation.

MGMT status classification based on distance-resolved ADC thresholds and majority voting from the PIZ subvolumes yielded an accuracy of 75%, which we found acceptable considering that classification was based on thresholds determined by using a simple statistical approach. We hypothesize that a sophisticated deep-learning approach could reach a higher accuracy. Nevertheless, the ROC analysis further highlights the difference between the PIZ of mMGMT and uMGMT and indicates that the prediction of the MGMT status by using MRI is feasible. In addition, for our cohort group, the distance-resolved subdivision of the PIZ into smaller subvolumes (from PIZ₁ to PIZ₅ with 1 voxel increment) and corresponding distance-resolved statistical analysis and ROC evaluation depicted ADC characteristics that were hidden in a larger volume such as the PIZ_{total}. This underlines the importance of distance-resolved evaluation of the PIZ, which may further increase the sensitivity of the analysis.

Although we obtained encouraging results, our study has some limitations, including its retrospective nature and single-center cohort group. Furthermore, we could not correlate ADC with neuropathologic and molecular data, eg, cell attenuation, pleomorphism, molecular signature in the PIZ, and explain our findings in the context of tissue characteristics, although this is a general problem of in vivo imaging research. To our knowledge, with current histologic methods, it is impossible to harvest and

analyze tissue samples of the PIZ with similar distance resolution as the one used here. Nevertheless, in the future, it would be of great interest to correlate distance-resolved quantitative MRI values in the PIZ with corresponding histologic analysis.

CONCLUSIONS

We presented here 3D volumetric evaluation of preoperative ADC in GBM that revealed volumetric tissue signatures imperceptible to the human eye on conventional MRI. We combined state-of-the-art 3D GBM segmentation with a novel distance-resolved analysis of the PIZ and analyzed volumetric mean ADC in 2 GBM subgroups: mMGMT versus uMGMT. Using our novel method, we demonstrated that mean ADC values around the tumor

Measured volumetric group mean ADC values ± standard deviation for mMGMT and uMGMT glioblastoma ^a		TC _{total}	TC	PIZ _{total}	PIZ ₁	PIZ ₂	PIZ ₃	PIZ ₄	PIZ ₅
mMGMT	Volume [cm ³]	42.8 ± 32	28.1 ± 16	98.6 ± 50					
	ADC × 10 ⁻⁶ mm ² /s	1397 ± 361	1272 ± 198	1431 ± 205	1298 ± 153	1369 ± 148	1422 ± 141	1451 ± 133	1459 ± 131
	ADC _{low} × 10 ⁻⁶ mm ² /s	892 ± 194	882 ± 156	916 ± 107	888 ± 118	935 ± 112	977 ± 103	1002 ± 90	1013 ± 87
	ADC _{high} × 10 ⁻⁶ mm ² /s	2005 ± 509	1765 ± 299	2020 ± 381	1711 ± 162	1763 ± 153	1804 ± 152	1828 ± 158	1840 ± 163
uMGMT	Volume [cm ³]	35.3 ± 28	25.1 ± 18.2	82.0 ± 53.1					
	ADC × 10 ⁻⁶ mm ² /s	1333 ± 302	1245 ± 214	1313 ± 179	1189 ± 124	1222 ± 131	1260 ± 133	1288 ± 136	1302 ± 145
	ADC _{low} × 10 ⁻⁶ mm ² /s	862 ± 175	862 ± 149	849 ± 109	837 ± 99	852 ± 100	874 ± 102	893 ± 97	901 ± 92
	ADC _{high} × 10 ⁻⁶ mm ² /s	1914 ± 524	1701 ± 343	1892 ± 387	1600 ± 179	1631 ± 176	1664 ± 178	1693 ± 192	1710 ± 214

^a PIZ₁₋₅ refer to the 5 distance-resolved subvolumes with 1 voxel increment.

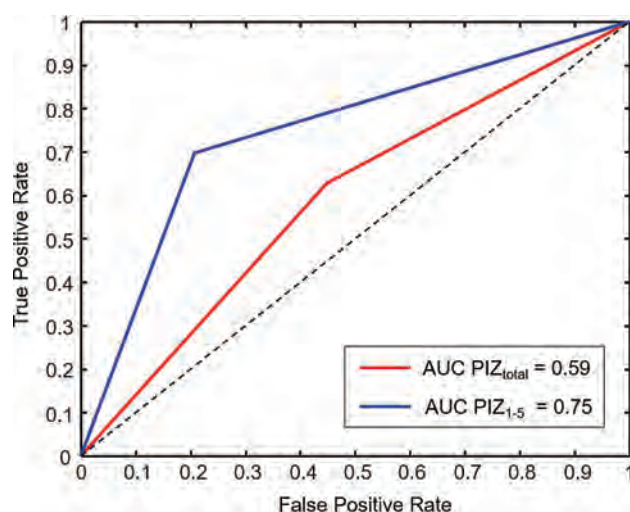


FIG 5. Receiver operating characteristic curves of predictors by using the determined group mean ADC values in the PIZ as the threshold for differentiation of mMGMT from uMGMT. The thresholds were determined as group mean ADC value of mMGMT in the 3D segment minus 50% of the SD: threshold = mean (ADC_{mMGMT}) – ($SD \times 0.5$). PIZ_{total} (including all 5 PIZ subvolumes) used 1 single threshold of $1.431 - (205 \times 0.5) = 1328.5 \times 10^{-6} \text{ mm}^2/\text{s}$ (Table). Tumors with mean ADC below $1328.5 \times 10^{-6} \text{ mm}^2/\text{s}$ for PIZ_{total} were classified as uMGMT. For MGMT prediction with distance-resolved ADC, the threshold was determined for each PIZ subvolume separately. Threshold was $1298 - (153 \times 0.5) = 1221.5$, $1369 - (148 \times 0.5) = 1295$, $1422 - (141 \times 0.5) = 1351.5$, $1451 - (133 \times 0.5) = 1384.5$, and $1459 - (131 \times 0.5) = 1393.5$ for PIZ_1 , PIZ_2 , PIZ_3 , PIZ_4 , and PIZ_5 , respectively (all in $\times 10^{-6} \text{ mm}^2/\text{s}$, Table). MGMT status was determined by using majority voting of the PIZ subvolumes. AUC was 0.59 (red curve) and 0.75 (blue curve) for PIZ_{total} and for the distance-resolved prediction (PIZ_{1-5}), respectively. Distance-resolved ADC thresholds resulted in higher classification accuracy than by using a single threshold for the entire PIZ.

core significantly increase as function of distance from TC toward the periphery of the perienhancing FLAIR hyperintensity. While group mean ADC of TC_{total} or TC showed no significant difference between mMGMT and uMGMT, distance-resolved 3D analysis of PIZ revealed a significant difference in ADC profile around the tumor core, indicating epigenetically influenced differences in perienhancing tissue characteristics between mMGMT and uMGMT GBM. The method presented here has the potential to provide a precise characterization of GBM tissue in the perienhancing region and could be applied to a number of other unresolved clinical challenges such as distinguishing between tumor infiltration and pure edema.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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“Synthetic” DSC Perfusion MRI with Adjustable Acquisition Parameters in Brain Tumors Using Dynamic Spin-and-Gradient-Echo Echoplanar Imaging

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ABSTRACT

BACKGROUND AND PURPOSE: Normalized relative cerebral blood volume (nrCBV) and percentage of signal recovery (PSR) computed from dynamic susceptibility contrast (DSC) perfusion imaging are useful biomarkers for differential diagnosis and treatment response assessment in brain tumors. However, their measurements are dependent on DSC acquisition factors, and CBV-optimized protocols technically differ from PSR-optimized protocols. This study aimed to generate “synthetic” DSC data with adjustable synthetic acquisition parameters using dual-echo gradient-echo (GE) DSC datasets extracted from dynamic spin-and-gradient-echo echoplanar imaging (dynamic SAGE-EPI). Synthetic DSC was aimed at: 1) simultaneously create nrCBV and PSR maps using optimal sequence parameters, 2) compare DSC datasets with heterogeneous external cohorts, and 3) assess the impact of acquisition factors on DSC metrics.

MATERIALS AND METHODS: Thirty-eight patients with contrast-enhancing brain tumors were prospectively imaged with dynamic SAGE-EPI during a non-preloaded single-dose contrast injection and included in this cross-sectional study. Multiple synthetic DSC curves with desired pulse sequence parameters were generated using the Bloch equations applied to the dual-echo GE data extracted from dynamic SAGE-EPI datasets, with or without optional preload simulation.

RESULTS: Dynamic SAGE-EPI allowed for simultaneous generation of CBV-optimized and PSR-optimized DSC datasets with a single contrast injection, while PSR computation from guideline-compliant CBV-optimized protocols resulted in rank variations within the cohort (Spearman's $\rho = 0.83$ – 0.89 , i.e. 31%–21% rank variation). Treatment-naïve glioblastoma exhibited lower parameter-matched PSR compared to the external cohorts of treatment-naïve primary CNS lymphomas (PCNSL) ($p < 0.0001$), supporting a role of synthetic DSC for multicenter comparisons. Acquisition factors highly impacted PSR, and nrCBV without leakage correction also showed parameter-dependence, although less pronounced. However, this dependence was remarkably mitigated by post-hoc leakage correction.

CONCLUSIONS: Dynamic SAGE-EPI allows for simultaneous generation of CBV-optimized and PSR-optimized DSC data with one acquisition and a single contrast injection, facilitating the use of a single perfusion protocol for all DSC applications. This approach may also be useful for comparisons of perfusion metrics across heterogeneous multicenter datasets, as it facilitates post-hoc harmonization.

ABBREVIATIONS: CBV = cerebral blood volume; DSC = dynamic susceptibility contrast; FA = flip angle; GBCA = gadolinium-based contrast agent; GBM = glioblastoma; GE = gradient echo; IDH = isocitrate dehydrogenase; IDH^m = IDH-mutant; IDH^{wt} = IDH-wild-type; 1p19q^{cod} = 1p19q codeleted; 1p19q^{int} = 1p19q intact; MRI = magnetic resonance imaging; nrCBV = normalized relative CBV; PCNSL = primary CNS lymphoma; PSR = percentage of signal recovery; Rec = recurrent; ROI = region of interest; SAGE-EPI = spin-and-gradient-echo echoplanar imaging; TE = echo time; TN = treatment-naïve; TR = repetition time

Dynamic susceptibility contrast (DSC) perfusion MRI of the brain¹ provides non-invasive information about vascularity, including measures of regional cerebral blood volume (CBV),

which has been shown to correlate with vascular density in brain tissue.^{1–3} In addition, from DSC time-intensity curves it is possible to compute the percentage of signal recovery (PSR), whose contrast appears to arise from the complex interplay of multiple tissue factors, including cellular architecture, vascular permeability,

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SUMMARY

PREVIOUS LITERATURE: Dynamic susceptibility contrast (DSC) perfusion MRI is routinely used to evaluate the normalized relative cerebral blood volume (nrCBV) and percentage of signal recovery (PSR) in brain tumors. nrCBV and PSR useful biomarkers for differential diagnosis and treatment response assessment in brain tumors. However, CBV-optimized DSC acquisition protocols have different acquisition parameters compared to PSR-optimized protocols, which makes it impractical to obtain simultaneous nrCBV and PSR measurements within the same MRI session. Additionally, heterogeneity in acquisition parameters across institutions is known to pose limitations in the universalizability of the quantification and interpretation of these DSC metrics.

KEY FINDINGS: Dual-echo DSC extracted from dynamic SAGE-EPI allows to generate synthetic DSC data with adjustable synthetic acquisition parameters (i.e., flip angle, echo time, repetition time, and preload simulation). Synthetic DSC experiments confirmed that nrCBV and PSR measurements are dependent on acquisition parameters. Comparisons with external cohorts showed that parameter-matched synthetic PSR in glioblastoma is significantly different from external cohorts of PCNSL.

KNOWLEDGE ADVANCEMENT: Synthetic DSC can simultaneously generate CBV-optimized and PSR-optimized DSC data with one acquisition and a single contrast injection, facilitating accurate nrCBV and PSR measurements within the same MRI session. Synthetic DSC has also the potential to achieve post-hoc harmonization of DSC parameters to improve the comparisons across heterogeneous multicenter datasets.

and vascular architecture.⁴⁻⁸ CBV⁹⁻¹² and PSR^{6,13} can inform the clinical management of brain tumors. Both have been shown to predict the molecular profile of gliomas, differentiate progressive disease from pseudoprogression during active treatment monitoring,¹⁴⁻¹⁹ and aid in differentiating between several tumor types including glioma, primary CNS lymphoma (PCNSL), and metastasis.^{2,8,20-26} Although CBV is more widely employed and is overall considered a more robust metric for most of these applications, PSR may be superior to CBV when distinguishing PCNSL from other tumor types.^{20,21}

Although both CBV and PSR provide potentially important information about tumor biology, obtaining optimal CBV and PSR measurements with a single-echo DSC acquisition is not possible, since CBV-optimized protocols^{27,28} differ significantly from PSR-optimized protocols.^{21,22} Indeed, DSC time-intensity curves are influenced by acquisition factors that impact the degree of relative T_2^* - and T_1 -weighting, including pulse sequence parameters (flip angle [FA], echo time [TE], and repetition time [TR]) and preload administration (P+ or P-). CBV-optimized protocols adopt various strategies to *reduce* the relative T_1 -weighting (e.g., low FA or P+) and increase CBV accuracy.^{27,29} Conversely, PSR-optimized protocols *maintain* T_1 -weighting (i.e., high FA and P-)^{21,22} so that DSC signal reflects the overall balance between T_1 and T_2^* post-bolus effects that depend on tissue factors.^{4,5,7} Therefore, either repeat single-echo DSC acquisitions are needed if both PSR-optimized and CBV-optimized protocols are desired, which doubles the scan time and the gadolinium-based contrast agent (GBCA) dose, or either CBV or PSR must be prioritized with a single acquisition.

Additionally, such dependency of DSC time-intensity curves upon acquisition factors causes a remarkable challenge in the standardization of CBV and PSR for clinical applications. Indeed, the heterogeneity in acquisition protocols across institutions has limited the availability of reliable thresholds for universal interpretation of DSC metrics. Of note, data quantifying the impact of acquisition parameters on DSC metrics *in-vivo* are scarce, and limited to the comparisons between P- and P+ protocols,³⁰⁻³² as

repeat DSC experiments are influenced by GBCA injections acting as preloads.

In this study, we propose to use the dual-echo gradient-echo (GE) datasets extracted from dynamic spin-and-gradient-echo echoplanar imaging (SAGE-EPI) to obtain “synthetic” DSC time-intensity curves with adjustable acquisition parameters (i.e., FA, TE, TR, and preload simulation), to overcome the limitations linked to parameter dependency in traditional single-echo DSC sequences. First, we anticipate that dual-echo GE will permit *simultaneous* acquisition of CBV-optimized and PSR-optimized synthetic DSC datasets, eliminating the need for double GBCA injection and repeated acquisitions, and we will evaluate the differences between these protocols. Second, we hypothesize that synthetic DSC datasets could represent a strategy for improving the generalizability of DSC by bypassing acquisition parameter heterogeneity across institutions. To test this, we will compare PSR values from synthetic DSC in our treatment-naïve glioblastoma cohort to external cohorts of PCNSL, after parameter-matching. Third, we propose that synthetic DSC can provide a framework to test the impact of acquisition factors (FA, TE, TR, P+/P-) on CBV and PSR *in-vivo*, which can be used to inform future recommendations on single-echo DSC protocols.

MATERIALS AND METHODS

Patient Selection

Patients with brain tumors were imaged prospectively as part of two research studies approved by the institutional review board (IRB#14-001261 and #21-000514) for which they provided written informed consent. Patients on study IRB #14-001261 were imaged between April 2015 and October 2020, and patients on study #21-000514 from October 2021 to June 2022. For the present study, we screened all the consecutive patients to select the ones with the following inclusion criteria: availability of dynamic SAGE-EPI datasets, contrast-enhancing tumor, histopathological diagnosis of adult-type glioma (either recurrent or treatment-naïve). The presence of excessive susceptibility artifacts affecting

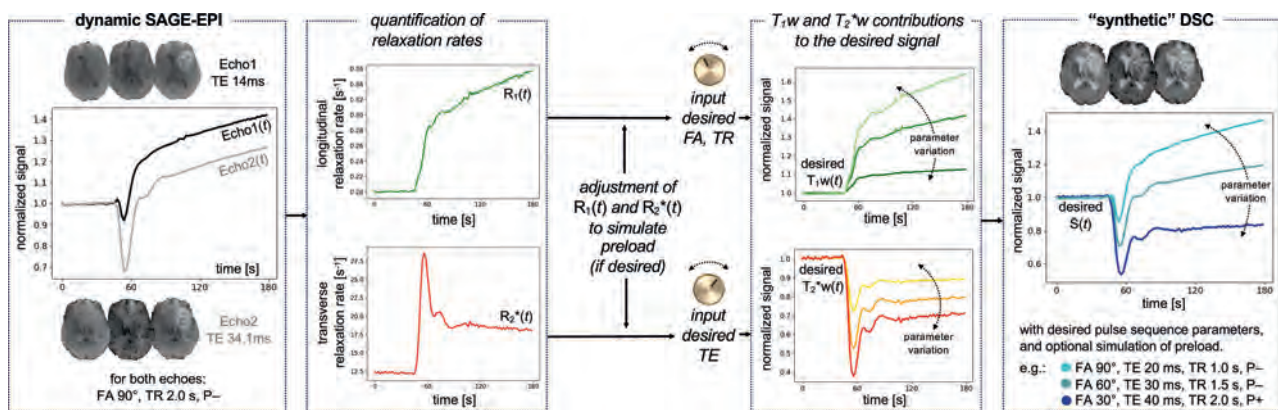


FIG 1. Image processing pipeline to obtain voxel-wise synthetic DSC datasets from dynamic SAGE-EPI. Echo1 (GE, TE = 14ms) and echo2 (GE, TE = 34.1ms) were used to compute $R_1(t)$ and $R_2^*(t)$. If desired, $R_1(t)$ and $R_2^*(t)$ were adjusted to simulate a preload administration. The desired $T_1w(t)$ component of the synthetic DSC was calculated from $R_1(t)$ by inputting the desired FA and TR in the Bloch equations. Similarly, the desired $T_2^*w(t)$ component of the synthetic DSC was calculated from $R_2^*(t)$ by inputting the desired TE in the Bloch equations. Finally, the synthetic DSC time-intensity curve is obtained by combining the desired $T_1w(t)$ and $T_2^*w(t)$. The final plot shows how different parameter combinations generate synthetic DSC time-intensity curves with different relative T1- and T2*-weighting.

the tumor region in dynamic SAGE-EPI was an exclusion criterion. A STROBE checklist was followed to design the study and report the results (see Supplemental Material).

MR Imaging

MR imaging was performed on a 3T Siemens Prisma (Siemens Healthineers) in compliance with the current standardized brain tumor imaging protocol (BTIP).^{28,33} Perfusion imaging was performed with a custom dynamic SAGE-EPI sequence (patent US 11,378,638 B2)^{3,7,34,35} with injection of one bolus of Gadavist (Gadobutrol, Bayer) (~0.1ml/kg) at a rate of ~4 ml/s, as per guidelines.³⁶ Dynamic SAGE-EPI included two gradient echoes (TE₁ = 14ms, TE₂ = 34.1ms), an asymmetric spin echo (TE₃ = 58.0ms) and a spin echo (TE₄ = 92.4ms) using the following acquisition parameters: TR = 2.0s, matrix size = 240x218mm, GRAPPA = 3, voxel size 1.875x1.875x5mm, 19 axial slices, 90 timepoints.

Image Analysis

The two gradient echoes (Echo1 and Echo2) were motion-corrected with FSL *mcflirt* (University of Oxford, <https://fsl.fmrib.ox.ac.uk/fsl/>), and the Bloch equations were used to compute the transverse relaxation rate over time, $R_2^*(t)$ [s⁻¹]^{7,37} (Fig 1, Suppl. Eq.1). The T₁-weighted signal contribution of the gradient echoes ($T_1w(t)$) was obtained by extrapolating the signal at TE = 0 ms, as previously described,^{7,37} and used to calculate the longitudinal relaxation rate over time $R_1(t)$ [s⁻¹] by assuming a fixed T₁ (T₁₀) [s] for the tissue (Fig 1, Suppl. Eq.2; refer to Suppl. Fig.1 for analyses reporting on the robustness of the methodology with respect to T₁₀ assumptions). When desired, $R_1(t)$ and $R_2^*(t)$ were adjusted to simulate a full-dose preload administration (P+) (Fig 1, Suppl. Eq.3), by assuming that a second bolus administration would cause the same change in relaxation rates $\Delta R_1(t)$ and $\Delta R_2^*(t)$.

$R_1(t)$ and $R_2^*(t)$ were then used in the Bloch equations to respectively compute the desired T₁-weighted component ($T_1w_{desired}(t)$) and T₂*-weighted component ($T_2^*w_{desired}(t)$) of the synthetic DSC with desired FA, TE, and TR (Fig1, Suppl. Eq.4-5). Finally, the

"synthetic" DSC time-intensity curve ($S_{desired}(t)$) was obtained by multiplying $T_1w_{desired}(t)$ and $T_2^*w_{desired}(t)$ (Fig 1, Suppl. Eq.6).

For inter-protocol comparisons, synthetic DSC datasets were generated with: one guideline-compliant CBV-optimized protocol with simulated preload (FA 60°, TE 30ms, TR 1.5s, P+)²⁷, one guideline-compliant CBV-optimized protocol without simulated preload (FA 30°, TE 30ms, TR 1.5s, P-),²⁷ and one PSR-optimized protocol (FA 90°, TE 30ms, TR 1.5s, P-).²¹ For comparisons with external cohorts acquired at 3T, synthetic DSC datasets were generated with acquisition parameters matching the ones reported in Cindil *et al.*²¹ (FA 90°, TE 30ms, TR 1.5s, P-, acquisition time 1min 23s) and Wang *et al.*²² (FA 90°, TE 30ms, TR 1.6s, both P- and P+, acquisition time 1min 36s). Note that we truncated our synthetic DSC time-intensity curves (3min) to match the external cohorts (1min 23s and 1min 36s), because the signal recovery depends on the acquisition time. Finally, to explore the impact of acquisition protocols on DSC metrics, we recursively generated synthetic DSC datasets while changing one parameter at the time.

$S_{desired}(t)$ was used to compute $\Delta R_{2, single_echo}^*(t)$ [s⁻¹] as in classic single-echo DSC studies, and rCBV maps were computed by integrating the positive values of $\Delta R_{2, single_echo}^*(t)$ (Suppl. Eq.7, Suppl. Fig.2A-B).³⁷ This step was repeated without model-based leakage correction, with bidirectional leakage correction,³⁸ and with Boxerman-Schminda-Weisskoff (BSW) leakage correction³⁹. Finally, nrCBV maps were generated with normalization to the contralateral white matter (Suppl. Eq.7).¹² PSR maps were generated from $S_{desired}(t)$ without leakage correction, as previously described (Suppl. Eq.8, Suppl. Fig.2C).^{7,20}

A neuroradiologist with 8 years of experience in neuroimaging (F.S.) used digital subtraction maps of pre- and post-contrast T₁-weighted images to segment the contrast-enhancing component of the lesion.^{7,40} Segmentations were registered to the perfusion space using FSL *flirt*.

Statistical Analyses

For comparisons across protocols, Spearman's correlation coefficient (ρ)⁴¹ and two-way mixed single score intraclass correlation

coefficient (ICC3)⁴² of median tumor PSR and nrCBV were obtained, and interpreted as in dedicated statistical articles.^{41,42} ρ tests whether the ranks of the tumor values are maintained across protocols, which influences the diagnostic performance of DSC metrics. The percent variation in ranks introduced by protocol variations was calculated as $(1-\rho^2) \times 100\%$ (Suppl.Eq.9). ICC3 tests the agreement of different protocols on the exact value of a certain DSC metric.⁴² The comparisons with external cohorts focused on PSR only, because the technical variability of PSR is entirely due to acquisition factors, without confounding aspects such as the leakage correction fit and the contralateral white matter signal. The PSR mean and standard deviation of our treatment-naïve glioblastoma subgroup was calculated and compared to the mean and standard deviation of external cohorts with two-sample t-tests. Neither non-parametric tests nor ROC curve computation were feasible, because the individual tumor-specific values of PSR of the external cohorts were not available.

RESULTS

Thirty-eight patients met the inclusion and exclusion criteria for the study (see the flow-chart in Suppl.Fig.3), with tumors of various grades and molecular status, either treatment-naïve or recurrent

Table 1. Demographic, clinical, and pathological features of the study cohort

Characteristics of the study cohort (n=38)	
Age (years, mean $\pm$ SD)	54.4 $\pm$ 14.0
Sex category (F)	
F	11 (28.9%)
M	27 (71.1%)
Main location	
Frontal	11 (28.9%)
Parietal	8 (21.1%)
Temporal	9 (23.7%)
WM/deep GM	4 (10.5%)
Multiple lobes	6 (15.8%)
Treatment status	
Treatment-naïve	14 (36.8%)
Recurrent	24 (63.2%)
Grade	
2	4 (10.5%)
3	4 (10.5%)
4	30 (78.9%)
Molecular status	
IDH ^m 1p19q ^{int}	10 (26.3%)
IDH ^m 1p19q ^{cod}	3 (7.9%)
IDH ^{wt}	25 (65.8%)

(Table 1). All recurrent lesions showed histopathologically-defined recurrent tumor (i.e., actively proliferating tumor cells, with or without evidence of treatment effects) in surgical specimens obtained in the weeks following the MRI acquisition. Of note, some analyses from this cohort were previously reported in an article with a substantially different aim and design.⁷

Plots of time-intensity curves from synthetic DSC with varying parameters were generated and a visual assessment revealed that the curve shapes changed consistently with previous findings (i.e., showing reduced relative T₁-weighting with lower FA, longer TE, longer TR, and with preload simulation P+) (Fig 2).

Comparison between CBV-Optimized and PSR-Optimized Protocols

Synthetic DSC permits generation of CBV-optimized and PSR-optimized DSC datasets from single acquisitions, which can be used in the clinical setting to simultaneously obtain nrCBV and PSR maps from synthetic optimal protocols (Fig 3). Conversely, obtaining PSR from CBV-optimized protocols can lead to inaccurate results. Median tumor PSR values computed with CBV-optimized protocols (FA 30° P- and FA 60° P+) had poor agreement (ICC3 = 0.20 and ICC3 = 0.34, respectively) with those computed with the PSR-optimized protocol (FA 90° P-), and showed 31% variation in ranks (ρ = 0.83) for FA 30° P- and 21% variation in ranks (ρ = 0.89) for FA 60° P+ (Fig 4A). Representative cases (tumors corresponding to the 20th, 40th, 60th, and 80th PSR percentile of our cohort) show how PSR maps from CBV-optimized protocols can yield different ranks compared to PSR-optimized ones (Fig4E-H). Notably, the agreement of PSR values between the two CBV-optimized protocols was only “good” (ICC3 = 0.79), and also introduced rank variations (21%, ρ = 0.89, Fig 4B).

Results suggested that nrCBV may be less influenced than PSR by acquisition factors, especially after bidirectional leakage correction,³⁸ with excellent agreement between PSR-optimized and CBV-optimized protocols (ICC3 = 0.96 and ICC3 = 0.97, respectively, Fig 4C), and with nearly perfect agreement between the two CBV-optimized protocols (ICC3 = 0.99, Fig 4D). BSW leakage correction³⁹ yielded almost similar results (Suppl.Fig.4A-B). nrCBV without leakage correction had only a “good” agreement between PSR-optimized and CBV-optimized protocols (ICC3 = 0.89 and ICC = 0.91, respectively, Suppl.Fig.4C) and an excellent agreement between the two CBV- optimized protocols (ICC3 = 0.97, Suppl.Fig.4D).

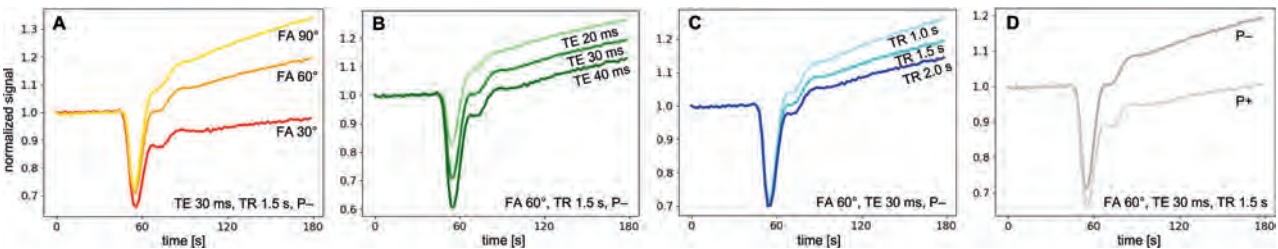


FIG 2. Examples of synthetic DSC time-intensity curves obtained with varying acquisition parameters in one representative tumor. As expected, lower FA (A), longer TE (B), longer TR (C), and the presence of preload simulation P+ (D) determined a reduced relative T₁-weighting and an increased relative T₂*-weighting in the time-intensity curve. This was observed in all tumors. Note that, while the median tumor signal was plotted for the visualization of this representative case, the synthetic DSC pipeline was performed voxel-wise for all the analyses.

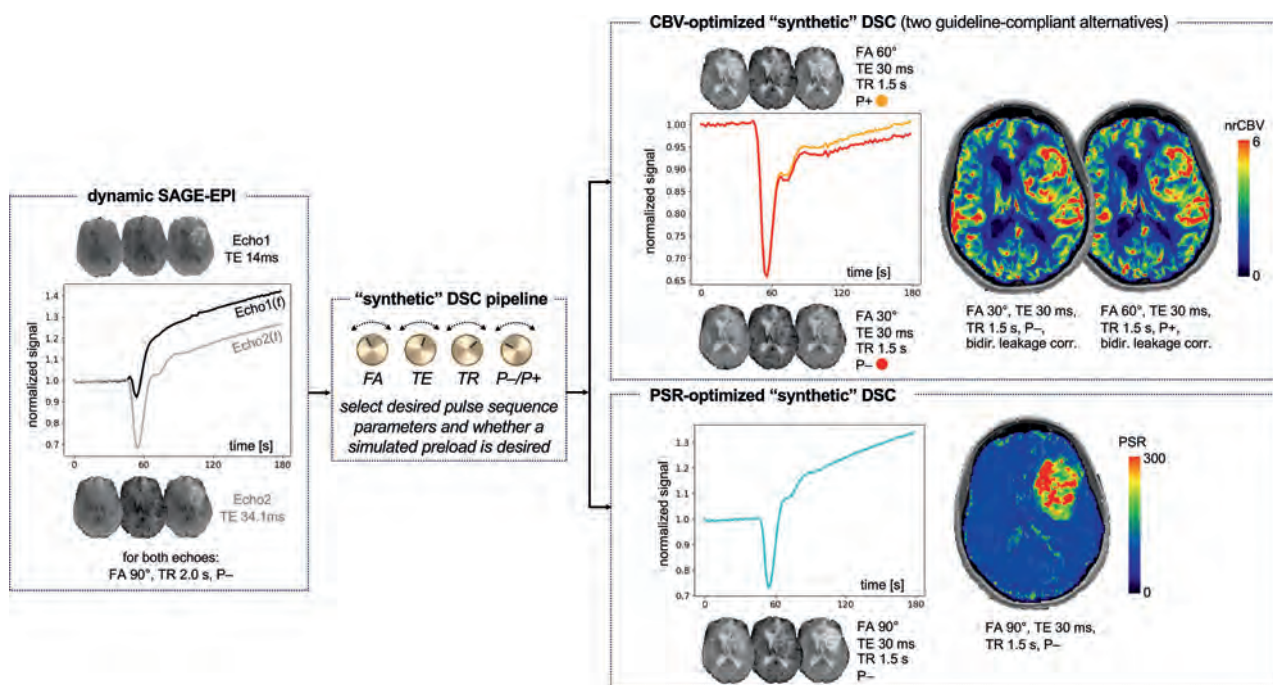


FIG 3. Clinical application of synthetic DSC to simultaneously generate CBV-optimized and PSR-optimized DSC datasets.

Comparison with External Cohorts

Results demonstrate the ability for synthetic DSC to generate datasets with consistent acquisition parameters to external cohorts, which may be useful for putting contemporary studies into historic context. For example, synthetic parameter-matched PSR values from our cohort of treatment-naïve IDH^{wt} glioblastomas were lower than the cohort of treatment-naïve PCNSL ($104.5 \pm 26.5\%$ vs $164.1 \pm 37.0\%$ $p < 0.0001$, Fig 5A) reported by Cindil *et al.*²¹ and not statistically different from their reported glioblastoma cohort ($104.5 \pm 26.5\%$ vs $95.3 \pm 20.1\%$ $p = 0.26$, Fig 5A). As for Wang *et al.*²², synthetic parameter-matched PSR (P-) from our glioblastoma cohort yielded significantly lower PSR values compared to their PCNSL cohort acquired without preload ($108.3 \pm 26.8\%$ vs $163.0 \pm 90.0\%$ $p < 0.0001$, Fig 5B). After preload adjustment (P+), our cohort showed PSR values overlapping with their PCNSL cohort acquired with preload ($89.4 \pm 12.3\%$ vs $70.0 \pm 71.0\%$ $p = 0.03$, Fig 5C). While there was a statistically significant difference between tumor groups, the overlap would arguably result in poor diagnostic performance. Suppl.Tab.1 reports clinical characteristics of the external cohorts, as well as details regarding imaging acquisition and analysis.

Impact of Acquisition Factors on DSC Metrics

When varying acquisition parameters to assess of the impact of acquisition factors on DSC metrics *in-vivo*, results showed that median tumor PSR values progressively decreased when lowering FA, increasing TE, increasing TR, and when adding a simulated preload (P+) (Fig 6A-B). Altering acquisition factors not only caused a remarkable change in PSR values but also affect their ranks within the cohort, suggesting measures of PSR and interpretation are highly dependent on the acquisition parameters. Similarly, median nrCBV values without leakage correction

tended to increase when lowering FA, increasing TE, increasing TR, and when adding a simulated preload (P+) (Fig 6C-D), which also effected the rank order among patients. Unlike PSR, however, nrCBV changes appear less predictable in terms of extent and directionality due to the interplay of the signal in the white matter, which is used for normalization. Bidirectional leakage correction remarkably mitigated the impact of acquisition factors on nrCBV estimates (Fig 6E-F). For reference, the BSW leakage correction showed comparable results (Suppl.Fig.5).

DISCUSSION

The current study proposes a novel methodology that generates multiple synthetic DSC datasets with adjustable pulse sequence parameters and optional preload simulation from a *single* dynamic SAGE-EPI sequence with a *single bolus* of contrast agent. Building on previous work showing how to disentangle T_1 and T_2^* contributions to DSC from *in-vivo* dual-echo data,^{7,37,43} this is the first study proposing the usage of these disentangled signals to compute a new combined signal with adjustable acquisition parameters.

First, the current study demonstrates the ability for dynamic dual-echo GE DSC extracted from dynamic SAGE-EPI to synthesize CBV-optimized and PSR-optimized DSC datasets in a single experiment. While PSR can technically be computed from CBV-optimized acquisitions, its usefulness may be limited by the weak relative T_1 -weighting of CBV-optimized acquisitions. Consistent with this hypothesis, data from the current study showed that PSR measurements from CBV-optimized protocols have poor agreement with measurements obtained with the recommended PSR-optimized protocols, also in terms of rank consistency across protocols, suggesting this may negatively impact not only accuracy but also diagnostic performance. Importantly, even PSR measurements computed with two different guideline-compliant

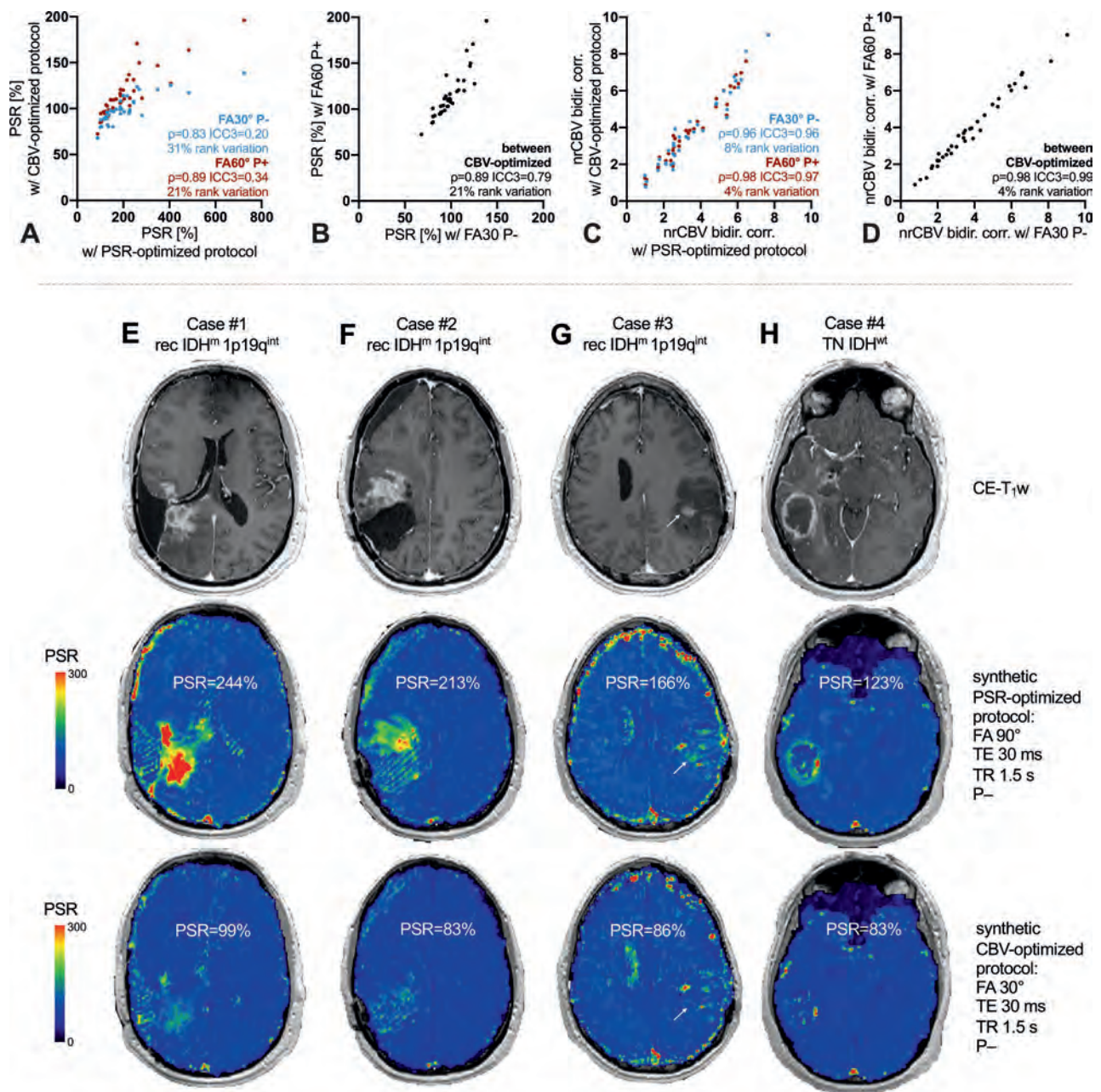


FIG 4. Comparisons of DSC metrics obtained with CBV- and PSR-optimized synthetic DSC protocols. PSR values (A, B) were strongly influenced by the acquisition factors, which impacted not only on the PSR value (reflected in the ICC3 test), but also on the ranks (reflected in the ρ value). nrCBV values with bidirectional leakage correction (C, D) were less influenced by the acquisition factors both in terms of agreement and rank consistency. Of note, the two CBV-optimized protocols yielded nrCBV values with nearly perfect agreement (D). Panels E-H show representative PSR maps for cases of lesions corresponding to the 20th, 40th, 60th, and 80th PSR percentile of our cohort, along with the median PSR tumor value. CBV-optimized protocols not only yield different PSR values, but also sometimes result in different ranks of the lesion within the cohort. For instance, the median values of case #2 and #3 swapped ranks when moving from PSR-optimized to CBV-optimized protocols.

CBV-optimized protocols only had “good” agreement (not excellent nor perfect), thus limiting the universalizability of diagnostic cutoffs given this dependence on acquisition parameters. Our results are consistent with previous studies suggesting that PSR should be computed from PSR-optimized protocols, since the diagnostic utility of PSR from PSR-optimized acquisitions is well documented. For instance, AUC ranged 0.88-0.98 across studies^{8,21,22} for the differentiation of PCNSL from glioblastoma, when using a PSR-optimized protocol (high FA, P-). Conversely,

in other cohorts, PSR differences between PCNSL and glioblastoma were reportedly either attenuated (AUC = 0.82)²⁰ or nullified (AUC = 0.53)²² when using CBV-optimized and/or preloaded protocols. Of note, only one study reported a very high diagnostic performance of PSR in distinguishing PCNSL using a preloaded protocol.²⁶ Overall, simultaneous PSR- and CBV-optimized synthetic protocols using dynamic dual-echo GE saves scan time and eliminates the need for double GBCA dose compared to duplicate experiments. Moreover, analyzing dynamic dual-echo GE is the

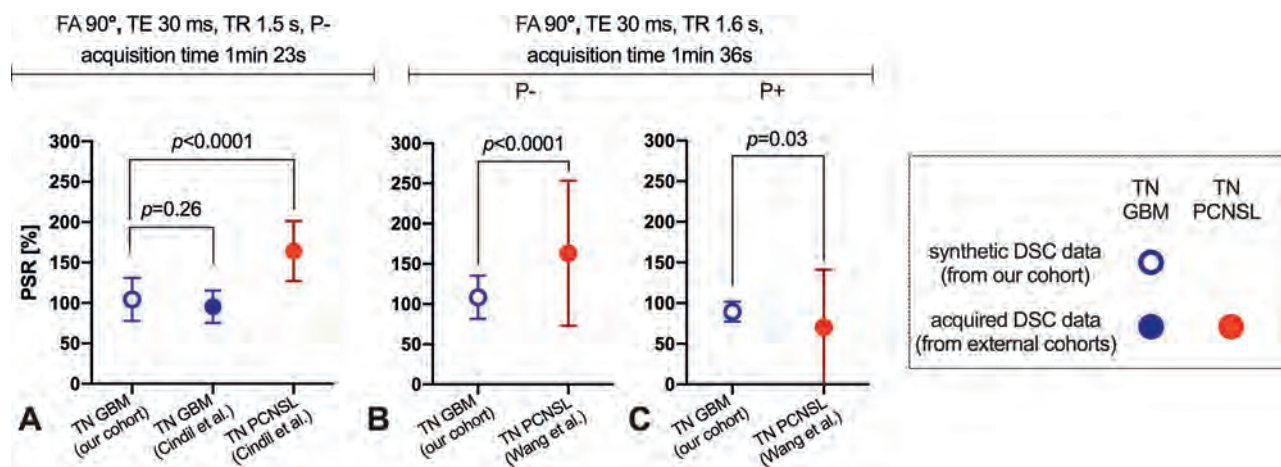


FIG 5. Clinical application of synthetic DSC to compare cohorts with different acquisition parameters. Median tumor PSR from our treatment-naïve glioblastoma cohort were lower than the PCNSL cohort reported by Cindil et al.,²¹ and not different from their glioblastoma cohort (A). Similarly, without preload (P-), median tumor PSR from our treatment-naïve glioblastoma cohort were lower than the PCNSL cohort reported by Wang et al.²². With preload, median tumor PSR from our treatment-naïve glioblastoma cohort overlapped with the other PCNSL cohort reported by Wang et al.²²

only feasible methodology to obtain DCE in addition to PSR-optimized DSC and CBV-optimized DSC.⁷ Indeed, single-echo acquisition schemes would not be suited to obtain all three, since both DCE and PSR-optimized DSC should be non-preloaded.

In addition to generating CBV- and PSR-optimized measurements, the current study demonstrates a framework for comparing prospectively acquired DSC data with external or historic data that was acquired under various acquisition parameters. For example, comparison of parameter-matched PSR values in the current study cohort of treatment-naïve glioblastoma with PSR values from external cohorts were able to replicate similar PSR differences reported in the original articles. In clinical trials, inter-institution heterogeneity and lack of standardization is one of main factors why DSC is excluded from the evaluation of treatment response in clinical trials, as per RANO criteria,⁴⁴ although this technique has been used to monitor treated glioblastomas for decades.^{1,27,45,46} Thus, synthetic DSC using dynamic dual-echo GE or SAGE-EPI can potentially allow real-time comparisons to external and historic cohorts through synthesis of specific acquisition parameters, and more generally, allows for better uniformity and standardization in multicenter studies. Of note, dynamic dual-echo GE and the historic cohorts must be acquired at the same field strength for this application.

Furthermore, synthetic DSC may represent a tool for investigating optimal DSC parameters for single-echo protocols aimed at specific clinical applications. Future studies may systematically permute synthetic acquisition parameters to find the optimal combination that can maximize PSR differences between PCNSL and glioblastoma, or maximize CBV differences between progression and pseudoprogession, or maximize the correlations between DSC metrics and histopathological findings such as vessel density. Other studies have proposed to investigate optimal DSC parameters by using digital reference objects (DROs) obtained from simulated *in-silico* analyses and validated with *in-vivo* datasets.⁴⁷⁻⁴⁹ Compared to the DRO approach, the synthetic DSC approach would have the advantage of being both agnostic

to any biophysical assumptions needed to model the simulated tissue structures, and not being restricted to the disease category represented in the DRO training cohort (i.e., glioblastoma). On the other hand, it would have the disadvantage of *not* providing ground truth model-derived tissue characteristics (e.g., vessel density, cell density) to test the accuracy of perfusion metrics.

Limitations

Some potential limitations should be addressed. First, we did not prospectively obtain a pre-contrast T_1 map, so an estimated value of T_{10} was chosen. However, our simulated data suggested that the absolute error derived from the assumed T_{10} estimation was minimal. Future studies should perform pre-contrast T_1 mapping to improve accuracy. Secondly, the proposed preload adjustment assumes that a second bolus of GBCA causes the same change in longitudinal and transverse relaxation rates as the first bolus. This assumption is overall justifiable for the longitudinal relaxation rate under the Tofts generalized kinetic model,⁵⁰ if an equal-dose bolus is injected close to the time of dynamic equilibrium. As for the transverse relaxation rate, this assumption is to be considered a simplification and it probably introduces some degree of inaccuracy that is not easily quantifiable, because the T_2^* effects are highly dependent on the tissue geometry.^{4,7,50,51} Future studies may employ two consecutive DSC acquisitions (a non-preloaded dual-echo as first, and a preloaded one as second) to quantify the potential inaccuracy of our proposed synthetic preload. Additionally, the current study had no available prospective dynamic SAGE-EPI datasets from patients with PCNSL, which would allow direct testing of the diagnostic performance of synthetic DSC using various parameters. Finally, the estimates of PSR are highly dependent on the duration of the “tail” of the post-injection DSC curve. When comparing to external cohorts, this issue was mitigated by truncating the duration of the time-intensity curves to match the acquisition time of the external cohort. Future studies should model the post-bolus signal and directly define PSR based on this model to lessen the dependency

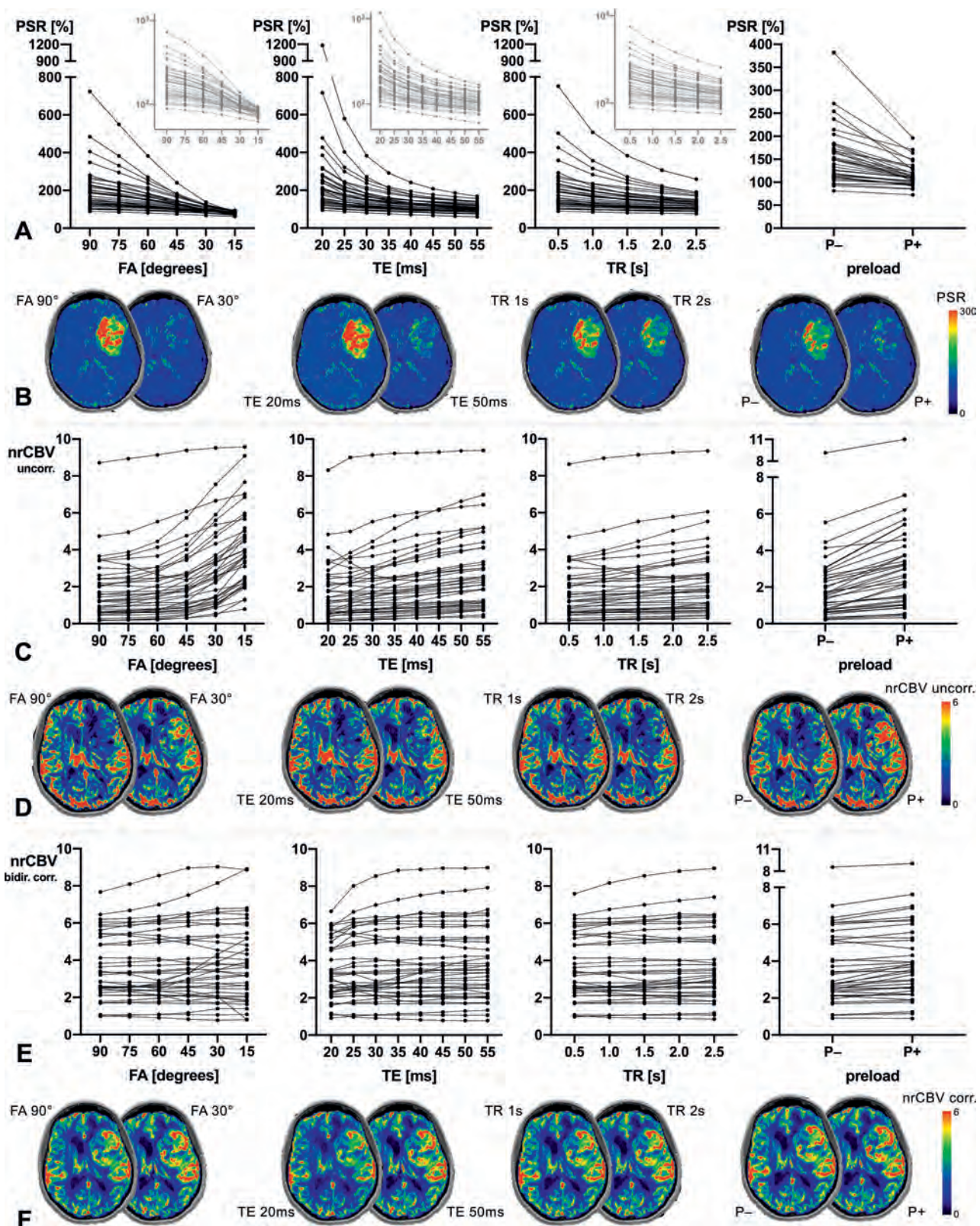


FIG 6. Research application of synthetic DSC to assess the impact of acquisition parameters on quantitative DSC metrics. Median tumor PSR and nrCBV were obtained from each subject, while systematically varying pulse sequence parameters and preload adjustment. Acquisition parameters were varied “one at the time”, and the “default” parameters were as follows: FA 60° TE 30ms TR 1.5s P-. PSR was highly sensitive to acquisition parameters, as shown in both dot plots (A, including linear scaling in black and log-transformed scaling in grey) and representative voxelwise maps (B). Varying parameters not only influenced PSR values, but also the relative ranks of the subjects within the cohort. Dot plots (C) and voxelwise maps (D) of uncorrected nrCBV demonstrate nrCBV variations with acquisition parameters, which are remarkably mitigated by model-based bidirectional leakage correction (E, F).

on the duration of data acquired after contrast injection. Finally, the long TR of our sequence may result in a reduced signal-to-noise ratio of the acquired T₁-weighted component in presence or high GBCA concentrations. Future studies may implement simultaneous multi-slice to shorten the TR and address this limitation.

CONCLUSIONS

The dual-echo GE datasets extracted from dynamic SAGE-EPI allow for direct synthesis of multiple DSC datasets with adjustable acquisition parameters and preload simulations. This method allows for simultaneous generation of CBV-optimized and PSR-optimized measurements with a single injection and acquisition, facilitating the use of a single perfusion protocol for all DSC parameters. Additionally, synthetic DSC from dynamic SAGE-EPI allows for real-time comparison to historic and external datasets acquired with variable acquisition schemes, increasing the rigor of prospective DSC studies in brain tumors.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Radiomics-Based Differentiation of Glioblastoma and Metastatic Disease: Impact of Different T1-Contrast-Enhanced Sequences on Radiomics Features and Model Performance

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ABSTRACT

BACKGROUND AND PURPOSE: Even though glioblastoma (GB) and brain metastases (BM) can be differentiated using radiomics, it remains unclear if the model performance may vary based on the contrast-enhanced sequence used. Our aim was to evaluate the radiomics-based model performance for differentiation between GB and brain metastases BM using MPRAGE and volumetric interpolated breath-hold examination (VIBE) T1-contrast-enhanced sequence.

MATERIALS AND METHODS: T1 contrast-enhanced (T1-CE) MPRAGE and VIBE sequences acquired in 108 patients (31 GBs and 77 BM) during the same MRI session were retrospectively evaluated. After standardized image preprocessing and segmentation, radiomics features were extracted from necrotic and enhancing tumor components. Pearson correlation analysis of radiomics features from tumor subcomponents was also performed. A total of 90 machine learning pipelines were evaluated using a 5-fold cross-validation. Performance was measured by mean area under the curve (AUC)-receiver operating characteristic (ROC), log loss, and Brier scores.

RESULTS: A feature-wise comparison showed that the radiomics features between sequences were strongly correlated, with the highest correlation for shape-based features. The mean AUC across the top 10 pipelines ranged between 0.851 and 0.890 with T1-CE MPRAGE and between 0.869 and 0.907 with the T1-CE VIBE sequence. The top-performing models for the MPRAGE sequence commonly used support vector machines, while those for the VIBE sequence used either support vector machines or random forest. Common feature-reduction methods for top-performing models included linear combination filter and least absolute shrinkage and selection operator for both sequences. For the same machine learning feature-reduction pipeline, model performances were comparable (AUC-ROC difference range, -0.078 – 0.046).

CONCLUSIONS: Radiomics features derived from T1-CE MPRAGE and VIBE sequences are strongly correlated and may have similar overall classification performance for differentiating GB from BM.

ABBREVIATIONS: AUC = area under the curve; BM = brain metastases; GB = glioblastoma; LASSO = least absolute shrinkage and selection operator; linComb = linear combinations filter; ML = machine learning; MRMR = minimum-redundancy maximum-relevance; NIFTI = Neuroimaging Informatics Technology Initiative; RF = random forest; ROC = receiver operating characteristic curve; SUSAN = Smallest Univalve Segment Assimilating Nucleus; SVM = support vector machine; T1-CE = T1 contrast-enhanced sequence; VIBE = volumetric interpolated breath-hold examination

Glioblastoma (GB) and brain metastases (BM) account for most malignant brain tumors. Gliomas account for about 81% of primary malignant brain tumors, with GB being the most common (57.3%). BM, on the other hand, are the most

common secondary malignant brain neoplasm. GB and BM have an annual age-adjusted incidence of 3.22 and 10 per 100,000 persons, respectively.^{1,2} Even though both entities have different therapeutic and prognostic implications and may be differentiated on the basis of conventional and advanced MRI techniques, accurate diagnosis may be challenging in cases with solitary metastasis or multifocal/multicentric glioma, both of which are not uncommon.³⁻⁵

Multiple prior radiomics-based studies have shown promising results for differentiating these entities.^{2,6} However, the impact on classification performance of models derived from different contrast-enhanced sequences for the same lesions remains unclear. It is also unclear if, and to what degree, the radiomics features from different contrast-enhanced sequences correlate for the same lesion. This issue is relevant because postcontrast T1 sequences

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SUMMARY

PREVIOUS LITERATURE: Radiomics-based differentiation of GB and BM is feasible. However, it is uncertain how well the radiomics features derived from different T1-CE sequences correlate or whether such differences impact eventual model performance.

KEY FINDINGS: We found that radiomics features derived from T1-CE MPRAGE and VIBE sequences showed moderate-to-strong correlation and comparable performances across multiple machine learning pipelines.

KNOWLEDGE ADVANCEMENT: Despite differences in acquisition parameters, comparable model performance from different T1-CE sequences is feasible. These findings may imply that conformity to a certain postcontrast sequence may be less restrictive in a multi-institutional setting.

may vary between institutions, with the commonly used sequences being 2D T1-spin-echo, 3D MPRAGE, volumetric interpolated breath-hold examination (VIBE), or variable flip angle refocusing pulse, fast spin-echo sequences such as sampling perfection with application-optimized contrasts by using different flip angle evolutions (SPACE; Siemens), Cube (GE Healthcare), or volume isotropic turbo spin-echo acquisition (VISTA; Philips Healthcare).^{7,8}

In the clinical setting, T1 contrast-enhanced sequences (T1-CE) are invariably performed in patients with brain lesions, either for treatment-planning, response assessment, surgical navigation, or stereotactic radiosurgery. The variability between the used postcontrast sequences and uncertainty about their impact on model classification performance can be a hindrance to multisite collaborations. This issue is important for a several reasons: First, if radiomics from any sequence is clearly superior for classification performance, it would seem reasonable to use it on a wider scale prospectively for tumor classification. On the other hand, if different sequences show similar classification performance and are strongly correlated, this result may imply that conformity to a certain postcontrast sequence may be less restrictive in a multi-institutional setting.

The MPRAGE sequence emphasizes gray-white matter contrast due to the inversion recovery preparation pulse and is often used in brain tumor clinical trials. The VIBE sequence, on the other hand, lacks an inversion recovery pulse but has higher demonstrated sensitivity to enhancing lesions.⁷ The aim of the current exploratory study was to determine whether the different radiomics features derived from these postcontrast sequences correlate and whether such correlation translates into similar model performance for differentiating between BM and GB using multiple machine learning (ML) pipelines post-uniform image preprocessing.

MATERIALS AND METHODS

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data Collection

The study was approved by the local institutional board and informed consent was waived, given the retrospective nature of the study. Using the DICOM header search functionality, the PACS database was searched for studies in which both MPRAGE

and VIBE sequences were acquired during the same session. Studies were sought between January 2016 and November 2021. A total of 288 patients were identified. Of these, cases were excluded after chart and imaging review for the following reasons: 1) patients with any diagnosis other than BM or GB ($n = 90$); 2) lesions previously biopsied or treated with surgery or radiation therapy ($n = 50$); 3) nonenhancing lesions or lesions with <1 cm of enhancement as demonstrated in either or both MPRAGE and VIBE sequences ($n = 27$); 4) images obtained without contrast ($n = 6$); and 5) the presence of artifacts impairing accurate image interpretation ($n = 7$). This process yielded a total of 108 subjects (GB = 31, BM = 77) who were further studied. All cases were pathologically-proved, either as GB or as BM. The underlying primary malignancy in BM cases is listed in Table 1.

Image Acquisition

Images were acquired on either a 1.5T Avanto or Aera or a 3T Magnetom Skyra scanner (Siemens). The sequence parameters of the 2 sequences on the various scanners on which the patients were scanned are provided in the Online Supplemental Data. All patients had MPRAGE and VIBE sequences performed in the same session in succession. T1-CE VIBE was acquired first for

Table 1: Demographic and clinical information of the patient cohorts

	GB	BM
Mean age (yr)	65.67 (SD, 11.12)	65.10 (SD, 11.06)
Sex		
Female	13	47
Male	18	30
Scanner		
1.5T	24	61
3T	7	16
Primary tumor	NA	
Lung	NA	29
Melanoma	NA	10
Breast	NA	6
RCC	NA	5
Mullerian	NA	5
Esophageal	NA	3
Germ cell tumor	NA	1
Adrenal	NA	1
Colorectal	NA	1
Anal	NA	1
Unknown	NA	15

Note:—RCC indicates renal cell carcinoma; NA, not applicable.

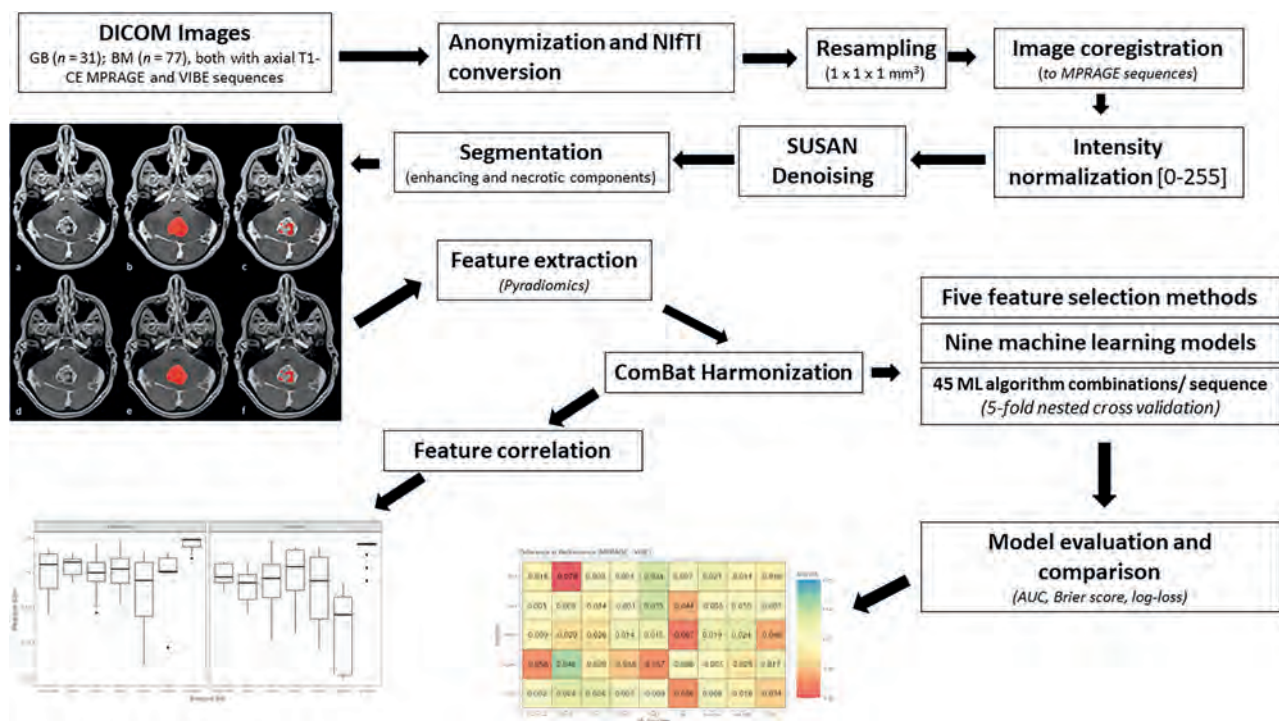


FIG 1. Schematic depicting the overall study workflow.

22 patients, and MPRAGE was acquired first for 86 patients. In general, the T1-CE VIBE duration was between 4 and 5 minutes, and T1-CE MPRAGE duration was between 5 and 6 minutes. The median time difference between the 2 acquisitions was 4.77 minutes. A gadobutrol (Gadavist; Bayer Schering Pharma) injection at a dose of 0.01 mmol/Kg body weight was used in all cases.

Image Processing

The overall study workflow is depicted in Fig 1. After deidentification and Neuroimaging Informatics Technology Initiative (NIfTI) conversion, MPRAGE and VIBE images were preprocessed using a series of image-processing steps. All sequences were first resampled to a voxel size of $1 \times 1 \times 1 \text{ mm}^3$ and registered to MPRAGE images using a rigid transformation. Then, the Smallest Univalve Segment Assimilating Nucleus (SUSAN) denoising technique was used to suppress the effects of noisy high-frequency features from the images.⁹ Following those steps, the image intensities were min-max normalized to 0-255. The resampling, intrasubject registration, and normalization steps were implemented using ANTsPy Version 0.2.9 (<https://pypi.org/project/antspyx/>), a python library that wraps the C++ biomedical image-processing library Advanced Normalization Tools (ANTs; <http://stnava.github.io/ANTs/>).¹⁰ The neuroimaging in python (Nipype) package, Version 1.7.0 (<https://nipy.readthedocs.io/en/latest/api/generated/nipype.html>) provides an interface to an FMRIB Software Library implementation of the SUSAN denoising method.¹¹⁻¹⁴

Tumor Segmentation

3D-segmentation of the tumor was performed using Layered Optimal Graph Image Segmentation for Multiple Objects and

Surfaces (LOGISMOS) software.¹⁵ In case of multiple lesions, only the largest lesion was segmented. For each segmented lesion, we created 2 masks: 1) a whole-tumor mask, consisting of both the solid and necrotic components; and 2) a necrotic mask, consisting of only the necrotic component. The mask for only the solid enhancing component was obtained by subtracting the necrotic component mask from the whole-tumor mask (Fig 2). The segmentations were performed by a radiology resident (C.G.Z., with 2 years of radiology experience) under the supervision of a board-certified neuroradiologist (G.B., with 19 years of radiology experience) with a Certificate of Added Qualification in neuroradiology. The users had access to all the standard MRI sequences in each case, even though the segmentation was performed only on the T1-CE sequences.

The segmentations were performed using semiautomated software and were manually editable with the same software to allow fine-tuning. Separate masks for the enhancing and necrotic components were used for analysis because some studies have shown better classification performance when using tumor subregions masks separately as compared to whole tumor masks.¹⁶ A region was considered “enhancing” when it showed an unequivocal increase in underlying signal intensity to the radiologist above the baseline noncontrast T1WI at the same level. The “necrotic” component, on the other hand, was defined as a persistently hypointense tumor subregion without any apparent increase in signal intensity postcontrast. Because there are documented differences in the contrast-to-noise and visual conspicuity ratings between the 2 sequences, separate segmentations were performed for both sequences instead of treating 1 sequence as a criterion standard and superimposing the ROI derived from one sequence on the other sequence.⁷ A few representative examples of tumor segmentations are provided in the Online Supplemental Data.

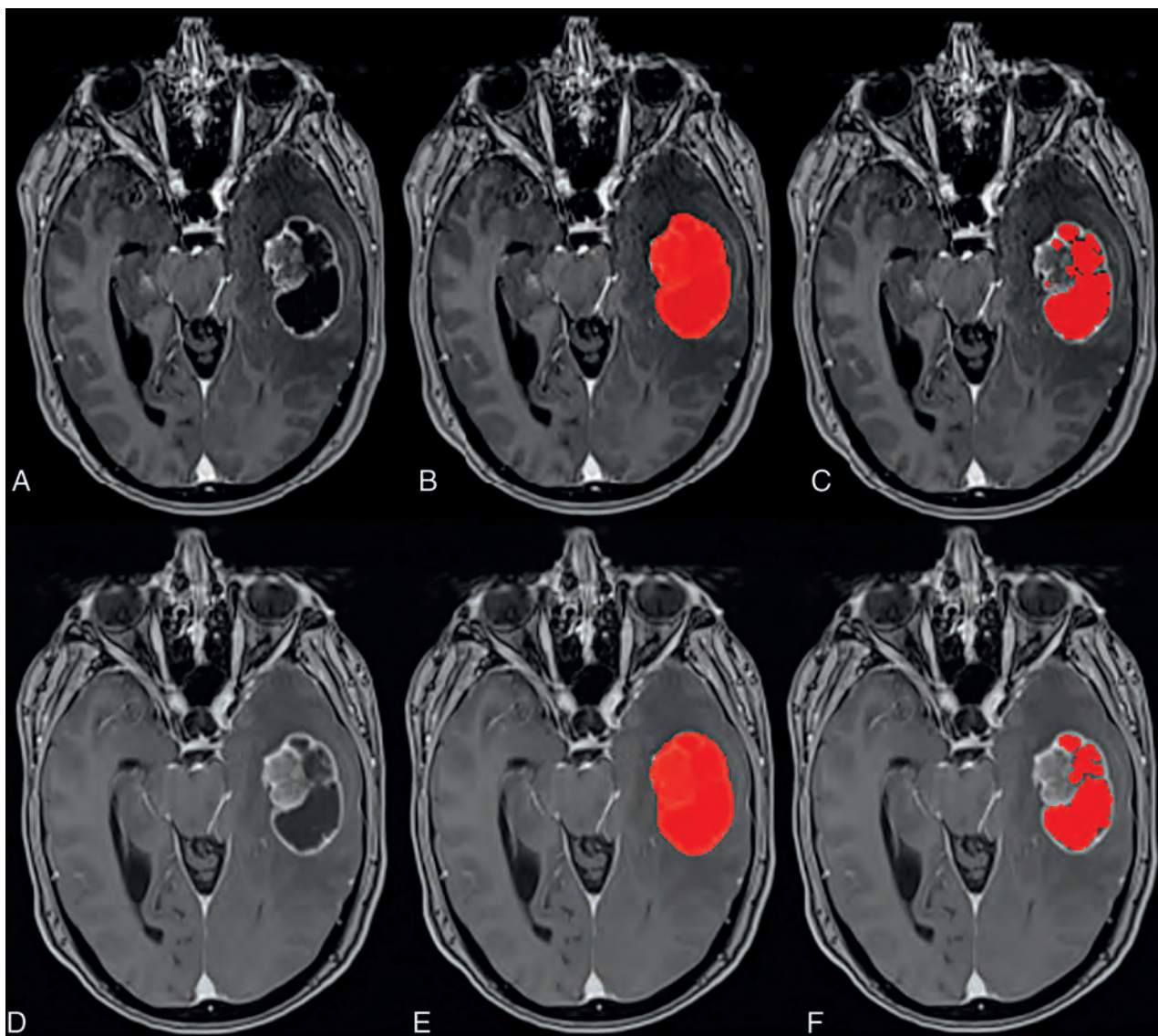


FIG 2. Representative images from a patient with BM demonstrating the baseline T1 postcontrast MPRAGE (A) and VIBE (D) images, the whole tumor mask (shaded in red) in MPRAGE (B) and VIBE (E), and the necrotic mask in MPRAGE (C) and VIBE (F). The mask for the solid-only enhancing component was obtained by subtracting the corresponding necrotic component mask (shaded in red) from the whole-tumor mask.

Feature Extraction

For each tumor, features were extracted using 2 masks: a solid enhancing tumor mask and a necrotic mask. Features were extracted using pyradiomics, Version 3.0 (<https://pypi.org/project/pyradiomics/>).¹⁷ Because there were 4 possible mask and sequence combinations (2 MRI sequences and 2 masks) on each of which 107 radiomic features were obtained, there were a total of 428 features.

Each set of 107 features included 3D shape features ($n = 14$), first-order features ($n = 18$), gray level co-occurrence matrix features ($n = 24$), gray level dependency matrix features ($n = 14$), gray level run length matrix features ($n = 16$), gray level size zone matrix features ($n = 16$), and neighboring gray tone difference matrix features ($n = 5$). The default value for the number of bins was fixed by a bin width of 25-Gy levels. Before feature selection, each covariate was standardized. There were no missing values, and imputation was not performed.

Modeling Scheme

To fully leverage all available data for training and testing, we adopted a nested cross-validation model-fitting design. Five outer folds were defined on the basis of stratified random sampling using MRI scanner strength (1.5 and 3T) and tumor status (GB and BM) as stratifying factors. Each outer fold then served as a distinct test data set for a model trained on the remaining 4 folds.

Feature Harmonization

Because the data were acquired from different MRI scanners (1.5 and 3T), there was a potential for the different signal intensities to lead to variations in the feature values. To account for this variation, we used the ComBat feature harmonization technique before model fitting.¹⁸ This technique has been shown to reduce feature dissimilarities among different scanners.¹⁹ Feature harmonization was implemented using the neuroCombat package in R Version 4.2.2, using the nonparametric adjustment method to

avoid making any distributional assumptions about the features.^{20,21} This was performed separately by sequence/mask combination and each of the 5 nested cross-validation based training datasets. Pretrained neuroCombat models were then applied to the remaining outfold data sets as part of the test set ML model classification.

Feature Selection

Feature selection was implemented through the recipes package in R, Version 4.2.2.²² Besides evaluating the models without any a priori feature selection (“none”), we used the following feature-selection/reduction techniques:

- 1) Linear combinations filter, which addresses both collinearity and dimension reduction by finding linear combinations of ≥ 2 variables and removing columns to resolve the issue. This process is repeated until the feature set is full rank.
- 2) Principal components analysis, in which the number of components retained is determined by specifying the fraction of the total variance that should be covered by the components (set to 0.90).
- 3) Least absolute shrinkage and selection operator (LASSO), in which 10-fold cross-validation was used to select the optimal tuning parameters based on minimized error (ie, more permissive than the One Standard Error Rule). A final LASSO model is then trained, and all features with nonzero coefficients are passed to the model training phase.
- 4) The minimum-redundancy maximum-relevance (MRMR) algorithm that ranks features according to the MRMR criterion. This requires specification of the number of features to extract, which was set to 50 (approximately a 75% feature set reduction).

Model Fitting

A total of 9 ML algorithms were considered, along with feature-reduction techniques as described above. These included support vector machine with polynomial kernel (SVM-Poly), support vector machine with Gaussian kernel (SVM-RBF), Elastic-net, LASSO, extreme gradient boosting, generalized boosted regression models, random forest (RF), neural networks, and K-nearest neighbors. A total of 45 ML pipelines were considered for each of the 2 MRI sequences by considering all possible combinations of the ML algorithm and feature-selection methods, and all pipelines were fed with radiomics data of both tumor subcomponents.

Models were fit using the caret package in R.²² The model training for hyperparameter tuning was based on 5-fold cross-validation, with 5 repeats, and optimal hyperparameter settings were identified on the basis of the cross-validated area under the receiver operating characteristic curve (AUC-ROC). Tuning grids were defined for each ML algorithm under default settings (tuneLength = 10) with the exception of extreme gradient boosting, SVM-Poly, and neural networks, for which custom grids were applied.

Evaluation

Pearson correlations were estimated for each radiomics feature derived from the respective sequence separately by mask. To evaluate the potential impact of scanner strength, we considered

correlation analyses without and with batch correction (using neuroCombat). For the latter, we aggregated batch-corrected radiomics data from the outerfolds of the nested cross-validation to constitute a single data set. Concordance of feature correlations with and without correction was assessed using the Lin concordance correlation coefficient separately by mask.

Model test set performance was measured by the mean AUC (with higher values indicating better performance), Log Loss (lower value indicating better performance), as well as the Brier score, which is a measure of the accuracy of the probabilistic predictions. A lower Brier score implies better prediction calibration. Finally, the top 20 radiomic features across the top performing 5 models were compared for both sequences. Given the nested cross-validation design, the 5 outfold test set performance measures for any given ML pipeline and MRI sequence were summarized by mean (SD). The study methodology in the Checklist for Artificial Intelligence in Medical Imaging (CLAIM) was followed.²³

RESULTS

Of the total patients ($n = 108$), 29% had GBs ($n = 31$) and 71% had BM ($n = 77$). Among the patients with BM, most tumors were known lung primaries ($n = 29$). In 18 cases, intracranial metastasis was the initial manifestation of the tumor, and the primary site remained unknown. Patient demographics and scanner information are provided in Table 1.

Figure 3 shows the Pearson correlation estimate distribution as boxplots for the enhancing and necrotic tumor components derived from the 2 sequences for the uncorrected data. This shows a moderate-to-strong correlation among features, with the strongest correlations for the shape-based features. In general, correlations were slightly higher for the enhancing tumor components. The Online Supplemental Data show the scatterplots of the individual Pearson correlation estimates after data set batch correction, with the Lin concordance correlation coefficient between batch corrected and uncorrected datasets for the 2 masks reported in the Online Supplemental Data. These feature correlations were noted to be highly concordant, indicating that the scanner had minimal impact on the feature correlation between sequences.

In terms of model classification performance, the best performing pipeline on MPRAGE masks showed a mean AUC of 0.890 (SD, 0.09) and was obtained using SVM-Poly with a linComb filter. For the VIBE sequence-derived radiomics models, SVM-RBF with linComb showed the best performance with a mean AUC of 0.907 (SD, 0.08). Table 2 shows the metrics for the top 5 models using the MPRAGE and VIBE sequences. Figure 4 shows the differences in AUC-ROC performance (MPRAGE-VIBE) between the sequences when using the same ML model and feature-reduction methodology. The performance showed only minimal differences (range, -0.078 – 0.046). The Online Supplemental Data show the scatterplot of the differences in AUC-ROC for the same pipelines, again redemonstrating the overall similar and correlated performance of the models. The Online Supplemental Data show the differences in model performance based on the ML algorithm and feature selection technique. Top-performing models for the MPRAGE sequence

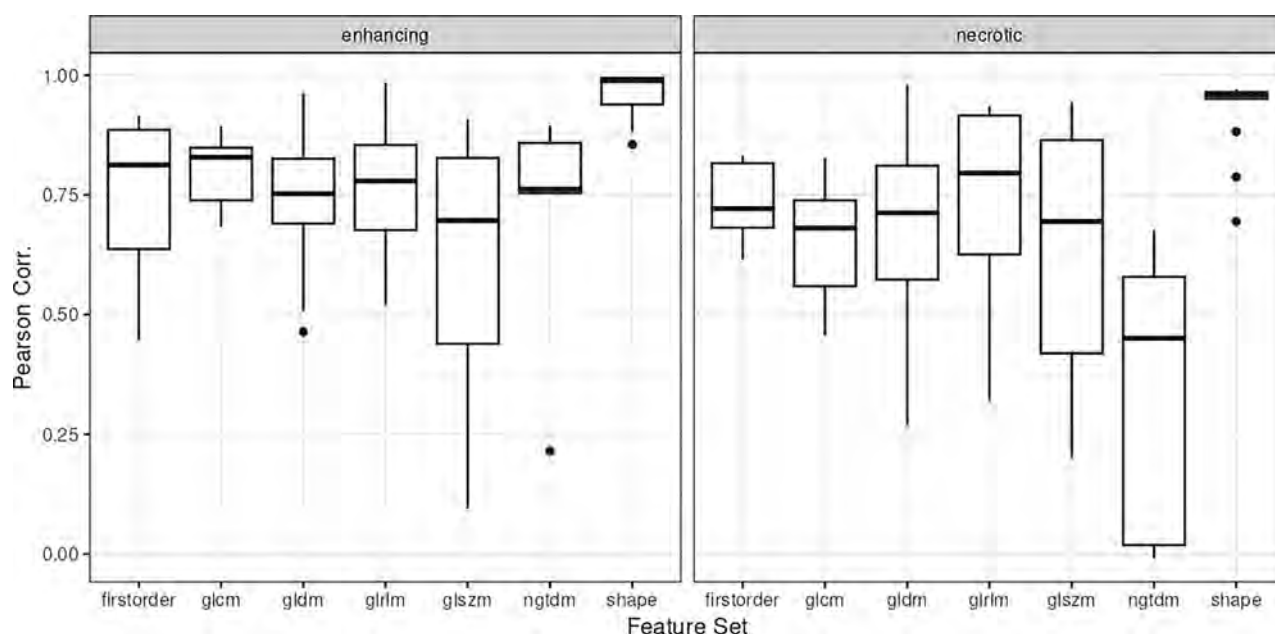


FIG 3. Boxplots showing Pearson correlation estimate distributions for the enhancing and necrotic tumor components derived from the 2 sequences for the uncorrected data. Corr. indicates Correlation.

Table 2: Performance metrics for the top 5 models using the VIBE and MPRAGE sequences

Table 2: Performance metrics for the top 5 models using the VIBE and MPRAGE sequences							
Model	Feature Selection	AUC-ROC		Log Loss		Brier Score	
		Mean	SD	Mean	SD	Mean	SD
VIBE							
SVM-RBF	LC	0.907	0.086	0.389	0.165	0.117	0.062
NNET	LC	0.896	0.056	0.678	0.425	0.144	0.041
SVM-Poly	LC	0.895	0.093	0.400	0.178	0.117	0.053
RF	MRMR	0.893	0.056	0.433	0.204	0.128	0.051
ENET	LC	0.893	0.085	0.454	0.138	0.132	0.039
MPRAGE							
SVM-Poly	LC	0.890	0.093	0.432	0.129	0.132	0.048
GBRM	LC	0.888	0.060	0.449	0.144	0.132	0.050
SVM-RBF	LC	0.882	0.106	0.430	0.213	0.133	0.071
SVM-RBF	MRMR	0.873	0.073	0.445	0.152	0.136	0.055
XGB	LC	0.871	0.091	0.475	0.226	0.143	0.067

Note:—ENET indicates elastic net; LC, linear combination filter; GBRM, generalized boosted regression model; NNET, neural network; XGB, extreme gradient boosting.

commonly used SVMs, while those for VIBE sequence used either SVMs or RF. Common feature-reduction methods for top-performing models included the linear combination filter and LASSO for both sequences. Finally, the Online Supplemental Data show the top 20 radiomics features for the top 5 models for both sequences. Sixteen of these top features were common, with approximately one-half of the features being shape-based. Equally important, all the top 20 radiomics features from both sequences were derived from the enhancing component of the tumor.

Because there were a total of 90 ML models, a detailed evaluation of the misdiagnosed cases for each model was beyond the scope of the current work. A preliminary assessment of cases most often misdiagnosed by the models was, therefore, performed. These were identified as cases with a median error of >0.80 across all models, implying that the cases were frequently misdiagnosed regardless of the ML algorithm or feature-reduction technique used. We identified 8 such cases (7 GB and 1 BM).

Representative images from these cases are provided in the Online Supplemental Data.

DISCUSSION

Our findings demonstrate that radiomics features derived from contrast-enhanced MPRAGE and VIBE sequences show moderate-to-strong correlation and have comparable model performance for differentiating between GB and BM. Our findings raise the possibility that similar ML pipelines may perform equally well with different sequences and pooling of data among different sites using different T1-CE sequences that may be less restrictive.

Even though several prior studies have evaluated differences in radiomics on the basis of different sequences, acquisition parameters, and scanner strengths, there is little information on the model performance when using different types of post-contrast sequences for the same classification task.²⁴⁻²⁸ We chose to address the model performance on T1-CE sequences

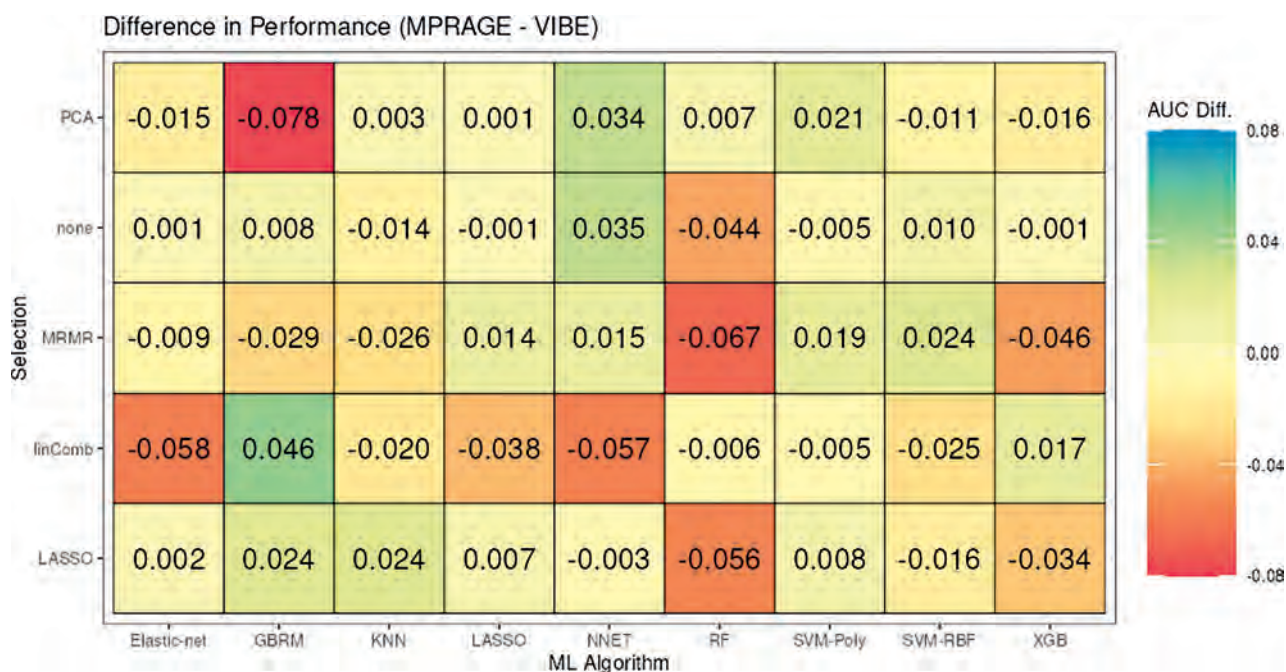


FIG 4. Differences in AUC-ROC performance (MPRAGE-VIBE) between the sequences when using the same ML model and feature-reduction methodology. PCA indicates principal components analysis; KNN, K-nearest neighbors; GBRM, generalized boosted regression model; XGB, extreme gradient boosting.

for several reasons. First, T1-CE sequences are one of the most important sequences in neuro-oncology and are almost always performed for tumor detection and assessment.^{2,6,7,16,29} Second, multiple prior studies have relied almost exclusively on the T1-CE-derived radiomics for classification problems, with some studies showing that the model performance of the T1-CE sequences may, at times, be comparable with that of multiparametric MRI-derived radiomics.^{2,16,29} Third, the variability in the type of T1-CE sequence, even with the same vendor, in terms of the 2D or 3D technique as well as the type of sequence used, lends itself to further interrogation. The variability in terms of underlying physics and actual lesion-detection performance can be considerable, as has been addressed in a few studies.^{7,8} These sequences can also have differences in radiomics features, as described by Ford et al,²⁶ who noted that the radiomics features can vary considerably among different T1-weighted pulse sequences. This issue, therefore, raises legitimate concerns about the generalizability of radiomics models when combining different sequences.

Our findings reveal that, at least for the 2 sequences evaluated in the current study, not only is the classification performance fairly similar but the individual radiomics features are also highly correlated. The precise reason for the high correlation is unclear. Both sequences are T1-weighted gradient recalled echo-based contrast-enhanced 3D sequences. Additionally, van der Reijdt et al,³⁰ in their study on hepatic metastasis, noted that T1-CE sequences were the most robust to segmentation variability. It is plausible that both of these factors contributed to the high correlation in radiomics features observed in the current study.

We also chose to evaluate models with radiomics derived from the solid-enhancing and necrotic components of the lesions separately, instead of the entire tumor combined. This evaluation

was performed because prior study by Priya et al¹⁶ showed improved model performance when evaluating radiomics from tumor subregions instead of the entire tumor. Another reason was to better evaluate the correlation between radiomics features derived from tumor subcomponents, an evaluation not feasible with whole-tumor segmentation.

Besides the high correlation between the radiomics features, the relatively similar performance of multiple ML pipelines in our study could potentially also be explained by the scanning parameters as well as the image-preprocessing techniques. Both T1-CE sequences in our study were 3D T1-CE sequences with slice thicknesses between 1 and 1.5 mm (MPRAGE) and 1.5 mm (VIBE). Mayerhoefer et al²⁷ previously noted that if the spatial resolution is sufficiently high, variations in the number of acquisitions, TR, TE, and sampling bandwidth have little effect on the results of pattern discrimination for a given sequence. Our preprocessing steps likely helped further homogenize the data sets in terms of image intensity and the radiomic features, which helped with achieving robust performance with similar ML pipelines despite different sequences. Another factor that potentially contributed to comparable performances was that most of the radiomics variables of importance were derived from shape-based features (Online Supplemental Data). In fact, of the top 20 radiomics features across the 5 best models in both sequences, 16 radiomics features were common to both sequences, and of these, there were 10 common shape-based features. Because shape features like shape flatness, maximum diameter, lesion volume, and so forth can be visually correlated by the radiologist, our findings suggest that their careful evaluation may be helpful when deciding between GB and BM.

Finally, a review of the most commonly misdiagnosed cases (Online Supplemental Data) was also performed. Most of these cases were GB ($n=7$), and 1 case was BM. Misdiagnosed GB

cases often tended to have a smaller enhancing component and/or well-defined margins and a more spherical appearance. The misdiagnosed BM case was large and had a prominent necrotic component. Given that some of the GB cases also had a larger, infiltrative nonenhancing component, it is possible that the use of multiparametric MRI or concurrent assessment by the model and human reader may further improve model performance.

Limitations of our study include its retrospective nature and lack of a larger data set. In our institution, the VIBE sequence is concurrently performed for neurosurgery stealth navigation in patients being considered for surgical intervention. Not all patients are, therefore, scanned with both 3D T1-CE sequences, introducing an element of selection bias, albeit random. Because the segmentation was performed by the radiology trainee under direct supervision of the neuroradiology attending physician, any impact of interreader segmentation on model performance could not be assessed. The relatively small sample size would preclude application of deep learning methodologies, which were, therefore, not pursued. Lack of external validation, model performance of 3D T1-CE SPACE, or pointwise encoding time reduction with radial acquisition (PETRA) sequences, and data from different vendors are other limitations that could be addressed in future studies and would further address the issue about broader generalizability of the T1-CE sequences across vendors and technical acquisition differences. Finally, reported performance measures among top models may be subject to some component of overfitting due to model selection, and interpretation of results should be constrained to the comparisons between sequences.

CONCLUSIONS

Radiomics features derived from MPRAGE and VIBE 3D T1-CE sequences are strongly correlated and can provide similar model performance for differentiating GB and BM despite differences in scanner strengths and acquisition parameters. These findings are encouraging and should be further validated for other intracranial space-occupying lesions and contrast-enhanced sequences. Ultimately, these may help guide future multisite collaborations between institutions using different T1-CE sequences, making the dependence on type of sequence less restrictive.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Predicting Post-Operative Side Effects in VIM MRgFUS Based on THalamus Optimized Multi Atlas Segmentation (THOMAS) on White-Matter-Nulled MRI: A Retrospective Study

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ABSTRACT

BACKGROUND AND PURPOSE: Precise and individualized targeting of the ventral intermediate thalamic nucleus for the MR-guided focused ultrasound is crucial for enhancing treatment efficacy and avoiding undesirable side effects. In this study, we tested the hypothesis that the spatial relationships between Thalamus Optimized Multi Atlas Segmentation derived segmentations and the post-focused ultrasound lesion can predict post-operative side effects in patients treated with MR-guided focused ultrasound.

MATERIALS AND METHODS: We retrospectively analyzed 30 patients (essential tremor, $n = 26$; tremor-dominant Parkinson's disease, $n = 4$) who underwent unilateral ventral intermediate thalamic nucleus focused ultrasound treatment. We created ROIs of coordinate-based indirect treatment target, focused ultrasound-induced lesion, and thalamus and ventral intermediate thalamic nucleus segmentations. We extracted imaging features including 1) focused ultrasound-induced lesion volumes, 2) overlap between lesions and thalamus and ventral intermediate thalamic nucleus segmentations, 3) distance between lesions and ventral intermediate thalamic nucleus segmentation and 4) distance between lesions and the indirect standard target. These imaging features were compared between patients with and without post-operative gait/balance side effects using Wilcoxon rank-sum test. Multivariate prediction models of side effects based on the imaging features were evaluated using the receiver operating characteristic analyses.

RESULTS: Patients with self-reported gait/balance side effects had a significantly larger extent of focused ultrasound-induced edema, a smaller fraction of the lesion within the ventral intermediate thalamic nucleus segmentation, a larger fraction of the off-target lesion outside the thalamus segmentation, a more inferior centroid of the lesion from the ventral intermediate thalamic nucleus segmentation, and a larger distance between the centroid of the lesion and ventral intermediate thalamic nucleus segmentation ($p < 0.05$). Similar results were found for exam-based side effects. Multivariate regression models based on the imaging features achieved areas under the curve of 0.99 (95% CI: 0.88 to 1.00) and 0.96 (95% CI: 0.73 to 1.00) for predicting self-reported and exam-based side effects, respectively.

CONCLUSIONS: Thalamus Optimized Multi Atlas Segmentation-based patient-specific segmentation of the ventral intermediate thalamic nucleus can predict post-operative side effects, which has implications for aiding the direct targeting of MR-guided focused ultrasound and reducing side effects.

ABBREVIATIONS: AC-PC = anterior commissure-posterior commissure; AUC = areas under the curve; ET = essential tremor; FGATIR = Fast Gray Matter Acquisition T1 Inversion Recovery; FTM = Fahn-Tolosa-Marín Clinical Rating Scale for Tremor; MRgFUS = MR-guided focused ultrasound; PD = Parkinson's disease; THOMAS = Thalamus Optimized Multi Atlas Segmentation; TH = thalamus; VIM = ventral intermediate nucleus

MR-guided focused ultrasound (MRgFUS) provides an incisionless therapeutic option for neurological disorders, utilizing high intensity ultrasound waves to ablate target tissue via thermocoagulation.¹⁻⁴ Clinically validated for its efficacy

and safety,^{2,5,6} MRgFUS has received FDA approval for managing essential tremor (ET) and tremor-dominant Parkinson's disease (PD), two prevalent movement disorders that substantially impact patients' quality of life. For patients with drug resistant tremor, MRgFUS targeting ventral intermediate nucleus (VIM)^{4,7} provides a non-surgical, incisionless solution, particularly benefiting the elderly population with PD and ET.^{1,8}

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SUMMARY

PREVIOUS LITERATURE: VIM-MRgFUS is an effective treatment for tremor in patients with essential tremor or Parkinson's disease. Precise targeting of the VIM is crucial but challenging due to its invisibility on standard MR imaging. While indirect targeting using the AC-PC line is common, it does not account for individual anatomical differences. Recently, the THOMAS method, an automated thalamic nucleus segmentation technique based on white-matter-nulled MRI, was developed. We seek to investigate its utility in predicting post-procedural side effect.

KEY FINDINGS: Spatial relationships between FUS-induced lesions and THOMAS-based thalamic segmentations can predict post-operative gait and balance side effects. Larger off-target lesion fraction and inferior displacement of lesion centroids relative to VIM were associated with increased side effects. Multivariate models using these imaging features achieved high predictive accuracy for side effects.

KNOWLEDGE ADVANCEMENT: This study provides quantitative evidence that THOMAS-based segmentation can be used for more precise VIM targeting in MRgFUS procedures, offering a objective and reliable method for VIM targeting and intra-operative adjustment. This advancement has significant implications for improving surgical outcomes and reducing post-operative side effects.

Accurate targeting of the VIM is essential for maximizing MRgFUS treatment efficacy and minimizing undesirable side effects. However, challenges arise from the insufficient contrast and poor delineation of the nucleus on standard anatomical MR images. The traditional VIM targeting relies on indirect targeting based on coordinates relative to the anterior commissure-posterior commissure (AC-PC) line. This technique, while widely adopted, has the limitation of lacking patient-specific anatomical consideration, such as age-related ventricle enlargement,⁹ which may directly alter the patient-specific VIM coordinates in relationship with the AC-PC line. The VIM targets are often adjusted based on the ventricle size, but the choice remains subjective.^{5,10,11} In addition, there is currently no consensus on the coordinates used. Commonly used coordinates are 10.5–15 mm lateral to the midline or 10–11 mm lateral to the ventricular wall for cases with enlarged ventricles, 6 mm posterior to the mid-commissural point or 25% of AC–PC distance anterior to the PC, and 0–2 mm superior to the AC–PC line.^{5,10–12}

Both the size and the location of the FUS-induced lesion have been associated with the incidence of post-procedural adverse effects.^{13–18} Gait ataxia and unsteadiness has been reported to be the most common neurological side effect, observed in 44–56% patients immediately after treatment (within 48 hours), 22–38% in the short-term (48 hours–3 months), and persisting in 24–38% of the cases beyond 3 months.¹⁹ The high complication rate was postulated to be associated with the small size of VIM and the close proximity of regions responsible for post-operative ataxia with those associated with clinical benefit. The pronounced prevalence of these adverse effects underscores a critical need for the improvement in MRgFUS planning strategies.

Recent advances in imaging techniques offer great promise in personalized VIM targeting, including tractography-based identification of the dentatorubrothalamic tract using DTI,^{20,21} proton density imaging²², and susceptibility MRI at ultrahigh field strength.^{23–26} Additionally, a combination of advanced sequences with the recent development of automated segmentation algorithms may further facilitate treatment planning. Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR), one of the

white matter-nulled contrast sequences has been developed for better visualization of the deep gray matter and intra-thalamic structures with high-resolution, including VIM.^{27–30} Compared to tractography and susceptibility imaging methods, this method can be acquired without specialized sequences or reconstruction algorithms and can be readily incorporated into the existing clinical protocol. Complementing this imaging technique, the Thalamus Optimized Multi Atlas Segmentation (THOMAS) tool has emerged as a novel method for automated delineation of thalamic nuclei.³¹ This combination of advanced imaging and an expert-level segmentation tool potentially allows for more precise and personalized MRgFUS treatment planning for the reduction of procedure-related side effects.

This study aims to integrate FGATIR and THOMAS for patient-specific VIM targeting. We hypothesize that the spatial relationships between post-FUS lesion and THOMAS segmentations will predict the post-operative side effects.

MATERIALS AND METHODS

Patients

We retrospectively analyzed 36 consecutive patients with medication-refractory essential tremor or Parkinson's disease who underwent unilateral VIM MRgFUS at our institution between May 2022 and June 2023. All patients were diagnosed by board-certified neurologists. We excluded six patients with absent or poor-quality pre-operative FGATIR images. Thirty patients were included in the analysis (21 males, age 75.0 ± 8.0 years) (Online Supplemental Data). This research was approved by the Institutional Review Board and informed consent was waived for the retrospective study.

Image Acquisition

We acquired FGATIR, T1-weighted MPRAGE, and 3D or 2D T2-weighted image for pre-operative scan, either a 3D T1-weighted fast spoiled gradient-echo or a 3D fast imaging employing steady-state acquisition during the operation, and T1-weighted MPRAGE and T2-weighted images for post-operative scan, which were

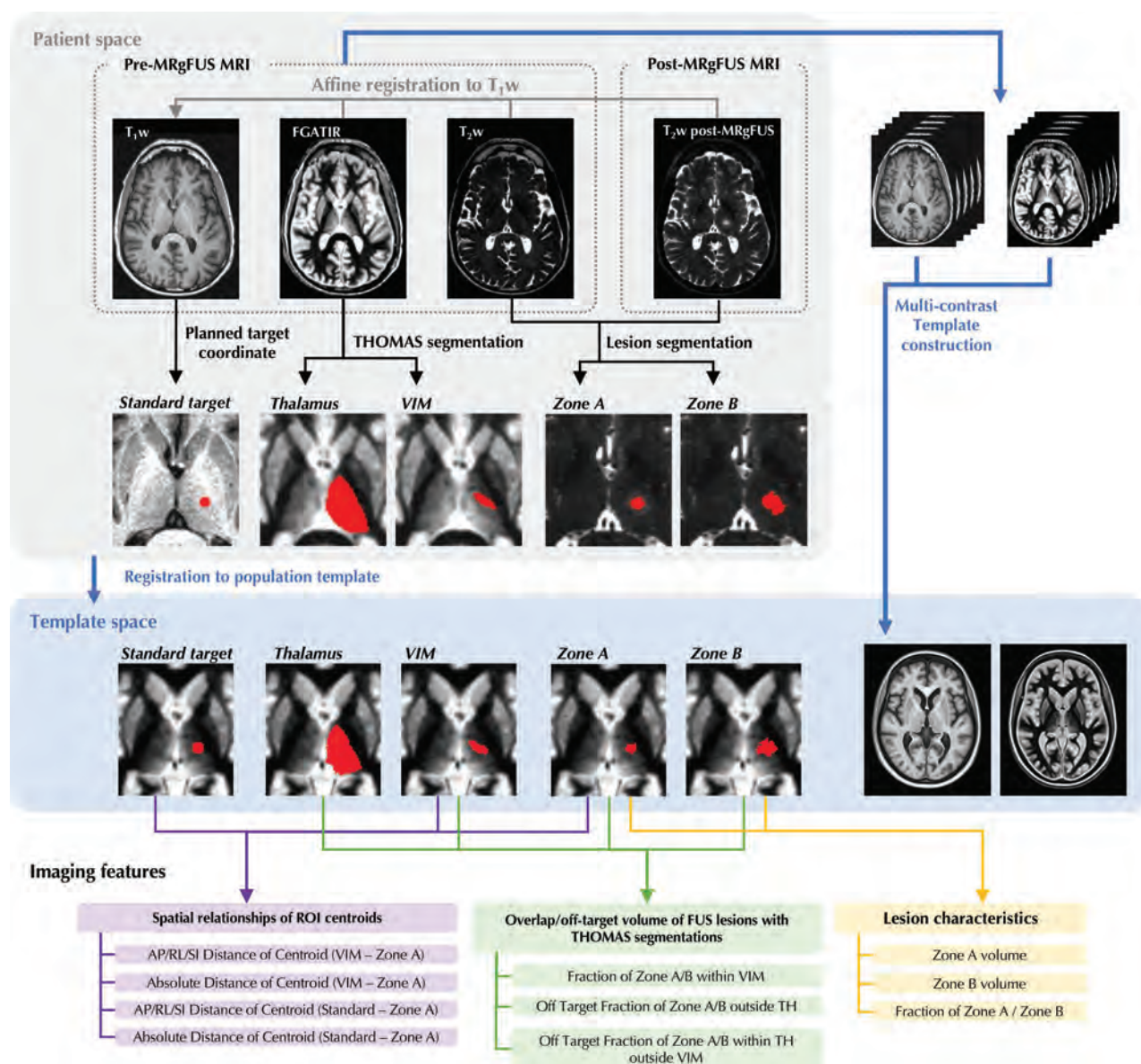


FIG 1. Imaging feature extraction pipeline. ROIs of standard target, FUS lesions and THOMAS segmentations were registered to the population-specific template generated from pre-operative T1-w and FGATIR images. Spatial relationships of ROI centroids, overlap of FUS lesions with segmentations and lesion volume characteristics were assessed. MRgFUS, MR-guided focused ultrasound; FGATIR, Fast Gray Matter Acquisition T1 Inversion Recovery; THOMAS, THalamus Optimized Multi Atlas Segmentation; VIM, ventral intermediate nucleus; TH, thalamus; AP, anterior-posterior; RL, right-left; SI, superior-inferior; ROI, region of interest.

acquired the following day of MRgFUS. Detailed sequence parameters are provided in the Online Supplemental Data.

MRgFUS Procedure

The therapeutic sonication of the targeted VIM was performed in an MRgFUS system (ExAblate Neuro, InSightec, Tirat Carmel, Israel). Details of the MRgFUS procedure have been described in prior studies.^{2,32} The ablation target coordinate was specified pre-operatively as one quarter of the length of the AC-PC line from the PC, 14 mm lateral to the midline or 11 mm lateral to third ventricle, and 3 mm superior to the AC-PC line, and fused to intra-operative MR images. Target localization was adjusted further intraoperatively by clinical monitoring of side effects and the reduction of tremor for each patient.

Image Post-processing

Five ROIs were generated in patient space for analysis, including the standard treatment target, thalamus segmentation, VIM segmentation, and two FUS lesion segmentations (Figure 1). All images were co-registered to the pre-operative T1-weighted image using an affine transformation in FSL (FLIRT; FMRIB Software Library, Oxford, England; <http://www.fmrib.ox.ac.uk/fsl/>) prior to subsequent processing.

Standard FUS Target. We generated the spherical ROI of the standard VIM ablation target with a radius of 4 mm centered on the coordinates of the first sonication recorded in the MRgFUS workstation, which was determined by the indirect targeting

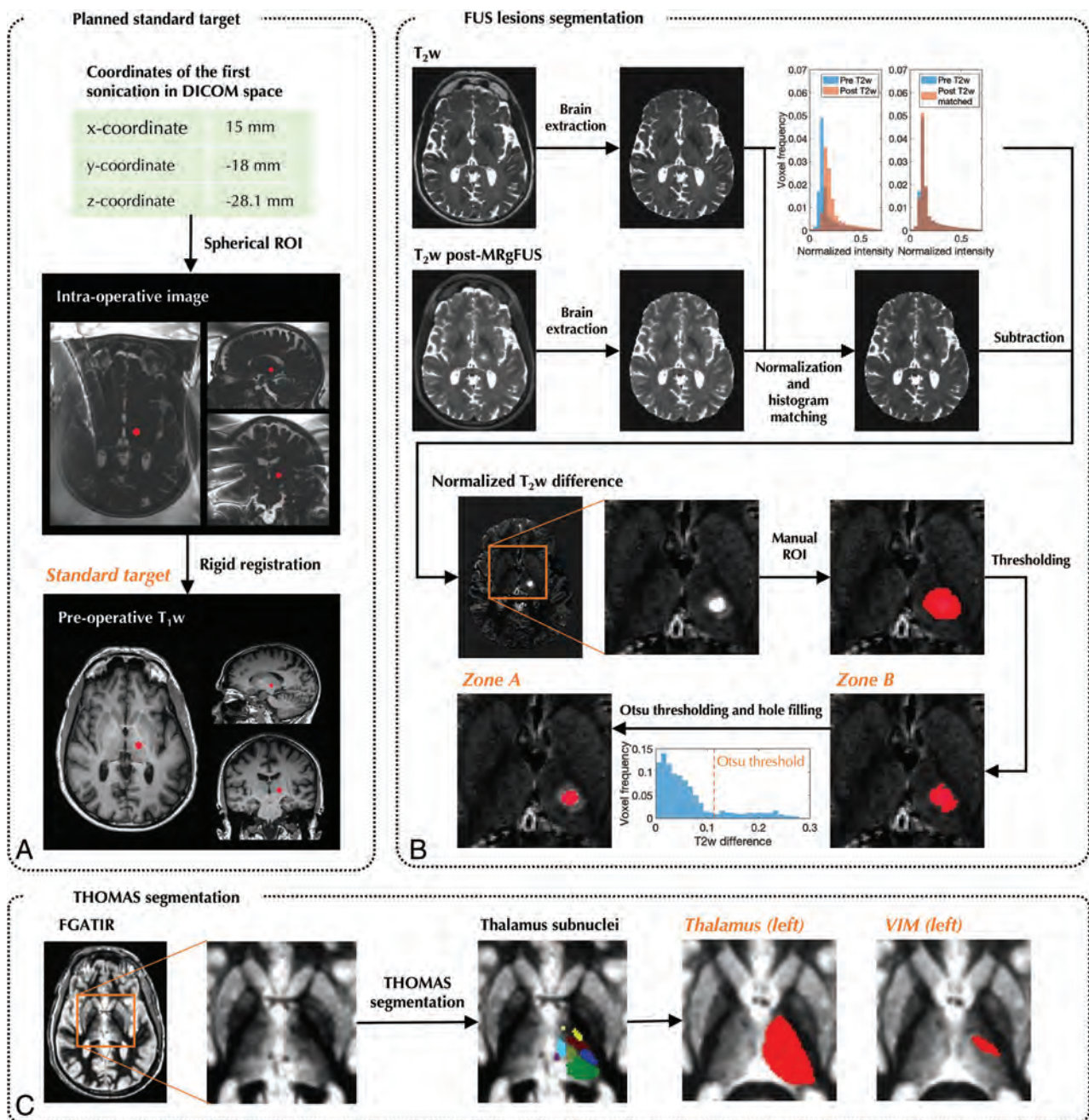


FIG 2. Procedures to create standard target, FUS lesions and THOMAS segmentations of thalamus and VIM. **A**, Standard target ROIs were created from coordinates of the first sonication. **B**, FUS lesions were generated by subtracting the pre-operative T₂-weighted image from the post-operative image and applying a thresholding method. **C**, The thalamus and VIM were segmented by applying THOMAS to pre-operative FGATIR images. The VIM here corresponds to the ventral part (inferior half) of the ventral lateral posterior nucleus in the Morel atlas. MRgFUS, MR-guided focused ultrasound; THOMAS, THalamus Optimized Multi Atlas Segmentation; VIM, ventral intermediate nucleus; FGATIR, Fast Gray Matter Acquisition T1 Inversion Recovery; ROI, region of interest.

method based on the AC-PC line as described in the previous paragraph (Figure 2A).

FUS Lesion Segmentations. Pre- and post-operative T₂-weighted images were used to identify FUS-induced lesions. We created the ROIs of Zone A, which includes a strongly hyperintense cytotoxic edema and a central hypointense coagulation necrosis on T₂-weighted images, and Zone B, which includes the Zone A and the peripheral slightly hyperintense area of vasogenic

edema.^{33–35} The ROIs were created by subtracting pre-operative T₂-weighted images from post-operative T₂-weighted images after registration, normalization, and histogram matching. Otsu thresholding method was applied to delineate the ROIs. The detailed procedure is described in the Online Supplemental Data and in Figure 2B.

THOMAS Segmentations. Pre-operative FGATIR images were processed with the THOMAS segmentation tool, a pipeline

designed to achieve optimal performance on white matter-nulled imaging contrasts (https://github.com/thalamicseg/thomas_new)³¹ to create segmentations of the thalamus (TH) and VIM of the treated side (Figure 2C).

Cohort Template Construction

We created an MRI template specific for the study population using the Advanced Normalization Tools multivariate template construction algorithm (*antsMultivariateTemplateConstruction*).³⁶ For each subject, the ROIs generated in previous steps were nonlinearly aligned to the population-specific template to enable direct comparisons across the subjects (Figure 1). The details of template creation and the figure of THOMAS segmentations on cohort template images are included in the Online Supplemental Data.

Imaging Features

We calculated the following imaging features: spatial relationships of ROI centroids (anterior-posterior [AP], right-left [RL], superior-inferior [SI] and absolute distances), overlap/off-target volume of FUS lesions with THOMAS segmentations, and lesion volume characteristics (Figure 1). Details are documented in the Online Supplemental Data.

Clinical Assessment

We reviewed the clinical records of self-reported and examination-based gait or balance disturbance on the day after MRgFUS and self-reported gait or balance disturbance at one-month post-procedure. The record of self-reported side effects at one month after surgery was not available for one patient. In order to assess the relationships between imaging features and treatment efficacy, we evaluated post-treatment Fahn-Tolosa-Marín Clinical Rating Scale for Tremor (FTM) scores of the treated side on the day after MRgFUS, and the reduction in drawing test scores from before to after the procedure, both of which were evaluated in the operating room. Details are documented in the Online Supplemental Data.

Statistical Analysis

We compared imaging features between patients with side effects and those without using Wilcoxon rank-sum test. Voxel-wise analysis was performed using a chi-square test to determine if the proportion of subjects with a Zone A lesion in that voxel differed between patients with and without side effects. In addition, we built multivariate prediction models of self-reported/exam-based side effects using three imaging features that showed the largest z-statistics in cross-sectional comparisons. We further evaluated models using features associated solely with THOMAS segmentations and lesion core (Zone A), to assess the potential of THOMAS segmentations for guiding the ablation procedure. The classification performance of the models was evaluated using the receiver operating characteristic curve analyses. Comparison of imaging features was also performed between patients with no side effects or with side effects that resolved within one month and those with persistent side effects after one month. Lastly, we assessed correlations between imaging features and FTM scores using Spearman's rank correlation. Benjamini-Hochberg (BH) correction was performed for multiple comparison and correlation tests. $P < 0.05$ after BH correction was considered statistically significant.

RESULTS

All patients demonstrated marked tremor improvement as suggested by low post-operative tremor scores and patients' self-report. Eighteen patients reported gait or balance disturbance on the day following MRgFUS procedure, with seven exhibiting these disturbances based on physical examination. One of these patients showed lower extremity weakness, while the others displayed gait instability or imbalance. Five out of 18 patients reported symptoms persisting after one month. Detailed clinical evaluations for each patient are provided in the Online Supplemental Data.

Example ROIs from two subjects are illustrated in Figure 3, depicting the FUS lesions and THOMAS segmentations, as well as their spatial relationships. In the patient with the gait and balance side effects, the FUS lesion extended further outside of the thalamus and VIM segmentations, compared to the patient without side effects. Figure 4 illustrates THOMAS-based thalamic nuclei segmentations, Zone A probabilistic maps, and standard targets of all subjects and subjects with or without side effects in the population-specific template space, and the result of voxel-wise analysis. Visually, the lesions in the group of patients with side effects were shifted more laterally and inferiorly relative to the VIM. The voxel-wise analysis indicates that voxels outside the VIM segmentation tend to have a higher proportion of patients with side effects compared to those without. The comparison of imaging features between patients with and without side effects are summarized in the Table and the Online Supplemental Data. Based on FUS lesion analysis, Zone B volume was significantly larger in patients with self-reported side effects (1.67 ± 0.70 ml vs. 1.04 ± 0.34 ml, $p_{\text{uncorrected}} = 0.01$, $p_{\text{BH}} = 0.03$). The fraction of Zone A/Zone B was smaller in both patients with self-reported side effects (0.20 ± 0.07 vs. 0.26 ± 0.07 , $p_{\text{uncorrected}} = 0.01$, $p_{\text{BH}} = 0.03$) and those with physical exam-based side effects compared to patients without (0.18 ± 0.05 vs. 0.24 ± 0.08 , $p_{\text{uncorrected}} = 0.04$), although the difference with physical exam-based side effects was not significant after BH correction.

We found that the volume fraction in Zone A or B overlapping with VIM was significantly smaller in patients with self-reported side effects (Figure 5A; Zone A within VIM: 0.31 ± 0.14 vs. 0.50 ± 0.17 , $p_{\text{uncorrected}} = 0.006$, $p_{\text{BH}} = 0.02$; Zone B within VIM: 0.14 ± 0.07 vs. 0.23 ± 0.07 , $p_{\text{uncorrected}} = 0.001$, $p_{\text{BH}} = 0.005$). Similarly, these measurements also trended smaller in patients with physical exam-based side effects, albeit without statistical significance after BH correction (Figure 5D; Zone A within VIM: 0.27 ± 0.12 vs. 0.43 ± 0.18 , $p_{\text{uncorrected}} = 0.03$; Zone B within VIM: 0.11 ± 0.05 vs. 0.20 ± 0.08 , $p_{\text{uncorrected}} = 0.01$). The off-target lesion volume fractions outside TH positively correlated with the presence of side effects, with higher off-target fractions found in patients with self-reported side effects (Figure 5B; Zone A outside TH: 0.33 ± 0.22 vs. 0.09 ± 0.07 , $p_{\text{uncorrected}} < 0.001$, $p_{\text{BH}} = 0.004$; Zone B outside TH: 0.52 ± 0.13 vs. 0.27 ± 0.08 , $p_{\text{uncorrected}} < 0.001$, $p_{\text{BH}} < 0.001$). The same features were also higher in patients with physical exam-based side effects (Figure 5E; Zone B outside TH: 0.57 ± 0.14 vs. 0.38 ± 0.15 , $p_{\text{uncorrected}} = 0.003$, $p_{\text{BH}} = 0.04$). There was no significant difference in imaging features between patients with and without persistent side effects at one month after BH multiple comparison correction, although our data showed a

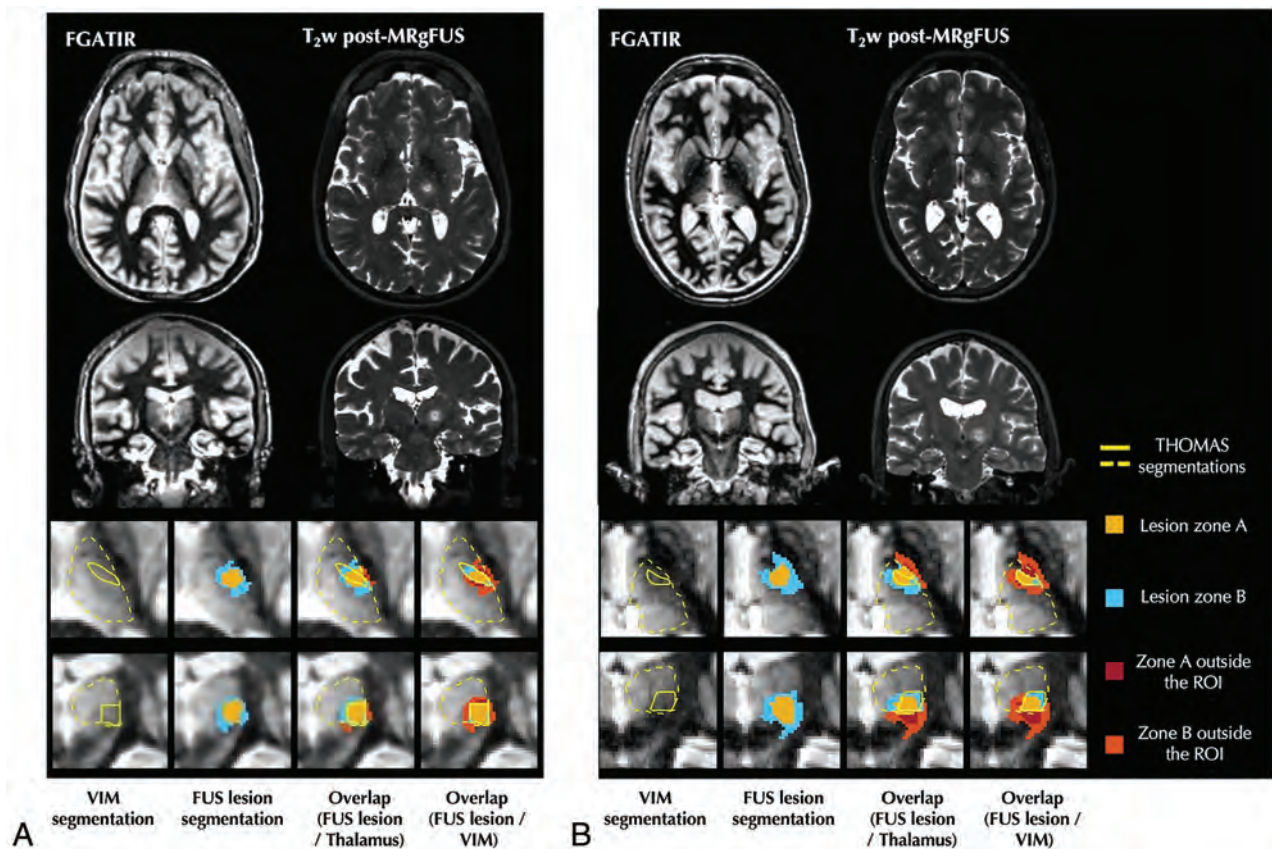


FIG 3. Example THOMAS segmentations (yellow line: thalamus; white line: VIM nucleus) and MRgFUS treated lesions (magenta: Zone A; cyan: Zone B) are shown in axial and coronal views. In the patient with side effects A, lesions extend farther out of the thalamus and segmented VIM, compared to the patient without side effects (B). FGATIR, Fast Gray Matter Acquisition T1 Inversion Recovery; MRgFUS, MR-guided focused ultrasound; THOMAS, Thalamus Optimized Multi Atlas Segmentation; VIM, ventral intermediate nucleus; ROI, region of interest.

trend where patients with persistent side effects showed a smaller fraction of Zone B overlapping with VIM and larger off-target fraction of Zone A or B outside TH compared to those without or with side effects that resolved at one month ($p_{\text{uncorrected}} < 0.05$).

As for the spatial relationships between FUS lesions and THOMAS segmentations, the centroid of Zone A tended to be more posterior, lateral and inferior in patients with self-reported side effects compared to those without, although only superior-inferior direction showed statistical significance (SI distance -2.77 ± 1.43 mm vs. -1.14 ± 0.96 mm, $p_{\text{uncorrected}} < 0.001$, $p_{\text{BH}} = 0.007$). Absolute distance between the centroids of Zone A and the VIM was significantly larger in patients with self-reported side effects (3.79 ± 1.33 mm vs. 2.55 ± 0.83 mm, $p_{\text{uncorrected}} < 0.001$, $p_{\text{BH}} = 0.02$). Absolute distance between the centroids of Zone A and the VIM was also higher in patients with exam-based side effect, although not significant after BH correction (4.20 ± 1.35 mm vs. 3.01 ± 1.17 mm, $p_{\text{uncorrected}} = 0.04$). As for the distance between FUS lesions and the standard planned FUS target, patients with physical exam-based side effects showed Zone A in a more posterior position relative to standard FUS target compared to those without side effects (-0.39 ± 0.69 mm vs. 0.63 ± 0.71 mm, $p_{\text{uncorrected}} = 0.005$). Plots of VIM and lesion centroids for patients with and without side effects in the population-specific template space are depicted in the Online Supplemental Data.

Multivariate regression models using the three most differentiating imaging features were established to predict side effects. The selected imaging features for predicting self-reported side effects include off-target fractions of Zone A/B outside TH, and off-target fraction of Zone B outside VIM and within TH. The multivariate model achieved the area under the curve (AUC) of 0.99 (95% CI: 0.88–1.00) with sensitivity of 100% and specificity of 92% (Figure 5C). For predicting physical exam-based side effects, the selected features include off-target fractions of Zone B outside TH, fractions of Zone B within VIM, and AP distance between the centroids of Zone A and standard coordinate. Similarly, the multivariate model achieved high AUC of 0.96 (95% CI: 0.73–1.00) with sensitivity of 86% and specificity of 100% (Figure 5F). Multivariate models using only the imaging features based on the spatial relationships between THOMAS segmentations and Zone A achieved AUC of 0.91 (95% CI: 0.71–0.99, sensitivity 72%, specificity 100%) for identifying patients with self-reported side effects and AUC of 0.78 (95% CI: 0.59–0.93, sensitivity 100%, specificity 65%) for identifying patients with physical exam-based side effects.

The results of the correlation between imaging features and tremor control, using post-operative tremor score and the reduction in drawing scores after MRgFUS, are shown in the Online Supplemental Data. Although no significant correlation between imaging features and FTM scores was found after BH multiple

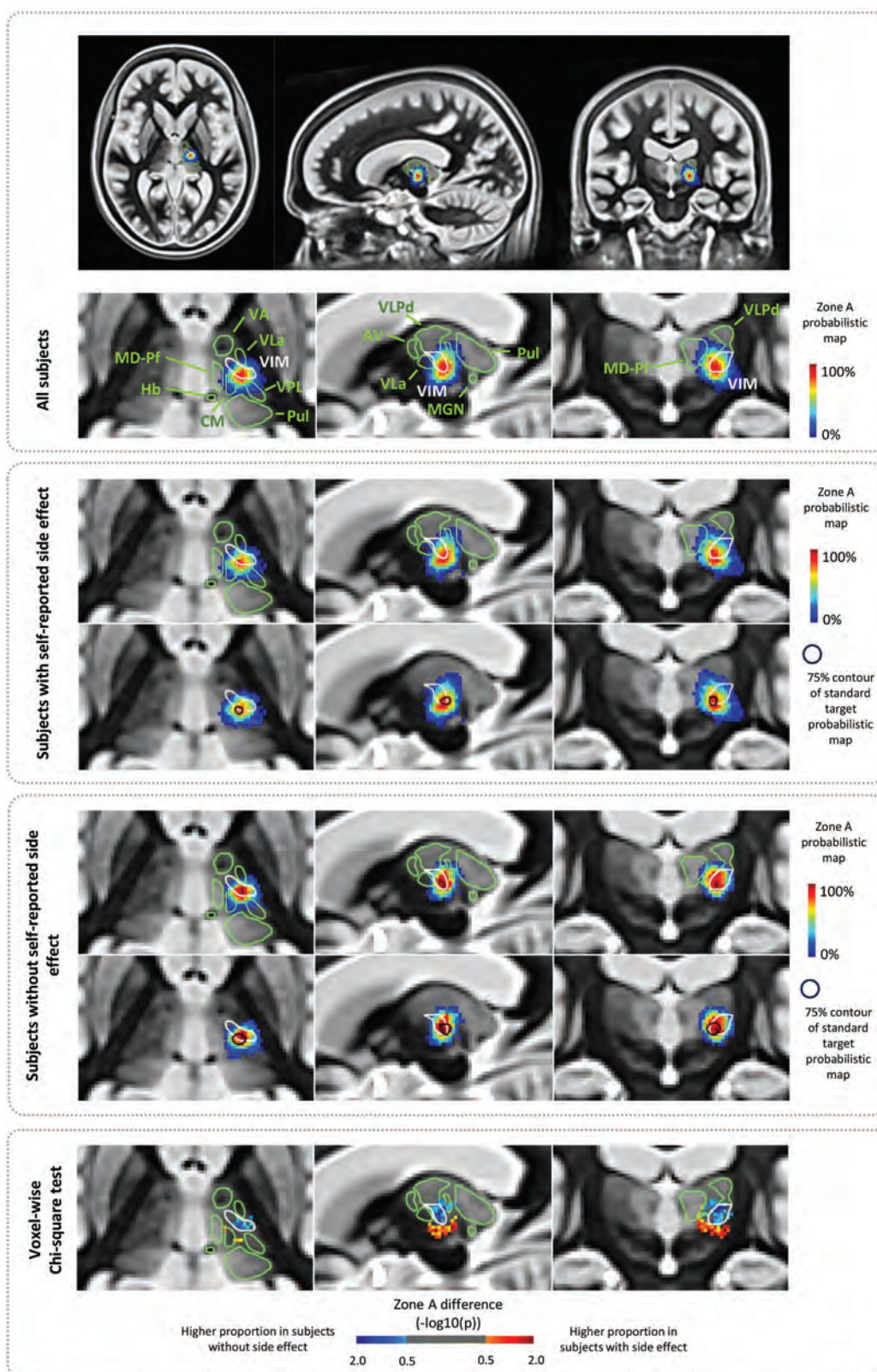


FIG 4. Probabilistic maps of Zone A in the population-specific template space. The spatial relationship between THOMAS-based thalamic nuclei segmentations, Zone A probabilistic maps, and standard targets are illustrated in different cohorts. The Zone A probabilistic map represents the voxel-wise percentage of FUS lesions across the subjects, and the standard target contour represents 75th percentile of standard coordinate ROI across the subjects. THOMAS, THalamus Optimized Multi Atlas Segmentation; FUS, focused ultrasound; VA, ventral anterior nucleus; VLa, ventral lateral anterior nucleus; VLP, ventral lateral posterior nucleus; VPL, ventral posterior lateral nucleus; VLPd, dorsal part of ventral posterior lateral nucleus; Pul, pulvinar nucleus; CM, centromedian nucleus; MD-Pf, mediodorsal-parafascicular nucleus; Hb, habenula; MGN, medial geniculate nucleus; ROI, region of interest.

Comparisons of imaging features between patients with and without side effect

MRI Features		Self-Reported Side Effect		Physical Exam-Based Side Effect
		Gait/Balance <i>p</i> -Value	Gait/balance > 1 Month <i>p</i> -Value	Gait/Balance <i>p</i> -Value
FUS lesion volume	Volume of Zone A	0.21	0.31	0.96
	Volume of Zone B	0.01	0.15	0.14
	Fraction of Zone A/Zone B	0.01	0.45	0.04
Overlap between FUS lesions and THOMAS segmentations	Fraction of Zone A within VIM ^a	0.006	0.09	0.03
	Fraction of Zone B within VIM ^a	0.001	0.01	0.01
	Off Target Fraction of Zone A outside TH ^b	< 0.001	0.02	0.02
	Off Target Fraction of Zone B outside TH ^b	< 0.001	0.008	0.003
	Off Target Fraction of Zone A within TH ^c	0.57	0.22	1
	Off Target Fraction of Zone B within TH ^c	< 0.001	0.07	0.05
Distance between FUS core lesion and THOMAS segmentations	AP Distance of Centroid (VIM - Zone A)	0.57	0.45	0.52
	RL Distance of Centroid (VIM - Zone A)	0.49	0.52	0.34
	SI Distance of Centroid (VIM - Zone A)	< 0.001	0.27	0.1
	Absolute Distance of Centroid (VIM - Zone A)	< 0.001	0.19	0.04
Distance between FUS core lesion and standard coordinate	AP Distance of Centroid (Standard - Zone A)	0.64	0.32	0.005
	RL Distance of Centroid (Standard - Zone A)	0.17	0.94	0.74
	SI Distance of Centroid (Standard - Zone A)	0.43	0.69	0.7
	Absolute Distance of Centroid (Standard - Zone A)	0.23	0.65	0.7

^a Volume of overlap between Zone A (or B) and VIM divided by that of Zone A (or B).

^b Volume of Zone A (or B) outside TH divided by that of Zone A (or B).

^c Volume of Zone A within TH but outside VIM divided by that of Zone A (or B).

P-values in the table represent uncorrected *p*-values. The bolded items represent statistical tests with Benjamini–Hochberg corrected *p*-values < 0.05.

Abbreviations: FUS, focused ultrasound; THOMAS, Thalamus Optimized Multi Atlas Segmentation; VIM, ventral intermediate nucleus; TH, thalamus; AP, anterior-posterior; RL, right-left; SI, superior-inferior.

statistics correction, lower positioning of Zone A relative to the VIM showed a tendency to correlate with a lower post-operative tremor score and a greater reduction in drawing score.

DISCUSSION

To examine the usefulness of FGATIR in combination with the thalamus segmentation algorithm, THOMAS, on improving VIM MRgFUS precision, we retrospectively assessed the relationships between FUS lesions, THOMAS segmentations derived from pre-FUS images, and the conventional target adopted during FUS procedures in 30 ET and tremor-dominant PD patients. Two main results emerged from our study: (1) patients with post-FUS gait and balance side effect exhibit significantly different spatial relationships between FUS lesions and THOMAS-based segmentations compared to those without; (2) multivariate models based on imaging characteristics of FUS lesions and THOMAS segmentations demonstrated high predictive accuracy for post-procedural side effects.

Our findings align with previous research,^{6,13,37} indicating that a larger volume of Zone B and a smaller fraction of Zone A/Zone B – indicative of a greater extent of vasogenic edema – are associated with gait and balance side effects. One potential explanation is that the larger area of vasogenic edema may lead to the disruption of the corticospinal and/or cerebellothalamic tracts. In addition to the adjustments to the duration and temperature of sonication during the procedure, hardware improvement to reduce the size of lesions could be an effective approach to minimizing side effects, while it is necessary to consider that excessively small lesions may lead to insufficient therapeutic efficacy.³⁸

Our results also showed that patients with acute gait and balance side effects exhibited a significantly smaller fraction of Zone

A or Zone B within VIM and a larger off-target lesion fraction outside TH, alongside a greater distance between Zone A and VIM. Although only superior-inferior direction showed statistical significance, there was a trend for the centroid of Zone A to be more posterior, lateral and inferior relative to the VIM, supporting previous evidence that lesions inferolateral to the thalamus were associated with an increased risk of acute adverse effects on gait and dysmetria.^{13,37,39} These results are associated with the finding that gait difficulties occur due to lesions impacting the corticospinal tract, which is located just lateral to the VIM.^{13,21} Our results add to the existing literature reporting lesion location as a significant factor impacting post-FUS side effect, and provides evidence that such off-target effects can be quantitatively evaluated using imaging features retrieved with a semi-automated processing procedure. These findings also highlight the utility of THOMAS-based segmentations in refining targets to reduce the acute side effects of MRgFUS. As demonstrated in previous literature, the dentatorubrothalamic tract, which is relayed by the VIM nucleus, also contributes to gait side effects. Therefore, even if the VIM is precisely targeted, side effects are still considered to occur with suboptimal size and temperature of the lesion.¹³ This explains the overlap in the locations of FUS lesions between patients with and without gait side effects in our study, as shown in Figure 5 and Supplementary Figure 2.

Among the 18 patients experiencing acute side effects post-MRgFUS, five reported persistent side effects one month later, a slightly lower incidence rate than previously reported.¹⁹ No significant differences were found in imaging features between patients with and without persistent side effects after BH correction. However, trends toward significance were observed in the overlap of Zone A/B with the VIM and the off-target Zone A/B

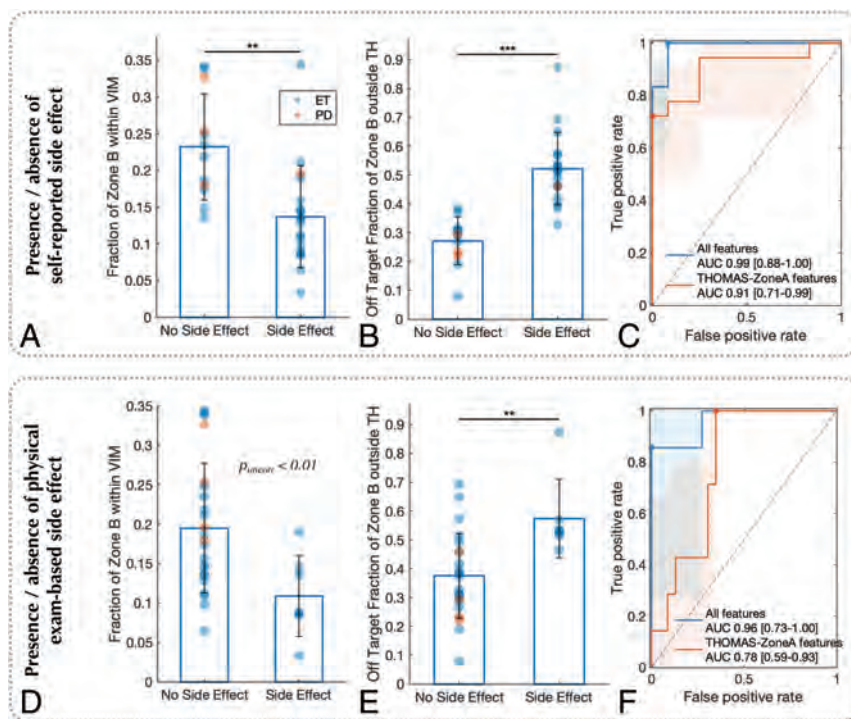


FIG 5. Results of imaging feature comparisons between patients with self-reported or physical exam-based gait/balance side effects and those without. In patients with side effects, Zone B shows less overlap with VIM segmentation and the off-target fraction of Zone B outside TH segmentation is greater (Graphs A–B and D–E). Graphs C and F show receiver operating characteristic curves of multivariate prediction models of side effects using imaging features. ET, essential tremor; PD, Parkinson's disease; VIM, ventral intermediate nucleus; TH, thalamus; AUC, area under the curve.

fraction outside the thalamic segmentation. Given that post-FUS lesion decreases over time and lesion shrinkage varies among individuals, future studies incorporating long-term follow-up MR imaging may assist the identification of specific imaging characteristics associated with persistent side effects.

THOMAS was developed using manual segmentations of 7T white matter-nulled MPAGE data guided by the Morel atlas.^{31,40} Similar to white matter-nulled MPAGE, FGATIR provides improved intra-thalamic contrast by highlighting grey matter structures that are surrounded by highly myelinated areas using preferential nullification of white matter signal.³⁰ Such unique contrast is thought to contribute to the reliability of THOMAS segmentation, as validated by high Dice coefficient scores when compared to the ground truth segmentation by expert neuroradiologist.³¹ The VIM segmentation obtained using THOMAS on pre-operative images can effectively guide target selection for pre-operative planning and assist with intra-operative adjustments. Despite its great potential, the clinical application of THOMAS in direct VIM targeting for neuromodulatory treatments like deep brain stimulation or MRgFUS has been scarcely evaluated. Notably, a recent study using THOMAS on 7T MRI found no correlations between overlap/spatial relationships of ablation lesions with VIM and 1-month post-treatment clinical outcome,¹⁷ which is consistent with our results. Expanding upon existing research, our study explores the link between FUS-induced imaging characteristics and side effects using THOMAS

with 3T MR images. While it is an expected finding that post-procedural side effects are associated with off-target ablation, our study provides rigorous quantitative evidence supporting this hypothesis. Additionally, the integration of FGATIR and THOMAS in our methodology can serve as a practical tool for objective and reproducible localization of VIM, for both pre-operative planning and intra-operative adjustments, reducing the reliance on neurosurgeons' experience and expertise.

There have been increasing efforts to improve the targeting of VIM for neuromodulation using various advanced imaging methods.^{1,21,41} VIM targets based on patient-specific dentatorubrothalamic tracts demonstrated by DTI were more anterior and medial than the indirect methods, which may help avoid regions at risk for motor and sensory adverse effects, and VIM targeting by DTI showed reduced post-procedure acute ataxia as compared to indirect targeting.^{19,42} Compared to tractography-based methods, segmenting FGATIR images using THOMAS offers several advantages. First, FGATIR has a higher resolution (about 1-mm isotropic) than DTI (about 2-mm isotropic). Second, FGATIR is less susceptible to image distortion compared to DTI.⁴³ Tractography based on DTI data may also suffer from inadequate representation of the underlying anatomy in areas with crossing fibers and within gray matter structures such as the thalamus.^{44,45} As such, its usefulness as the primary method of VIM targeting are still being debated.⁴⁶ Other direct VIM imaging methods include susceptibility weighted imaging^{23,25,26} and quantitative susceptibility mapping,²⁴ which have only been evaluated at ultrahigh field of 7T, but not at the more clinically-accessible field strength of 3T or lower. On the other hand, the THOMAS segmentation method we evaluated provides reliable high-resolution targeting of VIM using clinically available FGATIR images acquired by 3T MRI.

MRgFUS is influenced by various factors beyond targeting, such as low skull density ratios, which require higher energy to reach therapeutic temperatures.⁴⁷ Additionally, thermal ablation lesions in the focal zone form a prolate ellipsoid shape.⁴⁸ Techniques like CT-based aberration correction and echo focusing have been developed to stabilize lesion formation, but further research is needed to confirm their full effectiveness.⁴⁷

Our study has several limitations. First, a systematic pre-operative and long-term follow up tremor and side effect evaluations were not available. More rigorously controlled studies with adequate pre- and long-term tremor scores are necessary to evaluate the impact of VIM segmentation by THOMAS on tremor improvement and persistent side effects. Furthermore,

although we performed the additional analysis using physical exam-based gait and balance assessment to overcome the subjective bias of self-reported side effects, prospective studies of MRgFUS-associated side effect using quantitative measures such as Berg Balance Scale and standardized pre- and post-procedure neurologic exam protocols will provide a more comprehensive and robust evaluation of gait and balance impairment. Such methods are particularly crucial for ET and PD, which are prone to causing gait disturbances. Second, due to the limited number of patients, we did not assess other side effects including sensory and speech symptoms. While less common than gait disturbance, these side effects are critical for patients' quality of life.^{13,42} Lastly, the relatively small difference of distance observed between the two groups compared to MRI resolutions indicates that the precise targeting of VIM would benefit from techniques with improved imaging resolution. Future developments to enhance MRI resolution, including ultrahigh field MRI and super-resolution deep learning approaches may further increase the accuracy of THOMAS for direct targeting.

CONCLUSIONS

In conclusion, THOMAS segmentation derived imaging features predict post-operative gait/balance side effect in patients treated with VIM MRgFUS, and may provide a potential tool for aiding the direct targeting of VIM and reducing side effects in patients undergoing MRgFUS.

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Diagnostic Performance of ASL-MRI and FDG-PET in Frontotemporal Dementia: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: While the diagnosis of frontotemporal dementia (FTD) is based mostly on clinical features, [^{18}F]-FDG-PET has been investigated as a potential imaging standard in ambiguous cases, with arterial spin-labeling (ASL) MRI gaining recent interest.

PURPOSE: The purpose of this study is to conduct a systematic review and meta-analysis on the diagnostic performance of ASL MRI in patients with FTD and compare it with that of [^{18}F]-FDG-PET.

DATA SOURCES: A systematic search of PubMed, Scopus, and Embase was conducted until March 13, 2024.

STUDY SELECTION: Inclusion criteria were original articles, patients with FTD and/or its variants, use of ASL MR perfusion imaging with or without [^{18}F]-FDG-PET, and presence of sufficient diagnostic performance data. Exclusion criteria were meeting abstracts, comments, summaries, protocols, letters and guidelines, longitudinal studies, and overlapping cohorts.

DATA ANALYSIS: The quality of eligible studies was assessed by using the Quality Assessment of Diagnostic Accuracy Studies-2. Pooled sensitivity, specificity, and diagnostic odds ratio (DOR) for [^{18}F]-FDG-PET and ASL MRI were calculated, and a summary receiver operating characteristic curve was plotted.

DATA SYNTHESIS: Seven eligible studies were identified, which included a total of 102 patients with FTD. Aside from some of the studies showing, at worst, an unclear risk of bias in patient selection, index test, flow, and timing, all studies showed low risk of bias and applicability concerns in all categories. Data from 4 studies were included in our meta-analysis for ASL MRI and 3 studies for [^{18}F]-FDG-PET. Pooled sensitivity, specificity, and DOR were 0.70 (95% CI: 0.59–0.79), 0.81 (95% CI: 0.71–0.88), and 8.00 (95% CI: 3.74–17.13) for ASL MRI and 0.88 (95% CI: 0.71–0.96), 0.89 (95% CI: 0.43–0.99), and 47.18 (95% CI: 10.77–206.75) for [^{18}F]-FDG-PET.

LIMITATIONS: The number of studies was relatively small, with a small sample size. The studies used different scanning protocols as well as a mix of diagnostic metrics, all of which might have introduced heterogeneity in the data.

CONCLUSIONS: While ASL MRI performed worse than [^{18}F]-FDG-PET in the diagnosis of FTD, it exhibited a decent diagnostic performance to justify its further investigation as a quicker and more convenient alternative.

ABBREVIATIONS: 3DPCASL = 3D pseudocontinuous ASL; AD = Alzheimer disease; ASL = arterial spin-labeling; bvFTD = behavioral variant of frontotemporal dementia; DOR = diagnostic odds ratio; FN = false-negative; FP = false-positive; FTD = frontotemporal dementia; NLR = negative likelihood ratio; PASL = pulsed ASL; PLD = postlabel delay; PLR = positive likelihood ratio; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis; QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies-2; SROC = summary receiver operative characteristic; TN = true-negative; TP = true-positive

Frontotemporal dementia (FTD) is a spectrum of clinical syndromes characterized by progressive neurodegeneration and atrophy in the frontal and temporal lobes. More specifically, its most common behavioral subtype (behavioral variant of frontotemporal

dementia [bvFTD]) is characterized by impairments in behavior and language.^{1–3} With an estimated prevalence of 15 per 100,000 in people between 45 and 64 years of age,⁴ it is the second most common cause of dementia in patients under the age of 65.⁵ In patients older than 65, FTD is the third most common cause of dementia.

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Given the rapid functional decline and relatively short average survival time of 5 to 10 years for patients with FTD, early and reliable diagnosis remains critical.^{6,7} The premortem diagnosis of FTD is based mostly on clinical features, standardized cognitive tests, and consensus criteria.⁸ Unfortunately, symptoms can often mimic those of other neurodegenerative diseases like Alzheimer disease (AD) or even psychiatric conditions with prominent behavioral features, such as bipolar disorder and schizophrenia.⁹

[¹⁸F]-FDG-PET has been found to help with not only the diagnosis of FTD,¹⁰⁻¹² but also its differentiation from other dementias like AD.¹² [¹⁸F]-FDG-PET identifies metabolically active tissues throughout the body. As such, it can leverage the distinct atrophic and hypometabolic patterns of different dementias to achieve reliable diagnosis and differentiation.¹³ Unfortunately, [¹⁸F]-FDG-PET carries several disadvantages, including high costs and radiation exposure. Arterial spin-labeling (ASL) MRI has thus been investigated as an alternative to [¹⁸F]-FDG-PET, requiring no radiation exposure nor injection for the diagnosis of several dementias.¹⁴ Performing ASL MRI is convenient as patients with neurocognitive symptoms or suspicion of dementia are already likely to undergo structural MRI and it can thus be added as part of the protocol. Such investigation is based on the fact that areas of hypoperfusion and hypometabolism follow similar patterns.^{15,16} Further endeavors have been made to compare the performance of ASL MRI and [¹⁸F]-FDG-PET in the diagnosis of FTD within the same population with comparable yet variable results.¹⁷⁻²³

While some studies have tried pooling and systematically reviewing the available literature on the use of ASL MRI in several dementias,^{24,25} the same has not been done for FTD specifically. Therefore, the purpose of this systematic review and meta-analysis is to assess the diagnostic performance of ASL MRI versus [¹⁸F]-FDG-PET in patients with FTD.

MATERIALS AND METHODS

Search Strategy and Eligibility Criteria

The systematic review was conducted following an apriori-defined protocol (available from the authors upon request). It was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.²⁶ Two independent reviewers (R.D. and B.B.O., with more than 1–2 years of research experience, respectively) systematically searched the PubMed, Scopus, and Embase databases from inception to March 13, 2024, to identify studies investigating the use of ASL MR perfusion in patients with FTD and its variants. The detailed search string can be found in the Online Supplementary Data. The search was supplemented by citation checking and contacting the author of the eligible articles if necessary.

All search results were imported to EndNote 21 (Clarivate), where duplicates were automatically screened and deleted. The remaining references were imported into the Rayyan online platform,²⁷ where further duplicates were removed. Screening of titles and abstracts was performed by 2 independent reviewers (R.D. and B.B.O.). A third reviewer (L.P.L., neuroradiologist, 14 years of experience) examined all screening results, and discordant evaluations were resolved by discussion to reach a

consensus. All screening decisions are documented and outlined in the Online Supplemental Data.

Inclusion Criteria

Studies were included if they met all the following criteria: a) original articles published in English, b) inclusion of patients with FTD and/or its variants, c) studies that provided the diagnostic criteria for FTD and its variants used, d) used ASL MR perfusion imaging with or without [¹⁸F]-FDG-PET, and e) presence of sufficient data on the performance of ASL. There were no limitations regarding the age, nationality, race, sex, and disease stage of the participants.

Exclusion Criteria

Studies were excluded if they met any of the following criteria: a) duplicates; b) animal studies; c) did not provide qualitative or quantitative information about the diagnostic performance of ASL; d) longitudinal studies; e) studies with overlapping cohorts; and f) meeting abstracts, comments, summaries, protocols, letters and guidelines. In case 2, studies had overlapping cohorts; the most recent study was included.

Data Extraction

Data extraction was performed independently by 2 investigators (R.D. and P.A., 2 years of research experience). For each article, we extracted the following variables: a) authors, b) journal, c) year of publication, d) study design, e) target condition, f) sample size, g) patient demographics such as age and sex, h) ASL sequence and protocol, i) reference standard, j) study conclusions, k) sensitivity, l) specificity, and m) accuracy. If true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) were not explicitly provided, they were calculated by using the provided diagnostic numbers. The numbers for only patients with bvFTD were extracted.

Quality Evaluation

The quality assessment was conducted independently by 2 investigators (R.D. and P.A.) by using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).²⁸ Four domains were evaluated: patient selection, index test, reference standard, and flow and timing. The questions pertaining to each domain were answered with Yes, No, or Unclear, with a final score for each domain reached via consensus between the 2 investigators. Concerns about applicability and bias risk were graded as low, high, or unclear. All discordant evaluations were settled through discussion or by a third independent reviewer (L.P.L.).

Meta-Analysis

All statistical analyses were performed on STATA 17 (Stata). When needed, TP, FP, FN, and TP were calculated by using the sample sizes and diagnostic metrics provided by the studies. The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and the heterogeneity were calculated by a random-effects model with corresponding 95% CI by using the Clopper-Pearson method.²⁹ In addition, we summarized the joint distribution of TP and TN rates in a summary receiver operating characteristic (SROC) curve. The area under the curve represents an

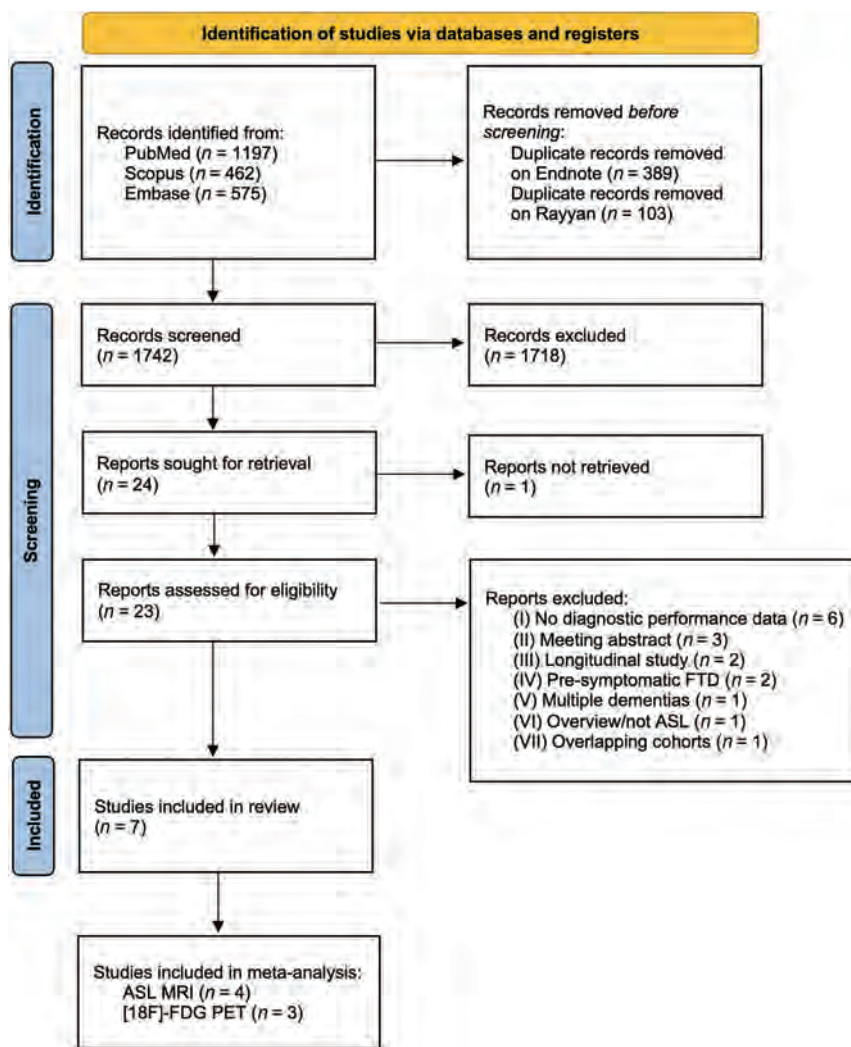


FIG 1. PRISMA flow diagram of the study selection process.

analytical summary of test performance and displays the trade-off between sensitivity and specificity. The pooled sensitivity, specificity, PLR, NLR, DOR, and SROC curves were calculated and plotted by using the metadta STATA command.³⁰ Statistical heterogeneity was quantified by using the I^2 statistic with the following interpretation: 0%–25% indicates low heterogeneity, 50%–75% indicates high heterogeneity, and >75% indicates large heterogeneity.³¹ Heterogeneity was also assessed visually on the SROC curve, with high heterogeneity suspected if individual studies substantially deviated from the SROC line.³² The same analysis was performed for ASL and [^{18}F]-FDG-PET separately.

RESULTS

Eligible Studies

The study selection process is summarized in Fig 1. After excluding duplicates ($n = 492$) and articles unrelated to our topic of interest based on the title and abstract ($n = 1718$), the full text of 23 articles was ultimately acquired and retrieved. Sixteen articles were excluded because of the following reasons, which are further detailed in the Online Supplemental Data: no diagnostic performance data ($n = 6$), meeting abstracts ($n = 3$), longitudinal studies

($n = 2$), presymptomatic genetic FTD ($n = 2$), multiple dementias lumped together ($n = 1$), overview/not ASL ($n = 1$), and overlapping cohorts ($n = 1$), leading to a total of 7 included studies.^{17–23} Because of a lack of diagnostic metric reporting, 3 studies^{19,22,23} were included in the review but not in the meta-analysis.

Study Characteristics

The Online Supplemental Data summarize the main characteristics of the included studies. The studies were published between 2006 and 2018. The studies were all cross-sectional, with all but one²⁰ happening at a single-center. All studies took place at specialized memory/dementia clinics, with other possibly overlapping diseases being excluded from all of them. In addition to FTD, some of the studies included other diseases like AD, progressive supranuclear palsy, and limbic encephalitis.^{18–23} One study²³ used a multidisciplinary team and follow-up approach as the standard for FTD diagnosis, whereas the rest used published consensus criteria. A total of 102 patients with FTD were included across all 7 studies, with a mean age of 60.8 years. Three studies^{17,20,23} relied on the visual assessment of their images for diagnosis, one¹⁹ on both visual and quantitative assessments, whereas the other 3 relied on quantitative measurements.

The studies by Verfaillie et al,²² Fällmar et al,¹⁹ and Weyts et al²³ did not provide diagnostic performance metrics to calculate TP, TN, FP, and FN, while Du et al¹⁸ did not study [^{18}F]-FDG-PET. Therefore, 83 patients were included in the subsequent meta-analysis on the performance of ASL, while 62 patients were included in the meta-analysis on the performance of [^{18}F]-FDG-PET.

The Online Supplemental Data summarize the ASL MRI scanning details of each study. One study¹⁸ used a 1.5T scanner, while the rest used 3T scanners. Two studies^{18,21} used pulsed ASL sequences, while the rest used 3D pseudocontinuous ASL (3DPCASL) sequences. Scanning parameters and voxel sizes were variable and heterogeneous across studies.

Quality Assessment

A summary of the quality assessment of the included studies by using the QUADAS-2 tool is illustrated in Fig 2. There was no suspicion of a high risk of bias or high applicability concerns regarding any category in all included studies. Three studies^{17,18,20} had an unclear risk of bias regarding patient selection due to unclear reporting of randomization/consecutiveness during the selection, while the rest had a low risk. Two studies^{18,21} showed an

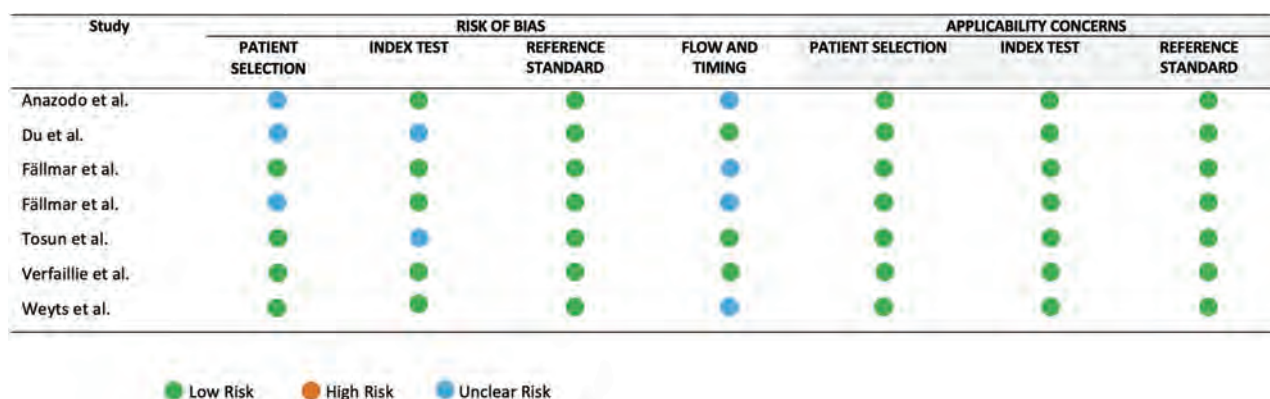


FIG 2. Summary of the QUADAS-2 results.

unclear risk of bias relating to the index test due to unclear reporting on the blinding of the index test readers, with the rest having a low risk. Three studies^{17,19,20,23} had an unclear risk of bias regarding flow and timing because not all patients were included in the analysis, while the rest had a low risk. No risk of bias was found regarding the reference standard in any of the studies, since all used published criteria or clinical follow-up for the diagnosis of FTD. There was also a low concern for applicability for the study population, index test, and reference standard since all 3 matched the review question in all the included studies.

Meta-Analysis

ASL MRI. Four articles reported enough diagnostic metrics to be included in our analysis. Fig 3A shows the forest plot of the calculated sensitivity and specificity of each study. Sensitivities ranged between 0.55 (95% CI: 0.32–0.77) and 0.78 (95% CI: 0.60–0.91). Specificities ranged between 0.60 (95% CI: 0.26–0.88) and 0.93 (95% CI: 0.68–1.00). The pooled sensitivity was 0.70 (95% CI: 0.59–0.79), while the pooled specificity was 0.81 (95% CI: 0.71–0.88). Fig 4A shows the forest plot for the DOR of each study. DOR values for each study ranged from 3.50 (95% CI: 0.55–22.30) to 50.00 (95% CI: 5.57–449.03), with a pooled DOR of 8.00 (95% CI: 3.74–17.13). Visual assessment of the SROC curve (Fig 5A) showed no prominent departures/outliers.

[¹⁸F]-FDG-PET. Three articles reported enough diagnostic metrics to be included in our analysis. Fig 3B shows the forest plot of calculated sensitivity and specificity of each study. Sensitivities ranged between 0.78 (95% CI: 0.60–0.91) and 0.95 (95% CI: 0.75–1.00). Specificities ranged between 0.55 (95% CI: 0.38–0.71) and 1.00 (95% CI: 0.78–1.00). The pooled sensitivity was 0.88 (95% CI: 0.71–0.96) while the pooled specificity was 0.89 (95% CI: 0.43–0.99). Fig 4B shows the forest plot for the DOR of each study. DOR values for each study ranged from 23.47 (95% CI: 2.85–193.61) to 105.40 (95% CI: 5.62–1976.82), with a pooled DOR of 47.18 (95% CI: 10.77–206.75). Visual assessment of the SROC curve (Fig 5B) showed no prominent departures/outliers.

DISCUSSION

FTD is one of the major causes of neurodegenerative dementia in adulthood, accounting for 20% of all degenerative dementia cases

in adults younger than 65.⁵ Presenting symptoms can mimic other neurodegenerative and psychiatric diseases, potentially leading to misdiagnosis and delays in intervention in a highly progressive disease.⁹ [¹⁸F]-FDG-PET has been found to be a useful tool in the diagnosis and differentiation of dementias, including FTD.^{10–12} ASL MRI is being investigated as a more convenient option for the diagnosis of FTD,^{17–23} requiring no radiotracer injection and given that it could be acquired during the same session as that of a standard structural MRI for the evaluation of cognitive symptoms. To our knowledge, our study represents the first systematic review and meta-analysis on the use of ASL MRI versus [¹⁸F]-FDG-PET in the diagnosis of FTD specifically.

Our search of the available literature yielded a total of 7 articles covering 102 patients. While all were assessed, evaluated, and reviewed, only 4 of them (and thus 83 patients) were included in the meta-analysis of ASL MRI performance, while only 3 (and thus 62 patients) were included in that of [¹⁸F]-FDG-PET. Our quality assessment showed an unclear risk of bias in several of the included studies regarding several of the categories. Nevertheless, visual and quantitative assessments showed the included data to be mostly in agreement.

Virtually all studies individually found that [¹⁸F]-FDG-PET still holds an advantage in diagnosing FTD, with its performance being at least as good as that of ASL MRI. Our analysis further substantiates this claim, with a pooled sensitivity of 0.88 versus 0.70, pooled specificity of 0.89 versus 0.81, and pooled DOR of 47.18 versus 8.00 for [¹⁸F]-FDG-PET versus ASL MRI, respectively. Such findings fall in line with what previous studies have found regarding the diagnostic performance of [¹⁸F]-FDG-PET and ASL MRI in all-type dementias. Dolui et al³³ found that ASL MRI and [¹⁸F]-FDG-PET hold comparable diagnostic power in AD and mild cognitive impairment, while Haidar et al²⁵ also found that [¹⁸F]-FDG-PET performed better in the diagnosis of all-type dementias. We suspect multiple reasons behind this finding. First, basi-frontal cortices physiologically experience relative hyperperfusion compared with the rest of the brain, normally leading to hyperperfusion artifacts and false suspicion of pathologically increased perfusion.³⁴ Given that the frontal and temporal lobes are primarily affected in FTD, the pathologic decrease in frontal lobe perfusion might not be enough to overcome its baseline relative hyperperfusion, leading to difficulty in

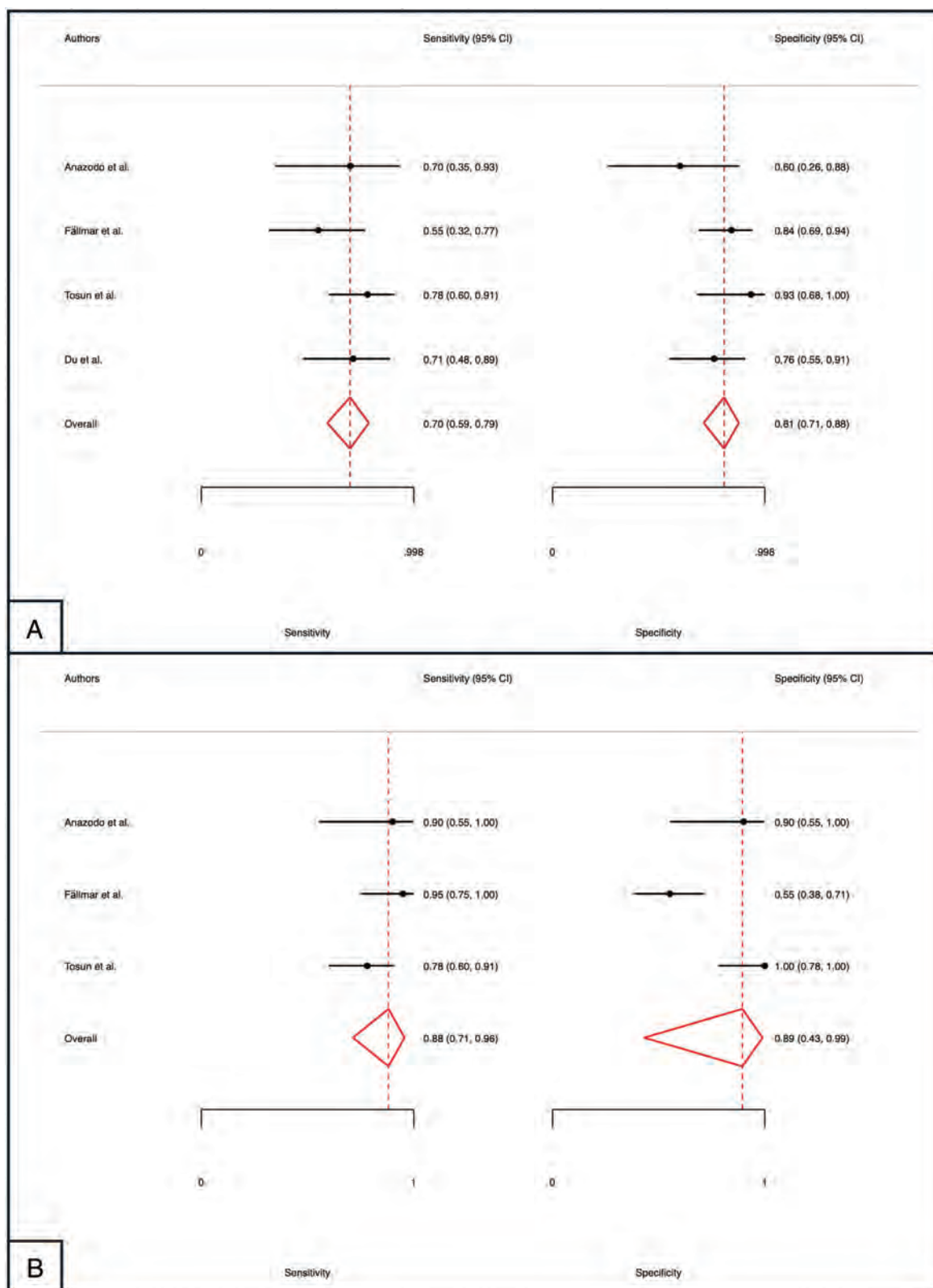


FIG 3. Forest plot of the studies' sensitivity and specificity for (A) ASL MRI and (B) [^{18}F]-FDG-PET.

its identification. Second, all studies used a fixed postlabel delay (PLD) for all of their patients during imaging. Because of the variable blood velocity from patient to patient depending on vessel patency, smearing or blurring of the signal could occur in

patients where PLD is not optimal, a phenomenon referred to as PLD artifact.^{34,35} Investigations have suggested using variable PLDs, depending on patient blood velocity, to minimize such artifact.³⁶ Third, glucose metabolism is one of the first markers

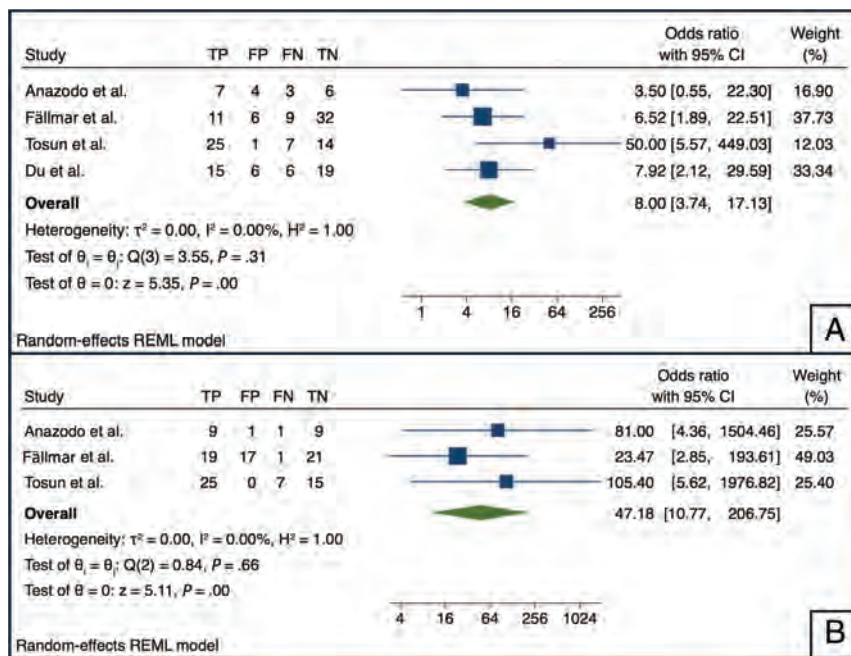


FIG 4. Forest plot of the studies' DOR for (A) ASL MRI and (B) $[^{18}\text{F}]$ -FDG-PET.

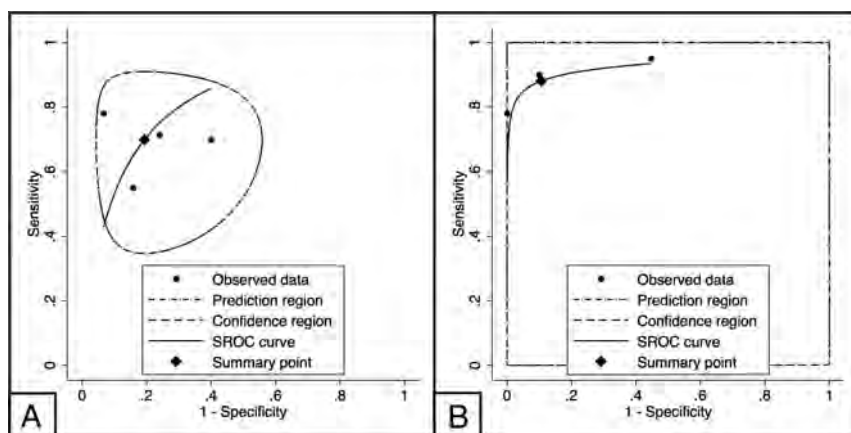


FIG 5. SROC plot of the studies for (A) ASL MRI and (B) $[^{18}\text{F}]$ -FDG-PET.

of neuronal activity change,³⁷ preceding any atrophy or changes in regional perfusion. As such, in diseases with rapid progression, hypoperfusion might lag behind hypometabolism,³⁸ at least in part explaining the difference in performance of their respective imaging techniques. Nevertheless, our analysis showed ASL MRI possessing a decent diagnostic power, making it a potential alternative for $[^{18}\text{F}]$ -FDG-PET in cases where clinical symptoms were too ambiguous.

ASL MRI presents itself as an alternative to $[^{18}\text{F}]$ -FDG-PET in cases where contrast injection is contraindicated, such as in diabetic patients. It can also be performed in addition to structural MRI as part of the work-up for neurocognitive symptoms, saving time and cost. For example, it can help rule in or out FTD where symptoms overlap with other diseases like AD, enabling early and more certain therapy, especially in light of emerging disease-

modifying anti-amyloid therapies. As a final step, and in cases where ASL did not yield satisfactory results, we suspect that $[^{18}\text{F}]$ -FDG-PET can be added to further increase sensitivity and specificity, especially in the case of double positives or double negatives. What remains to be overcome are the limitations inherent in the current state of ASL MRI. Notably, ASL suffers from a lack of standardization across scanner vendors,³⁹ leading to difficulties in consistent clinical applications. ASL also has a higher failure rate compared with both structural MRI and $[^{18}\text{F}]$ -FDG-PET. Finally, there are cases where both ASL and $[^{18}\text{F}]$ -FDG-PET cannot help easily distinguish between diseases with similar presentations to FTD. For example, the behavioral/dysexecutive variant of AD shares overlapping clinical and imaging features with FTD.⁴⁰ The clinical utility of both ASL MRI and PET in such cases remains to be studied.

There are several limitations to our study. First, the number of patients is still too small to draw any final conclusions. The fact that the studies did not show heterogeneity does not rule out the potential risks that arise from including low numbers in our statistical analysis. The cross-sectional design of included studies could have also introduced some bias, as FTD is best diagnosed via longitudinal assessments in addition to published criteria. Second, different scanner protocols were used in the study for both ASL MRI and $[^{18}\text{F}]$ -FDG-PET. More specifically, ASL acquisition was heterogeneous across papers, with some using 3DPCASL, others using pulsed ASL (PASL), and

none using 2DPCASL, introducing an added layer of variability in the data. This could, however, be considered a strength given that ASL was still found to be reliable. It is worth noting that PASL slightly outperformed 3DPCASL (sensitivity/specificity 0.75/0.82 versus 0.6/0.79), though the sample size is too small to draw any meaningful conclusions. Third, the studies used a mix of quantitative and visual assessment of the obtained images for diagnosis. While all studies assessed brain regions that were shown to be affected by FTD, different papers focused on different brain regions, with some leaving it up to the reader's impression. Fourth, most studies included studies that were assumed to address patients with bvFTD based on the provided numbers and definitions. As such, the diversity of included FTD subtypes remains limited, and generalization for all FTD, let alone frontotemporal lobar degeneration, cannot be certainly made. Therefore,

a more extensive network of studies is still needed to address all of these issues and allow subgroup analyses. Finally, it remains unclear how our findings directly translate into the real world, as all patients with FTD were selected with a predetermined diagnosis, and the clinicians evaluating the images were only diagnosing FTD versus normal instead of giving a differential diagnosis, including other possible diseases.

CONCLUSIONS

Our study shows that despite being lower compared with [^{18}F]-FDG-PET, the diagnostic performance of ASL MRI was still good enough to consider it as a potential safer alternative, with a pooled sensitivity of 0.70, specificity of 0.81, and DOR of 8.00. Further studies are still needed, however, to eliminate potential confounders and sources of variability in the data, allow for targeted subgroup analyses, and eventually explore its relevance in differentiating FTD from other neurodegenerative dementias.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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The “Outline Sign”: Thin Hyperenhancing Perimeter as an MR Imaging Feature of Meningioma. A Useful Tool in the Temporal Bone Region for Differentiating Meningiomas from Schwannomas and Paragangliomas

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ABSTRACT

BACKGROUND AND PURPOSE: This study investigates the practicality and utility of the “outline sign,” which refers to the thin curvilinear hyperenhancing line that may be seen along the margin of a meningioma on a spin-echo postcontrast T1-weighted image. For cases in which the differential diagnosis may include other tumors, visualization of the outline sign may help to increase the diagnostic confidence for a meningioma. Therefore, in the temporal bone region such as the cerebellopontine angle or jugular foramen, where differential considerations may include a schwannoma or paraganglioma, we additionally investigated whether the outline sign may be observed in these nonmeningioma lesions.

MATERIALS AND METHODS: A total of 39 clinical MRIs of meningiomas, schwannomas, and paragangliomas with confirmed histopathologic data were studied retrospectively. Two experienced head and neck radiologists independently assessed for the presence or absence of an outline sign and subsequently formed a consensus opinion while blinded to patient information and histopathologic data. Interreader reliability was assessed by Cohen κ statistics. Simple bivariate comparisons were performed on the consensus opinions to assess for statistical differences in presence of the sign in meningiomas versus schwannomas and paragangliomas. Sensitivity, specificity, and accuracy of the sign with respect to identifying an underlying meningioma were calculated.

RESULTS: Both readers displayed identical opinions in assessment of the outline sign in 34 of the 39 cases (87%), including 13 of the 14 meningiomas (93%), with substantial agreement (Cohen κ of 0.74). The outline sign was present in 12 of 14 meningiomas (86%), which was significantly greater in frequency compared with schwannomas (3 of 22, 14%) and paragangliomas (1 of 3, 33%). The outline sign demonstrated high sensitivity (86%), specificity (84%), and accuracy (85%) in identifying an underlying meningioma.

CONCLUSIONS: The outline sign can serve as a useful tool for diagnosing meningiomas. It may help distinguish meningiomas from other enhancing tumors, for example schwannomas and paragangliomas in the temporal bone region.

Meningiomas can occur intracranially and in the temporal bone region in various locations. They have imaging features that have been well described, including intermediate T2 signal, homogeneous enhancement (unless calcified), and presence of a dural tail on MRI, and adjacent bony hyperostosis on CT.¹

When located in the temporal bone region, differential diagnostic considerations could include a vestibular schwannoma (when in the internal auditory canal and/or cerebellopontine angle cistern), or a lower cranial nerve schwannoma

or jugular/jugulotympanic paraganglioma (when in the temporal bone region). To help distinguish between these entities, additional scrutiny for classic imaging features of schwannomas and paragangliomas is helpful. Schwannomas tend to be smooth lobulated lesions with fairly homogeneous enhancement, although they may have cystic components especially when large; they cause smooth expansile pressure scalloping of surrounding bone if they approach it. Paragangliomas enhance avidly, and may demonstrate internal flow voids due to their vascular nature; if they occur in regions surrounded by bone, as with a jugular or a jugulotympanic paraganglioma, the surrounding bone shows mottled, permeative changes.¹

Although these imaging features are helpful, there may be cases when they are absent or equivocal, or there may be overlapping characteristics, rendering interpretation and diagnosis challenging. In this retrospective study, we investigate another imaging feature, which we termed the “outline sign.” We have observed that meningiomas often exhibit a thin hyperenhancing

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SUMMARY

PREVIOUS LITERATURE: MR signal characteristics of the peripheral rim of meningiomas have been investigated in past decades. Among them, 2 studies reported observation of enhancement at the tumor periphery on contrast-enhanced T1-weighted imaging, supporting the theory of a rich capsule vascular supply rather than simply CSF space. Our study further investigated this rim enhancement phenomenon, which we termed the “outline sign,” and focused on its applicability in aiding the imaging diagnosis of meningiomas, and specifically in distinguishing meningiomas from schwannomas and paragangliomas when in the temporal bone region.

KEY FINDINGS: The outline sign was noted in a majority of histopathologically proven meningiomas, with substantial interreader agreement. It was noted much less frequently in schwannomas and paragangliomas. The outline sign demonstrated high sensitivity (85%), specificity (84%), and accuracy (85%) in identifying a meningioma.

KNOWLEDGE ADVANCEMENT: The outline sign is a useful tool that can aid in the MRI diagnosis of meningiomas. In the temporal bone region, visualization of an outline sign can help increase the suspicion for a meningioma over a schwannoma or paraganglioma.

perimeter on contrast-enhanced T1-weighted MR images, particularly noticeable on a spin-echo T1-weighted MR sequence, resembling a thin wire fence around the border of a farm, or the outline drawn with a sharp coloring pencil around a picture before coloring in the center. A variation of this has recently been described in the literature; a few studies reported peripheral/capsular enhancement in meningiomas, but on postcontrast T2 FLAIR sequence.²⁻⁴ At times, it may exhibit a serrated pattern due to surface CSF clefts.¹

In this study, we aimed to determine the effectiveness of the outline sign as an imaging marker for meningiomas. For the particular scenario of the temporal bone region, we examined the applicability of the outline sign in aiding differentiation of meningiomas from schwannomas and paragangliomas.

MATERIALS AND METHODS

Study Selection

This was performed as a retrospective study. The methodology proposed in the Standards for Reporting of Diagnostic Accuracy Studies 2015 checklist was followed. Imaging reports for MRI examinations retrieved from the Massachusetts Eye and Ear PACS database between September 1, 2023 and December 31, 2023 were queried separately for the terms “meningioma,” “schwannoma,” and “paraganglioma”/“glomus”/“carotid body

tumor.” This yielded a total of 270 distinct cases. Each full-length imaging report and the patient’s electronic medical records were then reviewed to confirm a history of pathology-proven meningioma, schwannoma, or paraganglioma, resulting in 44 histopathologically-proven cases. If the imaging study retrieved was performed subsequent to an antecedent surgical resection or intervention (e.g., biopsy), older imaging records were then reviewed to select the most recent preoperative or prebiopsy MRI, to ensure that imaging features of the original tumor were analyzed.

Exclusion criteria included absence of histopathologic confirmation, absence of preoperative imaging, absence of preoperative contrast-enhanced spin-echo T1-weighted sequences, and suboptimal image quality (e.g., motion degradation or hardware artifact). A final total of 39 cases (14 meningiomas, 22 schwannomas, and 3 paragangliomas) met all inclusion criteria and were included in our cohort (Fig 1).

MR Imaging Acquisition

MRI studies were performed on 1.5 or 3T units. All 2D contrast-enhanced spin-echo T1-weighted sequences from whole brain, skull base, internal auditory canal, or neck MRs were analyzed. Axial and coronal T1 spin-echo postcontrast images ranged from 2 to 4 mm in slice thickness.

Outline Sign

The included cases were reviewed for the presence or absence of an outline sign. An outline sign was considered present if there was thin (≤ 1 mm), curvilinear hyperenhancement along the perimeter of the lesion on a postcontrast spin-echo T1-weighted sequence in any imaging plane. This thin hyperenhancing perimeter may be complete (seen continuously all around the border of the mass), or incomplete (seen intermittently in short segments all around the border of the mass, or seen continuously but only along a portion of the border). This outline may often

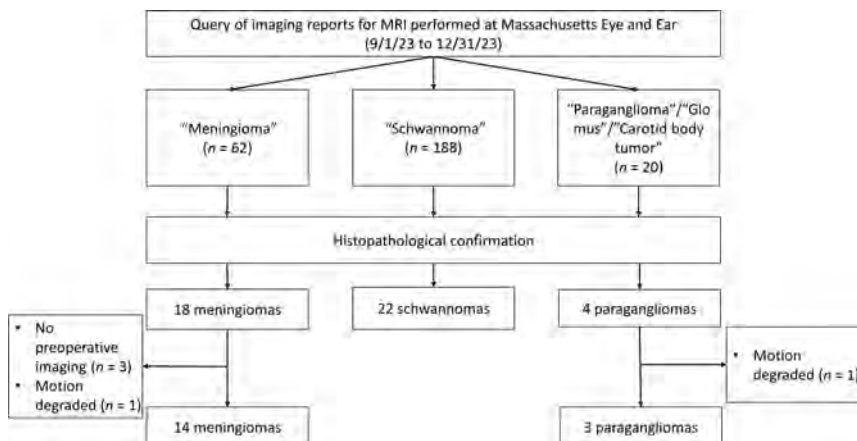


FIG 1. Study design.

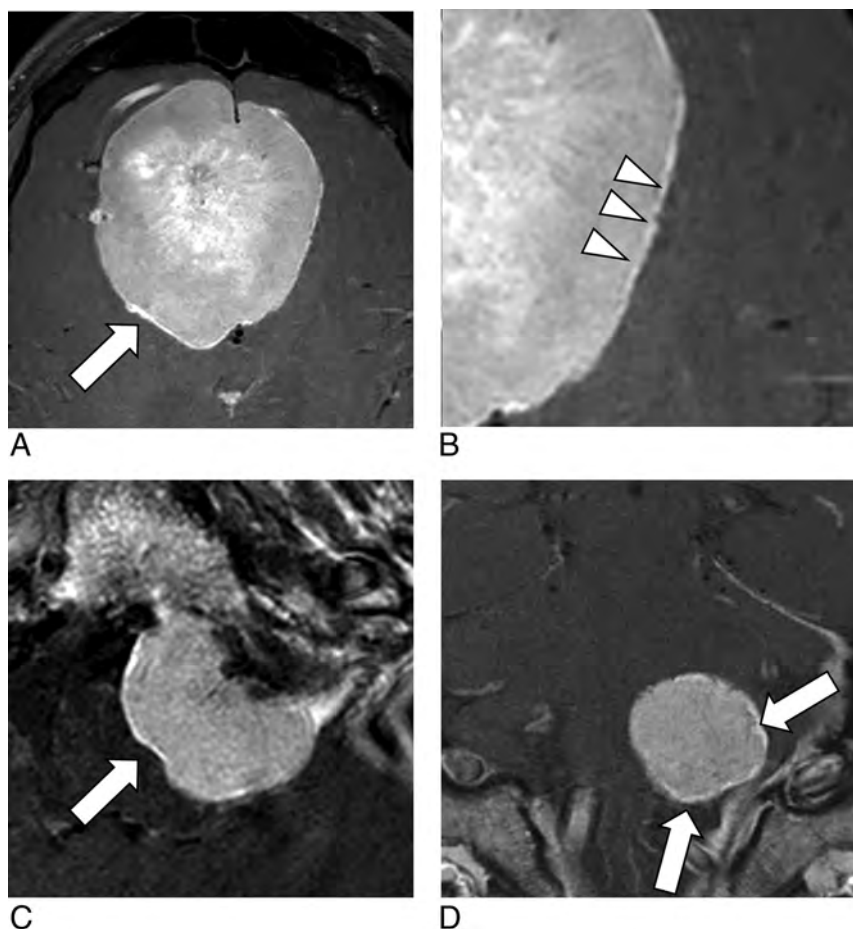


FIG 2. A, Contrast-enhanced axial T1-weighted image in a 46-year-old man demonstrates a large mass in the anterior cranial fossa continuing to the olfactory groove, which was subsequently resected and confirmed to be a meningioma. The mass demonstrates a thin rim of hyperenhancement (“outline sign”) that is especially prominent along its right posterolateral margin (arrow). B, A magnified view of this meningioma shows areas of rim enhancement (arrowheads) with a jagged appearance (“serrated edges”). Axial (C) and coronal (D) contrast-enhanced T1-weighted images in a 47-year-old with pathologically proven meningioma show an outline sign around the periphery of the lesion (arrows). Note the serrated pattern of this enhancing edge.

demonstrate a serrated pattern, a term that alludes to small intermittent indentations or “clefts” along the border of the mass, precluding a smooth margin; when a serrated pattern was observed, this was recorded as well. Examples of the outline sign and serrated edges are shown in Fig 2. Examples of what do not constitute the outline sign are shown in Fig 3. Of note, adjacent dural enhancement or dural tail were not considered as representative of the outline sign.

Image Review

Two head and neck radiologists at Massachusetts Eye and Ear with 7 years (K.L.R.) and 28 years (L.V.R.) of experience underwent a group training period to develop a consistent and reproducible technique for identifying the outline sign. They then independently reviewed a randomized, anonymized list of these 39 cases to determine the presence or absence of an outline sign. The readers also recorded the presence or absence of a serrated pattern to the outline sign. The readers were blinded to the original radiology reports, patient demographics, clinical information, histopathologic data, and the other reader’s findings. Subsequently,

the 2 readers reviewed discrepant cases together for consensus opinion.

Statistical Analysis

Interreader reliability was evaluated based on Cohen κ statistics for assessment of imaging characteristics (outline sign and serrated edges) between the 2 readers.

The consensus data set was used for additional statistical analysis. Simple bivariate comparisons were performed to assess the association between tumor and imaging characteristics. This was done by using Fisher exact test. Additionally, the tumor type was dichotomized to meningioma versus nonmeningioma groups and simple bivariate comparisons were repeated. Sensitivity, specificity, and accuracy of the outline sign in predicting final tumor histopathology (meningioma, schwannoma, or paraganglioma) were calculated.

All statistical analyses were performed by using R Version 4.2.3 (R Core Team, 2023) and 2-tailed P value less than 0.05 was used to determine statistical significance.

RESULTS

Clinical data regarding patient demographics and tumor location are presented in Table 1.

Both reader A and reader B independently identified the outline sign in a high percentage of meningiomas, as shown in Table 2 (86% and 93%, respectively). There was interreader agreement on the presence or absence of the outline sign in 34 of the 39 cases (87%), notably agreeing in 13 of the 14 meningiomas (93%). Findings yielded a Cohen κ index of 0.74, compatible with substantial agreement between readers. Interreader agreement in assessment of the presence or absence of serrated edges was lower, yielding a Cohen κ index of 0.49, suggesting only moderate agreement.

After reviewing discrepant cases by consensus opinion, an outline sign was identified among 12 (86%) of the 14 meningiomas (Table 3). The sign was identified far less frequently among schwannomas and paragangliomas, in only 14% (3 of 22) of schwannomas and 33% (1 of 3) of paragangliomas. These differences were found to be statistically significant ($P < .001$). Serrated edges were seen in only 57% of meningioma cases, which was still more frequently seen than in schwannomas (9%) and paragangliomas (33%) ($P = .0158$). These differences were also found to be statistically significant ($P = .0158$).

The presence of an outline sign as a diagnostic marker for meningioma shows promise, yielding a sensitivity of 86%, specificity of 84%, and accuracy of 85%.

DISCUSSION

In this study, we evaluated the utility of the outline sign, defined as the presence of any amount of thin, curvilinear hyperenhancement along the perimeter of the tumor on a postcontrast spin-

echo T1-weighted sequence, as a diagnostic marker for meningioma. Second, we selected the temporal bone region as an anatomic site for specific examination of the applicability of the outline sign in helping to distinguish meningiomas from other tumors that may arise in this area, such as schwannoma and paraganglioma. Assessment of the presence of this sign by 2 experienced head and neck radiologists showed substantial interreader agreement, suggesting that it can be reliably identified on MRI when present, rendering it suitable for practical application. This thin enhancing peripheral line may occasionally have a serrated pattern.

Our data suggest that the outline sign is highly indicative of a meningioma, which when seen would favor the diagnosis of a meningioma much over a schwannoma or a paraganglioma, should those be within differential diagnostic consideration based on anatomic location. Fig 4 is an example of an enhancing lesion in the right cerebellopontine angle/internal auditory canal that was thought to be a schwannoma based on MRI, given its location and shape, but was subsequently proven to be a meningioma

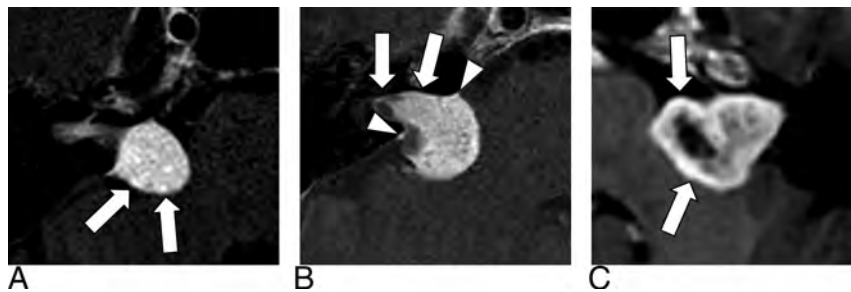


FIG 3. Potential pitfalls of the outline sign. A, Axial contrast-enhanced T1-weighted image in a 34-year-old with pathologically proven vestibular schwannoma shows small focal short/discrete (left arrow) or punctate/rounded/nodular (right arrow) areas of enhancement including some near the periphery (arrows). The short/discrete or punctate/nodular rather than thin curvilinear appearance is not consistent with the outline sign. B, Axial contrast-enhanced T1-weighted image in a 46-year-old with pathologically proven vestibular schwannoma. There is linear enhancement along the margin of the internal auditory canal (arrows), and it is difficult to determine whether this is intrinsic to the dural lining or if it is along the periphery of the tumor that may have cystic components at its lateral aspect. However, as this linear enhancement reaches the cerebellopontine angle cistern (arrowheads), it appears to continue along the posterior petrous ridge away from the tumor, favoring the former theory of being related to the dura. As such, this is equivocal for an outline sign. C, Axial contrast-enhanced T1-weighted image shows a pathologically proven left vestibular schwannoma in a 49-year-old patient. The central portion of the tumor shows diminished enhancement within areas of focal cystic change, falsely exaggerating the degree of mural enhancement (arrows). This enhancing periphery is thicker than 1 mm and does not have the thin appearance of the outline sign.

Table 1: Clinical features of meningiomas, schwannomas, and paragangliomas

	Meningiomas (n = 14)	Schwannomas (n = 22)	Paragangliomas (n = 3)
Mean age (standard deviation) in years	49.5 (19.1)	50.5 (13.0)	45.6 (14.8)
Sex	Woman (n = 9) Man (n = 5)	Woman (n = 14) Man (n = 8)	Woman (n = 2) Man (n = 1)
Tumor location	- Sphenoid wing (n = 6) - Olfactory groove (n = 2) - Tentorial leaflet (n = 2) - Frontal convexity (n = 1) - Cerebellopontine angle (n = 1) - Foramen magnum (n = 1) - Parafalcine (n = 1)	- Internal auditory canal/cerebellopontine angle (n = 18) - Cochlea (n = 1) - Meckel cave (n = 1) - Orbit (n = 1) - Submandibular region (n = 1)	- Carotid body tumor (n = 2) - Jugulotympanic paraganglioma (n = 1)

Table 2: Reader assessments on presence of outline sign performed independently and as a consensus opinion classified by tumor histopathology

Tumor Histopathology	# Positive Outline Sign—Reader A (%)	# Positive Outline Sign—Reader B (%)	# of Cases in Which There was Interreader Agreement, of the Total Number of Cases (%)
Meningioma (n = 14)	12 (86%)	13 (93%)	13/14 (93%)
Schwannoma (n = 22)	3 (14%)	4 (18%)	19/22 (86%)
Paraganglioma (n = 3)	1 (33%)	0 (0%)	2/3 (67%)

Table 3: Presence of outline sign and/or serrated edges (meningioma versus other tumor types) following consensus read

	Meningioma (n=14)	Schwannoma (n=22)	Paraganglioma (n=3)	P
Outline sign	12/14 (86%)	3/22 (14%)	1/3 (33%)	<.001
Serrated edges	8/14 (57%)	2/22 (9%)	1/3 (33%)	.0158

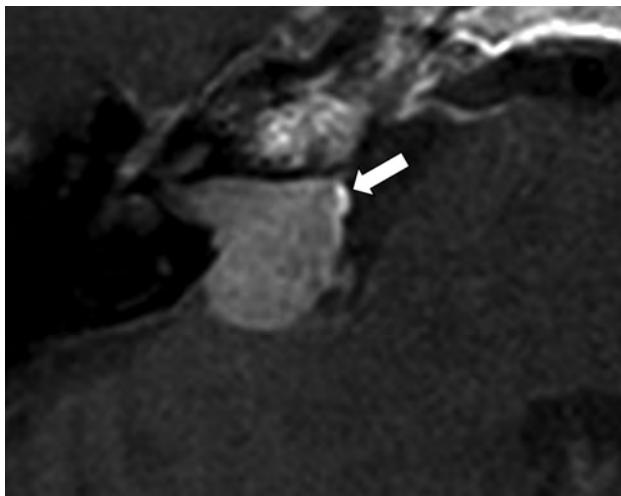


FIG 4. Contrast-enhanced axial T1-weighted image in a 40-year-old shows an enhancing lesion in the right cerebellopontine angle extending into the right internal auditory canal. The lesion was reported as a vestibular schwannoma by the interpreting radiologist. Histopathology upon resection revealed a meningioma. In retrospect, an incomplete rim of enhancement in keeping with an outline sign (arrow) is visible.

on histopathology. Review of the postcontrast T1-weighted images in retrospect suggested presence of an outline sign.

The MR signal characteristics of the peripheral rim of meningiomas have been a subject of investigation in prior studies. Several studies focused primarily on observations made on T2-weighted or FLAIR sequences.²⁻⁶ In 2014, Enokizono et al⁵ evaluated rim patterns of intracranial meningiomas on 3T MRI on nonenhanced and contrast-enhanced 3D FLAIR imaging, correlating signal intensity to surgical cleavability and histologic tumor grading. They noted that a more prominently visible rim on contrast-enhanced 3D FLAIR suggested prominent pial vascular supply to the tumor. A retrospective study by Panyaping et al⁴ in 2023 revealed rim enhancement on contrast-enhanced 3D FLAIR to be highly sensitive (89.2%), highly specific (93.5%), and the most accurate (90.2%) for a meningioma among their other studied imaging markers of interest, including presence of a dural tail, marrow edema, hyperostosis, and homogeneous tumoral enhancement.

A few studies included observations made on postcontrast T1-weighted imaging. In 2003, Oguz et al² studied 30 meningiomas on 0.5T MRI and examined T2-weighted fast spin-echo, T1-weighted spin-echo sequences, and fast FLAIR sequences before and following contrast administration, noting 21 with rim enhancement on fast FLAIR and only 1 on the spin-echo sequences. They suggested that this pattern may help to differentiate meningiomas from other extra-axial masses. That same year, Takeguchi et al⁶ examined the brain-meningioma interface of 50 meningiomas on 1T MRI, 41 of which were histologically proven. They noted FLAIR hyperintensity and T1-weighted postcontrast enhancement in a most of lesions, and concluded that the rim did not reflect a CSF cleft, but instead might reflect the capsule structure at the tumor surface. In 2016, Uchida et al⁷ focused on signal characteristics of the rim on T2-weighted sequence on 3T MRI in an effort to decipher the histologic correlate

for this finding. They examined 53 meningiomas, 22 of which underwent histopathologic analysis. They reported that of the 53 tumors, 37 showed a T2-hyperintense rim, of which 28 showed postcontrast T1-weighted enhancement at the brain-meningioma interface and therefore did not reflect CSF space, and rather was postulated to reflect a microvascular-rich capsule layer, endorsing the findings of Takeguchi et al⁶ 11 years earlier.

Our study focused primarily on signal characteristics of the periphery of meningiomas on contrast-enhanced spin-echo T1-weighted imaging and its applicability as a potential MR imaging marker for meningiomas. We found more intense enhancement around the peripheral margin of a meningioma compared with the main bulk of the tumor with high sensitivity and specificity. Given that spin-echo postcontrast T1-weighted imaging is a staple of MRI protocols at most institutions, scrutinizing MR features of a mass lesion for this imaging sign can readily be adopted in practice with existing imaging protocols, without the need for modifying protocols and/or adding extra sequences.

This phenomenon of rim enhancement in meningiomas has been attributed in the past to their dual arterial supply.^{2,4,5} Meningiomas are predominantly supplied by meningeal arteries, which supply the central portion of the tumor, generating a characteristic sunburst pattern on angiography. The relative hyperenhancement along the margins of the tumor is thought to be related to a separate arterial supply from pial vessels to a microvascular-rich tumor capsule. Presence of rim enhancement has been shown to be more common in meningiomas demonstrating visible pial arterial supply on digital subtraction angiography.⁵ Furthermore, this rim enhancement may be associated with the presence of increased microvascular density within the tumor capsule based on prior studies with histopathologic correlates.^{6,7} Indeed, the studies by Takeguchi et al⁶ and Uchida et al⁷ showed differences in MR enhancement characteristics between the rim and the bulk of the tumor that may reflect a hypervascular tumor capsule.

Limitations of this study include its retrospective nature and in the number of included imaging studies due to the criterion of requiring that there be histopathologic confirmation to serve as diagnostic gold standard. The imaging protocol was not identical for all included MRI studies, as each examination was tailored to its specific clinical area of interest. However, this in fact simulates the actual global radiology practice landscape where scanners and imaging parameters vary between institutions and facilities, and lends confidence to practical application of the sign in real life due to robustness of this imaging sign across variations in scanners and scan techniques.

We investigated the utility of the outline sign in aiding imaging diagnosis of meningiomas independent of tumor location; as such we included meningiomas in all locations within our study cohort. Second, we sought to apply this to the specific scenario of the temporal bone region, focusing on locations where schwannoma and/or paraganglioma may be reasonable differential diagnostic considerations based on tumor site. We investigated whether the outline sign may positively contribute to a correct diagnosis at these sites. With a focus on the temporal bone region and with the inclusion criterion of an available histopathologic diagnosis, an added limitation is the low number of cases of

histopathologically proven meningiomas, schwannomas, and paragangliomas specific to this location. This is in part related to an overall low surgical resection rate or biopsy rate, given extreme caution exercised when balancing the advantages of having a definitive histologic diagnosis against the downsides of potential damage to cranial nerves and vital function. Many are surveilled or radiated at times solely based on the degree of diagnostic confidence from imaging evaluation. Nonetheless, we thought it useful to study the cases available while ensuring satisfactory statistical power. In addition, the crucial role of imaging assessment informing clinical management highlights the necessity for increasing the radiologist's armamentarium of imaging diagnostic tools to increase our diagnostic confidence. Although this study did not exclusively examine cases in these locations in order to maintain a sufficient sample size, we believe our results are applicable to the differentiation of these 3 tumor types in the temporal bone region.

A few potential pitfalls were identified in the use of the outline sign by reviewing cases in which independent reader assessments were discordant. Linear enhancement along the tumor capsule in 1 dimension may appear as punctate enhancement in an orthogonal dimension. Lesions in close proximity to bone may result in a false-positive outline sign, possibly because areas of marginal enhancement may be related to the adjacent dura or dural-osseous interface rather than the peripheral portion of the tumor. Cystic changes within a tumor may result in diminished central enhancement and residual solid enhancement around the periphery, potentially leading to a false-positive thicker "pseudo-outline." In fact, this may potentially represent the "peritumoral halo" that has been described with schwannomas, where a rim of hyperenhancement is thought to reflect gadolinium extravasation along the margins of the tumor.⁸ This is distinct from the outline sign, which is thin and is thought to reflect enhancement of a tumor capsule.

CONCLUSIONS

The outline sign refers to thin curvilinear enhancement along the periphery of a meningioma that may be seen on spin-echo

postcontrast T1-weighted sequence. It is a practical and helpful imaging feature that can aid in the diagnosis of meningiomas. In the temporal bone region, such as the cerebellopontine angle or jugular foramen region, it is an added imaging feature that may help to distinguish meningiomas from other enhancing tumors such as schwannomas or paragangliomas. This finding is thought to reflect enhancement of a hypervascular meningioma tumor capsule.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Comparison of Imaging Findings between Granulomatosis with Polyangiitis and Eosinophilic Granulomatosis with Polyangiitis on Sinus CT: Importance of High-Density Opacification of the Paranasal Sinuses

 Inseon Ryoo,  Serena Poésy,  Artem Kaliev,  Karen Buch, and  Osamu Sakai

ABSTRACT

BACKGROUND AND PURPOSE: Granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) are the most common causes of chronic sinusitis from systemic granulomatous diseases. While both are small- to medium-sized vasculitis with necrotizing granulomas, they have different clinical courses and prognoses. High-density sinus opacification has been reported in allergic fungal sinusitis with eosinophilic infiltrates. Given that EGPA also has eosinophilic tissue infiltrates, we evaluated the differences in sinus CT findings, focusing on the sinus secretion attenuation between patients with GPA and EGPA, along with other previously described findings.

MATERIALS AND METHODS: This study included 31 patients with GPA and 22 patients with EGPA who underwent sinus CT. The attenuation of secretions within the paranasal sinuses was visually assessed, and the Hounsfield unit (HU) of the highest-density portions within each sinus was measured. Lund-Mackay scores (LMS), bony destruction, sclerotic wall changes, adjacent organ involvement, and nasal polyps were evaluated and compared between patients with GPA and EGPA. Multiple logistic regression analyses were conducted to determine which factors independently discriminated GPA from EGPA, and the diagnostic ability to differentiate between these 2 diseases was evaluated by using a receiver operating characteristic curve analysis.

RESULTS: More patients in the GPA group showed bony destructions, bone sclerosis, and involvement of organs adjacent to paranasal sinuses than in the EGPA group ($P = .006$, 0.048 , and 0.035 , respectively). The EGPA group had higher LMS and more nasal polyps than the GPA group ($P = .078$ and 0.333 , respectively). More patients in the EGPA group showed internal high-density opacification than in the GPA group, and patients with EGPA had higher mean HUs (both $P < .0001$). The presence of high-density opacification or mean HUs independently distinguished GPA from EGPA (OR, 53.67 and 1.07 ; 95% CI, 4.07 – 708.03 and 1.02 – 1.13 , respectively) and showed a greater ability to discriminate between these diseases compared with other findings.

CONCLUSIONS: Patients with EGPA had more high-density sinus opacification and higher mean HU on sinus CT than the patients with GPA. In addition to the previously reported CT findings, such as bony destruction, bone sclerosis, and adjacent organ involvement, evaluating secretion attenuation can assist in distinguishing between GPA and EGPA.

ABBREVIATIONS: AUROC = area under the receiver operating characteristic curve; EGPA = eosinophilic granulomatosis with polyangiitis; GPA = granulomatosis with polyangiitis; HU = Hounsfield unit; LMS = Lund-Mackay score; ROC = receiver operating characteristic

Chronic rhinosinusitis is a prevalent disease affecting 7%–14% of people in North America.^{1,2} It commonly presents with chronic nasal obstruction, rhinorrhea, and nasal crusting. Even

though many of the cases have an infectious or allergic etiology, these symptoms can be from systemic granulomatous diseases such as granulomatosis with polyangiitis (GPA, Wegener granulomatosis) or eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss syndrome). While both are small- to medium-sized vasculitis with necrotizing granulomas, they have different clinical courses and prognoses. Because paranasal sinusitis is an early manifestation of these diseases and may precede other organ involvement, it is important to differentiate and diagnose these diseases as early as possible based on sinus imaging characteristics.³

The prevalence of GPA in the United States is estimated to be 3 cases per 100,000 people.⁴ GPA involves the head and neck, lungs, kidneys, and central nervous system. Approximately 85% of

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SUMMARY

PREVIOUS LITERATURE: Granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) are the most common causes of chronic sinusitis from systemic granulomatous diseases. Both are small- to medium-sized vasculitis with necrotizing granulomas. While both diseases frequently appear as a nonspecific chronic sinusitis pattern in the early stages, they have different clinical courses and prognoses. Previous articles on allergic fungal sinusitis have shown that mucin with high eosinophilic infiltration in the paranasal sinuses has high attenuation on CT. Because EGPA also involves hypereosinophilic tissue infiltrates, the analysis of intrasinus attenuation on CT can help to differentiate between the 2 diseases.

KEY FINDINGS: The patients with EGPA had more high-density sinus opacification and higher mean HUs on sinus CT than the patients with GPA. The presence of high-density sinus opacification or mean HUs independently distinguished GPA from EGPA and showed higher diagnostic ability on CT to discriminate between these diseases compared with other CT findings.

KNOWLEDGE ADVANCEMENT: In addition to the previously reported CT findings, such as bone destruction, bone sclerosis, and adjacent organ involvement, evaluating secretion attenuation on sinus CT can assist in distinguishing between GPA and EGPA.

patients with GPA demonstrate head and neck involvement, with the sinonasal region being the most frequently involved.^{3,5} Isolated paranasal and sinonasal involvement is present in 25% of cases. GPA frequently manifests as a nonspecific chronic sinusitis pattern, especially early in the disease course.^{3,5}

The incidence of EGPA in the United States is 1–3 cases per 100,000 people per year.⁶ EGPA is characterized by marked eosinophilia and necrotizing granulomas with internal eosinophilic infiltrates. The nasal cavity and the paranasal sinuses are the most frequently affected regions.^{3,7} Chronic rhinosinusitis is the most common initial symptom and is present in up to 48%–86% of EGPA cases.^{3,7,8} In the prodromal stage, it shows rhinosinusitis and progresses to hypereosinophilia and eosinophilic tissue infiltrates. This is followed by the development of systemic vasculitis symptoms and multiorgan involvement, including the lungs, nerves, vascular systems, and kidneys.^{3,7} It was reported that approximately 12% of patients with EGPA died within a year without adequate diagnosis and treatment.⁹

In addition to the clinical, serologic and pathologic findings, imaging findings play an important role in developing an early differential diagnosis, defining the extent of the disease, and monitoring/surveillance disease activity during and after treatment of chronic granulomatous sinusitis. CT is the primary technique for diagnosing and assessing inflammatory diseases of the paranasal sinuses.¹⁰ Previous articles on allergic fungal sinusitis have shown that mucin with high eosinophilic infiltration in the paranasal sinuses has high CT attenuation.^{11–14} Because EGPA also involves hypereosinophilic tissue infiltrates, this study aims to compare the CT imaging findings between GPA and EGPA, focusing on the internal attenuation of the sinuses as well as other well-known CT findings.

MATERIALS AND METHODS

This retrospective study was performed across 2 large academic medical centers (Massachusetts General Hospital and Boston Medical Center). Institutional review board approval was obtained at each hospital, and a waiver of informed consent and Health Insurance Portability and Accountability Act authorization were obtained at each hospital. The methodology proposed in the Standards for Reporting of Diagnostic Accuracy Studies checklist was followed.

Patients

We reviewed all patients diagnosed with GPA or EGPA who underwent a noncontrast sinus CT between January 2001 and December 2023 at these 2 tertiary hospitals. Fifty-three patients with GPA and 32 patients with EGPA were identified. Among them, 22 patients with GPA and 10 with EGPA were excluded due to the lack of discernible sinusitis on CT or poor diagnostic image quality that hindered evaluation. A total of 31 patients with GPA and 22 patients with EGPA were included in this study: 17 patients with GPA and 12 patients with EGPA from 1 hospital, and 14 patients with GPA and 10 patients with EGPA from another hospital. The diagnosis of GPA and EGPA was made based on histologic diagnosis from biopsy specimens obtained from the kidney, nasal cavity, paranasal sinus, or lung in 9 patients with GPA and 8 patients with EGPA. Other patients were diagnosed based on the clinical criteria for each disease.

CT Imaging

All patients underwent noncontrast paranasal sinus CT scans with 16- to 64-detector row CT (IQon Spectral CT [Philips Healthcare]; LightSpeed VCT, Bright Speed, Discovery CT 750 HD, Revolution CT, Optima CT660, HiSpeed CT [GE Healthcare]; Somatom force, Biograph 64 [Siemens Healthineers]) by using a tube voltage of 90–140 kVp and a tube current of 160–275 mA. CT images, with 1.0- to 2.0-mm slice thickness, were reconstructed into axial, coronal, and sagittal images with soft tissue and bone algorithms by using iterative reconstruction algorithms on each vendor's scanner.

Imaging Analysis

Evaluation of High-Density Sinus Secretions. The attenuation of sinus secretions was visually assessed for the presence or absence of high-density material within the paranasal sinuses. This was defined as sinus secretions having a visually apparent or subjective high-density component compared with the adjacent mucosa or submucosa. The Hounsfield units (HUs) of the subjective high-density portion were also measured, and the HUs of the highest-density portion in the paranasal sinuses of all patients were measured.

Table 1: Characteristics of patients with GPA and EGPA

Group	GPA (n = 31)	EGPA (n = 22)
Age mean SD (years)	50.1 ± 20	50.8 ± 13.6
Sex (M:F)	15:16	13:9
ANCA status		
c-ANCA	20	0
p-ANCA	2	6
Both c-, p-ANCA	1	0
Negative	8	13
N/A	0	3
Eosinophil		
Eosinophilia (>8%)	1	20
Normal	30	0
N/A	0	2

Note:—SD indicates standard deviation; ANCA, antineutrophil cytoplasmic antibody; N/A, not available.

Evaluation of Other CT Findings. The presence of any bony destruction of the nasal cavities and paranasal sinuses (including the nasal septum), sclerotic changes of the paranasal sinus walls, adjacent organ involvement including the orbital cavity, nasolacrimal ducts, and intracranial region, and the presence of low-density nasal polyps were also assessed and recorded by using a binary scoring system (positive versus negative).

The CT images were also evaluated by using the Lund-Mackay score (LMS), which evaluates the extent of sinusitis in 10 regions derived from the left and right paranasal sinuses (maxillary, sphenoidal, anterior ethmoidal, posterior ethmoidal, and frontal) and assigned a grade of 0–2 based on the degree of involvement. The LMS also evaluates whether the ostiomeatal complex is obstructed on each side, and a score of 0 or 2 is assigned based on the extent of involvement. Twelve regions were evaluated for a total score of 24 points.^{15,16}

All images were evaluated independently by 2 head and neck radiologists with more than 10 and 25 years of experience, and the discrepancy was resolved by consensus.

Statistical Analysis

All statistical analyses were performed by using MedCalc software for Windows (MedCalc software V, 22.0.2.1). A 2-tailed *P* value ≤ .05 was considered significant for all statistical analyses. The HUs of the portion from the highest attenuation secretions in the paranasal sinuses were compared between the GPA and EGPA groups by using the unpaired Student *t* test. The presence of subjective high-density secretions, bone destruction, sclerotic change of the sinus walls, adjacent organ involvement, and nasal polyps was compared between the 2 groups by using the χ^2 test or Fisher exact test. The LMS was compared between the 2 groups by using the Mann-Whitney *U* test. The distribution of CT energy levels between the 2 groups was also compared by using Fisher exact test.

Multiple logistic regression analyses were conducted to determine which factors independently discriminated GPA from EGPA among the factors with a *P* value < .1 in a univariate analysis. First, it was conducted with the presence of subjective high-density lesions and then with the HU. All factors with a *P* value < .05 were considered independent factors to discriminate between the 2 diseases.

The diagnostic ability to differentiate between the 2 diseases was evaluated by generating a receiver operating characteristic (ROC) curve. The optimal cutoff values for differentiating between the 2 groups were identified by maximizing the Youden index.

RESULTS

Patient Characteristics

There were 15 men and 16 women in the GPA group and 13 men and 9 women in the EGPA group. The mean age of the GPA and EGPA groups was 50.1 ± 20 years (range, 19–88) and 50.8 ± 13.6 years (range, 25–79), respectively. No significant difference in patient age was noted between the GPA and EGPA groups (*P* = .889). Table 1 summarizes patient data on antineutrophil cytoplasmic antibody and eosinophil status. In the GPA group, 1 patient was scanned with 90 kVp, 4 patients with 140 kVp, and 26 patients with 120 kVp. In the EGPA group, 3 patients were scanned with 140 kVp and 19 patients with 120 kVp. There was no significant difference in the distribution of CT energy levels between the 2 groups (*P* = 1.0).

Analysis of High-Density Paranasal Sinus Secretions

Sixteen of 22 patients (73%) with EGPA showed subjective high-density material in the paranasal sinuses compared with 5 of 31 patients (16%) with GPA who had high-density material in the paranasal sinuses (*P* < .0001) (Figs 1, 2A, -B). The mean HUs of the subjective high-density components of the patients with EGPA and that of the patients with GPA were 94.1 ± 18.7 (range, 66.4–123.1) and 81.4 ± 20.8 (range, 62.9–114.5), respectively, which showed no significant difference between the groups (*P* = .674).

In the analysis of the HUs corresponding to the highest-density secretions in the paranasal sinuses of all patients, the mean HU of the patients with EGPA (77.8 ± 31.9; range, 24.1–123.1) was significantly higher than that of the patients with GPA (44.4 ± 20.2; range, 19.9–114.5) (*P* < .0001). The ranges of the HUs from the patients with EGPA and GPA who did not have subjective high-density components in the paranasal sinuses were 24.1–45.6 and 19.9–50.6, respectively.

Analysis of Other CT Findings

Fourteen of 31 (45%) patients with GPA had bone destructions, including nasal septa, sinus walls, orbital walls, and skull base (Fig 3). Two patients of the EGPA group (9%) showed destruction of the nasal septum (*P* = .006). The GPA group showed more sclerotic changes of the paranasal sinus walls (*n* = 16) (Figs 2C, -D, 3) than the EGPA group (*n* = 5) (*P* = .048). Six patients in the GPA group showed adjacent organ involvement (Fig 3), whereas no patients with EGPA showed adjacent organ involvement (*P* = .035). Nasal polyps were more prevalent in the EGPA group (10 of 22 patients) compared with the GPA group (10 of 31 patients) (Figs 1, 2A, -B), however, statistical significance was not achieved (*P* = .333).

The mean LMS of the EGPA group (13.1 ± 6.3; range, 4–21) was higher than that of the GPA group (10.1 ± 6.5; range, 2–24), however, statistical significance was not achieved (*P* = .078). All the paranasal sinus CT imaging findings of the patients with GPA and EGPA are summarized in Table 2.



FIG 1. A 28-year-old woman with eosinophilic granulomatosis with polyangiitis. *A and B*, Axial paranasal sinus CT images show high-density sinus opacifications in both maxillary and left sphenoidal sinuses and low-density nasal polyps in both nasal cavities. HU of high-density materials in the right maxillary, left maxillary, and left sphenoid sinuses are 66.7, 70.0, and 69.2, respectively. *C*, Coronal paranasal sinus CT image shows high-density materials in both maxillary sinuses and low-density nasal polyps in both nasal cavities.

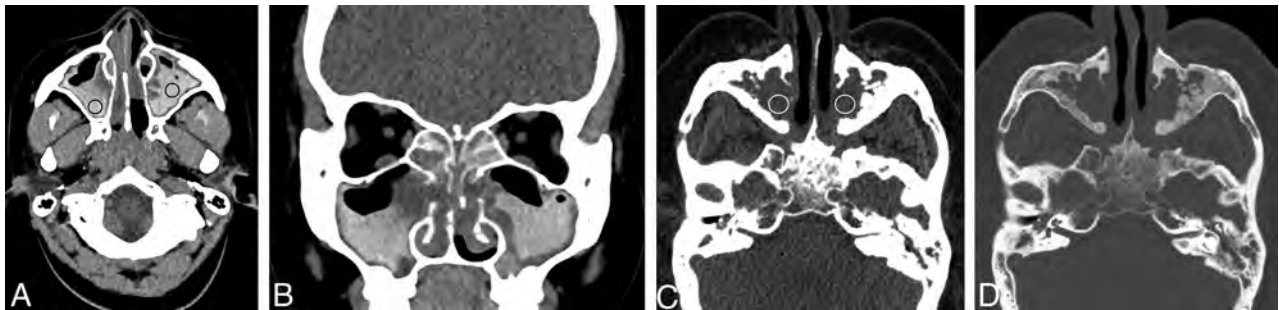


FIG 2. *A and B*, A 25-year-old woman with eosinophilic granulomatosis with polyangiitis. *C and D*, A 48-year-old man with granulomatosis with polyangiitis. *A*, Axial paranasal sinus CT image shows high-density sinus opacifications in both maxillary sinuses and low-density nasal polyps in both nasal cavities. HU of high-density materials in the right and left maxillary sinuses are 91.6 and 91.5 (black circular ROIs), respectively. *B*, Coronal paranasal sinus CT images show high-density materials in both maxillary and ethmoidal sinuses and low-density nasal polyps in both nasal cavities. *C*, Axial paranasal sinus CT image with soft tissue algorithm shows internal low-density materials in both maxillary sinuses. HU of low-density materials in the right and left maxillary sinuses are 43.5 and 41.5 (white circular ROIs), respectively. *D*, Axial paranasal sinus CT image with bone algorithm shows destruction of the medial walls and diffuse sclerosis of the anterior and posterior walls of maxillary sinuses bilaterally.

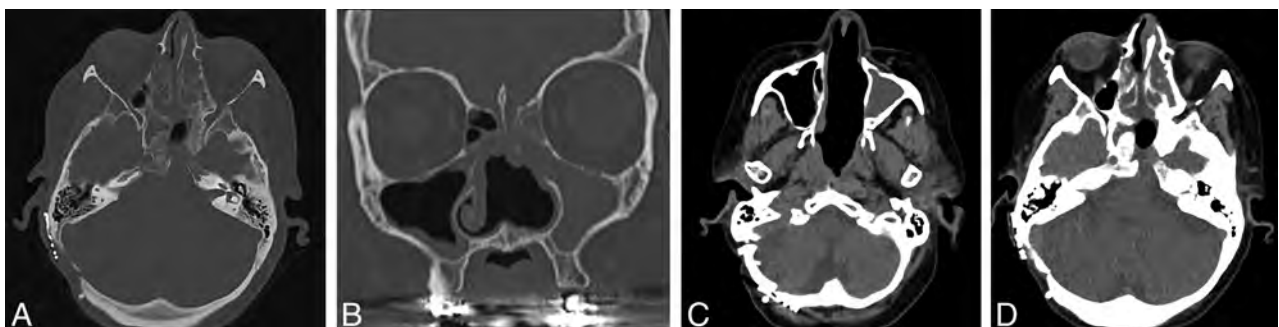


FIG 3. A 53-year-old woman with granulomatosis with polyangiitis. Axial (*A*) and coronal (*B*) paranasal sinus CT images with bone algorithm show diffuse sclerotic wall thickening of left sphenoidal sinus wall with posterior wall destruction (*A*) and bone destructions in nasal septum and nasal turbinates (*B*). Axial paranasal sinus CT images with soft tissue algorithm show left maxillary sinusitis without internal high-density (*C*) and suspicious intracranial extension of soft tissue attenuation lesion in the left sphenoidal sinus (*D*).

Multiple Logistic Regression Analysis

Multiple logistic regression analysis, including factors with a P value $< .1$ in the univariate analysis, showed that only the presence of subjective high-density sinus secretions ($P = .003$) or the mean HU of the highest-density portion of the secretions

($P = .005$) was able to differentiate GPA from EGPA on the paranasal sinus CT. The presence of bone destruction, sclerotic bone change, adjacent organ involvement, and LMS were not independent factors. The results of multiple logistic regression analyses, one with the mean HU of the highest-density portion

and another with the presence of subjective high density, are summarized in Table 3 and 4.

Diagnostic Ability Analysis

In the ROC curve analysis of the mean HUs from each group, the area under the receiver operating characteristic curves (AUROCs) for differentiating GPA from EGPA was 0.777 (95% CI, 0.642–0.88). The threshold discriminating between GPA and EGPA was 64.3. The AUROC for the presence of subjective high-density sinus secretions differentiating between the 2 diseases was 0.783 (95% CI, 0.648–0.884).

For other CT image findings, AUROCs for the presence of bone destruction, sclerotic bone change, and adjacent organ involvement for discriminating GPA from EGPA were 0.68, 0.597, and 0.644, respectively. All the AUROCs of imaging

findings in differentiation between GPA and EGPA with 95% CI, sensitivity, and specificity were summarized in Table 5.

DISCUSSION

Many systemic granulomatous diseases, such as GPA, EGPA, and sarcoidosis, may manifest as chronic rhinosinusitis. GPA and EGPA are the most common of these entities. Both diseases are systemic small-to-medium-sized vessel vasculitis with necrotizing granulomas, with rhinosinusitis being the most common presenting manifestation.^{3,17–19} However, as the name suggests, unlike GPA, EGPA lesions usually have eosinophilic tissue infiltrates along with hypereosinophilia.^{3,15,20}

Previous literature on allergic fungal sinusitis describes high-density opacifications in the paranasal sinus CT. Histologic examinations of these patients demonstrate sinus material containing allergic mucin composed of mucin, eosinophils, and Charcot Leyden crystals without fungal materials. This allergic mucin shows high attenuation on CT and low signal intensity on both T1- and T2-weighted MR images due to its high protein concentrations (more than 28%) and low free water.^{11–14}

In this study, the patients with EGPA showed higher mean HUs in the paranasal sinuses than the patients with GPA. In addition, more patients (73%) in the EGPA group showed subjective high-density secretions than in the GPA group. All the patients with subjective high-density secretions had HUs higher than 60 HU (the lowest value

Table 2: The paranasal sinus CT findings of patients with GPA and EGPA

	GPA (n = 31)	EGPA (n = 22)	P
HU (mean ± SD)	44.4 ± 20.2	77.8 ± 31.9	< .0001
High-density component (present:absent)	5:26	16:6	< .0001
Bone destruction			.006
Nasal septum	7	2	
Nasal septum + sinus wall	4	0	
Nasal septum + sinus wall + orbital wall	2	0	
Sinus wall + orbital wall + skull base	1	0	
None	17	20	
Sclerotic change (present:absent)	16:15	5:17	.048
Organ involvement			.035
Orbit	3	0	
Nasolacrimal duct	1	0	
Orbit + nasolacrimal duct	1	0	
Intracranial extension	1	0	
None	25	22	
Nasal polyp (present: absent)	10: 21	10: 12	.333
LMS (mean ± SD)	10.1 ± 6.5	13.1 ± 6.3	.078

Table 3: Multiple logistic regression analysis with the presence of subjective high-density in the paranasal sinuses

Imaging Finding	Coefficient (B)	Standard Error	P	OR	95% CI
High-density	3.983	1.316	.003	53.666	4.068–708.032
Bone destruction	−2.481	1.35	.066	0.084	0.006–1.18
Sclerotic change	−0.633	0.925	.494	1.884	0.307–11.552
Organ involvement	−19.417	6640.508	.998	3.69E-09	0-Exp (12,995)
LMS	−0.071	0.085	.401	0.932	0.789–1.099

Table 4: Multiple logistic regression analysis with the mean HU of the highest-density portion in the paranasal sinuses

Imaging Finding	Coefficient (B)	Standard Error	P	OR	95% CI
Mean HU	0.067	0.025	.005	1.072	1.021–1.125
Bone destruction	−1.842	1.224	.132	0.159	0.014–1.746
Sclerotic change	−0.033	0.877	.97	0.967	0.174–5.395
Organ involvement	−20.672	6485.543	.998	1.05E-09	0-Exp (12,689.9)
LMS	−0.056	0.074	.45	0.945	0.817–1.094

Table 5: The diagnostic ability of each paranasal sinus CT finding in differentiation between GPA and EGPA

Imaging Finding	AUROC	95% CI	Sensitivity	Specificity
HU	0.777	0.642–0.88	72.7	90.3
High-density component	0.783	0.648–0.884	72.7	83.9
Bone destruction	0.68	0.538–0.802	90.9	45.2
Sclerotic change	0.644	0.501–0.771	77.3	51.6
Organ involvement	0.597	0.453–0.729	100	19.4

was 62.9 HU), and all the patients who did not have subjective high-density secretions had HUs lower than 60 HU (the highest value was 50.6 HU). The subjective high-density paranasal secretions with HUs higher than 60 have been reported to contain abnormal contents, such as allergic mucin with eosinophilic infiltrates, compared with common secretions in bland cases of rhinosinusitis. The mucus of acute sinus secretions is known to have an attenuation of 10–25 HUs, with the chronic state becoming more viscous and having a higher attenuation of 30–60 HUs.²¹ Furthermore, the mean HU of the highest attenuation portion of the paranasal sinuses and the presence of subjective high-density secretions showed better diagnostic performance in differentiation between GPA and EGPA, compared with bone destruction, sclerotic bone change, and adjacent organ involvement. However, there were also 5 patients with GPA with subjective high-density secretions in the paranasal sinuses. Because patients with GPA sometimes present with epistaxis, the high density may reflect hemorrhagic contents.^{18,19}

Forty-five percent of the patients with GPA and 9.1% of the patients with EGPA had bone destruction in the present study. Two patients with EGPA showed nasal septal perforations as their only manifestation of bony destruction. This result is within the range of previously published studies reporting that approximately 35.9%–75% of patients with GPA showed bone destruction.^{4,5,22–27} It is thought that avascular necrosis resulting from the occlusion of small arteries by an inflammatory cell infiltrate leads to the pathophysiologic process of bone destruction in patients with GPA.^{4,28}

Previous literature has reported that up to 50% of patients with GPA had neo-osteogenesis, resulting in a characteristic sclerotic bony appearance with a leading edge of a well-corticated bone.^{4,5,22,25} The maxillary sinuses are known to be mainly affected.²⁵ Approximately one-half of the patients with GPA (52%) in this study also showed sclerotic bone change (Figs 2C, -D, 3); all of the patients except for 1 had maxillary sinus involvement. In contrast, only 1 patient among the 5 patients showing sclerotic bone changes in the EGPA group had involvement of the maxillary sinuses.

GPA is also well known for involving other head and neck regions along with the nasal cavities and paranasal sinuses, including orbits, nasolacrimal ducts, skull base, ear, and intracranial extension.^{4,5,19,29–31} The orbit has reportedly been involved in 18%–58% of patients with GPA.¹⁹ We also found that 16% of the patients with GPA had orbital or nasolacrimal duct involvement, with 1 patient having intracranial extension (Fig 3D). However, no patient showed additional organ involvement in the EGPA group.

Patients with EGPA usually have sinonasal polyposis, and previous reports have described 52%–76% of these patients as having sinonasal polyps. Patients with EGPA have been described as having nasal polyps more frequently than the GPA group.^{7,17,20,26} Our cohort showed a slightly lower prevalence of nasal polyps in the EGPA patient group (45.5%) than in previous studies. However, it still demonstrated a higher prevalence than the GPA group (32.3%).

The mean LMS of the GPA group and the EGPA group were similar to the results of previous studies.^{15,24,26,32} The patients with EGPA had slightly higher LMS values than the patients with GPA. However, there was no statistically significant difference. A

study with eosinophilic sinus diseases reported that EGPA had a milder form of sinus opacification than other eosinophilic sinus diseases.¹⁵ This might be the reason for the lesser difference in LMS between EGPA and GPA.

There are several limitations in this study. First, the study population was small, and the results of this study may not be generalizable to a large patient population. Further studies on a larger patient cohort are needed to strengthen our results. Second, because most patients did not undergo paranasal sinus surgery, histopathologic confirmation could not be performed for the high-density material in the paranasal sinuses. Only 3 patients in the EGPA group had pathologic results of hypereosinophilic infiltrates from the paranasal sinuses and showed subjective high density on the sinus CT. However, all the subjective high-density sinus opacification had HUs higher than 60, which was beyond the level of usual secretions in chronic sinusitis.

CONCLUSIONS

Patients with EGPA had more subjective high-density paranasal sinus secretions on CT compared with patients with GPA. Additionally, the mean HU of the patients with EGPA was higher than that of the patients with GPA. The HU threshold value to discriminate between GPA and EGPA was 64.3. The presence of subjective high density in the paranasal sinuses or the mean HU of the highest-density portion of the paranasal sinuses independently differentiates EGPA from GPA. In addition to the previously reported CT findings, such as bone destructions, sclerotic bone changes, and adjacent organ involvement, evaluating the high-density opacification in the paranasal sinuses on CT can aid in differentiating sinusitis between the GPA and EGPA.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Pre- and Postoperative Imaging of Cochlear Implantation in Cadaveric Specimens Using Low-Dose Photon-Counting Detector CT

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ABSTRACT

BACKGROUND AND PURPOSE: Anatomically adapted cochlear implantation and efficient postoperative cochlear implant-fitting strategies benefit from reliable and highly detailed imaging techniques. Since image quality in CT is related to the applied radiation dose, this study aimed to evaluate low-dose cochlear imaging with a photon-counting detector by investigating the accuracy of pre- and postoperative cochlear analysis.

MATERIALS AND METHODS: Photon-counting CT images of 10 temporal bone specimens were acquired with 3 different radiation dose levels (regular dose: 27.1 mGy, low dose: 4.81 mGy, and ultra-low dose: 3.43 mGy) before and after cochlear implant electrode carrier insertion. A clinical scan protocol was used with a tube potential of 120 kV in ultra-high-resolution scan mode (detector collimation 120×0.2 mm). The accuracy of cochlear duct length measurements for the organ of Corti and electrode contact determination was investigated for all applied settings by 2 independent otosurgeons.

RESULTS: No substantial differences were ascertained between photon-counting CT scans performed with standard dose and dedicated low-dose imaging regarding the accuracy of neither pre- and postoperative cochlear analysis nor postoperative cochlear implant electrode analysis. Radiation dose reduction of 82.3% (low dose) and 87.3% (ultra-low dose) could be realized compared with the clinical standard protocol.

CONCLUSIONS: Ultra-high-resolution cochlear imaging is feasible with very low radiation exposure when using a first-generation photon-counting CT in combination with dedicated low-dose protocols. The accuracy of pre- and postoperative cochlear analysis with the applied dose reduction settings was comparable with a clinical regular-dose protocol.

ABBREVIATIONS: AID = angular insertion depth; CDL = cochlear duct length; CDL_{LW} = cochlear duct length of the lateral cochlea wall; CDL_{OC} = cochlear duct length of the organ of Corti; $CTDI_{vol}$ = volume CT dose index; DLP = dose-length product; EID = energy-integrating detector; ICC = intraclass correlation coefficient; IL = insertion length; LD = low dose; PCD = photon-counting detector; RD = regular dose; SD = standard deviation; ULD = ultra-low dose

Successful hearing rehabilitation by cochlear implantation depends on implementing information about the patient's cochlear characteristics into the surgical procedure.^{1,2} Preoperative analysis of cochlear anatomy allows for appropriate length selection of the cochlear implant electrode carrier to achieve full cochlear coverage with the electrode lead. This enables electric stimulation of all relevant frequencies for pitch perception.³⁻⁷ By

extracting anatomic and tonotopic information about the cochlea, precise insertion of the chosen electrode carrier becomes feasible.^{8,9} As a result, the patient's hearing outcome can benefit from transferring delicate information about the cochlear duct length (CDL), the number of turns, and the frequency bandwidth distribution into the insertion process.¹⁰⁻¹² Insertion depth, insertion angle, and electrode placement can influence the audiological outcome of the patient.^{3,13,14}

Despite precise implantation, postoperative cochlear implant electrode contacts may deviate from preoperatively targeted locations, leading to a "frequency-to-place mismatch." This mismatch between electrode distribution and cochlear tonotopy can impair speech perception in patients.¹⁵ Despite adjusting each cochlear implant electrode contact to the anatomically correct natural frequency location during postoperative fitting, frequency-to-place mismatches remain a concern,¹¹ particularly for patients with bilateral cochlear implants to reduce tonotopic asymmetry between the ears.¹⁵ Recent studies addressed the need for precise electrode

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SUMMARY

PREVIOUS LITERATURE: Comparative studies emphasize the advantages of photon-counting detectors over conventional CT scanners regarding spatial resolution, tissue contrast, and radiation dose reduction. However, the extent to which photon-counting CT improves imaging in the context of cochlear implantation has not yet been investigated.

KEY FINDINGS: In 10 temporal bone specimens, no substantial difference was ascertained between regular-dose and low-dose photon-counting CT in terms of preoperative cochlear analysis and postoperative electrode contact determination. However, extensive radiation dose reduction was achieved compared with the clinical standard protocol.

KNOWLEDGE ADVANCEMENT: Our findings indicate that photon-counting CT facilitates highly accurate pre- and postoperative cochlear analysis with very little radiation dose. Children and young adults needing cochlear implant surgery especially may benefit from this radiation exposure reduction.

contact determination in accordance with a patient's tonotopic characteristics for anatomically correct postoperative fitting.^{9,16,17} Cochlear analysis with surgical planning software can accurately show the position of the cochlear implant electrodes after insertion. Knowing the exact locations of each electrode contact within the cochlea helps audiologists and electrophysiologists minimize the frequency-to-place mismatch.¹⁵

To evaluate cochlear structures, various imaging options are available, including conventional energy-integrating detector (EID) CT, conebeam CT with flat panel detectors,^{18,19} and now, photon-counting detector (PCD) CT.

CDL measurement varies considerably, especially depending on the imaging and measurement techniques used.^{7,20-23} Frequently used CT scanners in clinical routine employ EID.²⁴⁻²⁷ In recent years, the dose reduction potential of the less efficient EID technology has been mostly exhausted because of the technical constraints originating from the detector architecture.²⁸ Simultaneously, radiation protection, particularly in infants, who constitute a substantial portion of the patient group undergoing perioperative temporal bone CT scans, becomes crucial.²⁹

Therefore, PCD-CT, representing a promising alternative for conventional EID-CT, is gaining the attention of not only radiologists but also otosurgeons.³⁰ The only commercially available and clinically approved PCD consists of a semiconductor material (cadmium-telluride).^{31,32} PCD-CT facilitates improved contrast-to-noise ratios, reduction of the pixel size, and overall improvement of dose efficiency.³²⁻³⁵ The potential radiation dose reduction in temporal bone scans was described to be up to 80% compared with conventional EID-CT in recent preclinical analysis.³⁶

This study was conducted by using cadaveric specimens to ensure optimal comparability between scans. Its primary objective was to assess preoperative planning and positions of cochlear implants. The evaluation of the cochlea was supported by dedicated software, which enabled the comparison of pre- and postoperative scans at various dose levels by analyzing the cochlear duct length. Additionally, the study investigated whether the dose level influences the outcomes.

MATERIALS AND METHODS

Image Acquisition

PCD-CT studies were performed with a first-generation dual-source scanner (NAEOTOM Alpha, Siemens Healthineers) equipped with a cadmium-telluride detector system. Three protocols with

different radiation dose levels were investigated: A clinical regular-dose protocol (PCD-CT_{RD}) with a volume CT dose index (CTDI_{vol}) of 27.1 mGy, a low-dose protocol (PCD-CT_{LD}) with a CTDI_{vol} of 4.81 mGy, and an ultra-low-dose (PCD-CT_{ULD}) protocol with 3.43 mGy. Other scan parameters are summarized in Table 1. Effective radiation exposure was calculated by multiplying the dose-length products (DLP) with an established conversion factor of $0.0021 \text{ mSv} \times \text{mGy}^{-1} \times \text{cm}^{-1}$.³⁷

Specimens and Practical Approach

Cochlear implant electrode carrier insertion was performed in 10 human petrous bone specimens by an experienced cochlear implant surgeon by using a mastoidal approach after preoperative PCD-CT imaging. The temporal bone specimens used in this study were used following appropriate guidelines and procedures for obtaining and using human tissue in concordance with the Bavarian law. No further ethics committee approval was obtained.

In all specimens, a Flex²⁸ cochlear implant electrode array (MED-EL) was inserted. Postoperative PCD-CT data were acquired in all specimens with the same scan protocols used for preoperative imaging (Fig 1 and Fig 2). Figure 1 provides a representation of the adjusted pre- and postoperative cochlear view in one of the temporal bone specimens. Minor differences between the freeze frames in Fig 1 resulted from adjustments for each scan mode. The oblique coronal view of the basal turn of the cochlea was individually aligned by inserting projection axes through the center of each basal turn and the modiolus. The differences depicted in Fig 1 did not affect the measurements as they were performed in 3 planes (axial, sagittal, and cochlear view) in a dynamic process.

To ensure the comparability of scan lengths, the specimens were brought in an anatomically correct position, and the CT planning was performed based on the anatomic structures visible on scout images. CDL measurement was performed before and after electrode carrier insertion. Cochlear implant electrode contact determination was investigated postoperatively.

Primary Data Analysis

Pre- and postoperative CDL measurements were performed separately for the lateral cochlea wall (CDL_{LW}) and the organ of Corti (CDL_{OC}). After transferring the Digital Imaging and Communications in Medicine (DICOM) data sets into a dedicated viewer software (Horos, Version 3.3.5, Nimble Co LLC d/b/a Purview), a 3D-curved multiplanar reconstruction of the

cochlea was performed by an otosurgeon with 4 years of training in multiplanar reconstruction measurements. The reconstruction technique enables a precise determination of CDL_{LW} by fitting in a manually placed Bézier path directly to the lateral wall of the cochlea that is projected in the “cochlear view”.^{5,21,38,39} The

Bézier path extends from the center of the round window to the apex of the cochlea by defining multiple marker dots in different planes as described by Wuerfel et al.³⁸ A minimum intensity projection with 1.0-mm thickness was used to optimize the visualization of the highest point of the spiral canal.^{20,40}

The DICOM data set was then transferred to a specialized otological planning software (Otoplan, Version 3, CAscination AG, and MED-EL) to measure CDL_{OC} (Supplemental Video V1). CDL_{OC} measurement by using this software is based on equations by Alexiades et al⁴¹ and Schurzig et al.⁴² The calculation of the tonotopic frequency map of the cochlea is based on preliminary work by Greenwood,⁴³ in which the relationship between the frequency and the location of maximum basilar membrane excursion was first described. The formula used by Greenwood⁴³ was supplemented by Stakhovskaya et al⁴⁴ with the inclusion of cochlear angle measurements (in

Table 1: Scan and reconstruction parameters

Scan Protocol	Regular Dose	Low Dose	Ultra-Low Dose
Pixel size at the iso-center [mm ²]		0.15 × 0.176	
Collimation [mm]		120 × 0.2	
Tube voltage [kVp]		120	
Effective tube current [mAs]	158	28	20
CTDI _{vol} [mGy]	27.1	4.81	3.43
Spiral pitch factor		0.2	
Rotation time [sec]		1	
Convolution kernel [line pairs/cm at 50% and 10% of the modulation transfer function]		Hr98 ($\rho_{50} = 39.04$; $\rho_{10} = 42.91$) ^a	
Iterative reconstruction strength		QIR level 3	
Slice thickness [mm]		0.2 mm (0.1 mm increment)	
Matrix [pixel]		512 ²	
Reconstruction field of view [mm]		50	
Reconstruction mode		Polychromatic (T3D)	

^aThe ρ_{50} and ρ_{10} values represent manufacturer-specified metrics, indicating the maximum resolution of the reconstruction kernel.

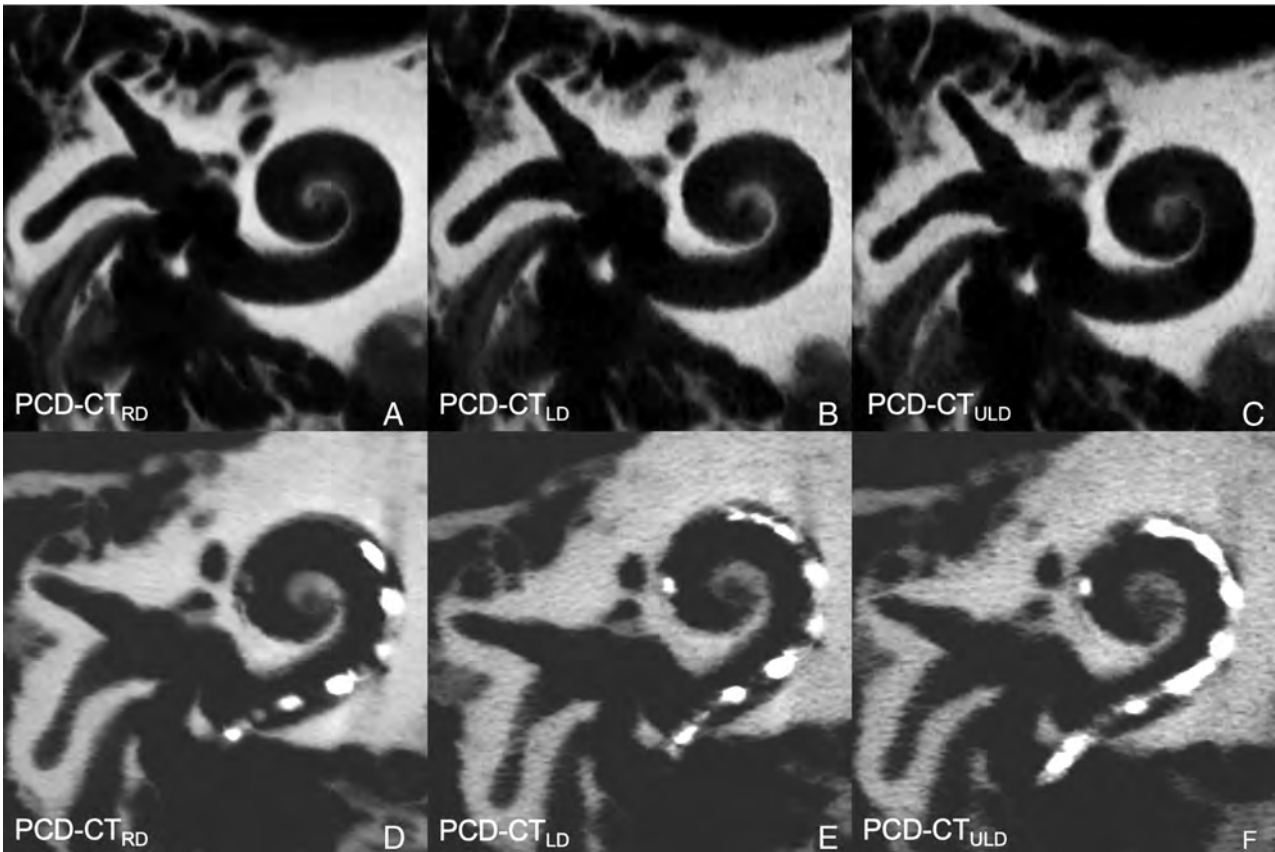


FIG 1. Representative PCD-CT images of the same temporal bone scan before and after cochlear implant insertion show the “cochlear view” with different radiation dose levels. PCD-CT_{RD} scans were acquired with a CTDI_{vol} of 27.1 mGy (A, PCD-CT_{RD} before cochlear implant insertion, D, PCD-CT_{RD} after cochlear implant insertion). PCD-CT_{LD} scans were acquired with a CTDI_{vol} of 4.81 mGy (B, PCD-CT_{LD} before cochlear implant insertion, E, PCD-CT_{LD} after cochlear implant insertion). PCD-CT_{ULD} scans were acquired with a CTDI_{vol} of 3.43 mGy (C, PCD-CT_{ULD} before cochlear implant insertion, F, PCD-CT_{ULD} after cochlear implant insertion). Minor differences concerning cochlear implant visibility between the freeze frames resulted from individual cochlear view adjustment for each scan mode.

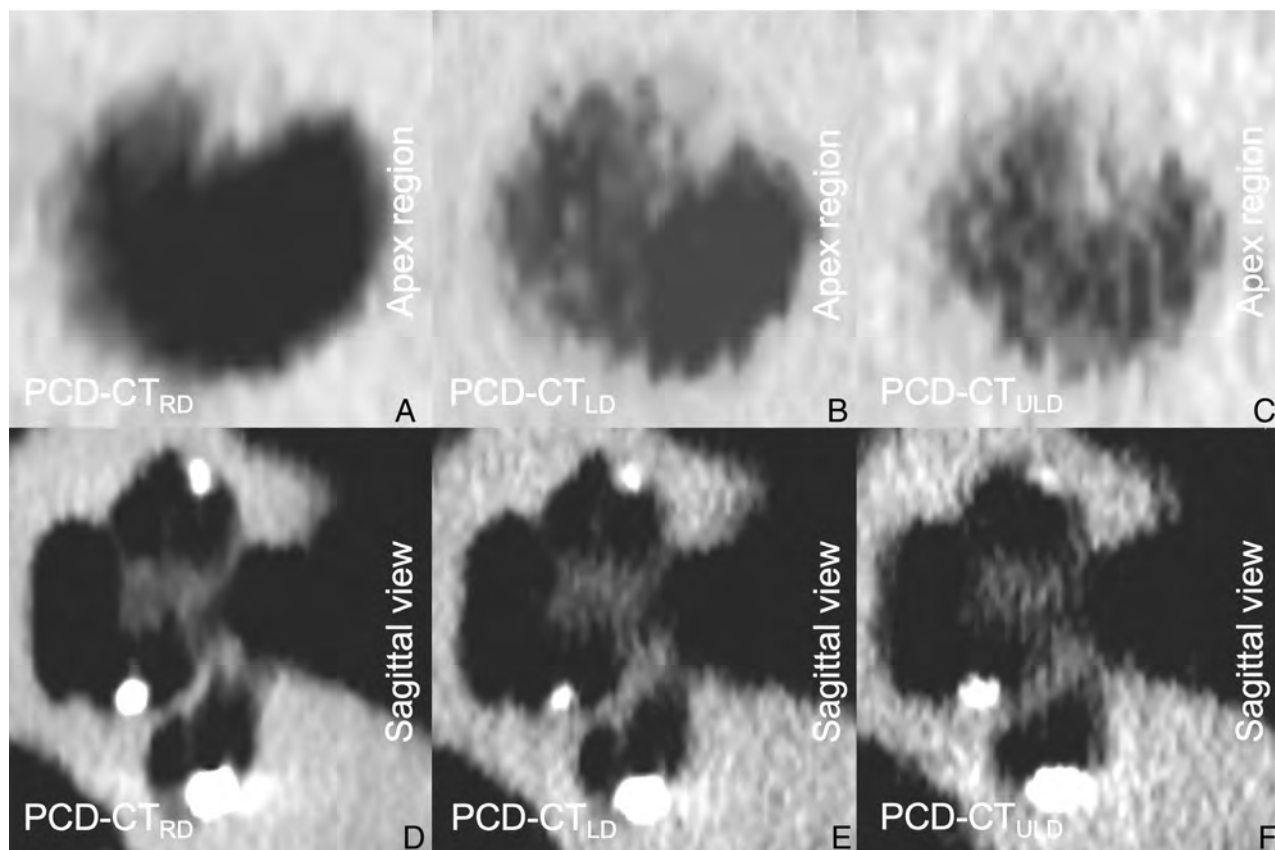


FIG 2. Representative PCD-CT images of 1 temporal bone scan after cochlear implant insertion showing the apex region (A–C) and the sagittal view (D–F) of the same cochlea dependent on different radiation dose levels.

degrees) to determine the location within the cochlea. Postoperative cochlear implant electrode contact determination within the software was performed in 2 ways, automatically and manually, by 2 independent otosurgeons with 6 and 4 years of clinical training in the field, respectively. Measurements were performed in 2 sessions (before and after cochlear implant insertion) with observers blinded to the respective scan protocol. Electrode contact determination enabled analysis of the angular insertion depth, insertion length, and tonotopic mapping of each electrode contact. The manually performed electrode contact determination represented the ground truth of electrode positioning. It was performed by placing 12 individual fiducials precisely in the center of each electrode contact using the axial, sagittal, and cochlear view. Starting with the C12 electrode contact in the basal turn of the cochlea right next to the round window niche, the examiner placed one fiducial after another along the cochlear turns up to the apex region where the most apical electrode, ie, the C1 electrode contact, was positioned. Angular insertion depth (AID), insertion length (IL), and frequency location were then calculated by the software, which was dependent on the individual CDL_{OC} computed before. Since it is also possible to let the software place the 12 fiducials automatically, the manual fiducial placement was compared with the automated electrode detection (Online Supplemental Data). Accuracy levels were determined based on the differences between automated and manual measurements and were

calculated for all radiation dose protocols. Interrater variability was analyzed.

Subjective Image Quality Analysis

In addition to quantitative analyses, a subjective assessment of overall image quality was performed by 3 board-certified radiologists with 7–10 years of experience. Blinded to any scan protocol-related information, the observers analyzed all pre- and postoperative data sets in randomized order by using standard PACS software (Merlin, Phönix-PACS). Personal window preferences, ie, width and center, could be used for each read. An equidistant 7-point scale was used to evaluate the overall image quality (7 = excellent, 6 = very good, 5 = good, 4 = satisfactory, 3 = fair, 2 = poor, 1 = very poor). To estimate interrater agreement, the intraclass correlation coefficient (ICC) was computed based on absolute agreement of single measures in a 2-way random effects model. ICC values were interpreted as: ICC > 0.90 = excellent; 0.75–0.90 = good; 0.50–0.75 = moderate; and < 0.50 = poor reliability.

Statistics

Normal distribution was assessed by using the d'Agostino-Pearson test. One-way repeated measures analysis of variance (ANOVA) was used for metric data in case of normal distribution, whereas the Friedman or Wilcoxon test was applied for non-normal items. A type 1 error level of < 0.05 was considered indicative of statistical significance and a confidence level of 95%

Table 2: Pre- and postoperative cochlear duct length measurements with different radiation dose levels

Image Acquisition	Regular Dose		Low Dose		Ultra-Low Dose	
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
CDL _{OC} (mm)						
Mean	37.23	37.33	37.16	37.25	37.15	37.05
SD	2.66	2.72	2.56	2.62	2.71	2.64
95% CI	35.33–39.13	35.38–39.28	35.33–38.99	35.37–39.13	35.21–39.09	35.16–38.94
Range	7.40	7.40	6.80	7.10	7.20	7.20
Minimum	32.80	32.80	33.00	33.10	32.50	32.30
Maximum	40.20	40.20	39.80	40.20	40.30	39.50
CDL _{LW} (mm)						
Mean	40.76	40.99	40.90	40.74	40.88	40.96
SD	2.73	2.88	2.58	2.72	2.61	2.57
95% CI	38.81–42.71	38.93–43.05	39.06–42.74	38.79–42.69	39.02–42.74	39.12–42.80
Range	8.40	8.90	8.00	8.40	7.70	7.50
Minimum	36.10	35.90	36.60	35.80	36.70	36.50
Maximum	44.50	44.80	44.60	44.20	44.40	44.00

was preset. Interrater variability was statistically analyzed and graphically displayed via Bland-Altman plots for all measurement groups. A CDL deviation of more than ± 1.5 mm was determined as clinically relevant and defined as an error range.^{5,45} All statistical analyses were performed by using dedicated software (GraphPad Prism, Version 8.3.0, GraphPad Software).

RESULTS

Radiation Dose

The regular-dose protocols were associated with a DLP of 153.19 ± 43.45 mGy $\times$ cm, while the LD and ULD protocol resulted in a mean DLP of 27.19 ± 7.71 mGy $\times$ cm and 19.36 ± 5.49 mGy $\times$ cm, respectively. This corresponds to effective dose values of 0.32 ± 0.09 mSv for regular dose, 0.06 ± 0.016 mSv for low dose, and 0.04 ± 0.01 mSv for ultra-low-dose imaging.

Influence of Radiation Dose on CDL_{OC} and CDL_{LW} Measurements

Normally-distributed metric data read as mean $\pm$ standard deviation (SD) (Table 2). PCD-CT_{RD} scans showed a preoperative CDL_{OC} of 37.23 ± 2.66 mm and a preoperative CDL_{LW} of 40.76 ± 2.73 mm. The postoperative measurements revealed a CDL_{OC} of 37.33 ± 2.72 mm and CDL_{LW} of 40.99 ± 2.88 mm. PCD-CT_{LD} scans had a preoperative CDL_{OC} of 37.16 ± 2.56 mm and a preoperative CDL_{LW} of 40.90 ± 2.58 mm. Postoperatively, a CDL_{OC} of 37.25 ± 2.62 mm and a CDL_{LW} of 40.74 ± 2.72 mm were measured. The scan protocol with the lowest radiation dose, PCD-CT_{ULD}, resulted in a preoperative CDL_{OC} of 37.15 ± 2.71 mm and a CDL_{LW} of 40.88 ± 2.61 mm. PCD-CT_{ULD} showed a postoperative CDL_{OC} of 37.05 ± 2.64 mm and a CDL_{LW} of 40.96 ± 2.57 mm. Data comparison revealed no statistically significant difference between the tested groups. Moreover, there were no significant differences between pre- and postoperative measurements within the same scan protocol group (Fig 3).

Influence of Radiation Dose on Postoperative Electrode Contact Determination

Accuracy of Automated Frequency Determination. The overall difference between automated and manual frequency determination across all cochlear implant electrode contacts was 31 ± 8 Hz for

PCD-CT_{RD}, 32 ± 8 Hz for PCD-CT_{LD}, and 34 ± 7 Hz for PCD-CT_{ULD}. There was no difference concerning the accuracy levels for automated frequency determination between PCD-CT_{RD} and PCD-CT_{LD} ($P > .99$), between PCD-CT_{RD} and PCD-CT_{ULD} ($P = .53$), or between PCD-CT_{LD} and PCD-CT_{ULD} ($P = .79$).

Accuracy of Automated Insertion Length Determination. The overall mean difference between automated and manual IL determination across all cochlear implant electrode contacts was 0.058 ± 0.011 mm for PCD-CT_{RD}, 0.056 ± 0.016 mm for PCD-CT_{LD}, and 0.062 ± 0.014 mm for PCD-CT_{ULD}. There was no significant difference concerning the accuracy levels for automated IL determination between PCD-CT_{RD} and PCD-CT_{LD} ($P = .93$), between PCD-CT_{RD} and PCD-CT_{ULD} ($P = .71$), or between PCD-CT_{LD} and PCD-CT_{ULD} ($P = .29$).

Accuracy of Automated Angular Insertion Depth Determination. The overall mean difference between automated and manual AID determination across all cochlear implant electrode contacts was $1.3 \pm 0.4^\circ$ for PCD-CT_{RD}, $1.2 \pm 0.3^\circ$ for PCD-CT_{LD}, and $1.3 \pm 0.4^\circ$ for PCD-CT_{ULD}. The accuracy levels for automated AID determination between PCD-CT_{RD} and PCD-CT_{LD} showed no significant difference ($P = .43$). This was the same for comparisons between PCD-CT_{RD} and PCD-CT_{ULD} ($P = .89$) and between PCD-CT_{LD} and PCD-CT_{ULD} ($P = .19$) (Fig 4).

Influence of Radiation Dose on Interrater Variability

Interrater variability of pre- and postoperative CDL_{OC} was low for all measurements independent of the applied radiation dose (Table 3). No unacceptable errors were found. The lowest interrater variability was seen in the PCD-CT_{ULD} group with a bias of 0.12 ± 0.38 preoperatively and 0.11 ± 0.47 postoperatively. PCD-CT_{RD} showed a bias of 0.35 ± 0.40 preoperatively and 0.18 ± 0.49 postoperatively. The bias of PCD-CT_{LD} was 0.17 ± 0.35 preoperatively and 0.47 ± 0.35 postoperatively (Online Supplemental Data).

Subjective Image Quality

PCD-CT_{RD} was considered to feature the best image quality overall (median 7 [interquartile range 7–7]). Both PCD-CT_{LD} (6 [5–6])

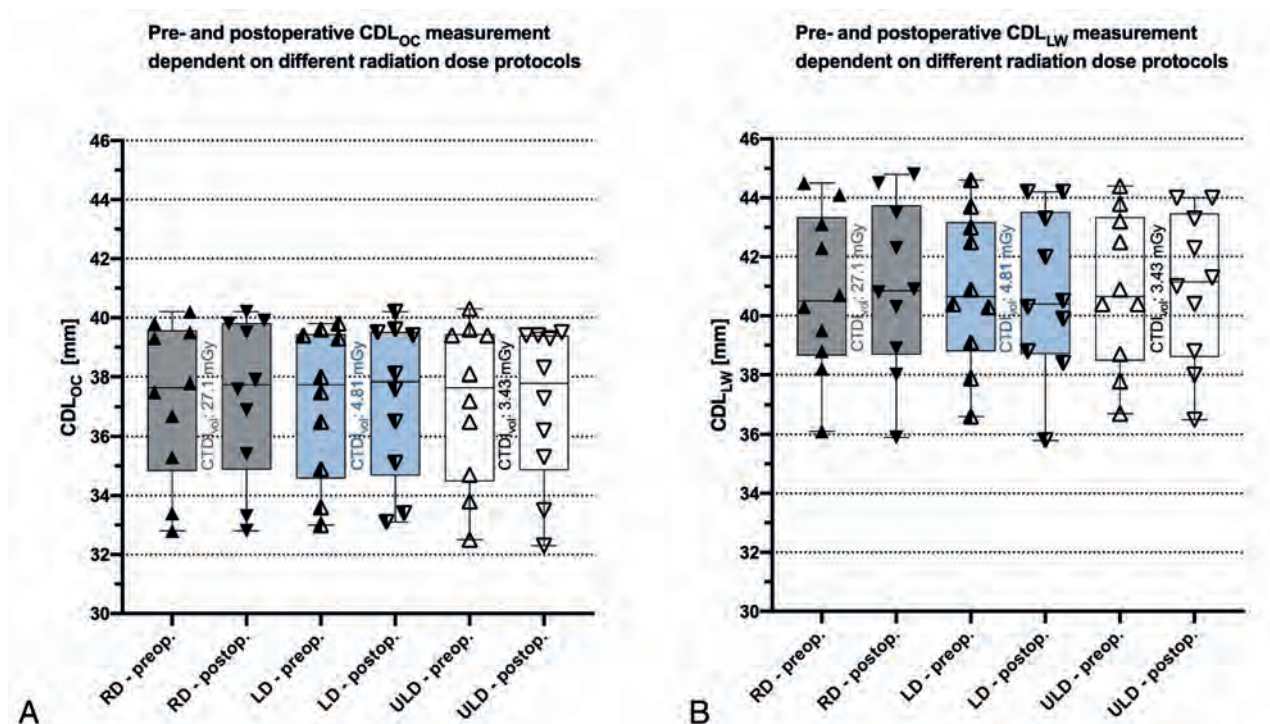


FIG 3. CDL measurement with different radiation dose levels. *A*, Pre- and postoperative CDL_{OC} measurement with the otological planning software showing no significant differences between the tested groups. *B*, Reveals no significant differences between all groups concerning CDL_{LW} measurement by 3D-curved MPR analysis.

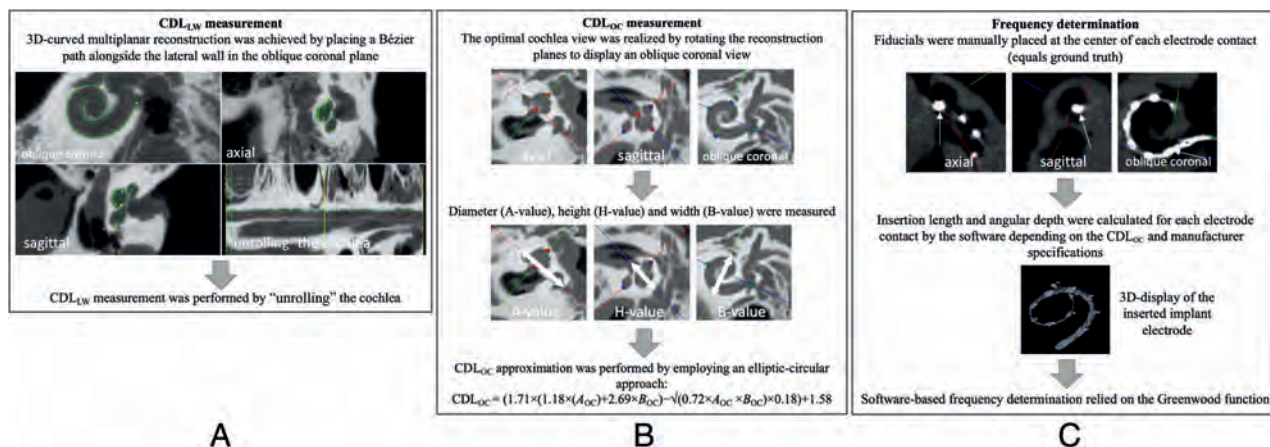


FIG 4. Illustration of cochlear analysis by using 3D-curved multiplanar reconstructions (*A*) and the otological planning software (*B* and *C*): Measurements of CDL_{LW} (*A*) were performed by fitting in a Bézier path to the lateral wall of the cochlea projected in the “cochlear view.” Multiple marker dots were placed in different planes extending from the center of the round window (RV) to the apex of the cochlea. CDL_{OC} (*B*), as well as insertion length, angular insertion depth, and frequency distribution (*C*) were calculated with otological planning software. Calculation of CDL_{OC} is based on an elliptic circular approximation formula described by Alexiades et al.⁴¹ and Schurzig et al.⁴² Calculation of the related frequency location is based on formulas described by Greenwood⁴³ and Stakhovskaya et al.⁴⁴

and PCD-CT_{ULD} (4 [3–4]) received considerably inferior ratings (all $P < .001$). Notably, preoperatively acquired data sets were deemed superior compared with postoperative images in PCD-CT_{LD} (6 [6–6] versus 5 [5–6]; $P < .001$) and PCD-CT_{ULD} (4 [4–5] versus 3 [3–4]; $P < .001$). In contrast, no significant difference was ascertained among acquisitions before and after cochlear implant insertion in PCD-CT_{RD} (7 [7–7] versus 7 [7–7]; $P = .21$). Interrater reliability was good, indicated by a single measures ICC of 0.89 (95% CI: 0.84–0.93; $P < .001$).

DISCUSSION

High-resolution temporal bone scans in the context of otosurgical procedures are increasingly in demand since preoperative knowledge of individual anatomic conditions can substantially influence the surgical outcome. For cochlear implant surgery, the selection and implantation of an anatomically fitting cochlear implant electrode, as well as postoperative coding and fitting strategies of the audio processors, are all influenced considerably by the quality of the CT images.^{6,16,46–48} However, radiation

Table 3: Influence of radiation dose on electrode contact determination and interrater variability

Image Acquisition	Regular Dose		Low Dose		Ultra-Low Dose	
Accuracy of automated frequency determination (Hz)						
Mean	31		32		34	
SD	8		8		7	
95% CI	25–37		27–38		29–39	
Range	26		22		25	
Minimum	23		27		19	
Maximum	49		49		44	
Accuracy of automated insertion length determination (mm)						
Mean	0.058		0.056		0.062	
SD	0.011		0.016		0.015	
95% CI	0.050–0.066		0.045–0.067		0.051–0.073	
Range	0.040		0.050		0.040	
Minimum	0.040		0.030		0.040	
Maximum	0.080		0.080		0.080	
Accuracy of automated angular insertion depth determination (° [degree])						
Mean	1.3		1.2		1.3	
SD	0.4		0.3		0.4	
95% CI	1.0–1.6		1.0–1.4		1.1–1.6	
Range	1.1		0.9		1.0	
Minimum	0.9		0.8		0.9	
Maximum	2.0		1.7		1.9	
Influence of CDL _{OC} measurement and radiation dose on interrater variability (mm)						
	Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
Bias	0.35	0.18	0.17	0.47	0.12	0.11
SD	0.40	0.49	0.35	0.35	0.38	0.47

protection remains a concern, particularly for vulnerable patient groups like pediatrics, limiting access to high-resolution imaging techniques. This temporal bone study explores a new imaging approach by using PCD-CT with dedicated low- and ultra-low-dose protocols for pre- and postoperative scans in cochlear implant surgery.

Our results indicate that with PCD-CT, metal artifacts from cochlear implants do not interfere with CDL measurements, although established artifact suppression techniques, such as iterative metal artifact reduction and virtual monoenergetic imaging, were not employed in the present study. We refrained from applying these methods, because they cannot be combined with ultra-sharp convolution kernels as of this writing. In 2022, Waldeck et al²⁸ presented the first scientific study on PCD-CT for cochlear implant surgery. In their study, they investigated temporal bone scans of human body donors with an inserted cochlear implant electrode, comparing PCD-CT to conventional EID-CT. While PCD-CT scans were performed with a tube potential of 120 kV, an image slice thickness of 0.4 mm, and CTDI_{vol} of 5.44 mGy, EID-CT images were acquired in dual-energy scan mode with a tube potential of 80 kV/Sn 150 kV, an image section thickness of 0.6 mm, and CTDI_{vol} of 4.16 mGy. In this investigation, PCD-CT scans showed an improved contrast enhancement for metal-to-bone transitions enabling a more accurate cochlear implant electrode contact visualization with an improved visualization of the interelectrode wire. While metal artifacts are often problematic in CT imaging, the cochlear

implant electrode contacts had no effect on the cochlear analyses in the presented study.²⁸

To the best of the authors' knowledge, this study is the first to assess dedicated low-dose protocols in temporal bone PCD-CT for pre- and postoperative cochlear analysis in cochlear implant surgery. It includes a comprehensive analysis of cochlear parameters crucial for anatomically based cochlear implants, including CDL measurement; electrode contact determination; and analysis of AID, IL, and frequency assessment. In conclusion, CDL_{OC} and CDL_{LW} measurements by using scan protocols with reduced radiation dose showed no significant difference from regular-dose scans. Furthermore, there was no difference between pre- and postoperative CDL measurements within each group.

Postoperative electrode contact frequency determination was equally accurate with low- and ultra-low-dose protocols, matching the established regular-dose protocol. Comparable results were seen for postop IL and AID measurements. Both reduced-dose protocols exhibited no interrater variability or unacceptable errors. These findings indicate that dose reduction efforts must not necessarily entail a significant measurement error compared with a regular-dose protocol. In the present study, the low-dose protocol enabled a dose reduction of 82.3%, while the dose reduction was even higher for the ultra-low-dose protocol with 87.3%. While the subjective ratings for PCD-CT_{LD} and PCD-CT_{ULD} were lower compared with the regular dose protocol, it is important to note that both objective and subjective results indicate that the respective clinical questions could still be adequately

addressed. Depending on the individual's needs, one could perform preoperative planning by using the low-dose protocol and postoperative control by using the ultra-low-dose protocol. This approach would offer a balanced solution, maximizing both dose efficiency and clinical efficacy.

In a prior study, Tada et al⁴⁹ examined radiation dose exposure with 2 temporal bone scan protocols in children by using conventional multislice CT. In 9 cases, a standard-dose 120 kV protocol was employed with filtered back-projection for image reconstruction. CTDI_{vol} and effective dose were 19.9 mGy and 0.42 mSv, respectively. In 13 children, the authors tested a dedicated low-dose protocol with a CTDI_{vol} of 9.9 mGy and an effective dose of 0.21 mSv.⁴⁹ Despite methodologic and technical differences, these numbers underline the quantum leap in dose reduction made possible by the emergence of PCD-CT. Our clinical reference protocol yielded an effective dose of 0.196 mSv, comparable with the low-dose protocol in Tada et al. However, our ultra-low-dose PCD-CT protocol resulted in only 0.025 mSv, just 11.9% of the low dose in Tada et al.⁴⁹

There is only a limited number of studies focusing on temporal bone imaging with a PCD-CT scanner thus far. Zhou et al⁵⁰ investigated temporal bone scans of human body donors and compared the image quality to a high-resolution EID-CT scanner. According to the authors, the radiation dose was set to a clinical examination level with a CTDI_{vol} of 61 mGy for both CT scanners. Of note, this is more than twice as high as the regular-dose protocol in the present study. Zhou et al⁵⁰ report that PCD-CT allowed for approximately 40% image noise reduction compared with EID-CT with the same image section thickness. Based on this finding, they quantified the potential for radiation dose reduction to be about 64% if the same image noise is targeted. Moreover, the authors postulate better image quality concerning delicate anatomic structures of the middle and inner ear, eg, the incudomalleolar joint, the stapes footplate, and the cochlear modiolus.

Another study from Benson et al⁵¹ conducted a comparable study comparing PCD-CT and EID-CT temporal bone scans in 13 patients. PCD-CT scans were performed by using a tube potential of 120 kV, a sharp kernel type (Hr84), and an image section thickness of 0.2 mm, resulting in a CTDI_{vol} of 35.6 mGy. The EID-CT scans were performed by using a clinical routine scan protocol with a tube potential of 120 kV, a slice thickness of 0.4 mm, and a CTDI_{vol} of 51.5 mGy. Despite a radiation dose reduction of 31%, the authors describe a substantially improved overall image quality for PCD-CT compared with EID-CT.⁵¹

Several methodologic limitations have to be considered. First, the presented study did not include intact head specimens. Although the temporal bone is naturally covered by only a small amount of soft tissue, our radiation dose results may not be transferable to full-head scans. It is to be expected that the radiation dose reduction potential in full-head specimens with more surrounding soft tissue and air spaces is lower than in extracted temporal bone specimens. Second, no histologic preparation was performed. All data were collected in 10 temporal bone specimens, which have been shown to be a sufficient number in previous temporal bone studies.^{5,13,21,52-54} Third, since fresh-frozen bones were utilized for all scans, the thawing process may have

resulted in a minor systematic error, which was deemed acceptable for the feasibility of the experiment. Fourth, electrode models from different manufacturers were not inserted to reduce confounders. Fifth, Hr98 represents the sharpest applicable convolution kernel for head imaging. However, the maximum resolution may not be achievable under low-dose conditions. Therefore, it appears reasonable for clinical practice to adjust reconstruction parameters to the applied radiation dose. This optimization was not performed in the present investigation but may be necessary if the goal is to reduce the dose even further. Finally, despite being common practice for several high-contrast imaging tasks, such as lung cancer screening and urolithiasis, in the era of EID-CT, tin prefiltration was not employed in this investigation since earlier studies have demonstrated a substantial loss of image contrast and a limited effect on the dose reduction potential in temporal bone studies by using PCD-CT.³⁶

CONCLUSIONS

Ultra-high-resolution cochlear imaging is feasible with very low radiation exposure when using first-generation photon-counting CT in combination with dedicated low-dose protocols. The accuracy of pre- and postoperative cochlear analysis with the applied dose reduction settings was comparable to a clinical regular-dose protocol.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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The Association of Vascular Loops within the Internal Auditory Meatus or Contacting the Vestibulo-Cochlear Nerve with Audiovestibular Symptoms: A Systematic Review and Meta-Analysis

Jake E. Cowen, Mehrshad Sultani Tehrani, and Steve E.J. Connor



ABSTRACT

BACKGROUND: Intrameatal vascular loops (IVL) entering the internal auditory meatus and neurovascular contact (NVC) with the vestibulocochlear nerve (cranial nerve [CN] VIII) have been proposed to have a relationship with audiovestibular symptoms.

PURPOSE: This systematic review and meta-analysis aimed to determine whether the presence of IVLs and CN VIII NVC on MRI is associated with tinnitus, sensorineural hearing loss (SNHL), or vertigo and any specific subtypes.

DATA SOURCES: All studies comparing the presence of IVL or CN VIII NVC in ears with these audiovestibular symptoms and controls were identified through MEDLINE, EMBASE, the Web of Science Core Collection, Scopus, and the Cochrane Register of Controlled Trials databases.

STUDY SELECTION: Sixteen studies and 3455 ears (1526 symptomatic ears and 1929 control ears) were included.

DATA ANALYSIS: Meta-analysis was performed using a bivariate random effects model. Pooled ORs were calculated, and heterogeneity was evaluated with the Cochran Q test with statistical significance defined as $P < .05$.

DATA SYNTHESIS: There was no significant association between the presence of undefined tinnitus or SNHL and IVL (OR, 0.90; 95% CI, 0.47–1.70; OR, 0.67; 95% CI, 0.36–1.25) or CN VIII NVC (OR, 1.15; 95% CI, 0.68–1.95; OR, 0.89; 95% CI, 0.33–2.40). However, the subgroup of sudden onset SNHL was associated with IVL (OR, 1.34; 95% CI, 1.04–1.73) ($P = .02$). There was no significant difference in the prevalence of IVL (OR, 0.97; 95% CI 0.64–1.48) or CN VIII NVC (OR, 0.99; 95% CI, 0.42–2.32) between ears with undefined vertigo and control ears. However, there was an association between the presence of CN VIII NVC and the specific diagnosis of vestibular paroxysmia (OR, 13.19; 95% CI, 2.09–83.16) ($P = .006$).

LIMITATIONS: Our meta-analysis is limited by selection bias, the small number of eligible studies, and moderate heterogeneity.

CONCLUSIONS: IVL or CN VIII NVC on MRI is unrelated to symptoms of undefined tinnitus, SNHL, and vertigo. However, CN VIII NVC is associated with vestibular paroxysmia, while IVL is associated with sudden onset SNHL.

ABBREVIATIONS: CN = cranial nerve; IAM = internal auditory meatus; IVL = intrameatal vascular loop; NVC = neurovascular contact; SNHL = sensorineural hearing loss; SoSNHL = sudden onset sensorineural hearing loss

Vascular loops are frequently identified within the internal auditory meatus (IAM) on MRI. While this is most commonly

due to the anterior inferior cerebellar artery, the posterior inferior cerebellar artery, superior cerebellar artery, or venous structures may also be responsible.¹ Authors have speculated that these intrameatal vascular loops (IVLs) may be responsible for tinnitus, sensorineural hearing loss (SNHL), and vertigo.² It is hypothesized that such audiovestibular symptoms may result from altered neural conduction due to cranial nerve (CN) VIII neurovascular contact (NVC), reduced vascular perfusion of the nerves due to disturbed blood flow, or increased transmission of sound through the CSF of the IAM.^{1,2} Symptoms due to NVC are considered most common when a vessel contacts the centrally myelinated portion of the CN or the transition zone between central and peripheral myelin.³

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Determining an association between the presence of an IVL or CN VIII NVC and audiovestibular clinical presentations would guide the selection of appropriate diagnostic MRI sequences and interpretation of the imaging findings. There are also potential therapeutic implications because vascular decompression surgery has been performed to alleviate such symptoms.⁴ An association between these vascular variants and audiovestibular clinical presentations remains uncertain, with variable outcomes from previous case-controlled studies and with no contemporary pooling of the statistical outcomes.

This systematic review and meta-analysis aimed to determine whether there is an association between IVLs or CN VIII NVC and specific audiovestibular symptoms.

MATERIALS AND METHODS

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁵ and enrolled in the Prospective Register of Systematic Reviews (PROSPERO), CRD42023447065.

Search Strategy

The search strategy was designed using population; intervention or exposure; comparator/control; outcome; study design (PICOS). “Population” was defined as ears with specific audiovestibular symptoms; “exposure,” as the presence of an IAM vascular loop or CN VIII NVC; “control,” as ears without audiovestibular symptoms; “outcome,” as the presence of an IAM vascular loop or CN VIII NVC relative to the reporting of audiovestibular symptoms; and “study design,” as case-controlled cross-sectional studies. Search terms were adapted after a pilot search to include relevant synonyms (Online Supplemental Data).

Searches were performed in MEDLINE, EMBASE, the Web of Science Core Collection, Scopus, and the Cochrane Register of Controlled Trials databases. The search was performed from database inception onward. The searches were last performed on January 8, 2023. Manual forward and backward searches were performed for all eligible review articles. The 5 most frequently cited journals were hand-searched (2009–2023) (Online Supplemental Data). EndNote Web (<https://endnote.com/>) was used as a reference manager to identify and collate the literature and allow the manual removal of duplicates.

Selection of Studies

Two independent reviewers (J.E.C. and M.S.T.) applied the piloted screening tool to the titles and abstracts with the following inclusion criteria: a defined patient group with audiovestibular symptoms; analysis using MRI; and reference to a vascular loop/variant or anomaly. Case studies, review articles, foreign language literature, and duplicated studies were excluded. The full text was independently assessed for eligibility by both reviewers according to the PICOS criteria. Studies were included when there were data that could be extracted into a 2×2 contingency table comparing the presence of an IVL or CN VIII NVC in ears with and without tinnitus, SNHL, or vertigo. Because vertigo is not lateralized to either ear, patients with vertigo were compared with subjects without vertigo, with the prevalence of an IVL or CN VIII NVC in either ear being recorded. When a symptomatic

subtype was defined by specific criteria, then this subtype was analyzed separately.

Reasons for exclusion are listed in the Online Supplemental Data. Discrepancies were resolved by discussion (J.E.C., M.S.T., S.E.J.C.).

Data Extraction

Two reviewers (J.E.C., M.S.T.) independently extracted data regarding the following: 1) study characteristics: authors, year of publication, retrospective versus prospective, case and control group size, IVL classification scale applied, specified audiovestibular symptoms; 2) control group type: asymptomatic contralateral ears, healthy volunteer ears, or ears of patients with an unrelated condition; and 3) demographic and clinical characteristics: age and sex of the case and control groups, and unilateral or bilateral cases. Contingency tables (2×2) were constructed comparing the presence of the audiovestibular symptom (criterion standard) with the presence of an IVL or CN VIII NVC on MRI (index test). Details of specific classifications for the assessment of IVL and CN VIII NVC are provided in the Online Supplemental Data. Any discrepancies in the data collection were resolved by revisiting the article in a consensus meeting.

Quality Assessment

The methodologic quality of the eligible studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies, Version 2 (QUADAS-2; <https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/>) tool by 2 independent reviewers (J.E.C., M.S.T.).⁶ The signaling questions were tailored specifically to the review (Online Supplemental Data).

Statistical Analysis

Bivariate random effects meta-analysis was performed with R 4.3.1 (package “meta”; <http://www.r-project.org/>) and R Studio (Version 2023.09.0 + 463; <http://rstudio.org/download/desktop>) to evaluate the association between audiovestibular symptoms and the presence of an IVL or CN VIII NVC. The results were tabulated with corresponding forest plots. Pooled ORs were calculated with 95% CIs and *P* values. Heterogeneity was assessed by the Cochran Q test. Further quantification of heterogeneity was provided with τ^2 and I^2 statistics. Statistical significance was defined as $P < .05$.

RESULTS

Systematic Review

The screening tool identified 77 potentially eligible articles. After full text review, 15 studies were included. One additional relevant article was identified via citation searching, totaling 16 eligible studies (Fig 1).

Study Characteristics

The demographics of the patients from eligible studies and the number of case (with audiovestibular symptoms) and control ears are documented in Table 1.^{1,7–21} A total of 1526 symptomatic ears and 1929 control ears were included. The mean ages ranged between 43 and 54.1 years. Study characteristics are demonstrated in the Online Supplemental Data. Eligible studies comprised ears

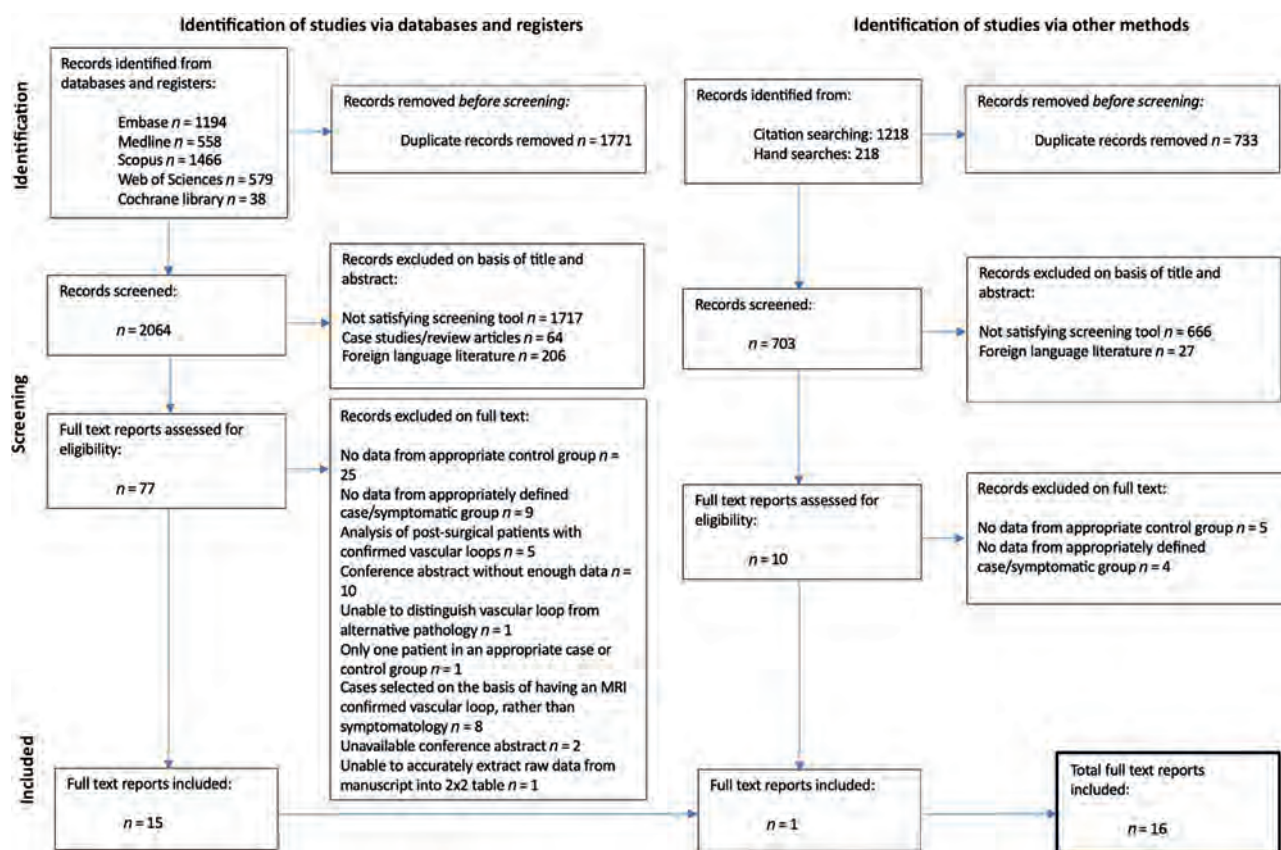


FIG 1. Flow chart summary of the systematic literature review process.

Table 1: Eligible studies and patient demographics

Author (yr)	Case Ears/ Control Ears (n)	Bilateral Cases Included Y/N (n)	Age (Cases)	Sex (Cases)	Age (Controls)	Sex (Controls)
Bae et al (2017) ⁷	16/14	Y (1 bilateral)	54.1 (27–84)	5 m/10 f	NA	NA
Best et al (2013) ⁸	40/40	NA	47.2 (SD, 14.7) (17–78)	8 m/12 f	48.4 (SD, 14.9) (25–77)	8 m/12 f
Beyazal Celiker et al (2017) ⁹	356/478	NA	50.1 (SD, 17.3)	63 m/115 f	42.1 (SD, 18.9)	119 m/120 f
Ezerarslan et al (2017) ¹⁰	68/76	N	45.3 (SD, 14.6) (18–77)	36 m/32 f	48.6 (SD, 14.0) (26–81)	21 m/17 f
Gorrie et al (2010) ¹¹	58/56	N	NR	31 m/27 f	NA	NA
Gultekin et al (2008) ¹²	68/128	Y (13 bilateral)	48.5 (18–78)	23 m/32 f	42.2 (19–88)	9 m/34 f
Kierig et al (2023) ¹	36/36	NA	52.6 (SD, 18.1) (28–84)	12 m/6 f	50.3 (SD, 16.5) (10–84)	5 m/13 f
Kim et al (2019) ¹³	49/49	N	45.0 (SD, 15.3)	58 m/40 f	NA	NA
Leng et al (2022) ¹⁴	136/136	N	43 (SD, 13)	60 m/76 f	NA	NA
Maruyama et al (2020) ¹⁵	248/392	N	51.1 (SD, 17.2) (8–84)	121 m/127 f	55.2 (SD, 16.8) (23–79)	77 m/67 f
Ozan and Arslan (2017) ¹⁶	92/85	N	53.6 (SD, 14.2) (20–84)	42 m/50 f	52.2 (SD, 15)	39 m/46 f
Peters et al (2020) ¹⁷	48/49	N	52 (23–76)	24 m/25 f	NA	NA
Sivarasan et al (2019) ¹⁸	9/20	N	48.4 (SD, 14.0)	5 m/4 f	NA	NA
Yoo et al (2011) ¹⁹	85/173	Y (29 bilateral)	47.3 (SD, 12.7)	30 m/44 f	NA	NA
Zhang et al (2023) ²⁰	77/77	N	47.6 (SD, 14.3)	45 m/34 f	NA	NA
Zidan and Almansor (2020) ²¹	140/120	N	47.6 (SD, 15) (11–73)	47 m/51 f	45.6 (SD, 11.7) (19–88)	28 m/32 f

Note:—n indicates number of patients; Y, yes; N, no; NA, not available; NR, not recorded; m, male; f, female.

with tinnitus ($n = 5$), SNHL ($n = 7$), and vertigo ($n = 6$). Specific symptomatic subtypes studied were “typewriter tinnitus,” sudden onset sensorineural hearing loss (SoSNHL), and vestibular paroxysmia. The diagnostic criteria for these subtypes are defined in

the Online Supplemental Data. Control groups comprised the contralateral ear ($n = 8$), a healthy asymptomatic patient cohort ($n = 5$), or a patient cohort with an unrelated condition (eg, trigeminal neuralgia) ($n = 3$).

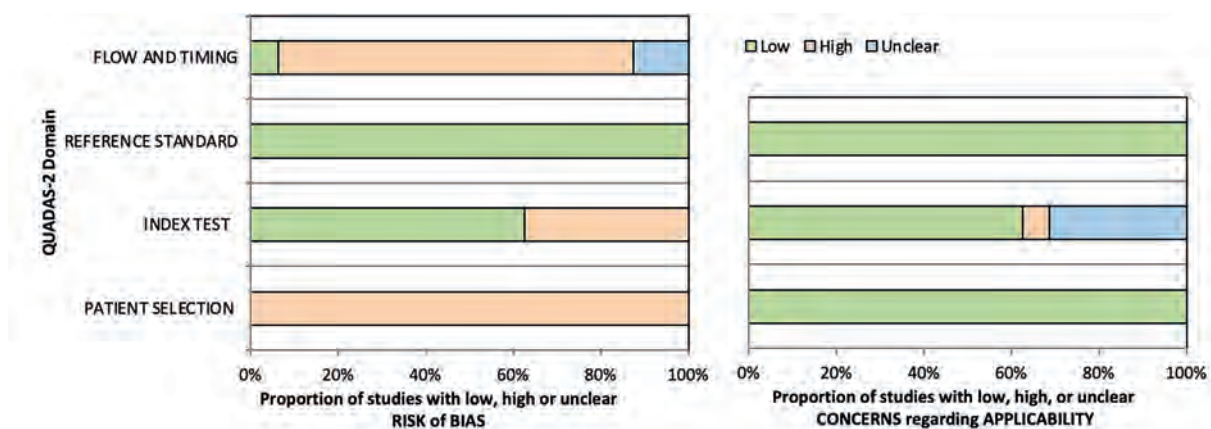


FIG 2. QUADAS-2 tool. Bar charts quantify studies by risk of bias (A) and for the 16 eligible studies included in the meta-analysis concerns (B).

Table 2: Pooled ORs, 95% CIs, and *P* values for the association between IVL or CN VIII NVC and audiovestibular symptoms

Audiovestibular Symptom	MRI Vascular Loop Variable	No. of Studies	Pooled OR (95% CI)	<i>P</i>
Tinnitus (undefined)	IVL	3	0.90 (0.47–1.70)	.73
Tinnitus (undefined)	NVC	3	1.15 (0.68–1.95)	.60
SNHL (undefined)	IVL	2	0.67 (0.36–1.25)	.21
SNHL (undefined)	NVC	2	0.89 (0.33–2.40)	.82
SoSNHL	IVL	5	1.34 (1.04–1.73)	.02
SoSNHL	NVC	3	1.16 (0.61–2.20)	.65
Vertigo (undefined)	IVL	2	0.97 (0.64–1.48)	.90
Vertigo (undefined)	NVC	3	0.99 (0.42–2.32)	.98
Vestibular paroxysmia	NVC	3	13.19 (2.09–83.16)	.006

Eleven articles analyzed the relationship of audiovestibular symptoms to IVL, while 13 articles analyzed the association with CN VIII NVC. The most adopted classification regarding the position of the IVL was that proposed by Chavda in McDermott et al.²² A standardized classification for NVC was seldom used, with that established by Gorrie et al¹¹ adopted in 3 articles (Online Supplemental Data).

Quality of Studies

QUADAS-2 evaluation showed high bias within the “patient selection” and “flow and timing” domains. Patient selection always resulted in high bias due to all included studies being case-controlled. High bias was reported for the index test when it was unclear whether readers were blinded to the clinical details. Because the diagnosis of an audiovestibular symptom (criterion standard) always preceded index test evaluation, all studies were low bias in this domain. Only 1/16 studies was deemed low risk with regard to flow and timing because others were either retrospective or included post hoc exclusions (Fig 2).

Relationship between Audiovestibular Symptoms and an IAM Vascular Loop or CN VIII NVC

Pooled odds ratios are presented in Table 2. Forest plots are shown in Fig 3.

There was no significant association demonstrated between the presence of tinnitus (undefined) and IVL (OR, 0.90; 95% CI, 0.47–1.70) or CN VIII NVC (OR, 1.15; 95% CI, 0.68–1.95) ($P > .05$). The single study of the typewriter tinnitus subtype showed

no significant difference in the prevalence of symptoms in ears with either IVL ($P = .73$) or NVC ($P = .15$).⁷

There was no relationship demonstrated between ears with SNHL (undefined) and the presence of IVL (OR, 0.67; 95% CI, 0.36–1.25) or CN VIII NVC (OR, 0.89; 95% CI, 0.33–2.40) ($P > .05$). In studies of the SoSNHL subtype alone, there was also no relationship between symptomatic ears and CN VIII NVC (OR, 1.16; 95% CI, 0.61–2.20) ($P > .05$); how-

ever, there was an association with an IVL (OR, 1.34; 95% CI, 1.04–1.73) ($P = .02$).

There was no significant difference in the prevalence of IVL or CN VIII NVC between ears with vertigo (undefined) and control ears (OR, 0.97; 95% CI, 0.64–1.48 and OR, 0.99; 95% CI, 0.42–2.32) ($P > .05$). However, there was a strong association between the presence of CN VIII NVC and the specific diagnosis of the vestibular paroxysmia subtype (OR, 13.19; 95% CI, 2.09–83.16) ($P = .006$). No included studies investigated the association of IVL and vestibular paroxysmia.

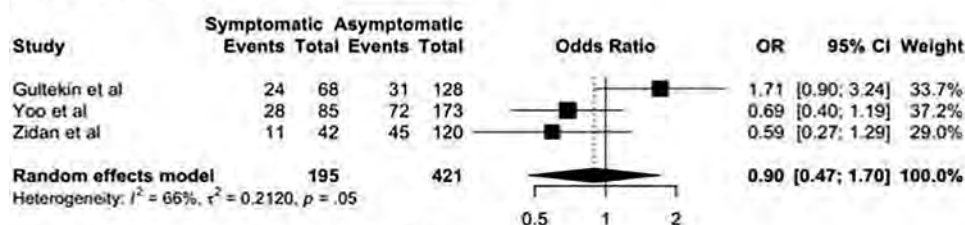
Heterogeneity

Considerable heterogeneity was detected in 1 subgroup for articles comparing the presence of CN VIII NVC in patients with vertigo (undefined) ($P < .01$), with an I^2 of 84%. All other analyses demonstrated nonsignificant P values (range, .05–.71). I^2 quantification suggested moderate heterogeneity for 5 subgroup analyses and substantial heterogeneity for 2 further subanalyses. The subgroup analysis comparing IVL and SNHL demonstrated an I^2 of 0%. A guide for the interpretation of I^2 has been included in the Online Supplemental Data.

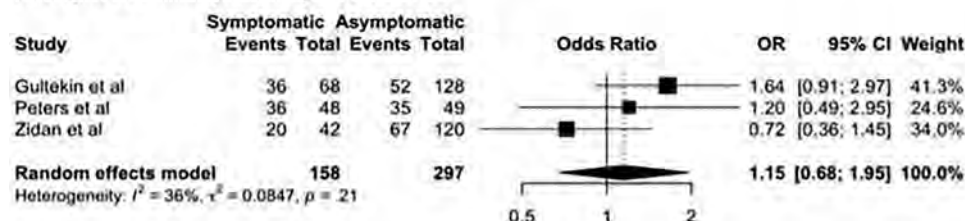
DISCUSSION

This systematic review and meta-analysis sought to quantify the relationship between IVL or CN VIII NVC and specific audiovestibular symptoms. Pooled data from 16 case-controlled studies demonstrated no statistically significant association between the

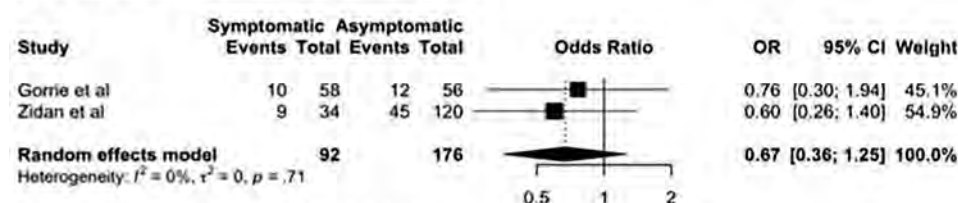
Forest plot for tinnitus (undefined) and presence of an IVL



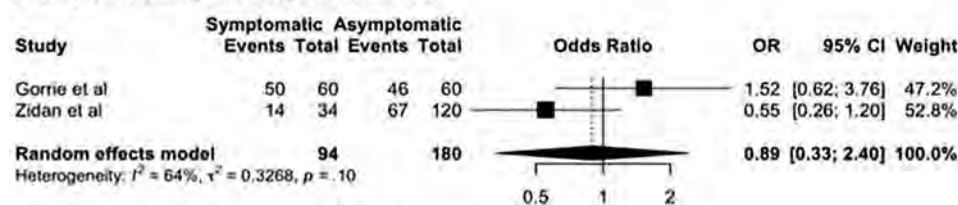
Forest plot for tinnitus (undefined) and CN VIII NVC



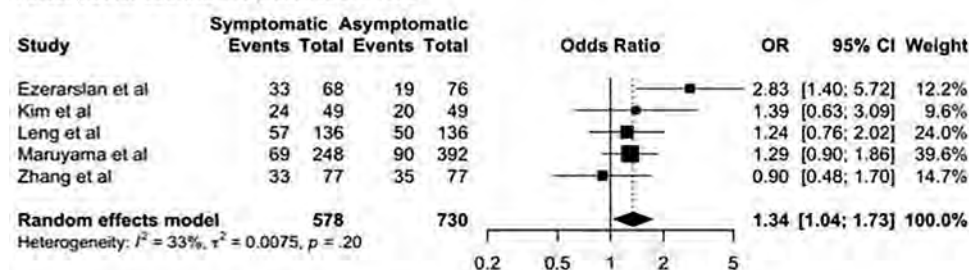
Forest plot for SNHL (undefined) and presence of an IVL



Forest plot for SNHL (undefined) and CN VIII NVC



Forest plot for SoSNHL and presence of an IVL



Forest plot for SoSNHL and CN VIII NVC

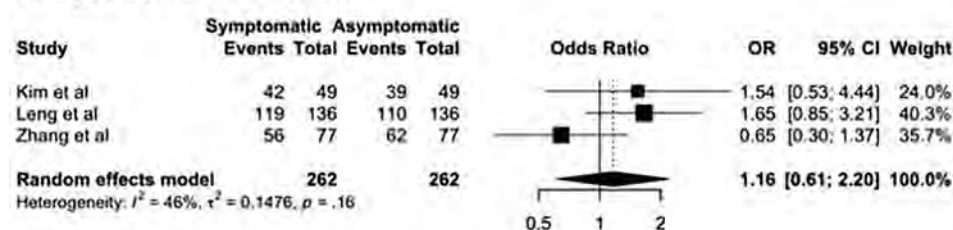
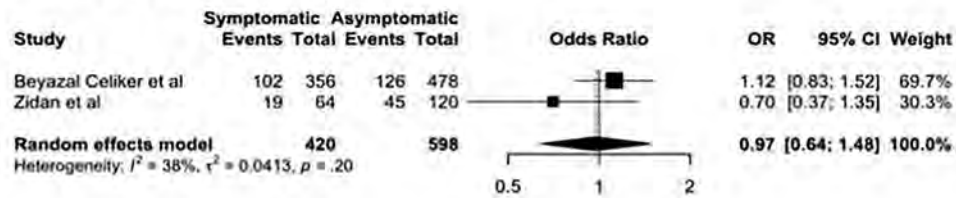


FIG 3. Forest plots for each audiovestibular symptom and corresponding MRI variable (IVL or CN VIII NVC).

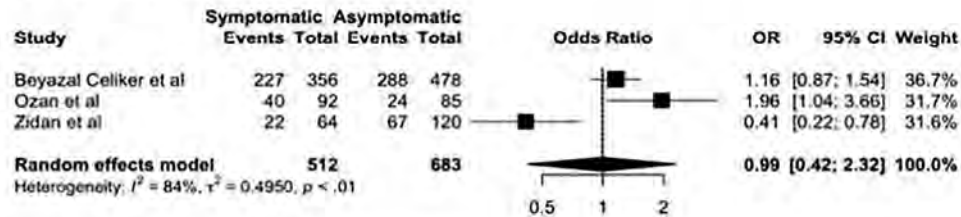
presence of an IVL or CN VIII NVC and either tinnitus (undefined) or SNHL (undefined), while there was also no relationship between IVL or vertigo (undefined) or CN VIII NVC and vertigo (undefined). However, the symptomatic

subtype of SoSNHL demonstrated a significant association with the presence of an IVL, while the symptomatic subtype of vestibular paroxysmia was associated with CN VIII NVC (Fig 3) (Table 2).

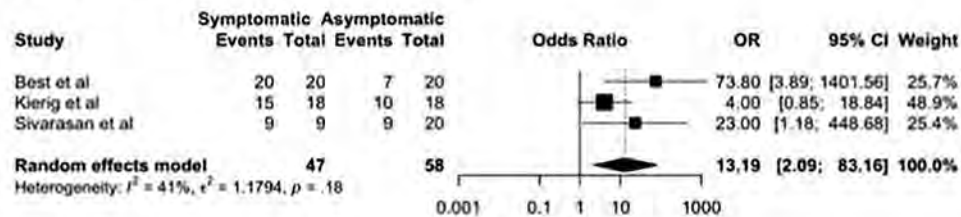
Forest plot for vertigo (undefined) and IVL



Forest plot for vertigo (undefined) and CN VIII NVC



Forest plot for vestibular paroxysmia and CN VIII NVC



Events – presence of a vascular loop within the IAM or CN VIII contact

OR – odds ratio

CI – confidence interval

IVL – intrameatal vascular loop

NVC – neurovascular compression

FIG 3. Continued.

Few attempts have been made to formally synthesize the body of literature before now. Chadha and Weiner²³ performed a systematic review of 5 articles in 2008, but this comprised studies with heterogeneous and largely noncomparable methodology. Two of the eligible studies concurred with our finding of no significant association between CN VIII NVC and unilateral tinnitus; however, an association was demonstrated between CN VIII NVC and sensorineural hearing loss ($P < .05$; OR, 1.99).²³ In addition, a more recent meta-analysis found no significant association between ipsilateral SoSNHL and NVC, though substantial differences in the eligibility criteria and the interpretation of IVL/NVC grading exist between their work and the present study.²⁴

The results of the current study should serve to inform both radiology and surgical colleagues alike. While dedicated 3D T2-weighted sequences will be required to exclude other pathologies in patients with undefined audiovestibular symptoms, there will not be a requirement for the radiologist to report either CN VIII NVC or IVL. Similarly, our analysis indicates that IVL and CN VIII NVC are unlikely to be an etiology for undefined SNHL, tinnitus, and vertigo and would not benefit from surgical intervention. A previous meta-analysis of 35 studies and 572 patients who underwent microvascular decompression of CN VIII NVC found that only 28% of patients with tinnitus and 32% of those with

vertigo reported complete relief of symptoms, with substantial complication rates following treatment.⁴

The results of the current study demonstrate an association between an IVL and SoSNHL. Identifiable causes of SoSNHL are found in a minority of patients, with a vascular etiology and altered neural perfusion in the context of an IVL a possible pathophysiologic explanation.²⁵ However, of the 5 articles included in the subanalysis, one demonstrated an OR of >1 , suggesting low statistical power for this association. Moreover, there may be several confounding factors responsible for the altered vascular supply to the inner ear, with a recent meta-analysis demonstrating increased rates of concomitant diabetes, hypertension, and increased cholesterol in patients with SoSNHL.²⁶

The demonstrated association of CN VIII NVC with vestibular paroxysmia also warrants a consideration of potential pathophysiology. While this study indicates an association rather than causality, it may be postulated that the association of CN VIII NVC with the characteristic short-lived paroxysmal vertigo of vestibular paroxysmia is more likely to be related to direct pulsatile compression of the vulnerable long VIII transition zone resulting in ephaptic discharges.²⁷

Limitations of the current study should be appreciated. First, a body of non-English language literature was not reviewed,

possibly missing eligible or noteworthy studies. Second, the low number (range, 2–5) of eligible studies for each analysis and the generally small study cohorts have the potential to increase type II errors. In this regard, some substantial case-controlled studies were not considered eligible because it was not possible to identify the specific audiovestibular symptom experienced. For instance, Makins et al²⁸ studied “auditory symptoms,” and Lei et al²⁹ investigated a cohort with Meniere disease, neither of which showed a significant association with IVLs. Third, case-controlled studies analyzing IVL or CN VIII NVC were not available for all relevant symptom subgroups, including for pulsatile tinnitus. Finally, despite attempts to reduce heterogeneity in our meta-analysis and *P* values $\geq .05$ in 7/8 plots, there remained a moderate-substantial degree of variance with I^2 ranging from 0% to 84% for each subanalysis. Explanations are likely multifaceted and comprise clinical heterogeneity between studies and a small number of included articles. Any future studies should aim to collect patients consecutively, with a sample size that allows appropriate power, and to adopt an established grading system for vascular loops and a control group of healthy volunteers.

CONCLUSIONS

This systematic review and meta-analysis evaluated the association between the presence of a vascular loop within the IAM (IVL) or contacting the vestibulocochlear nerve (CN VIII NVC) and audiovestibular symptoms. There was no statistically significant correlation between IVL or CN VIII NVC and tinnitus, SNHL, or vertigo, except for specific subtypes of vestibular paroxysmia and SoSNHL.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Quantitative Susceptibility Mapping with Source Separation in Normal Brain Development of Newborns

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ABSTRACT

BACKGROUND AND PURPOSE: Quantitative susceptibility mapping is an emerging method for characterizing tissue composition and studying myelination and iron deposition. However, accurate assessment of myelin and iron content in the neonate brain using this method is challenging because these 2 susceptibility sources of opposite signs (myelin, negative; iron, positive) occupy the same voxel, with minimal and comparable content in both sources. In this study, susceptibilities were measured in the healthy neonate brain using susceptibility source separation.

MATERIALS AND METHODS: Sixty-nine healthy neonates without clinical indications were prospectively recruited for MRI. All neonates underwent gradient-echo imaging for quantitative susceptibility mapping. Positive (paramagnetic) and negative (diamagnetic) susceptibility sources were separated using additional information from R2* with linear modeling performed for the neonate brain. Average susceptibility maps were generated by normalizing all susceptibility maps to an atlas space. Mean regional susceptibility measurements were obtained in the cortical GM, WM, deep GM, caudate nucleus, putamen, globus pallidus, thalamus, and the 4 brain lobes.

RESULTS: A total of 65 healthy neonates (mean postmenstrual age, 42.8 [SD, 2.3] weeks; 34 females) were studied. The negative susceptibility maps visually demonstrated high signals in the thalamus, brainstem, and potentially myelinated WM regions, whereas the positive susceptibility maps depicted high signals in the GM compared with all WM regions, including both myelinated and unmyelinated WM. The WM exhibited significantly lower mean positive susceptibility and significantly higher mean negative susceptibility than cortical GM and deep GM. Within the deep GM, the thalamus showed a significantly lower mean negative susceptibility than the other nuclei, and the putamen and globus pallidus showed significant associations with neonate age in positive and/or negative susceptibility. Among the 4 brain lobes, the occipital lobe showed a significantly higher mean positive susceptibility and a significantly lower mean negative susceptibility than the frontal lobe.

CONCLUSIONS: This study demonstrates regional variations and temporal changes in positive and negative susceptibilities of the neonate brain, potentially associated with myelination and iron deposition patterns in normal brain development. It suggests that quantitative susceptibility mapping with source separation may be used for early identification of delayed myelination or iron deficiency.

ABBREVIATIONS: CGM = cortical gray matter; DGM = deep gray matter; PMA = postmenstrual age; QSM = quantitative susceptibility mapping

The early postnatal period is a crucial phase characterized by rapid brain development, which is an ongoing process that

started prenatally, including myelination in the CNS.¹ Early studies have reported the spatiotemporal patterns of myelination in the fetal and neonatal brain using histology^{2,3} and conventional T1- and T2-weighted MRI.⁴⁻⁶ Recently, more advanced MRI techniques, such as DTI, multicomponent relaxometry, and magnetization transfer imaging, have provided greater insights into WM maturation at a microstructural level during infancy and early childhood.⁷⁻⁹

Quantitative susceptibility mapping (QSM) is an emerging MRI method that offers another means of characterizing tissue composition.¹⁰ This technique is used to measure the volume magnetic susceptibility of each voxel, which represents intrinsic properties of materials within the voxel. Myelin is the predominant source of negative magnetic susceptibility (ie, diamagnetism) in

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SUMMARY

PREVIOUS LITERATURE: Assessment of myelin and iron content in the early neonate brain may be useful for accurately evaluating neurodevelopment. Conventional quantitative susceptibility mapping can be used to investigate myelination and iron deposition, but measuring the individual contributions of myelin and iron content in the neonate brain is challenging because these 2 susceptibility sources have opposite signs and occupy the same voxel, with minimal and comparable content in both sources. Recent studies have demonstrated the feasibility of performing quantitative susceptibility mapping with source separation in the adult brain, which may be applied to the neonate brain.

KEY FINDINGS: Significantly lower positive and higher negative susceptibilities were observed in WM compared with GM. In the deep GM, the thalamus showed significantly lower negative susceptibility than the other deep GM subregions. The occipital lobe exhibited significantly higher positive and lower negative susceptibilities than the frontal lobe.

KNOWLEDGE ADVANCEMENT: Regional and temporal variations in positive and negative susceptibilities measured in the neonate brain using quantitative susceptibility mapping with source separation may be associated with myelination and iron deposition. These measures can potentially be used for early identification of impaired neurodevelopment in the neonate brain.

the WM, making QSM an effective tool for evaluating myelination.¹¹ While DTI, currently the most commonly used technique for WM assessment, provides indirect measures of myelination due to its reliance on axonal organization (eg, axonal diameter, cell swelling, and axonal packing density),¹² QSM may allow measurements more specific to myelin due to the direct contributions of the lipid layers and proteins in the myelin sheath to the measured diamagnetism. Furthermore, QSM provides a sufficiently accurate evaluation of iron distribution in the brain, which exhibits positive magnetic susceptibility (ie, paramagnetism).¹⁰ Iron is essential for neurodevelopment, because oligodendrocytes, the iron-containing cells, play a primary role in myelin production. Altered neurotransmitter metabolism due to iron deficiency further disturbs neurodevelopment beyond impairment in myelination.¹ Therefore, QSM may serve as an effective, noninvasive tool to study brain development in neonates, with quantitative evaluation of myelination and iron deposition.

In previous studies applying QSM to the developing brain, magnetic susceptibility was found to decrease in the WM and increase in the deep gray matter (DGM) with advancing age, reflecting the progressive WM myelination and DGM iron deposition throughout infancy and early childhood.^{11,13–15} While these studies primarily demonstrated the temporal evolution of magnetic susceptibility during the first few years of life, there is a lack of investigation focused on magnetic susceptibility in the first 1–2 months of life, particularly in the context of normal brain development. Evaluating myelin and iron content of the neonate brain on the basis of the conventional QSM is challenging because it measures the average magnetic susceptibility within each voxel. In the neonate brain with a minimal amount of myelin and iron content, the effects of opposing signs of susceptibility from iron (positive) and myelin (negative) may be comparable and can cancel each other within the same voxel in most regions.

In this study, we measure the individual contributions of positive and negative susceptibilities within the voxels for more accurate assessment of myelin and iron content in early normal brain development. We use QSM with source separation^{16–20} based on additional information of R2* measurements. While the bulk susceptibility is the sum of positive and negative susceptibilities

within a voxel (resulting in a canceling effect), R2* relates to the sum of the absolute values of positive and negative susceptibilities within a voxel (resulting in an amplifying effect). Therefore, R2* can be used along with the bulk susceptibility to differentiate these 2 susceptibility contributions. Considering the regional differences in myelination and iron deposition, we characterize regional magnetic susceptibility of the neonate brain by comparing magnetic susceptibilities between different regions and correlating magnetic susceptibilities with neonate age.

MATERIALS AND METHODS

Study Population

In this prospective study, we enrolled 61 neonates from the Children's National Hospital (Washington, DC) and 8 neonates from Weill Cornell Medicine (New York, New York). All neonates were healthy with a normal perinatal history of screening and ultrasound studies and without any clinical indication for MRI. The study was approved by the institutional review boards of both Children's National Hospital and Weill Cornell Medicine, and written informed consent was obtained from the parents of each infant.

Data Acquisition

All MRI scans were performed on MR 750 3T scanners (GE Healthcare) using 8- or 32-channel head coils. All infants were scanned during natural sleep using the “feed and bundle” approach without sedation. A 3D multiecho gradient-echo sequence was performed using imaging parameters of TR = 55–60 ms, 7–9 TEs ranging from 5 to 44 ms with an echo spacing of 5–6 ms, bandwidth ≥ 50 kHz, flip angle = 20°, field of view = $160 \times 160 \times 100$ mm³, and acquired spatial resolution = $0.38 \times 0.4 \times 2$ mm³ or $0.5 \times 0.63 \times 2$ mm³. The total scan time was approximately 5 minutes with parallel imaging ($R = 2$) and elliptical k -space coverage (70%). Anatomic images were acquired using a 3D T2-weighted fast-spin-echo Cube (GE Healthcare) sequence with TR = 2.5 seconds, TE = 68–84 ms, bandwidth = ± 50 kHz, field of view = $160 \times 160 \times 130$ mm³, spatial resolution = $1 \times 1 \times 1$ mm³, and a scan time of approximately 4 minutes with parallel imaging ($R = 2$). In 8 neonates, dual-echo fast-spin-echo imaging was performed for R2 mapping using TR = 4450 ms, TE =

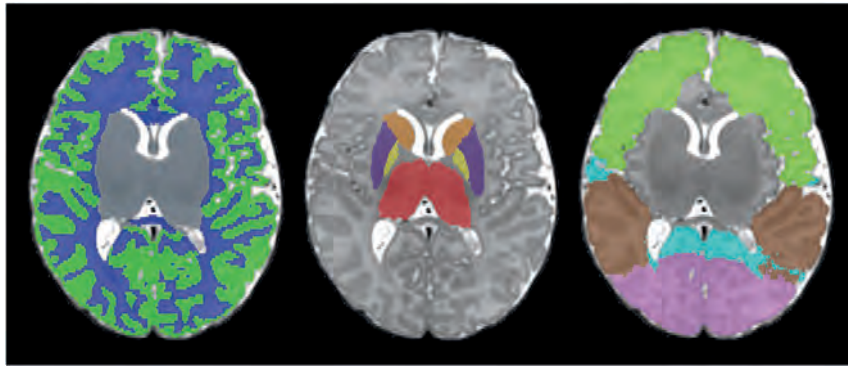


FIG 1. Example of segmentation in 1 representative neonate brain (PMA = 46.3 weeks). Segmented ROIs are overlaid on the anatomic image in different colors: green, CGM; blue, WM; gray, DGM; orange, caudate nucleus; purple, putamen; yellow, globus pallidus; red, thalamus; light green, frontal lobe; light blue, parietal lobe; brown, temporal lobe; light purple, occipital lobe.

21 and 126 ms, bandwidth = ± 31.25 kHz, field of view = $160 \times 160 \times 120\text{--}132$ mm³, spatial resolution = $0.5 \times 0.83 \times 2$ mm³, and a scan time of approximately 5 minutes with parallel imaging ($R = 2$).²¹

QSM Reconstruction

In each infant, the whole brain was manually segmented on the gradient-echo first-echo magnitude images using ITK-SNAP software²² (www.itksnap.org) to generate masks required for QSM processing. Background field was removed using the variable-kernel sophisticated harmonic artifact reduction for the phase data method with a maximum sphere radius of 12 mm.^{23,24} Dipole inversion was performed using the morphology-enabled dipole inversion method with a regularization parameter of 1000 and model error reduction through iterative tuning.^{25,26} Bulk susceptibility measures were referenced to the mean susceptibility of the whole brain, which is considered a stable reference region due to its large size.¹⁰ For $R2^*$ -based source separation, the following complex signal model of gradient-echo MRI was applied, assuming a linear correlation between $R2^*$ and $R2'$: ($R2^* = \alpha \cdot R2' + \beta$): $R2^*(r) + i2\pi \cdot \Delta f(r) = \alpha \cdot D_r^+ \cdot |\chi^+(r)| + \alpha \cdot D_r^- \cdot |\chi^-(r)| + \beta + i2\pi \cdot D_f(r) * [\chi^+(r) + \chi^-(r)]$, where $\Delta f(r)$ is the frequency shift, α and β are calibration parameters, D_r^+ and D_r^- are relaxometric constants (137 Hz/parts per million), $D_f(r)$ is a dipole kernel, and the asterisk denotes a convolution operation. This equation was formulated as a minimization problem and was solved iteratively using a conjugate gradient descent algorithm.^{16–18} $R2^*$ and $R2'$ maps were generated using the multi-echo gradient-echo and dual-echo fast-spin-echo data, respectively. The relationship between $R2^*$ and $R2'$ ($R2^* - R2'$) in the neonate brain was approximated in 8 neonates using a linear regression model and was applied to all neonates.^{16,17} For this regression analysis, mean $R2^*$ and $R2'$ values were measured within the cortical gray matter (CGM) and WM, each divided into the frontal, parietal, temporal, and occipital lobes, as well as DGM, resulting in a total of 9 ROIs per neonate.

Image Registration and Segmentation

Reconstructed susceptibility maps were registered to T2-weighted anatomic images in each neonate using the rigid image

registration algorithm of Advanced Normalization Tools (ANTs; <http://stnava.github.io/ANTs/>).²⁷ The gradient-echo first-echo magnitude images were first registered to anatomic images, creating a transformation matrix. This matrix was then used to move the susceptibility maps to the anatomic image space. The ROIs for mean susceptibility measurements included the CGM, WM, and DGM. Within the DGM, the caudate nucleus, putamen, globus pallidus, and thalamus were further segmented. The brain was also segmented into the frontal, parietal, temporal, and occipital lobes, with each lobe including both CGM and WM. All these

ROIs were initially segmented on the anatomic images using the Draw-EM tool kit (<https://github.com/MIRTK/DrawEM>)²⁸ and further refined manually using ITK-SNAP (Fig 1). The manual corrections were minor but were applied to almost all subjects by the same rater (K.K.), who had >8 years of experience in neonatal brain MRI segmentation. The mean susceptibility of each ROI was calculated by averaging the susceptibility of all voxels within the ROI of each neonate. Furthermore, susceptibility templates were generated by normalizing the susceptibility maps of all neonates to a high-definition spatiotemporal neonatal brain atlas.²⁹ The neonatal brain atlas for a postmenstrual age (PMA) of 43 weeks was used in accordance with the mean PMA at the MRI of our cohort. The registered images of all neonates were manually inspected to confirm that there were no major registration errors.

Statistical Analysis

We used descriptive statistics to determine the baseline characteristics of our cohort. We used the Wilcoxon signed-rank test to determine the differences in regional mean susceptibility and mean $R2^*$ among different ROIs. To examine the association between mean susceptibility and PMA in each ROI, we calculated Pearson correlation coefficients, corresponding P values, and linear regression lines. Bonferroni correction was used to correct for multiple comparisons. After the correction, the significance level was .0008 (.05/60) for comparing different ROIs and .0011 (.05/44) for estimating associations with PMA.

RESULTS

Study Population

Of the 69 neonates enrolled, 3 neonates were excluded from our study due to a 5-minute Apgar score of <7. No MRI scans had substantial motion artifacts. One infant was further excluded due to unexplained artifacts in the raw gradient-echo images. The characteristics of the remaining 65 infants (PMA at MRI, 42.8 [SD, 2.3] weeks; 30 females) are summarized in Table 1.

$R2^*$ -Based Source Separation

Figure 2A shows the linear regression between the mean $R2^*$ and mean $R2'$ of 72 ROIs from 8 neonates (PMA at MRI, 43.3 [SD,

1.7] weeks; range, 40.9–45.6 weeks), with a relationship of $R2^* = 1.40 \times R2' + 4.96$ ($r = 0.93$). Figure 2B demonstrates the validation of the $R2^*$ -based source separation by comparing it with the $R2'$ -based method. The susceptibilities from the 2 different source separation algorithms demonstrated good agreement ($r = 0.99$).

Qualitative Analysis

Figure 3 shows the original susceptibility images (ie, before registration) acquired in 3 representative neonates with different PMAs at MRI (40.3, 44.4, and 47.4 weeks). In individual neonates, the DGM nuclei were not clearly distinguishable from the surrounding WM on all susceptibility and $R2^*$ maps, being the primary difference from typical susceptibility maps obtained in the adult brain. There was also indistinct contrast between the CGM and WM on the conventional susceptibility

maps; however, positive susceptibility maps revealed increased CGM-WM contrast. Additionally, high signal intensities were found in the cerebral veins on the positive susceptibility maps. On the other hand, the averaged susceptibility templates demonstrated common contrast across all neonates while suppressing individual variations (eg, pial and cortical vein signals), as shown in Fig 4. The negative susceptibility maps revealed high signal intensities in areas of WM linked to early myelination, such as the posterior limb of the internal capsule, corpus callosum, and corticospinal tracts, which were best visualized on the axial, sagittal, and coronal planes, respectively. However, most other WM regions potentially unmyelinated showed slightly lower diamagnetism than the CGM. Interestingly, the positive susceptibility maps indicated low paramagnetism in both the aforementioned myelinated WM regions as well as unmyelinated WM regions at birth, such as the corona radiata, optic radiation, and external capsule. The thalamus, brainstem, and cerebellum exhibited elevated signal intensities on the negative susceptibility maps. The thalamus also showed high signals on the positive susceptibility maps. In addition, the primary sensorimotor cortex demonstrated high signals on both the positive and negative susceptibility maps.

Table 1: Characteristics of the study cohort (n = 65)

Perinatal Characteristics	
Gestational age at birth (mean) (wk)	39.2 (SD, 1.3) (36.4–41.6) ^a
Birth weight (mean) (g)	3327 (SD, 453)
Female	34 (52%)
Ethnicity	
White	40
Black	9
Hispanic	7
Other	9
Apgar (mean) 1 min	8.0 (SD, 1.1) (4–9) ^a
Apgar (mean) 5 min	8.8 (SD, 0.6) (7–9) ^a
Maternal age (mean) (yr)	34.8 (SD, 5.7) (21.8–50.9) ^a
Cesarean delivery	25 (38%)
MRI characteristics	
PMA at MRI (mean) (wk)	42.8 (SD, 2.3) (38.6–48.7) ^a
Days of life at MRI (mean) (days)	25.4 (SD, 13.8) (5–62)
Weight at MRI (mean) (g)	4022 (SD, 804)

^a Data in parentheses are ranges.

Quantitative Analysis

All regional mean susceptibilities and $R2^*$ are summarized in Table 2, and pair-wise comparisons within each ROI group are illustrated in Fig 5. While there were no significant differences in conventional susceptibility among the CGM, WM, and DGM, the CGM and DGM showed significantly higher mean positive susceptibility and significantly lower mean negative susceptibility compared with the WM ($P < .0001$). Of note, despite the higher diamagnetic signals in the potentially myelinated WM regions, the overall WM showed significantly higher mean negative susceptibility than the CGM and DGM. Among the DGM subregions,

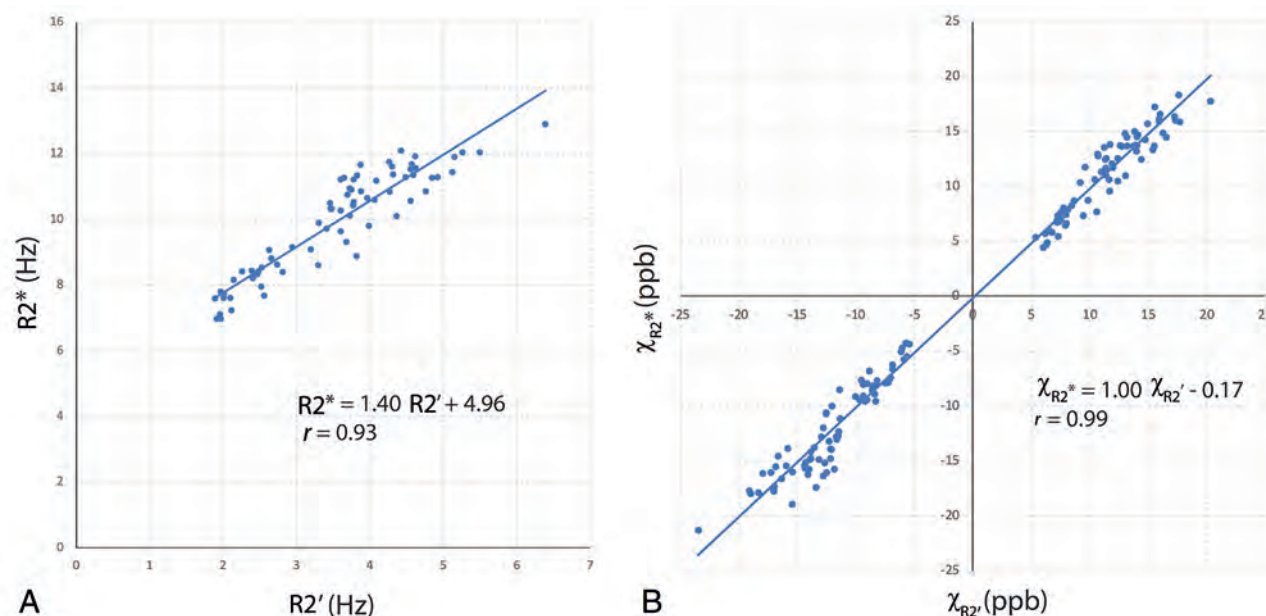


FIG 2. A, Linear regression of mean $R2^*$ and mean $R2'$. B, Linear regression of mean χ_{R2^*} ($R2^*$ -based source separation) and mean $\chi_{R2'}$ ($R2'$ -based source separation). ROIs in these analyses include the frontal, parietal, temporal, and occipital lobes of CGM and WM as well as DGM in 8 neonates. ppb indicates parts per billion.

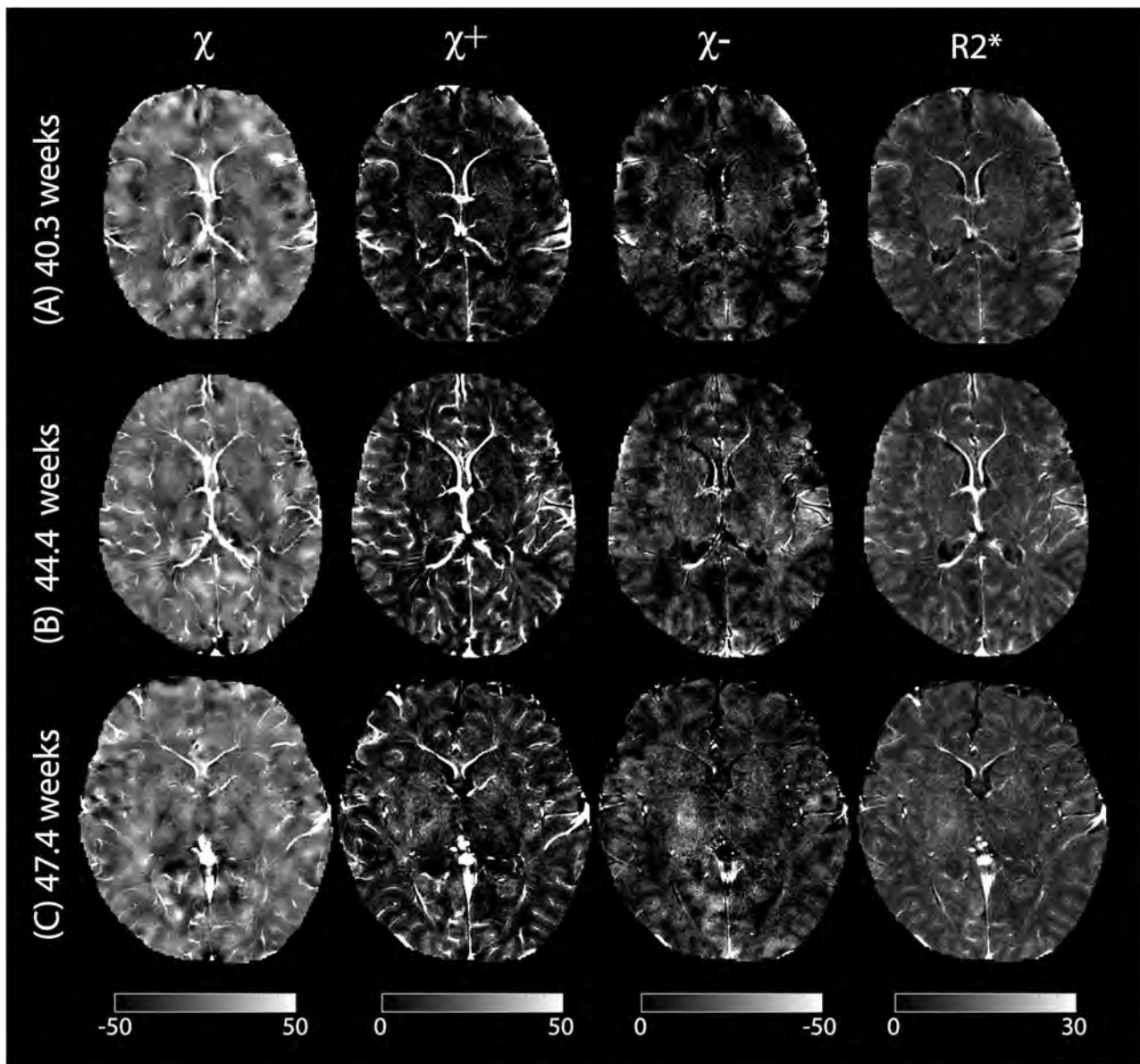


FIG 3. Original susceptibility (in parts per billion) and R2* (in hertz) maps before registration, acquired in 3 neonates with different PMAs at MRI of 40.3 (A), 44.4 (B), and 47.4 (C) weeks. χ , χ^+ , and χ^- denote conventional, positive, and negative susceptibilities. High paramagnetism was found in the veins on the conventional susceptibility and positive susceptibility maps. Positive susceptibility maps also show increased contrast between CGM and WM compared with conventional susceptibility maps.

the thalamus showed significantly lower mean negative susceptibilities than the other subregions ($P < .0001$). Among the 4 brain lobes, the occipital lobe showed significantly higher mean positive susceptibility and significantly lower mean negative susceptibility than the frontal lobe ($P < .0001$). Table 3 contains the results of linear regression between the regional mean susceptibility (or R2*) and PMA in only those ROIs showing significant associations. The Online Supplemental Data show the distributions of mean susceptibilities and mean R2* across PMA in these ROIs. While there was no significant association of conventional susceptibility with PMA, there were significant associations of positive and negative susceptibilities with PMA: the putamen (χ^+ , χ^-) and globus pallidus (χ^+). Among all these ROIs, the globus pallidus showed the highest rate of temporal change (0.527 parts per billion/week).

DISCUSSION

In this study, we measured the magnetic susceptibilities of the normal neonate brain in the first 2 months of life, separating positive and negative susceptibility sources. On the conventional susceptibility maps, we visually observed lower susceptibilities along most WM fiber tracts. However, when decomposed into the positive and negative susceptibilities, the magnetic susceptibility exhibited different patterns in the WM. While negative susceptibility maps demonstrated high diamagnetism only in the myelinated WM tracts, positive susceptibility maps demonstrated low paramagnetism in both myelinated and unmyelinated WM regions. Negative susceptibility maps also depicted high diamagnetism in other regions associated with early myelination, including the thalamus and brainstem. In the quantitative analysis, we confirmed that the mean positive

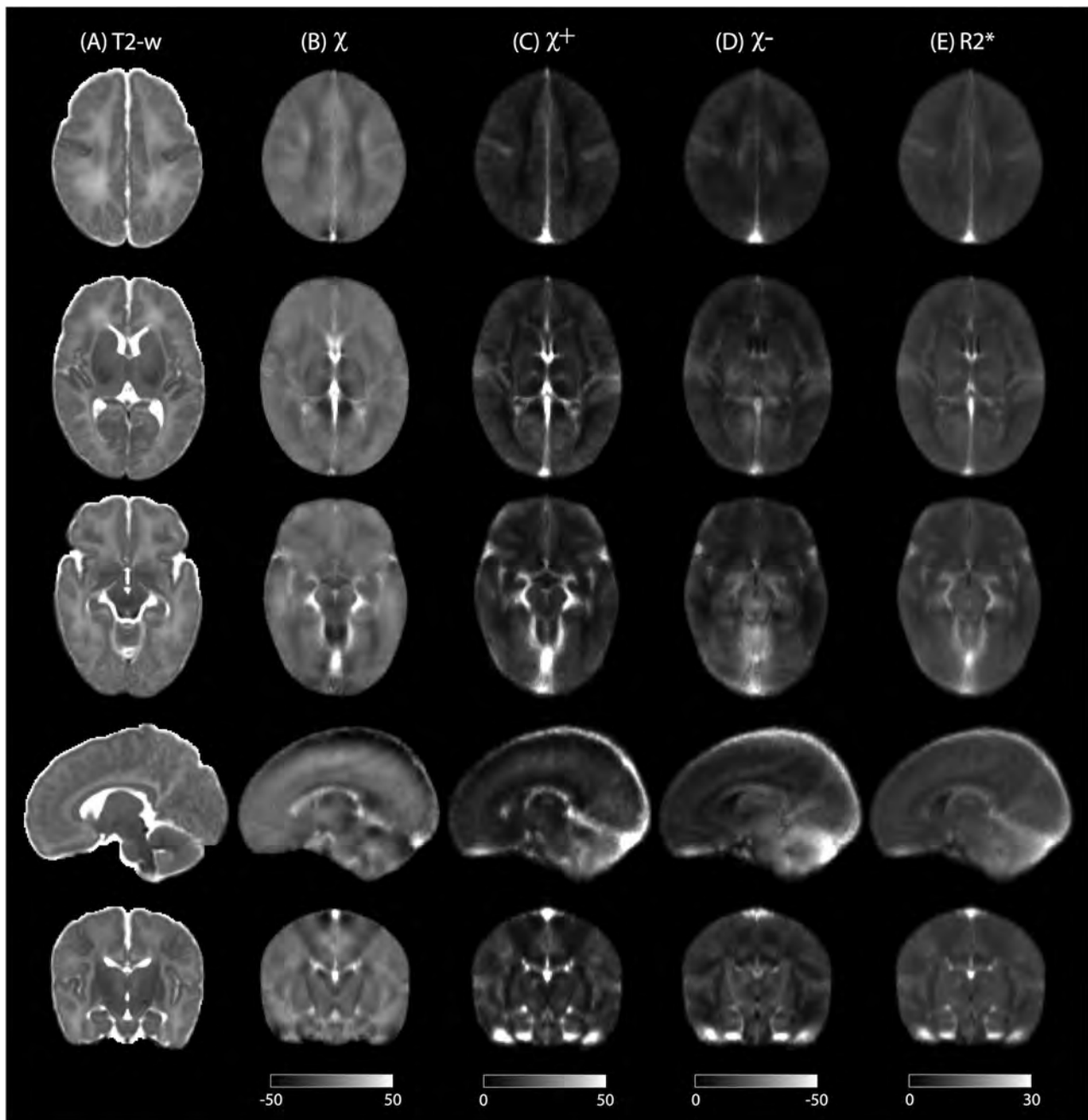


FIG 4. Templates of T2-weighted anatomic images (A) and conventional (B), positive (C), and negative (D) susceptibility maps (in parts per billion), and R2* maps (in hertz, E) in the axial (3 different levels), sagittal, and coronal planes. Averaged susceptibility maps revealed substantial contrasts in several regions that were invisible on the maps from individual neonates. These regions included the thalamus, brainstem, sensorimotor cortex, and WM fiber tracts, such as the corona radiata, optic radiation, external capsule, posterior limb of the internal capsule, corpus callosum, and corticospinal tract. T2-w indicates T2-weighted.

susceptibility was significantly lower in the WM than in the CGM and DGM. We also found that the mean negative susceptibility was significantly higher in the WM than in the CGM and DGM due to large unmyelinated WM regions with lower diamagnetism. Among the DGM nuclei, the thalamus demonstrated the lowest mean negative susceptibility, and the putamen and global pallidus exhibited mean positive and/or mean negative susceptibility significantly associated with PMA. Among the 4 brain lobes, the occipital lobe showed significantly higher mean positive susceptibility and significantly lower mean negative susceptibility than the frontal lobe.

CGM-WM Contrast of Susceptibility

In the adult brain, QSM with source separation has demonstrated that highly paramagnetic susceptibility is mainly found in the GM, whereas highly diamagnetic susceptibility is mainly limited to the WM. These separate susceptibility patterns are relatively straightforward to interpret and align with earlier findings based on conventional QSM with histologic validation. In contrast, source-separated susceptibilities measured in our neonate cohort revealed intriguing findings that require careful interpretation. Prior MR studies based on T1- and T2-weighted imaging have

Table 2: Means of regional mean magnetic susceptibilities^a (in parts per billion) and R2* (in hertz) in each ROI

ROI	χ	χ^+	χ^-	R2*
CGM	-1.95 (SD, 0.92)	14.87 (SD, 2.31)	-15.50 (SD, 2.11)	10.50 (SD, 0.78)
WM	-2.16 (SD, 0.89)	8.20 (SD, 2.20)	-8.96 (SD, 2.26)	7.87 (SD, 0.83)
DGM	-2.01 (SD, 2.02)	13.59 (SD, 1.56)	-14.42 (SD, 1.74)	10.20 (SD, 0.58)
Caudate nucleus	0.08 (SD, 3.11)	12.53 (SD, 2.23)	-11.64 (SD, 1.83)	9.41 (SD, 0.73)
Putamen	-0.12 (SD, 2.30)	11.87 (SD, 2.29)	-11.92 (SD, 2.04)	9.41 (SD, 0.78)
Globus pallidus	0.21 (SD, 4.41)	12.56 (SD, 2.95)	-12.81 (SD, 2.64)	9.74 (SD, 0.94)
Thalamus	-5.02 (SD, 3.37)	13.43 (SD, 2.16)	-16.09 (SD, 2.49)	10.49 (SD, 0.79)
Frontal lobe	-1.98 (SD, 0.93)	10.08 (SD, 1.87)	-10.77 (SD, 2.01)	8.63 (SD, 0.71)
Parietal lobe	-2.82 (SD, 1.62)	10.30 (SD, 2.87)	-11.18 (SD, 3.07)	8.72 (SD, 1.08)
Temporal lobe	-1.88 (SD, 0.96)	13.35 (SD, 2.54)	-14.11 (SD, 2.33)	9.84 (SD, 0.92)
Occipital lobe	-2.66 (SD, 2.15)	14.12 (SD, 3.25)	-15.26 (SD, 3.05)	10.33 (SD, 1.12)

^a χ , χ^+ , and χ^- denote conventional, positive, and negative susceptibilities.

reported myelination at birth in the brainstem, thalamus, posterior limb of the internal capsule, and corticospinal tract.^{4,5} Similarly, highly negative susceptibilities were visually observed in these regions in the present study. However, except for these regions with early myelination, most WM regions, which are potentially unmyelinated, exhibited lower diamagnetism than the CGM. This CGM-WM difference in diamagnetism may be attributed to regional variation of macromolecular content. Early CT studies have suggested a higher macromolecular concentration in the CGM than in the WM of the neonate brain,^{30,31} which is corroborated by shorter relaxation times³² and a higher magnetization transfer ratio⁹ in the CGM than in the WM in neonates. On the other hand, the higher paramagnetism in the CGM than in the WM is potentially caused by higher iron content in the CGM, similar to the adult brain results reported by histochemical studies.³³

Iron concentration has been reported to be higher in the WM than in the CGM in the neonatal rat brain,^{34,35} but this finding has not been confirmed in the human brain. Nevertheless, the observed high paramagnetic susceptibility in the sensorimotor cortex is likely related to high iron levels. In the cerebral cortex, the motor cortex has previously been found to have the highest iron content across the life span, followed by the occipital cortex and sensory cortex.³⁶ Another potential source of higher positive susceptibility in the CGM is its higher macromolecular content. Macromolecules not only exhibit diamagnetism but also induce a positive frequency shift due to the chemical exchange between water and macromolecular protons.³⁷⁻⁴⁰ The apparent high paramagnetism in the neonate CGM may be caused by this effect on magnetic susceptibility. In the adult brain, there are more abundant macromolecules in the WM, such as lipids, cholesterol, and proteins associated with myelin, and studies have suggested that the effect of chemical exchange on the frequency shift is smaller than on the opposite frequency shift induced by diamagnetic susceptibility. However, the level of these 2 effects is dependent on the molecular types, size, and content and, therefore, may be different in the neonate CGM compared with the adult WM.⁴⁰ Further investigation into the contribution of macromolecular and iron content to susceptibility contrast between the CGM and WM in the neonate brain is warranted in future studies.

Susceptibility in the DGM

Unlike the adult brain, the neonate DGM exhibited no high paramagnetism due to insufficient iron deposition, making it difficult

to distinguish the DGM from the surrounding WM on all susceptibility and R2* maps in individual infants. However, the averaged susceptibility maps on the template space revealed high diamagnetism and high paramagnetism in the thalamus. The mean negative susceptibility measured in the thalamus was also significantly lower than those of the other subregions in the DGM. This finding is potentially attributed to early myelination in the thalamus of the neonate brain. Previous studies have documented that the first regions to be myelinated in the neonate cerebrum are the DGM nuclei; and specifically, the thalamus is one of the myelinated regions at birth.²⁻⁵ Along with myelination, iron deposition is expected to progress in the DGM simultaneously. The globus pallidus and putamen showed significant associations of positive susceptibility with PMA. Particularly, the globus pallidus demonstrated the most rapid temporal change in susceptibility among all ROIs. This feature appears to be supported by a postmortem iron study by Hallgren and Sourander,³⁶ which has demonstrated that the globus pallidus shows the most rapid increase in iron content during brain development. Additionally, the putamen also showed significantly decreasing negative susceptibility with advancing PMA, possibly due to progressive myelination. The significant temporal increase in R2* in the putamen may indicate an amplifying effect of iron and myelin content on R2*, whereas this outcome results in a canceling effect on conventional susceptibility.¹⁶⁻²⁰

Susceptibility in the 4 Brain Lobes

There were significant differences in both mean positive and mean negative susceptibilities among the 4 lobes of the neonate brain, though these were challenging to visually confirm in the susceptibility maps. These regional susceptibility variations may be associated with different degrees of myelination and iron deposition. Global patterns of myelination in the developing brain have been described in the literature as proceeding from the central sulcus outward to the poles, with the occipital lobe myelinating before the frontal lobe (so-called caudal-to-rostral direction).^{4,6,8,14} In line with these findings, the mean negative susceptibility was the lowest in the occipital lobe and the highest in the frontal lobe. Similarly, variation of iron distribution among the 4 brain lobes has previously been studied, demonstrating the highest and lowest iron content in the occipital and frontal cortices, respectively.³⁶ In accordance with this previous study, the mean positive susceptibility of our neonate brain cohort was significantly higher in the occipital lobe than in the frontal lobe.

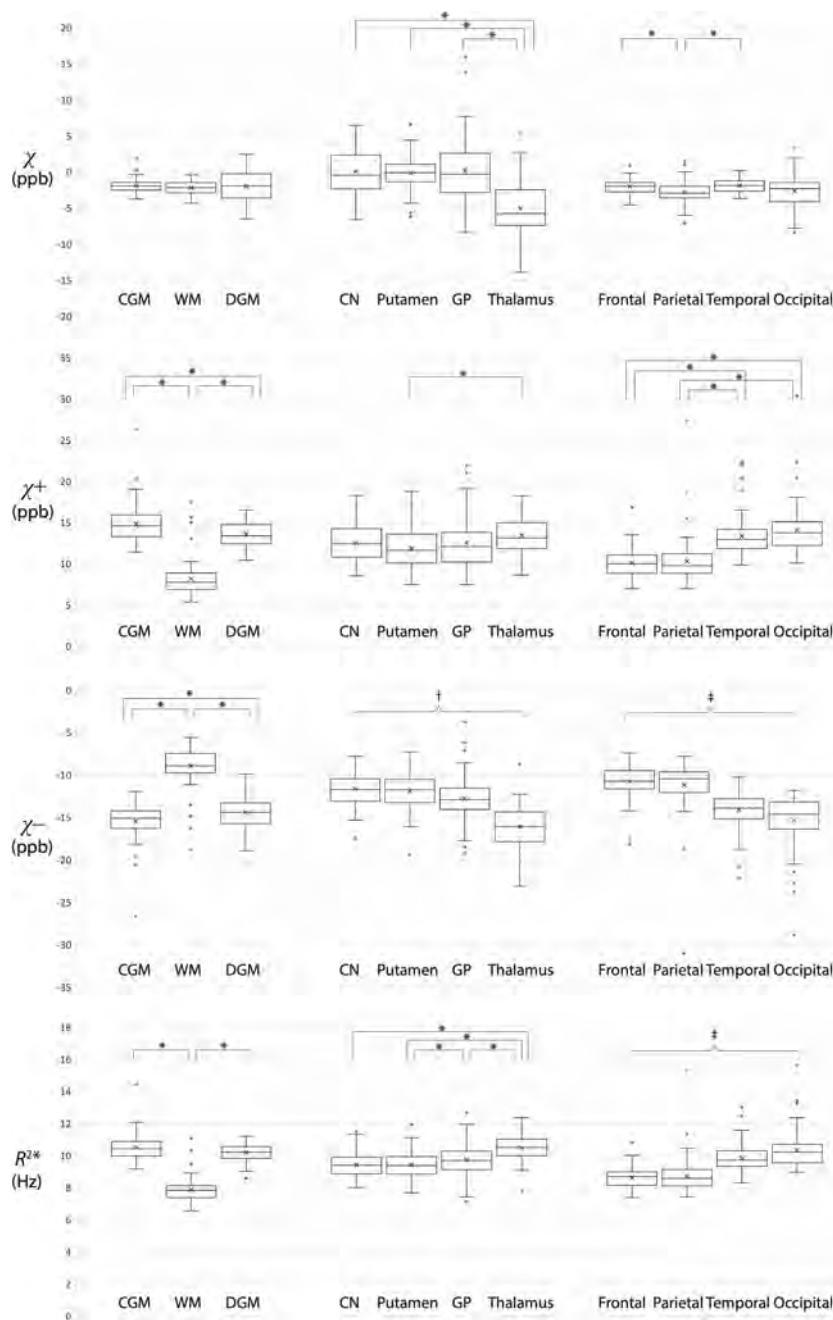


FIG 5. Comparison of mean susceptibilities and $R2^*$ between ROIs within each ROI group. Each asterisk indicates a significant difference ($P < .0008$). † indicates significant differences between all possible pairs within the ROI group except for the comparison between the caudate nucleus and putamen ($P < .0008$). ‡ indicates significant differences between all possible pairs within the ROI group except for the comparison between the frontal and parietal lobes ($P < .0008$). Open circles represent outliers, defined as data points that are beyond 1.5 times the interquartile range, larger above the third quartile or below the first quartile. ppb indicates parts per billion.

Limitations

This study has limitations. First, validating susceptibility source separation in the neonate brain as a means to assess myelin and iron content is necessary but remains challenging. Even with reliable separation of paramagnetic and diamagnetic susceptibilities, estimating myelin or iron content using these measures may be complicated by the potential presence of nonmyelin

macromolecules, especially in GM regions. Their contribution to susceptibility is typically considered negligible in the adult brain, though this consideration may not hold true for the neonate brain. Ultimately, accurate correlations between susceptibilities and iron or myelin content could be assessed through postmortem studies using tissue specimens, but this method may be impractical for healthy cohorts. Second, our measurement of mean regional susceptibility was limited to the supratentorial areas due to potential errors in susceptibility measurement around the cerebellum. The neonate brain often exhibits large off-resonance near the back of head and neck regions due to air-tissue interface with the relatively high curvature compared with adults. This effect is commonly observed as blooming artifacts in neonatal functional MRI studies and was also evidenced by high $R2^*$ values in the present study. With incomplete background field removal, this feature may lead to spurious susceptibility measurements. In future studies, more robust background field removal approaches optimized for the neonate brain should be investigated to filter out the field perturbation in these regions and prevent error propagation into susceptibility maps.

CONCLUSIONS

Unlike the adult brain, where either myelin or iron serves as the primary source of magnetic susceptibility in specific regions, there is no single predominant source of magnetic susceptibility in each region of the neonate brain, highlighting the necessity for source separation in neonate brain QSM. The present study provides new insight into regional magnetic susceptibility in the healthy neonate brain by evaluating the contributions of paramagnetic and diamagnetic susceptibility sources separately. The regional variations and

temporal changes observed in positive and negative susceptibilities are likely associated with myelination and iron deposition patterns in normal brain development. These findings suggest that QSM with source separation may have the potential for early detection of impaired neurodevelopment by measuring altered regional susceptibilities induced by delayed myelination or iron deficiency.

Table 3: Parameters of linear regression between the measurement (susceptibility or R2*) and PMA in the ROIs showing significant associations (*P* < .001)

Measurement = A × PMA + B					
Measurement	ROI	A (ppb or Hz/week)	B (ppb or Hz)	<i>P</i>	<i>r</i>
χ ⁺	Putamen	0.464	−8.0	<.0001	0.459
	Globus pallidus	0.527	−10.0	.0008	0.405
χ [−]	Putamen	−0.390	4.8	<.0001	−0.433
R2*	Putamen	0.177	1.9	<.0001	0.515

Note:—ppb indicates parts per billion.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Dextromethorphan-Associated Neurotoxicity with Cerebellar Edema Syndrome in Young Children: Neuroimaging Features

 Smily Sharma,  Sarbesh Tiwari, Lokesh Saini,  Taruna Yadav, Sujatha Manjunathan,  Ananya Panda, Bharat Choudhary, and Daisy Khara



ABSTRACT

SUMMARY: Dextromethorphan toxicity in young children (especially those 4 years of age or younger) can have an extremely poor prognosis if untreated. However, if timely recognized and optimally managed, it can have a good clinical outcome despite a profound initial insult. We present 3 pediatric cases (younger than 5 years of age) with sudden unresponsiveness following ingestion of cough medications containing dextromethorphan. All these children showed cytotoxic edema in the cerebellar hemispheres on MR of the brain, with diffusion-restricting foci in the supratentorial white matter in 2 patients. These features resemble the recently described acute opioid toxidrome in children, pediatric opioid use–associated neurotoxicity with cerebellar edema (POUNCE). Hence, we named this entity dextromethorphan-associated neurotoxicity with cerebellar edema (DANCE) to increase the awareness of dextromethorphan toxicity in young children and the need to promptly recognize it to initiate optimal management.

ABBREVIATIONS: DANCE = dextromethorphan-associated neurotoxicity with cerebellar edema; IgG = immunoglobulin G; POUNCE = pediatric opioid use–associated neurotoxicity with cerebellar edema

Dextromethorphan-associated neurotoxicity in young children is less well-described in the literature. POUNCE syndrome, the term used for pediatric opioid use–associated neurotoxicity with cerebellar edema is a recently recognized clinico-radiologic entity in children, occurring secondary to acute opioid toxicity. It is extremely rare with fewer than 20 cases published in the literature.¹ We report 3 pediatric patients (younger than 5 years of age) who presented to our institution during a span of 2 years with clinical and radiologic features like POUNCE syndrome but with an antecedent history of ingestion of over-the-counter cough medications containing dextromethorphan for fever, cough, and coryza. We, therefore, named this entity dextromethorphan-associated neurotoxicity with cerebellar edema (DANCE) syndrome due to its striking resemblance to the POUNCE syndrome. We consider it different from POUNCE syndrome because it did not occur directly due to opioid ingestion, rather occurred secondary to ingestion of an opioid analog with a slightly different mechanism of action. Our intention is

to increase awareness of this entity in children 4 years of age or younger for whom over-the-counter antitussive medications containing dextromethorphan are otherwise not recommended but are still used in a few parts of the world.

CASE SERIES

Clinical Presentation

Case 1. A 4-year-old girl presented with low-grade fever, cough, and coryza for 2 days. She was given a cough syrup containing dextromethorphan hydrobromide (dextromethorphan dose of 1 mg/kg), chlorpheniramine maleate, and phenylephrine hydrochloride from a local physician. Three hours after ingestion of the cough syrup, she presented with sudden unresponsiveness. A similar presentation was elicited at the same time in her younger sibling of 2 years of age, who died before reaching hospital. There was no history of any animal bites or exposure to other toxins like organophosphorus compounds or opioids. At arrival, the child was unconscious with a Glasgow Coma Scale score of 4 (E1V1M2) and had bilateral pinpoint pupils. She was febrile and tachycardic and had an elevated blood pressure of 131/67 mm Hg, a low oxygen saturation level of 75% at room air, and a low blood glucose level of 43 mg/L. Examination revealed generalized hypotonia with brisk deep tendon reflexes and bilateral extensor plantar.

Case 2. A 2-year-old boy presented with fever and upper respiratory tract illness for 1 day, for which a cough syrup containing

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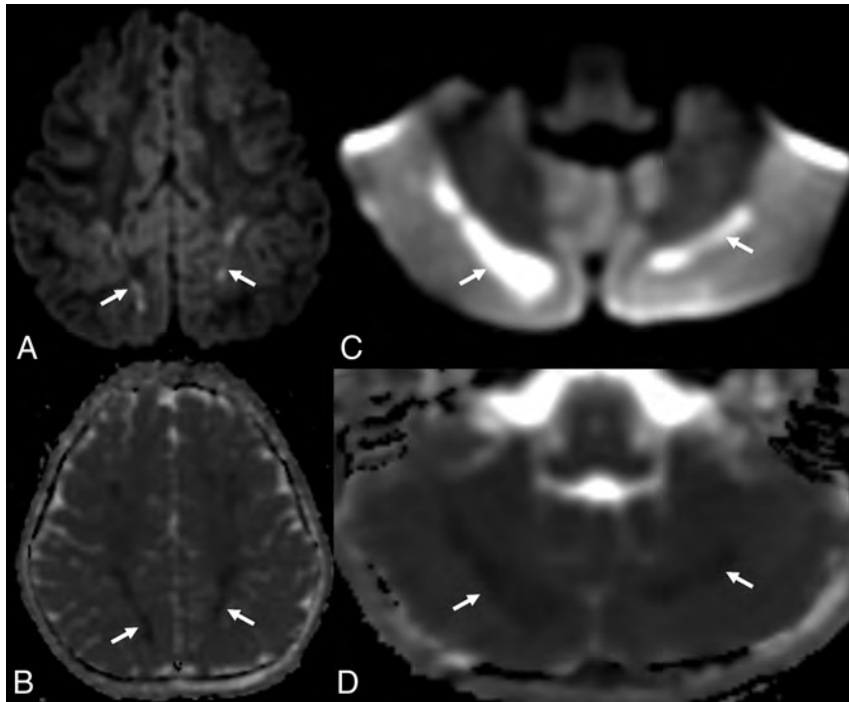


FIG 1. Image of a 4-year-old girl who presented with sudden unresponsiveness and pinpoint pupils 3 hours following ingestion of a cough syrup containing dextromethorphan hydrobromide (dextromethorphan dose of 1 mg/kg), prescribed to her for low-grade fever, cough, and coryza from an outside hospital. Axial MR brain images: diffusion-weighted images (A and C) and their corresponding ADC maps (B and D) show near-symmetric linear diffusion-restricting foci in the bilateral centrum semiovale (arrows in A and B). Symmetric and confluent diffusion-restricting areas are seen in the bilateral cerebellar hemispheres (arrows in C and D), indicating cerebellar edema.

dextromethorphan hydrobromide (dextromethorphan dose of 1.6 mg/kg) was prescribed in a local clinic. One hour after ingestion of the syrup, the child was found to be unresponsive. On the way to the hospital, he had 7 brief episodes of generalized tonic-clonic seizures, each lasting for 3–5 minutes. On arrival, the child was unconscious and febrile and had tachycardia, bilateral pinpoint pupils, and generalized hypotonia with brisk deep tendon reflexes and bilateral extensor plantar.

Case 3. A 1.5-year-old girl presented with intermittent fever and dry cough for 2–3 days and decreased responsiveness for the last 2 hours. She had an episode of abnormal body movements in the form of clenching of teeth and frothing from mouth, with bluish discoloration of the body 1 hour before reaching our hospital. She had been given a similar oral cough syrup containing dextromethorphan hydrobromide like the previous 2 patients at a local private hospital for her respiratory illness. On examination, the child was lethargic with Glasgow Coma Scale of 7 (E1V2M4) and had bilateral constricted pupils. She developed respiratory failure with a venous oxygen saturation level of 54% at room air and was found to have hypoglycemia.

All the children had normal CSF examination findings. Patient 1 had positive immunoglobulin G (IgG) antibodies for coronavirus disease 2019 (COVID-19). Hematologic and biochemical investigations revealed elevated transaminases (AST/ALT [IU/L] in patient 1: 56/197, patient 2: 118/41, and patient 3:

128.9/43.9). Patient 3 had raised creatine kinase-MB level (61.4) and creatine kinase level (1095) with hyperkalemia, indicating rhabdomyolysis. She also had a high interleukin 6 value of 133 pg/mL (normal value: <4.4).

Imaging Findings

After initial resuscitation, the patients underwent MRI of the brain within 6 hours of their presentation. MRI brain in all patients consistently showed confluent T2-FLAIR hyperintensities in the bilateral cerebellar hemispheres with restricted diffusion on the corresponding DWI sequence, suggestive of cytotoxic edema. Multiple other punctate and linear foci of restricted diffusion were seen in the bilateral centrum semiovale and corona radiata in patients 1 and 2 (Figs 1 and 2). Patient 3 did not have supratentorial involvement. The basal ganglia or hippocampi were not involved except in patient 2 in whom a few diffusion-restricting foci were seen in the left caudate nucleus and bilateral posterior putamina (Fig 2). None of the patients showed cerebral cortical involvement, blooming/bleeds on SWI, enhancement on postcontrast T1-weighted sequences, or any evidence

of vascular stenosis/occlusion on TOF-MRA. These features strongly resembled the recently described typical features of POUNCE syndrome.¹

Treatment and Follow-Up

Emergent measures were performed in all the children by securing the airway with intubation and administering a 10% dextrose bolus for hypoglycemia. Considering dextromethorphan-induced encephalopathy, they were given bolus doses of naloxone followed by an infusion for 48 hours along with measures to reduce intracranial pressure. In view of cerebellar edema, they were given methylprednisolone pulse therapy for 5 days, followed by oral prednisolone for 2 weeks. All the children showed dramatic improvement in the sensorium after methylprednisolone therapy. They were discharged in stable condition without any residual deficits after a brief hospital stay varying from 5 to 10 days and had normal neurologic examination findings on a 2-week follow-up. Follow-up MR 2 weeks later in patient 3 showed significant resolution of T2-FLAIR hyperintensities in the cerebellum with normalization of restricted diffusion (Fig 3). The Online Supplemental Data summarize the clinical and imaging features, treatment, and follow-up of the patients in the clinical report.

DISCUSSION

Dextromethorphan-associated neurotoxicity in young children is a little-known entity. We describe 3 pediatric patients who

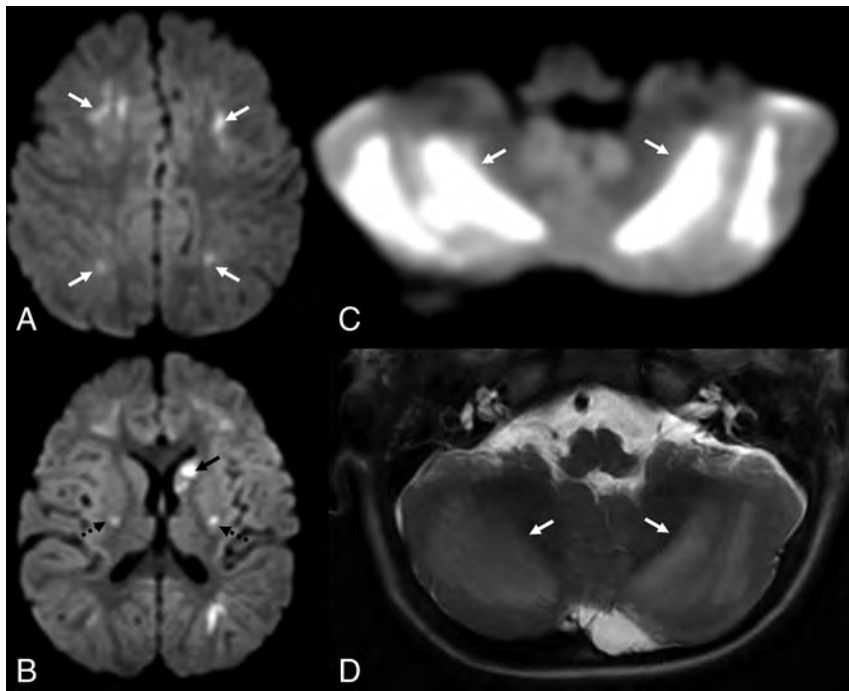


FIG 2. Image of a 2-year-old boy who presented with unresponsiveness, brief episodes of generalized tonic-clonic seizures, and bilateral pinpoint pupils 1 hour following ingestion of a cough syrup containing dextromethorphan hydrobromide (dextromethorphan dose of 1.6 mg/kg), prescribed to him for upper respiratory tract illness. Axial MR brain images (A, B, and C, Diffusion-weighted sequence. D, T2-weighted sequence) show features of DANCE syndrome. Symmetric linear diffusion-restricting foci with corresponding low values on the ADC map (not shown) are seen in the bilateral centrum semiovale (arrows in A) and deep white matter (B). A few diffusion-restricting foci are seen in the left caudate nucleus (black solid arrow in B) and bilateral posterior putamina (black dashed arrows in B). Confluent areas of diffusion restriction (with low values on the ADC map, not shown) are seen in the bilateral cerebellar hemispheres (arrows in C), with corresponding hyperintense signal on T2-weighted images (arrows in D).

presented with significant neurologic deterioration after ingestion of over-the-counter antitussive medications containing dextromethorphan for their short febrile respiratory illness. The patients in our series had strikingly similar clinical features and MRI of the brain appearances like those of the recently described POUNCE syndrome.¹

POUNCE syndrome is a term coined by Kim et al¹ for a distinct clinico-radiologic syndrome caused by acute opioid toxicity in children. It is characterized by cerebellar edema in the form of T2-FLAIR hyperintensities with or without restricted diffusion. It is often accompanied by some degree of supratentorial white matter injury, predominantly in the deep and periventricular white matter, seen as punctate or confluent T2-FLAIR hyperintensities, which may show restricted diffusion in the early stages.¹ A few of the previously published reports on pediatric opioid toxicity have also described similar cerebellar and white matter injury, often with malignant cerebellar edema leading to complications, including cerebellar tonsillar herniation, compression of brainstem, and rapidly evolving obstructive hydrocephalus. These complications may lead to dreaded consequences, including death if not addressed in early stages by antiedema measures or posterior fossa decompression or placement of an external ventricular drainage tube if necessary.¹⁻¹²

All the children in our report presented with profound encephalopathy and respiratory failure and had cerebellar edema on

MRI. Two of them showed supratentorial involvement. None of the children showed hemorrhages or contrast enhancement, though hemorrhage has been reported in a few of the previously published cases of POUNCE.⁶ Our patients did not show significant compression of the brainstem or upstream hydrocephalus and did not require surgical measures, likely due to early recognition and administration of appropriate therapy.

Dextromethorphan, an over-the-counter antitussive medication, is a D isomer of levorphanol, which is a synthetic analog of codeine, an opioid receptor agonist. Its cough-suppressant actions in regular doses are mediated via its action on σ opioid receptors in the medulla. Due to its stereochemistry, it does not bind to μ and δ opioid receptors, which are commonly involved in manifestations of opioid toxicity.^{13,14}

Although definite histopathologic evidence is lacking to date, POUNCE is postulated to occur due to direct neurotoxic effects of the opioid agents on glial and neuronal cells, with contributions from factors like apoptotic upregulation due to mitochondrial injury and potentiation of these mitochondrial pathways from anoxic insults secondary to respiratory depression.^{1,2,4} Predominant cerebellar involvement in POUNCE is

proposed due to an abundance of μ receptors in the cerebellum, which are the primary target for opioid toxicity.¹

Although dextromethorphan primarily binds with σ opioid receptors, due to a striking resemblance of the clinical and radiologic syndrome in all the cases of our series with POUNCE, we postulate the occurrence of DANCE syndrome in small children with dextromethorphan toxicity and propose a similar mechanism with the possibility of cross-reactivity with μ receptors. Over-the-counter cough remedies containing dextromethorphan have been largely prohibited for children younger than 2 years of age and are not recommended for use in those younger than 4 years of age.¹⁴⁻¹⁶ The occurrence of DANCE syndrome in young children in our report further emphasizes the necessity of this precaution. A recently published case report has highlighted clinical features of opioid toxidrome secondary to dextromethorphan toxicity in children, but it is extremely rare and there is a paucity of knowledge about the associated neuroimaging features.¹⁷ Although never proved, the occurrence of dextromethorphan toxicity in only young children may be due to the enhanced sensitivity of the receptors in this age group, leading to a heightened effect even at doses less than the toxic range. Further research into this matter is warranted.

Because all the children in our series had a respiratory illness and showed good response to methylprednisolone, one of them

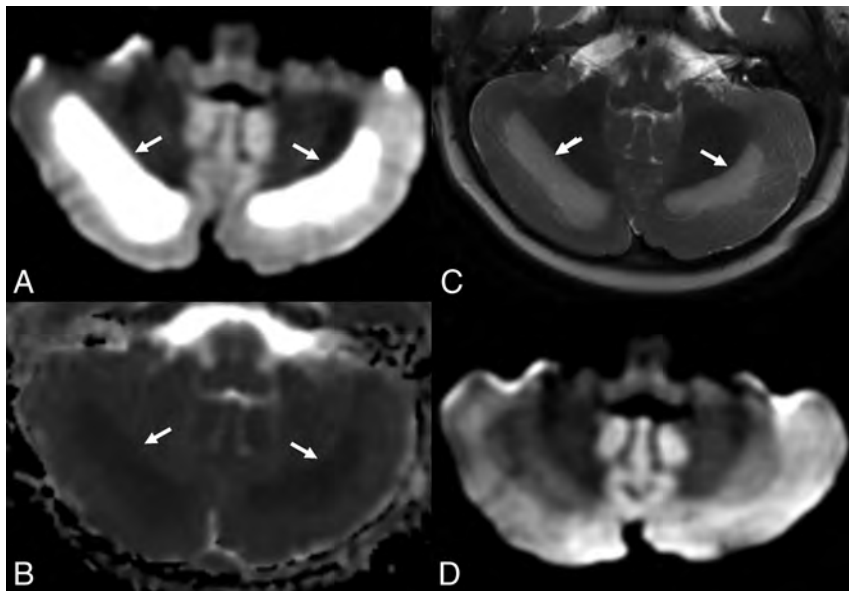


FIG 3. Image of a 1.5-year-old girl who ingested oral cough syrup containing dextromethorphan hydrobromide for intermittent fever and dry cough and now presented with decreased responsiveness, a seizure episode, and bilateral constricted pupils. Axial MR brain images (A, Diffusion-weighted sequence. B, ADC map. C, T2-weighted sequence) show features of DANCE syndrome. Symmetric and confluent areas of restricted diffusion (arrows in A) with low values on the ADC map (arrows in B) and corresponding hyperintense signal on T2-weighted sequence (arrows in C) are seen in the bilateral cerebellar hemispheres, indicating cerebellar edema. No diffusion-restricting foci were seen in supratentorial white matter in this case (not shown). D, Follow-up MR image (diffusion-weighted sequence) obtained 2 weeks later in the patient shows no residual diffusion restriction in cerebellum.

had high interleukin-6 levels, and one had positive IgG for COVID-19, the possibility of an underlying parainfectious immunologic phenomenon and the role of viral infection in the increasing predisposition to DANCE syndrome also need to be investigated. In this context, the most important differential of DANCE syndrome remains viral/infectious cerebellitis. However, a specific MR pattern involving both the cerebellum (in all the children) and supratentorial white matter (in 2 of the 3), a remarkably similar clinical context with features including pinpoint pupils, a striking resemblance to POUNCE syndrome, a lack of contrast enhancement, and normal findings on blood and CSF investigations despite extensive infectious disease work-up make the diagnosis of an infectious/viral cerebellitis less likely than DANCE. Hypoxic-ischemic encephalopathy is another major clinical differential of DANCE syndrome in patients with sudden unresponsiveness and respiratory failure. Predominant involvement of the cerebellar white matter and centrum semiovale without cortical and basal ganglia involvement on MRI of the brain makes the distinction from hypoxic-ischemic encephalopathy possible, when the cerebellum is usually involved late.^{1,18,19}

A similar predilection for the cerebellum and white matter in cases of “chasing the dragon” leukoencephalopathy occurring due to chronic rather than acute inhalation of heroin and the recently described cerebellar, hippocampal, and basal nuclei transient edema with restricted diffusion syndrome and opioid-associated amnesic syndrome occurring secondary to acute opioid toxicity in adults suggests that all these disorders may represent a continuum of similar pathophysiology.^{18–21} Nevertheless, there

are differences (Online Supplemental Data) among these entities possibly due to varying binding affinity of opioid receptors in different parts of the brain in children and adults.²²

Our report has a few limitations. We could not determine the serum levels of dextromethorphan in the children in our series. The lack of supratentorial involvement in the third child in our study could not be explained. This may be related to the difference in the sensitivity of the brain receptors at different ages because the third child was the youngest of the 3 (younger than 2 years of age), but we refrain from making a definite assumption without any histopathologic or other conclusive evidence from the literature. Due to logistic reasons, MR follow-up was not available in 2 of the 3 patients. However, normal neurologic examination findings were reassuring and indicated a definite clinical improvement in these patients.

DANCE syndrome can have an extremely poor prognosis if untreated as could be seen in the sibling of the patient in case 1 who succumbed to death before reaching our hospital. However,

if timely recognized and optimally managed, it can have a good clinical outcome despite a significant initial insult as seen in all the patients of our series, likely owing to the neuroplasticity of the pediatric brain.¹ This experience highlights the importance of early neuroimaging and the need to promptly recognize the specific DANCE pattern and urgently treat this rare entity. The case series reiterates the adverse effects of dextromethorphan in young children and the need to monitor its use, especially in children younger than 4 years of age.

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Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Reversible Perfusion Changes during Acute Attacks in Glucose Transporter Type 1 Deficiency Syndrome: A Pediatric Case Series

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ABSTRACT

SUMMARY: Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is an uncommon condition represented by an infantile-onset disorder, frequently arising from heterozygous mutations in the *SLC2A1* gene. Individuals with GLUT1-DS may present with early-onset seizures (typically manifesting before 4 years of age), developmental delay, and complex movement disorders. In fewer cases, stroke-like events or hemiplegic migraine-like symptoms are also reported, defined by unilateral paresis affecting 1 side of the body and/or one-half of the face, occasionally accompanied by speech impairment. Currently, the pathomechanism underlying these acute transient clinical manifestations is poorly understood. MR imaging studies performed in the absence of acute manifestations frequently reveal nonspecific imaging signs associated with this syndrome. We present findings obtained using the arterial spin-labeling technique for perfusion imaging and MRA during the acute onset of stroke-like episodes in a series of 4 pediatric patients with GLUT1-DS. We observed reversible hypoperfusion in the left hemisphere and associated reversible attenuation of distal MCA branches on MRA. A notable association between unilateral cerebral hypoperfusion and transient crossed cerebellar diaschisis was evident on perfusion maps as well.

ABBREVIATIONS: ASL = arterial spin-labeling; EEG = electroencephalography; GLUT1 = glucose transporter 1; GLUT1-DS = glucose transporter type 1 deficiency syndrome; pCASL = pseudocontinuous arterial spin-labeling

Glucose transporter type 1 deficiency syndrome (GLUT1-DS) is a rare congenital disease caused by a deficiency of glucose transporter 1 (GLUT1), which is primarily expressed in endothelial cells and astrocytes forming the BBB. The main gene involved is *SLC2A1*, with most cases resulting from autosomal dominant de novo heterozygous mutations.¹ The hallmark of the disease is reduced glucose concentration in the CSF, despite normoglycemia.

Epilepsy is frequently the initial symptom, with absence seizures (before 4 years of age) being the most common presentation; generalized seizures are more likely to occur than focal ones.¹⁻³ The most frequent electroencephalographic (EEG) abnormalities are 2.5- to 4-Hz generalized spike and wave discharges,^{4,5} though interictal EEG often has normal findings.⁶ Within the spectrum of GLUT1-DS, spasticity, ataxia, and movement disorders such

as dystonia, chorea, and tremor have also been described.^{1,3} Microcephaly and intellectual disability, ranging from mild to severe, may also be present.¹ It has been recently reported that GLUT1-DS-affected patients may experience recurrent acute transient focal neurologic deficits, including episodes that could be classified as alternating hemiplegia of childhood, hemiplegic migraine, or more generally stroke-like events.^{1,7} The exact percentage of patients with GLUT1-DS who develop stroke-like events is not known, though in a study of 42 patients between 6 and 38 years of age, 8 presented with an acute onset of neurologic disturbances.⁸

Despite the growing awareness of the phenotype associated with the disorder, there is a limited understanding of the underlying mechanisms by which low GLUT1 contributes to brain dysfunction. The energy deficit related to this uniport channel impairment seems to play the main role in GLUT1-DS, and a ketogenic diet, as an alternative energy source to brain metabolic needs, is reported to control epilepsy and motor symptoms.⁹ GLUT1 is also involved in endothelial metabolism and function, with implications for CNS development and BBB integrity.¹⁰

Patients with GLUT1-DS have been reported to have nonspecific subcortical white matter T2-weighted hyperintensities, prominent Virchow-Robin spaces, and delayed myelination; however, approximately 25% present with normal findings on brain MR

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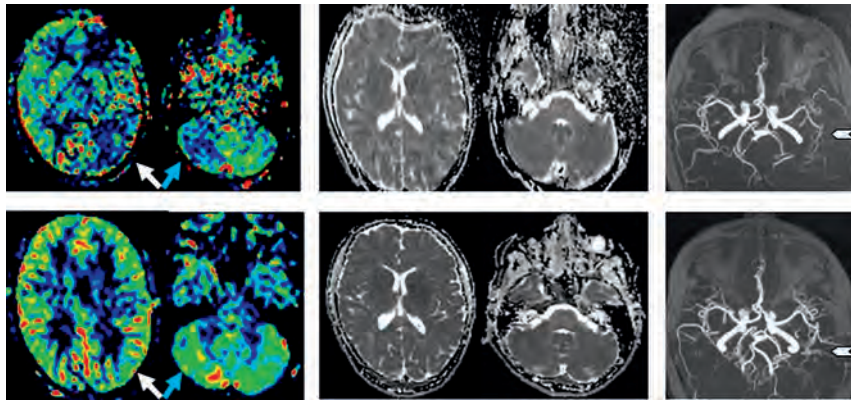


FIG 1. Case 1. MR examinations from left to right: 3D-pCASL, ADC map, and MRA-MIP. The *upper* row shows images acquired during the acute phase: hypoperfusion in the left cerebral hemisphere (white arrow) and in the contralateral cerebellar hemisphere (blue arrow). No ADC map changes are seen. Note reduced representation of the distal branches of the left MCA (white arrowhead). The *lower* row shows the follow-up examination 4 days later with normalization of all the findings.

imaging.¹ Possible imaging findings related to stroke-like events have been poorly investigated. In this report, we present novel MR imaging findings from a series of 4 patients with GLUT1-DS. These patients, despite ketogenic therapy, experienced stroke-like events, and they underwent imaging during the acute phase. All patients were diagnosed with pathogenic variants in the *SLC2A1* gene and underwent a lumbar puncture to test glucose levels in the CSF; all of them had a glycemia/glycorrachia ratio lower than 0.5 (see the Online Supplemental Data for details). Genetic testing excluded mutations in genes related to hemiplegic migraine (*CACNA1A*) and alternating hemiplegia of childhood (*ATP1A2*).

CASE SERIES

This was a single-center retrospective study, reporting 4 patients.

These cases were collected as consecutive imaging observations during the acute onset of stroke-like episodes and were followed up between the third and seventh day. Patients' imaging data were retrieved and evaluated from the PACS and internal medical records between 2022 and 2024. Imaging assessment was performed by our senior author (A.R. with >20 years' experience in pediatric neuroradiology). The study complied with institutional regulations for anonymized retrospective studies and was related to the approved study by the ethics committee of Area 1 of Milan (2021/ST/004).

MR procedures were performed on the latest-generation 3T scanner (Magnetom Vida; Siemens) for case 1, case 2, and case 4, and on a 1.5 T scanner (Ingenia; Philips Healthcare) for case 3, including conventional T1- and T2-weighted sequences, 2D T2 FLAIR, arterial spin-labeling (ASL) by a 3D pulsed continuous arterial spin-labeling (pCASL) acquisition, DWI, and TOF-MRA. In cases 2 and 3, SWI was also performed, and in case 2, single-voxel (TE = 144 ms) proton MRS was performed during the acute phase.

For details about ASL sequence parameters and data analysis refer to the Online Supplemental Data.

Case 1

A 12-year-old girl presented with acute-onset aphasia, ataxia, dysmetria, vomiting, and right-arm weakness. Ketone levels at onset were 0.6 mmol/L, increasing to 2.9 mmol/L within 4 hours. EEG showed a slow activity in the left hemisphere with slower δ - θ waves in the anterior and left temporal regions (Online Supplemental Data). No abnormal findings were detected on T2 and T2 FLAIR sequences, while 3D-pCASL revealed hypoperfusion in the left cerebral hemisphere, accompanied by hypoperfusion in the contralateral cerebellum (Fig 1). Additionally, MRA showed a diminished representation of distal branches of the left MCA. Within 24 hours, symptoms totally subsided. A follow-up examination

4 days later showed resolution of all abnormalities. No focal signal anomalies were ever noted on conventional imaging and ADC maps.

Case 2

A 7-year-old girl presented with symptoms including acute-onset aphasia, dysarthria, sialorrhea, confusion, irritability, and right-arm weakness. After 2 hours, she developed headache and vomiting. Initial ketone levels were 2.6 mmol/L. EEG showed interhemispheric asymmetry with hypovolted activity in the left hemisphere, while normal background activity was detected in the right one (Online Supplemental Data). The MR examination did not show any findings on T2 and T2 FLAIR sequences; a perfusion study demonstrated left cerebral hemisphere hypoperfusion on 3D-pCASL and bilateral cerebellar hypoperfusion, more pronounced in the contralateral hemisphere (Fig 2). SWI showed a mild-to-moderate increase in the conspicuity of cortical veins on the left side, and MRA revealed a reduction in the representation of distal branches of the left MCA. Proton MRS showed no lactate peak (Online Supplemental Data). The patient fully recovered within 6 hours. On follow-up 3 days later, all abnormalities, including SWI findings, had resolved on MR imaging. No focal signal anomalies were ever noted on conventional imaging and ADC maps.

Case 3

A 16-year-old girl presented with acute onset of right-arm weakness, dysarthria, and a right-sided facial nerve deficit. Within 30 minutes, only aphasia and the facial deficit persisted. Her initial ketone levels were 1.2 mmol/L (Online Supplemental Data). EEG was not performed during the acute phase. The MR scan revealed left cerebral hemispheric hypoperfusion, along with a mild reduction in the contralateral cerebellar hemisphere (Fig 3). Notably, a cortical atrophic-gliotic area was identified in the right cerebellar hemisphere, but no additional findings were detected on T2 and T2 FLAIR sequences. SWI showed a mild increase in the conspicuity of cortical veins on the left side, and

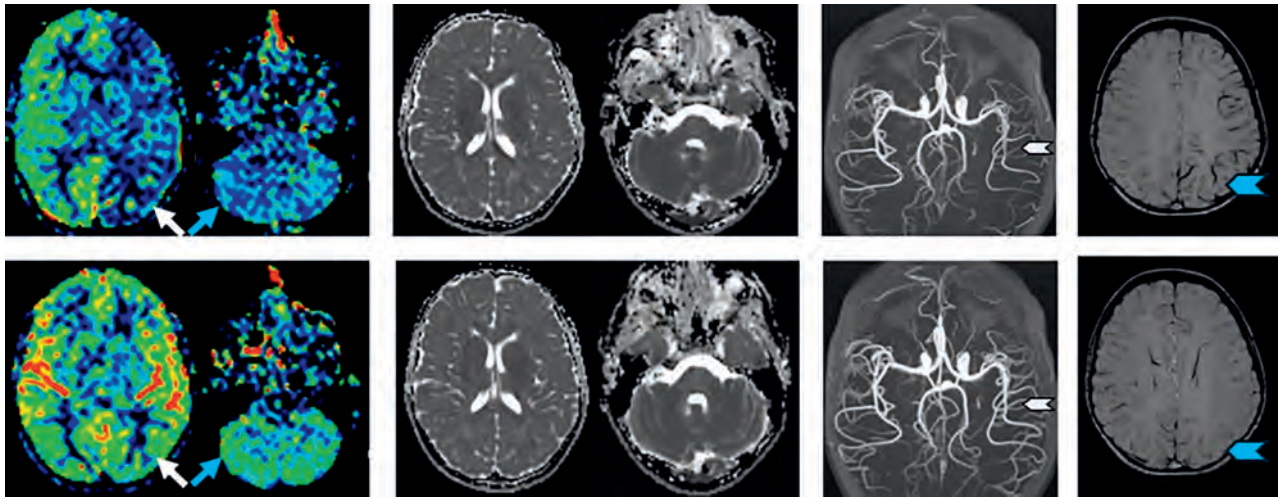


FIG 2. Case 2. MR examinations from left to right: 3D-pCASL, ADC map, MRA-MIP, and SWI. The *upper* row shows the acute onset: hypoperfusion in the left cerebral hemisphere (*white arrow*) and in cerebellar hemispheres but more pronounced in the right cerebellar hemisphere (*blue arrow*). No ADC map changes are seen. Note reduced representation of the distal branches of the left MCA (*white arrowhead*) and a mild increase in the conspicuity of cortical veins on the left side on SWI (*blue arrowhead*). The lower row shows the follow-up examination after 3 days, with normalization of all the findings.

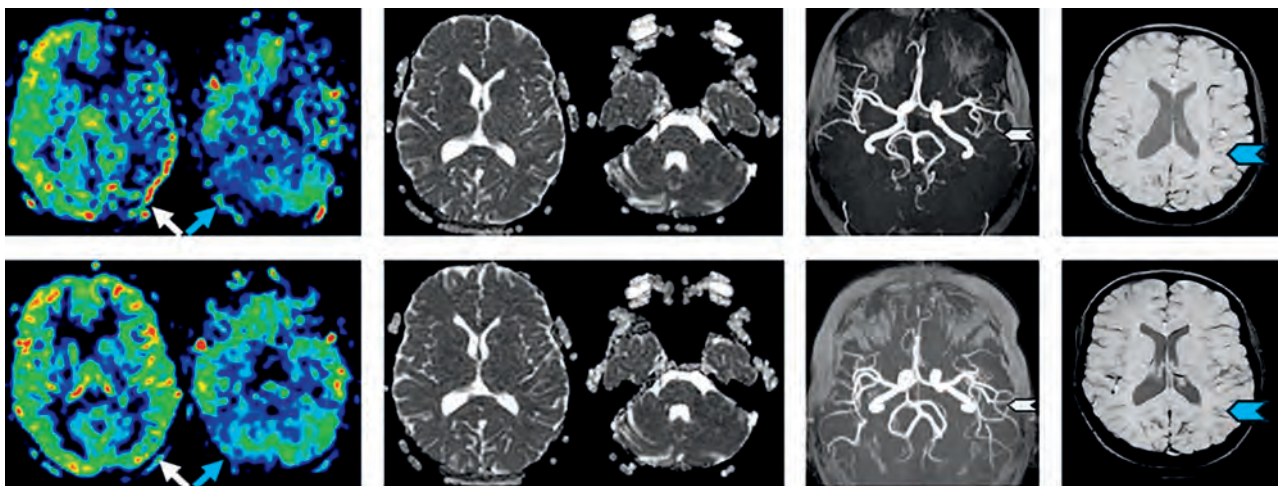


FIG 3. Case 3. MR examinations from left to right: 3D-pCASL, ADC map, TOF-MIP, and SWI. The *upper* row shows the acute phase findings: hypoperfusion of the left cerebral hemisphere (*white arrow*) and of the contralateral cerebellar hemisphere (*blue arrow*). No ADC map changes are seen. Note reduced representation of distal branches of the left MCA (*white arrowhead*) and a mild increase in the conspicuity of cortical veins on the left side on SWI (*blue arrowhead*). The lower row shows the follow-up examination after 7 days, with normalization of all acute findings. There is persistent-but-improved hypoperfusion of the right cerebellar hemisphere proportional to what would be expected for the known background encephalomalacia in this region (*blue arrow*).

MRA indicated a reduction in the representation of distal branches of the left MCA. A follow-up 7 days later showed normalization of all acute findings, including on SWI. No focal signal anomalies were ever noted on the ADC map.

Case 4

A 15-year-old girl presented with acute-onset headache, right-arm weakness, and pain, followed by multiple vomiting episodes within 30 minutes. Her initial ketone levels were 1.5 mmol/L. EEG showed slow activity in the left hemisphere with slow epileptic discharges in the frontal centrottemporal regions (Online Supplemental Data). The MR examination did not show any findings on T2 and T2 FLAIR sequences; the

perfusion study revealed hypoperfusion in the left cerebral hemisphere on 3D-pCASL and a mild reduction in perfusion in the contralateral cerebellar hemisphere (Fig 4). Additionally, MRA demonstrated a decreased representation of distal branches of the left MCA. No focal signal anomalies were noted on conventional imaging or ADC maps. No follow-up MR study was performed.

DISCUSSION

All presented patients have common features of acute symptom onset caused by single cerebral hemisphere disfunction, accompanied by a congruous unilateral cerebellar hemisphere (the left one)

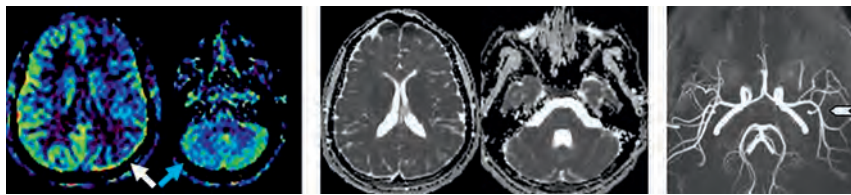


FIG 4. Case 4. MR examination from left to right: 3D-pCASL, ADC map, and MRA at the acute onset of symptoms: hypoperfusion of the left cerebral hemisphere (white arrow) and of the contralateral cerebellar hemisphere (blue arrow). No ADC map changes are seen. Note reduced representation of the distal branches of the left MCA (white arrowhead).

reversible hypoperfusion, reduced MRA arterial representation, and decreased EEG activity (Online Supplemental Data). Notably, a contralateral cerebellar hemisphere transient hypoperfusion was also noted as a novel sign of very likely functional crossed cerebellar diaschisis in these subjects with GLUT1-DS. The predominant symptoms in patients with GLUT1-DS seem to depend on the age of the patient. In younger patients, GLUT1-DS manifests as clusters of tonic-clonic seizures, absence seizures, and myoclonus. Meanwhile, in older patients, it presents as paroxysmal dyskinesia or paroxysmal weakness of the lower limbs. Muscle stiffness, gait abnormalities, and dysarthria are also evident in older patients. Behavioral problems are reported as remarkable features within the spectrum related to this condition. Therefore, GLUT1-DS should be considered a condition with a large spectrum of symptoms with varying degrees of severity. According to the work of Winczewska-Wiktor et al,¹¹ the presentation can vary widely, even within the same family and with the same genetic background. The ketogenic diet has been shown to be very effective in treating epilepsy and, to a lesser extent, motor and behavioral problems. In some cases, such as the one reported by Klepper et al,¹² it has also been effective to counter delayed demyelination.

Currently, conventional MR imaging does not have a specific diagnostic role in GLUT1-DS management; rather, it is predominantly performed to rule out alternative etiologies such as stroke in children, because conventional imaging findings are frequently normal¹³⁻¹⁵ or may show some delayed myelination.^{2,15} Additionally, we were able to evaluate the presence of crossed cerebellar diaschisis, which had not been previously reported. Our case series differs from others because it includes only pediatric patients for whom a complete follow-up protocol with MRI and pCASL was available. Our cases show that MR imaging can play a role during acute events in these patients and that sequences such as ASL and MRA should be included in the imaging protocol.

Our data corroborate the single observation of Almuqbil et al,¹⁶ who reported a 9-year-old child affected by GLUT1-DS with reversible attenuation of the distal branches of right MCA on MRA and ipsilateral reduced perfusion on ASL during acute-onset left hemiparesis and altered mental status.

Proton MRS was only performed in 1 case (case 2) during the acute phase and demonstrated no evidence of a lactate peak (Online Supplemental Data). Meanwhile, ADC values remained normal as in all other cases. One interpretation is that despite the unequivocal blood flow reduction, any possible transient cell energy dysfunction or failure (reduced EEG activity) may have

remained below the decompensation threshold (cytotoxic edema) detectable by ADC mapping. Whether unilateral hypoperfusion was the cause or the epiphenomenon of transient cerebral functional impairment remains to be established.

Given that GLUT1 is predominantly expressed by the endothelial cells of the BBB and astrocytes, it can be hypothesized that acute cortical hypometabolism, resulting from inadequate glucose

supply and consequent decrease in regional cerebral perfusion (neurovascular coupling), underpins these acute episodes. The detrimental effects of neuroglycopenia, similar to cellular “starvation,” may act on the endothelium and nervous tissue, altered by the transporter deficiency.

One of the hypotheses is that the vasospasm-like events in patients with GLUT1-DS are similar to those observed during the acute phase of hemiplegic migraine, which shares similar symptom patterns¹⁷ and in which acute vasospasm has also been occasionally reported on MRA.¹⁸ The etiology of hemiplegic migraine is not completely understood, but 1 prevailing theory suggests that a depolarization wave during the aura phase triggers cerebral perfusion changes, initially causing hypoperfusion followed by hyperperfusion, potentially resulting in damage to the BBB.¹⁹ Consistent EEG findings were observed in patients with hemiplegic migraine and GLUT1-DS during episodes of acute transient neurologic symptoms, characterized by contralateral EEG slowing.²⁰ The phenomenon of spreading depression, hypothesized to precipitate migraine attacks, is typified by a widespread depolarization propagating through the cortex, leading to suppression of neuronal electrical activity. The elevation of extracellular potassium ions (K^+) is believed to be associated with the depolarization of neighboring cells.²¹ Perfusion imaging of migraine attacks accompanied by an aura demonstrates a distinct pattern: an initial phase of hypoperfusion during the aura period, followed by hyperperfusion in regions extending beyond the boundaries of individual vascular territories.²² It is conceivable that a similar mechanism may underlie the observations documented in patients diagnosed with GLUT1-DS during acute events. Nevertheless, elucidating the precise trigger for spreading depression in these individuals poses a challenge.

Furthermore, the transient increased conspicuity of vein depiction observed with SWI in 2 cases has no univocal explanation. This finding has also been reported to be associated occasionally with migraine attacks.²³ It is not currently clear whether it may represent a reactive venous side vascular dilation consequent to arterial bed reduction or an increased oxygen extraction with consequent deoxyhemoglobin production. The cases also showed some transient contralateral cerebellar hypoperfusion suggestive of a functional crossed cerebellar diaschisis phenomenon. It is commonly defined as a reduction in neuronal activity in the cerebellar hemisphere contralateral to a cerebral hemisphere affected by a lesion.²⁴ Cerebellar hypoperfusion was transient as supratentorial flow changes. Crossed cerebellar diaschisis was more pronounced in case 1; notably, this patient was also the

one who presented with cerebellar signs such as ataxia and dysmetria and also had the most symptom-resolution delay (Online Supplemental Data). In case 2, the difference in cerebellar hemisphere perfusion was milder, and there was a significant variation in perfusion levels across both cerebellar cortices during follow-up. Case 4, which lacked a follow-up study, seemed to exhibit a mild crossed cerebellar diaschisis during the acute phase. In case 3, mild crossed cerebellar diaschisis was evident in the presence of a gliotic-atrophic area in the ipsilateral cerebellar hemisphere. The patient lacked a documented history of prior stroke-like incidents; however, she exhibited a documented history of epileptic events. Hypothetically, this scenario could be interpreted as the permanent sequelae of multiple previous crossed cerebellar diaschisis episodes.

Transient functional crossed cerebellar diaschisis has also been reported in a small fraction of patients with migraine during the acute phase such as in the article by Kellner-Weldon et al,²⁵ in which a cohort of patients was scrutinized during migraine episodes using MR perfusion imaging with a dynamic susceptibility contrast technique, unveiling oligemia in a cerebral hemisphere in 23 of 106 patients, most of whom manifested an aura. Cerebellar hypoperfusion was evident in 12 of the 23 patients. While crossed cerebellar diaschisis was documented in 9 of the 23 patients with oligemia, none of their patients presented with DWI restriction. It is possible that the 2 conditions may share some similar pathophysiologic aspects regarding the functional consequences on cerebellar status of defaulting supratentorial structures.

Moreover, all our patients had left cerebral hypoperfusion at presentation, and all were right-handed with left-sided hemispheric dominance. While this feature could be happenstance related to the small sample size, it is possible that the left hemisphere might be more at risk, perhaps due to higher energy demand. Observations in a larger number of cases would be needed to address this issue.

Morphologic and functional observations in patients with stroke-like episodes and GLUT1-DS are scant. Other case reports have primarily centered on clinical findings, in which the reported features were generally like those in our series: acute onset of hemiplegia, ataxia, speech disorders, and facial nerve deficit.²⁶⁻²⁸ The use of some functional techniques such as perfusion assessment by ASL matched with water diffusion imaging, MRA, and EEG data may add some insight into the pathophysiology of this rare and intriguing condition.

Limitations

One of the inherent drawbacks our study is that it consists of a limited case series of patients with clear-cut acute stroke-like symptoms, so it might not be representative of the general population of patients with GLUT1-DS. There may have been bias in selecting the subset of patients with GLUT1-DS who experienced stroke-like symptoms. Moreover, smaller possible variations among subjects in this cohort may have been obscured by the different time-frames in which acute evaluation and follow-up were conducted. While ASL-based perfusion imaging allows imaging without the need for contrast agents, setting the appropriate parameters such as postlabel delay can be challenging, depending

on the patient's age. Different parameters apply to neonates, children, and adults respectively.²⁹ Moreover, when using ASL, one must be aware of artifacts resulting from low cardiac output or vessel stenosis (which can cause arterial transit artifacts), the "ring of fire" caused by the labeling of CSF water protons, the shunt effect in arteriovenous malformations, and motion artifacts.³⁰ Therefore, we recommend minimizing potential artifacts and hazards when using this perfusion approach, selecting the appropriate postlabel delay for the respective age group, and performing MRA to evaluate arterial tortuosity.

CONCLUSIONS

Drawing from our data and supported by a thorough review of the literature, we propose that hypoperfusion in the cerebral hemisphere and reduction in the representation of distal branches of the MCA in association with crossed cerebellar diaschisis may be more common in this patient population than previously recognized. The parallels observed between patients with hemiplegic migraine and GLUT1-DS experiencing acute stroke-like events could imply some shared pathophysiology. Further cohort studies are needed to extend our observations.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Safety and Technical Performance of Bilateral Decubitus CT Myelography Using Standard versus Increased Intrathecal Iodinated Contrast Volume

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ABSTRACT

BACKGROUND AND PURPOSE: Lateral decubitus CT myelography (LDCTM) is one of the main studies for the detection of CSF-venous fistulas, but detection of CSF-venous fistulas is dependent on intrathecal contrast attenuation. The purpose of this investigation was to assess the tolerability and technical performance of increased intrathecal doses of myelographic contrast compared with standard doses.

MATERIALS AND METHODS: This is a retrospective series of 24 patients who underwent LDCTM following administration of either 10 or 20 mL of intrathecal iodinated contrast media (300 or 320 mg/mL of iodine content). Patients were scanned in the initial lateral decubitus position and then turned to the contralateral side and re-scanned in the same session. The safety and tolerability of the 20 mL dose was assessed from clinical records. The technical performance of the studies was compared between groups (10 or 20 mL) by measuring attenuation values over the lateral thecal sac at standardized levels. Both the initial scan and the scan after turning the patient to the contralateral side were assessed.

RESULTS: No moderate or severe adverse event was recorded in either group. The 20-mL group showed higher attenuation values, which were statistically greater on the second side examined compared with the standard-dose group.

CONCLUSIONS: Increased volume of intrathecal contrast was well-tolerated and improved the technical performance of LDCTM in this limited series. Further assessment of the safety and impact on diagnostic yield using larger patient cohorts is warranted.

ABBREVIATIONS: CVF = CSF-venous fistula; IOCM = iodinated contrast media; LDCTM = lateral decubitus CT myelography

CSF-venous fistulas (CVFs) result from abnormal connections between the spinal subarachnoid space and neighboring paraspinal veins, leading to the onset of spontaneous intracranial hypotension.¹ Lateral decubitus CT myelography (LDCTM) and lateral decubitus digital subtraction myelography are the primary methods for identifying CVFs.¹ Both examinations rely on decubitus positioning to promote dense layering of iodinated contrast media (IOCM) over the lateral aspect of the thecal sac to enhance visualization of CVFs.^{2,3} When a fistula is not identified on the first side examined, the contralateral side needs to be investigated. Because of the need for digital subtraction and thus an initial

masking image without contrast on each side, bilateral lateral decubitus digital subtraction myelography is necessarily performed on 2 separate days.^{3,4} With LDCTM, because there is no masking/subtraction constraint, evaluating both sides in the same session is feasible.^{1,5–7} However, contrast media tends to dilute within the thecal sac the more patients change their position, potentially decreasing the sensitivity of the evaluation on the second side. Thus, some centers opt to also perform bilateral LDCTM on 2 separate days, requiring a repeat lumbar puncture.^{4,7}

Although package inserts and much of the medical literature on the intrathecal use of IOCM advises a limit of 3.0–3.2 g of iodine/day (ie, 10 mL of IOCM containing 300 or 320 mg/mL of iodine),⁸ recent literature suggests that higher doses could be safe.^{6,8,9} The authors have thus started performing LDCTM using such higher doses of contrast and hypothesized that this use might be safe and may promote higher contrast density over the dependent portion of the thecal sac during LDCTM performed for suspected CVF. The purpose of this investigation was to review preliminary safety and tolerability data from those cases and to assess the impact on contrast density in LDCTM cases in which both lateral decubitus positions were assessed after a single intrathecal contrast injection.

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SUMMARY

PREVIOUS LITERATURE: LDCTM is one of the main imaging modalities for the detection of CSF-venous fistulas, but studying both sides of the spine in the same session has limitations. Using an increased dose of contrast media to overcome these limitations has not been extensively studied previously, with 1 small case series describing a 2-injection technique.

KEY FINDINGS: There were no relevant adverse reactions to 20 mL of iodinated contrast media in this series. Increased contrast dosage was associated with higher attenuation values within the subarachnoid space, especially on the second side examined during a single-session bilateral LDCTM.

KNOWLEDGE ADVANCEMENT: LDCTM with a single bolus of 20 mL of IOCM appears safe and effective for the bilateral evaluation of the spine in patients with suspected CSF-venous fistulas.

MATERIALS AND METHODS

This is a retrospective case-control series of patients undergoing LDCTM examinations between April 2023 to February 2024, which were performed by the same team of radiologists on the same CT scanner (Somatom Definition AS; Siemens). A checklist from the Strengthening the reporting of observational studies in epidemiology (STROBE) was used to guide the methodology of this study.

Inclusion criteria were the following: 1) LDCTM performed with a single bolus injection of either 10 or 20 mL of iodinated contrast media; 2) bilateral LDCTM during the same examination; 3) study performed for a suspicion of CVF; and 4) study performed with elevation of the head and hips to concentrate the contrast bolus in the thoracic spine. All consecutive patients meeting these criteria were enrolled, and no patients were excluded. Only the first examination meeting these criteria for each patient was considered. The control group was defined as subjects who received the standard 10 mL of intrathecal iodinated contrast media; and the study group, as those who received 20 mL of contrast.

Intrathecal Contrast Dose Selection

Our standard protocol before June 2023 involved the administration of 10 mL of intrathecal contrast (either 300 mg/mL [total dose of 3 g of iodine] or 320 mg/mL [total dose of 3.2 g of iodine]). From June 2023 onward, we have progressively changed our protocol and standardized the use of 20 mL of intrathecal contrast, consistently using the isosmolar agent Iodixanol 320 (320 mg/mL [total dose of 3.2 g of iodine]), which, in some of the authors' anecdotal experience, might be associated with fewer neurologic adverse effects than other agents with higher osmolality.

Myelography Technique

Patients are positioned in the lateral decubitus position on the CT table (usually on the right side, except if the operator had a particular suspicion for the left side, eg, more diverticula, doubtful finding on a previous conventional CTM, and so forth), with the head, trunk, and hips at the same height. The lumbar thecal sac is then accessed under CT fluoroscopic guidance with a 25G pencil-point Whitacre needle (Becton, Dickinson and Company). After measuring the CSF opening pressure and before the injection of contrast, the patient's head is elevated with pillows to prevent the contrast from flowing into the head, which can potentially induce headache and decrease the density of intrathecal contrast in

the spine. Either 10 or 20 mL of iodinated contrast media is then injected. The patient is monitored for adverse effects that might cause the operator to stop the contrast injection. Mild pain, subjective heaviness, or burning sensation during injection are expected adverse effects of the contrast medium and would usually not prompt discontinuation of injection. The needle is withdrawn, and the patient's hips are elevated with a foam wedge, creating a gravity-dependent concavity on the midthoracic spine. A scan is obtained with the patient in the first decubitus position. Subsequently, the wedge is removed, and the patient is carefully rolled over on his or her back into the contralateral decubitus position. The hips are again elevated using a wedge, and a second scan with the patient in the contralateral decubitus position is acquired. Occasionally >1 scan is performed in each decubitus position with differing degrees of hip elevation to adjust the cranial or caudal movement of the contrast bolus. The time between scans usually varies from 2 to 6 minutes and does not seem to be an important factor under this protocol in our experience. All examinations are performed with the patient under local anesthesia without sedation.

Evaluation of Safety and Tolerability

All procedural notes were reviewed for immediate relevant adverse events (moderate or severe as per the Society of Interventional Radiology Adverse Event Classification¹⁰), including but not limited to severe or prolonged headache, seizure, loss of consciousness, or need for hospitalization. Charts were also reviewed to identify hospital admission or emergency department visits during the following 4 weeks after the procedure. If present, telephone follow-up notes were also reviewed.

Technical Performance Evaluation

For each myelogram, quantitative analysis of the intrathecal contrast density was performed. Analysis was separately conducted on both decubitus scans for each patient. If >1 scan was obtained in a single decubitus position, the scan with the most complete coverage of the thoracic spine was used. Four standardized levels were assessed to represent the contrast density and spread throughout the thoracic spine: C7, T3, T9, and T12. Levels C7 and T12 were considered peripheral levels, to represent how often the entire thoracic spine was well-opacified, while T3 and T9 were considered central levels, to represent the quality of the remaining concentrated contrast bolus.

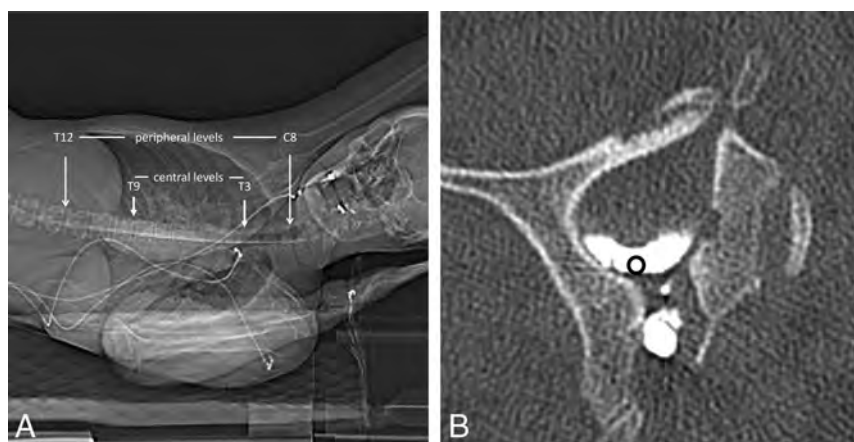


FIG 1. Technique for measurement of attenuation in the lateral thecal sac. A, CT scout image indicating the levels assessed on each scan. B, Axial CT image shows representative placement of an ROI immediately caudal to the dural emergence of the nerve root.

General characteristics of the population under study

	Age	Sex	Opening Pressure	Contrast Volume	Contrast Type	Iodine Dose	First Decubitus	CVF	Bern Score
1	41	F	13	20	Iodixanol 320	6.4	Left	L T8	4
2	59	F	5	20	Iodixanol 320	6.4	Right	L T8	7
3	64	F	11	20	Iodixanol 320	6.4	Right	R T2	8
4	20	M	25	20	Iodixanol 320	6.4	Right	None	4
5	34	M	18	20	Iodixanol 320	6.4	Right	None	0
6	52	F	16	20	Iodixanol 320	6.4	Right	None	0
7	42	F	—	20	Iodixanol 320	6.4	Right	None	0
8	40	F	18	20	Iodixanol 320	6.4	Left	None	0
9	15	M	14	20	Iodixanol 320	6.4	Right	None	2
10	64	F	—	20	Iodixanol 320	6.4	Left	R T9	6
11	63	M	8	20	Iodixanol 320	6.4	Right	None	0
12	31	M	27	20	Iodixanol 320	6.4	Right	None	0
13	41	F	11	20	Iodixanol 320	6.4	Left	None	0
14	51	M	7	20	Iodixanol 320	6.4	Right	R T7	6
15	51	F	10	20	Iodixanol 320	6.4	Right	R T10	4
16	68	M	1	20	Iodixanol 320	6.4	Right	None	0
17	70	M	7	20	Iodixanol 320	6.4	Right	R T6	7
18	46	F	11	20	Iodixanol 320	6.4	Right	R T11	6
19	65	F	28	10	Iohexol 300	3.0	Right	None	1
20	44	F	10	10	Iohexol 300	3.0	Left	None	2
21	40	F	12	10	Iodixanol 320	3.2	Left	R T7	9
22	30	M	16	10	Iohexol 300	3.0	Right	R C8	9
23	29	F	15	10	Iohexol 300	3.0	Right	None	0
24	61	M	13	10	Iodixanol 320	3.2	Right	None	0

Note:—R indicates right; L, left; en dash, information not available or not measured; M, male; F, female.

On each sampled level, a 0.05-cm² ROI was placed immediately caudal to the dural emergence of the corresponding nerve root, within the most lateral dependent part of the thecal sac, measuring the mean attenuation in Hounsfield units (Fig 1).

Three average attenuation values were then calculated for each side: total thoracic attenuation average (from all 4 sampled levels), central thoracic attenuation average (from T3 and T9), and peripheral thoracic attenuation average (from C7 and T12).

We also assessed the number of levels that exhibited adequate opacification of the lateral margin of >1500 HU within a 0.05-cm² ROI positioned immediately medial to the corresponding exiting nerve root sleeve.

Because of the small sample size, we did not compare the diagnostic yield for CVFs between groups, because the study

would likely not have been powered adequately to make this assessment. However, when CVFs were detected, the side and vertebral level of the CVF were recorded.

Statistical Analysis

We compared each average attenuation value (total, central, and peripheral) for each side (first side and second side) between the control group and the 20-mL group using a Student *t* test. The side of the first scan of each patient (decubitus position in which the contrast had been injected) was considered the first side, and the side after rolling the patient over was considered the second side, regardless of it being the right or the left side. *P* values < .05 were considered statistically significant.

RESULTS

Twenty-four examinations performed between April 2023 and February 2024 met the inclusion criteria. Of these, 6 examinations were performed using 10 mL of intrathecal contrast, and 18 examinations were performed with 20 mL. The Table summarizes the patient population.

Safety and Tolerability

No moderate or severe adverse effects were identified in either group following intrathecal contrast administration. There were no cases of hospital admission or emergency department visits related to the adverse events from the CTM immediately after the procedure or in the following 3 months (there were 8 new admissions for transvenous embolization and 4 visits for blood patches). Telephone follow-up informa-

tion was available for all patients in the 20-mL study group and for most of the control group (4/6), with contact time varying between 24 hours and 5 days after the examination. Two patients in the 20-mL group reported mild erythematous skin reactions in the trunk region, with mild itching approximately 8 and 12 hours after the procedure, both of which were considered delayed mild allergic reactions treated with antihistamines and resolved after 24 and 48 hours, respectively. No other adverse effects were reported. Mild symptoms without the need for medication, either during or immediately after the CTM, such as short-lasting headache or nausea, are considered normal and not routinely entered in the patient's notes, so they could have been present in either group and could not be compared.

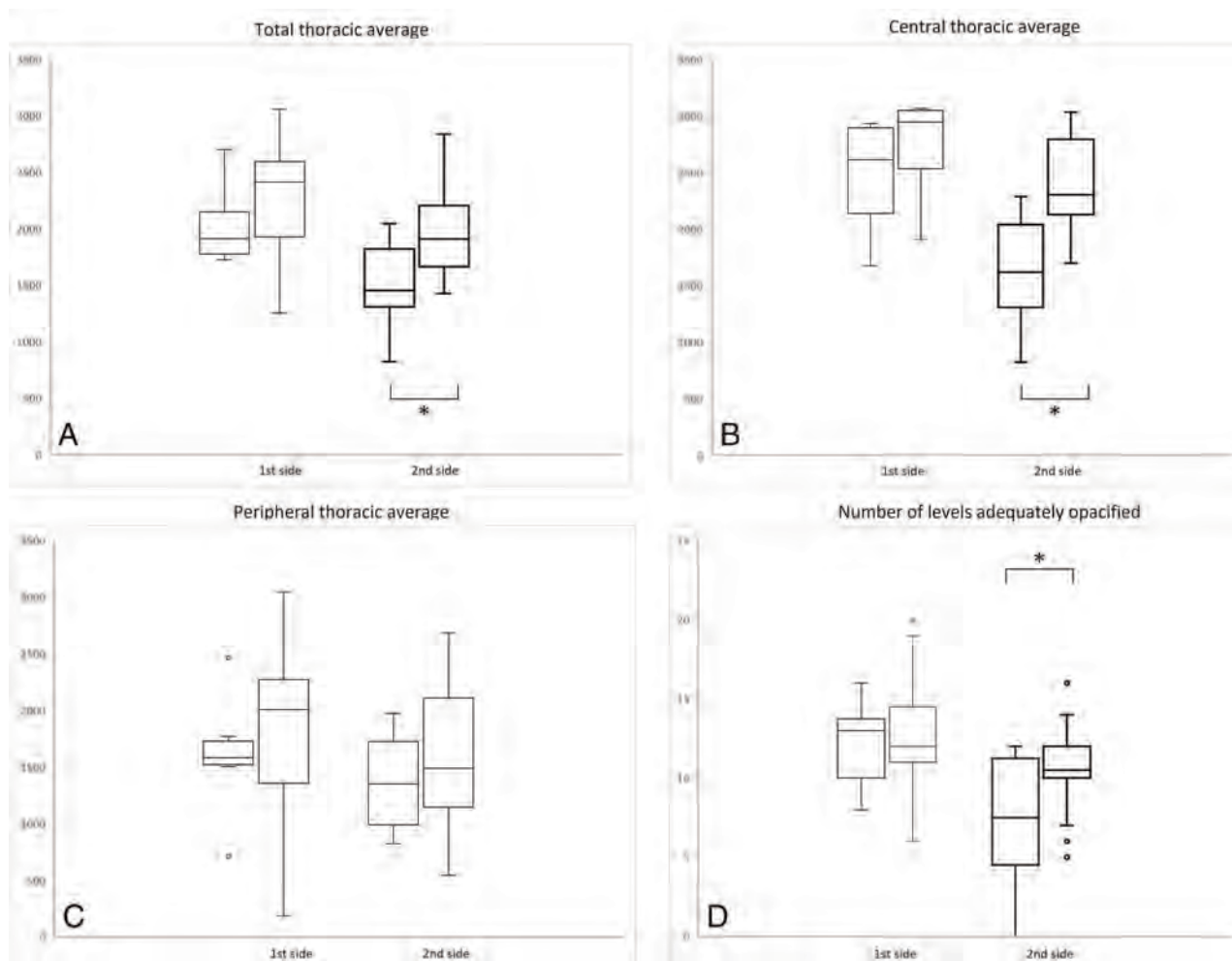


FIG 2. Box-and-whisker plots summarizing the technical performance of the 10-mL control and 20-mL study groups. The distribution of average attenuation within the lateral-most part of the thecal sac on the total (A), central (B), and peripheral (C) portions of the thoracic spine is shown. The number of levels adequately opacified by contrast (D) is also shown. Boxplots highlighted using bold lines, Asterisks in A, B, and D indicate groups showing statistically significant differences.

Technical Performance

Differences in intrathecal attenuation in the thoracic spine and in the number of adequately opacified vertebral levels between the control and study groups are shown in Fig 2. The total thoracic attenuation average on the first side examined was 2034 HU in the control group and 2272 HU in the 20-mL group ($P = .31$). The second contralateral side measurements for these values were 1497 HU and 2007 HU, respectively ($P = .02$).

The central thoracic attenuation average (T3 and T9) followed the same pattern, with a smaller non-statistically significant difference on the first side examined (2468 versus 2747 HU; $P = .18$) and a larger statistically significant difference on the second side examined (1623 versus 2426 HU; $P = .001$).

The peripheral thoracic attenuation average (C8 and T12) did not show a statistically significant difference between groups, but in both cases, the average attenuation was higher in the 20-mL group (1604 HU versus 1797 HU [$P = .6$] on the first side, and 1371 HU versus 1589 [$P = .45$] on the second side). Again, the same trend was noticeable, with a greater difference in attenuation on the second side examined.

For reference, the Online Supplemental Data illustrate the difference in the quality of the opacification relative to the

measured attenuation on the lateral part of the thecal sac on different levels.

The average number of vertebral levels with adequate opacification of the dural sac on the first side examined was 12.2 in the control group and 13.1 in the 20-mL group ($P = .51$). This difference was more pronounced and statistically significant on the second side examined, with 7.2 well-opacified levels in the control group versus 10.7 in the 20-mL group ($P = .04$).

A total of 10 CVFs were identified in 10 different patients (2 in the control group and 8 in the 20-mL group). Three of these (1 in the control group and 2 in the 20-mL group) were identified on the second side of the examination (Fig 3).

DISCUSSION

Our investigation found that higher volumes of intrathecal IOCM (up to 6.4 g of iodine) were safe and well-tolerated, consistent with previous investigations.^{5,7,8} Additionally, we found that the higher 20-mL contrast dose improved contrast density and the number of levels well-opacified on the second decubitus scan obtained after turning the patient following the initial decubitus scan. Although not statistically significant in this small

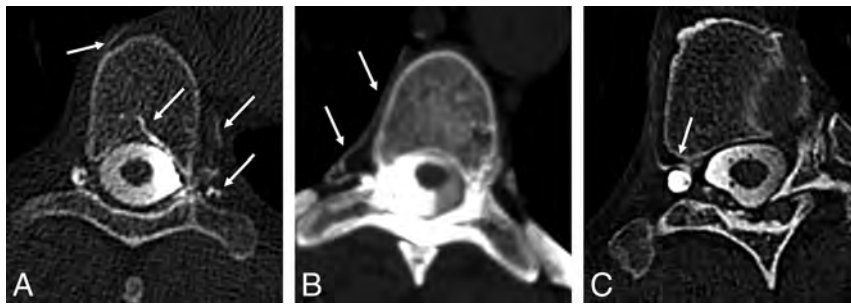


FIG 3. Cases in which a CVF was found on the second side examined. A, Axial CT image shows a left T8 CVF in a patient who had received 20 mL of contrast. B, Axial CT MIP image shows a right T7 CVF in a patient who had received 10 mL of contrast. C, Axial CT image shows a right T9 CVF in a patient who had received 20 mL of contrast. Arrows in all images point to opacified draining veins from the CVFs.

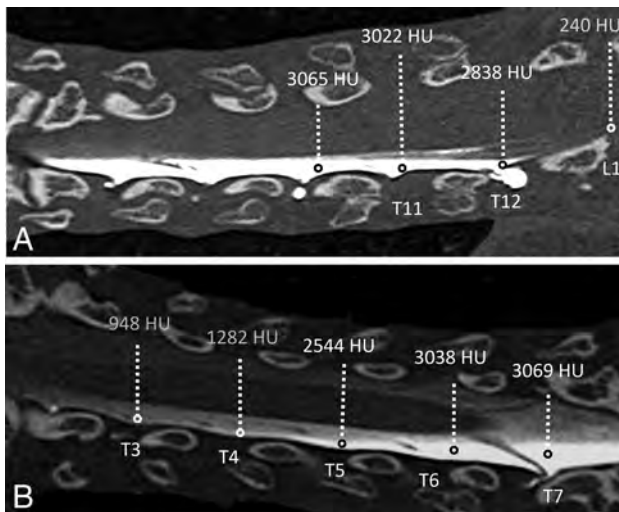


FIG 4. Coronal CT reformats showing the cranial and caudal margins of an IOCM bolus on the first side examined (A) and on the second side examined (B) of a patient who had received 20 mL of IOCM. Notice that a peripheral level may have very poor opacification even if a large and dense bolus of contrast is still present adjacently.

sample size, trends toward higher attenuation values and the number of levels adequately opacified on the initial decubitus scan were also observed. These results suggest the need for larger studies capable of assessing rare complications and further evaluating the technical performance and effect on the diagnostic yield in patients with suspected CVF.

In our study, all intrathecal contrast attenuation averages were higher in the 20-mL dose group than in the control group, with larger and statistically significant differences on the second decubitus scan. This difference was more pronounced with the central thoracic average, in which the absolute difference averaged 802 HU higher in the 20-mL group, a 50% increase in attenuation. This difference reflects the gravitationally dependent settling of IOCM when the patient is positioned in the lateral decubitus position with the head and hips elevated with respect to the midthorax.²

Of note, none of the patients who had received 20 mL of IOCM had a central thoracic average of <1500 HU on the second side examined, while one-half of the patients in the control group did. This effect could potentially limit the degree to which the

contrast pool can be repositioned to other levels of interest by adjusting the height of the head or hips if such repositioning was needed.

Lower attenuation values could theoretically impair the ability to detect CVFs. Previous literature shows that an increased attenuation, such as that achieved by lateral decubitus myelography, enables the identification of previously unnoticed fistulas.^{2,3} Specifically, Kranz et al² described a gain in diagnostic confidence of CVF by performing the CT myelography acquisition with the patient in the lateral decubitus

position, which provided a mean increase in intrathecal attenuation of 1215 HU.

The peripheral thoracic attenuation average was higher in the 20-mL group compared with the control group, but the difference was not statistically significant. Although our study may have been underpowered for the inference of these smaller differences, we hypothesize that the number of levels covered by contrast (and thus the average attenuation on peripheral levels) is less influenced by the contrast dose and more by the patient's position, particularly the degree of lateral concavity formed by the spine (Online Supplemental Data). A high degree of concavity formed by elevating the patient's hips and head may result in a sharp drop of contrast attenuation outside of the region of dependent contrast layering (Fig 4). While this possibility may occasionally restrict the evaluation of the entire spine in a single acquisition, subsequent manipulation of the hips and head seems to be effective in ensuring a complete assessment. While the initial coverage of IOCM was somewhat unpredictable, shifting the contrast column both cranially and caudally proved highly effective, particularly in the 20-mL group in which the central bolus consistently maintained a strong concentration (Fig 5).

One previous article reported that among 48 CVF diagnoses, only one of those came from contralateral decubitus repositioning without a dedicated injection (2% of their diagnoses),¹¹ while, in our population, 33% of cases had such an outcome, a difference that may be explained by our positioning scheme as well as by our increased contrast dose. In addition, we have achieved a 100% diagnostic yield for CVF detection in the high-suspicion subgroup according to brain MR findings, here defined as a Bern score ≥ 5 , which is a yield similar to or higher than that of previous articles using either decubitus digital subtraction myelography or decubitus CT myelography in patients with high Bern scores or positive findings on brain MR when the Bern score was not directly assessed, which all fall in the range of 67%–100%.^{12–16} Notably, most of these articles relied on dedicated injections on each side. This information could suggest that contralateral repositioning with an increased dose might be equivalent to a dedicated contralateral injection. In fact, in our data, contrast concentration on the second side examined in a 20-mL dose was similar to that of the first side examined with the usual 10-mL dose.

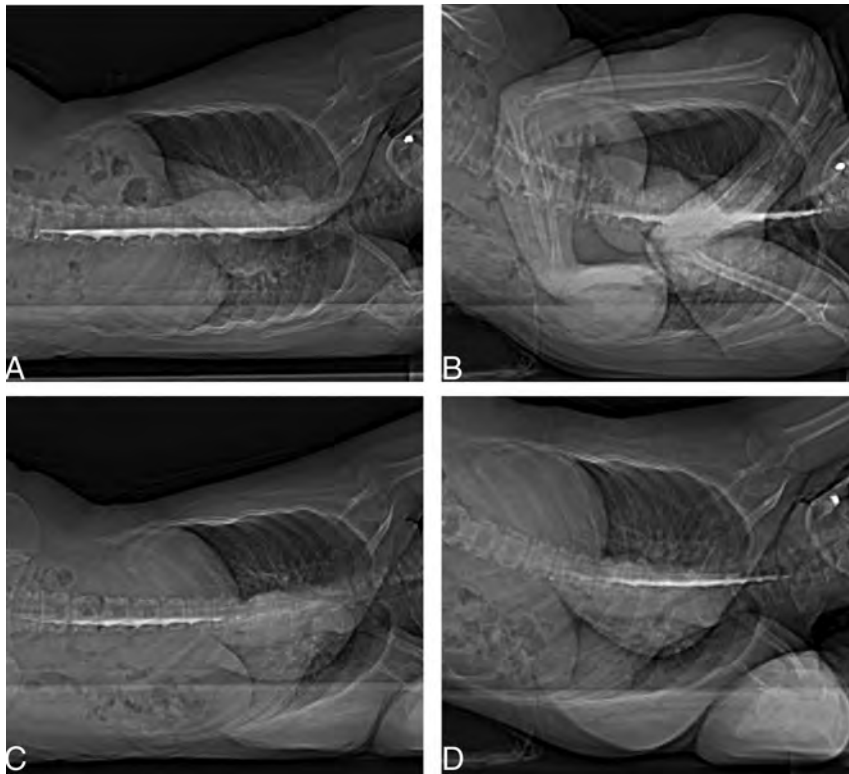


FIG 5. Anterior-posterior scout images of a patient who had received 20 mL of IOCM, demonstrating that the residual contrast bolus stays dense, even after the patient is repositioned a few times. Patient positioning is shown as follows: right decubitus, hips neutral (A); right decubitus, hips elevated (B); left decubitus, hips neutral (C); and left decubitus, hips elevated (D).

Our study has several limitations. It was retrospective in nature and not randomized, thus subject to confounding. Some possible confounding factors such as patients' sizes (height and weight) were not considered. Another possible confounding factor was the fact that the 20-mL dose group exclusively received Iodixanol as contrast agent, while the control group mostly used iohexol. However, there is little reason to believe that different IOCMs should differ considerably except for their density/concentration, and concentration of the IOCM used is directly related to the total iodine dose, which was our subject of investigation.

The sample size was small and likely underpowered for some of the associations we tried to evaluate. The small sample size also precluded the evaluation of diagnostic yield. Further studies investigating the diagnostic yield of higher contrast volumes directly or assessing the effect of attenuation values on CVF detection rates would be useful. This particular scan protocol is obtained with a static pool of contrast at the time of scanning and differs from other "dynamic" CTM protocols in which contrast is moving during scanning.^{7,17} The effect of increased contrast volumes on such dynamic CT myelography protocols may differ. Finally, the small study size limits the ability to detect uncommon safety events.

CONCLUSIONS

The increased volume of intrathecal contrast was well-tolerated and improved the technical performance of LDCTM in this

limited series. Further assessment of the safety and impact on diagnostic yield using larger patient cohorts is warranted.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Azygos Vein Stenosis in Frontotemporal Dementia Sagging Brain Syndrome

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ABSTRACT

BACKGROUND AND PURPOSE: Symptoms indistinguishable from behavioral-variant frontotemporal dementia (bvFTD) can develop in patients with spontaneous intracranial hypotension associated with severe brain sagging. An underlying spinal CSF leak can be identified in only a minority of these patients and the success rate of nondirected treatments, such as epidural blood patching and dural reduction surgery, is low. The disability associated with bvFTD sagging brain syndrome is high and, because of the importance of the venous system in the pathophysiology of CSF leaks in general, we have investigated the systemic venous circulation in those patients with recalcitrant symptoms.

MATERIALS AND METHODS: We reviewed the medical records and imaging studies of 21 consecutive patients with bvFTD sagging brain syndrome in whom no spinal CSF leak could be found and who underwent imaging of the systemic venous circulation (MR- or CT-venography). An SIH Disability Assessment Score (SIHDAS) questionnaire was completed to assess the severity of the symptoms.

RESULTS: The mean age of the 3 women and 18 men was 50 years (range, 26–68 years). Seven patients were found to have venous stenosis. Endovascular stent placement of moderate to high-grade azygos vein stenosis in 3 patients resulted in prompt and remarkable improvement of symptoms in 2 patients (SIHDAS: very severe disability to no or mild disability) and mild improvement in 1 patient (SIHDAS: very severe disability to severe disability). Treatment of internal jugular vein and inferior vena cava stenosis in 2 patients each did not result in any improvement of symptoms. Endovascular (5 patients) or surgical (2 patients) interruption of multiple epidural spinal venous pathways did not result in any clinical improvement.

CONCLUSIONS: The azygos vein is the main conduit between the spinal CSF space and the systemic venous circulation and this study demonstrates that isolated azygos vein stenosis may be a cause of spinal CSF loss and sagging brain syndrome. In this study, the yield of finding a clinically important treatable venous lesion among patients with recalcitrant bvFTD sagging brain syndrome was relatively low (15%). However, high quality and safe noninvasive imaging of the systemic venous system is available, eg, MR-venography, and should be considered for those patients who have exhausted treatments for this devastating condition, focusing on the azygos system.

ABBREVIATIONS: AP = antero-posterior; bvFTD = behavioral-variant frontotemporal dementia; DSM = digital subtraction myelography; IJV = internal jugular vein; IVC = inferior vena cava; SIH = spontaneous intracranial hypotension; SIHDAS = SIH Disability Assessment Score

Patients with spontaneous intracranial hypotension (SIH) typically present with orthostatic headaches, but a wide variety of

other neurologic manifestations have been reported.¹ When SIH is accompanied by severe brain sagging, a depressed level of arousal can lead to coma, distortion of the brainstem, and cranial nerves can cause hemifacial spasm or trigeminal neuralgia, and distortion and compression of the brainstem and cerebellum and sagging of the frontal and temporal lobes can be associated with symptoms indistinguishable from behavioral-variant frontotemporal dementia (bvFTD) usually along with daytime hypersomnolence after the headaches have abated.^{1–8} The symptoms of bvFTD consist of progressive changes in comportment, social cognition, personality, and intellect.^{9,10} It is a devastating condition for both patients and their families. Unlike other patients

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SUMMARY

PREVIOUS LITERATURE: Patients with sagging brain syndrome display symptoms indistinguishable from behavioral variant frontotemporal dementia. It is a devastating condition for both patients and their families. An underlying spinal CSF leak is found in less than one-half of these patients.

KEY FINDINGS: In this study of 21 patients with sagging brain syndrome and no detectable spinal CSF leak we investigated the systemic venous circulation and found significant azygos vein stenosis in 3 patients. Stent placement of the azygos vein stenosis resulted in prompt and dramatic resolution of symptoms in 2 of these patients.

KNOWLEDGE ADVANCEMENT: Azygos vein stenosis may be a reversible cause of excessive spinal CSF loss in patients with sagging brain syndrome, representing a novel mechanism of disease.

with SIH and an abnormal brain MRI where the source of spinal CSF loss, ie, a spinal CSF leak, can be identified in most patients,^{1,11} a CSF leak can be identified in only approximately 40% of patients with bvFTD sagging brain syndrome.⁷ The success rate of nontargeted treatments in these patients is only approximately 25% and we have been aggressively pursuing other potential sources of spinal CSF loss and their treatment in those with recalcitrant symptoms.⁷ Recent studies have suggested an important role for the systemic or craniocervical venous circulation in SIH and we now report our experience with the investigations into the venous circulation in patients with recalcitrant bvFTD sagging brain syndrome and their treatment.

MATERIALS AND METHODS

Since January 2001, all patients with SIH evaluated by us in person at Cedars-Sinai Medical Center in Los Angeles, California, have been enrolled prospectively in a registry. Patients evaluated remotely with the use of telehealth were not included. Using this registry, we reviewed the medical records and radiographic studies of a group of consecutive patients with SIH and persistent symptoms of bvFTD who underwent dedicated imaging of the venous system after treatments for bvFTD sagging brain syndrome had been exhausted. The diagnosis of SIH was based on the criteria of the International Classification of Headache Disorders, third edition, with minor modifications.¹² These criteria require objective evidence of SIH, consisting of brain MRI showing stigmata of SIH (ie, pachymeningeal enhancement, brain sagging, or subdural fluid collections), spinal imaging showing a CSF leak (ie, the presence of extradural CSF or a CSF-venous fistula), or low CSF opening pressure (ie, <6.0 cm H₂O). The modification consists of also including patients who do not have headaches but whose symptoms are best explained by SIH.

The clinical diagnosis of bvFTD was based on the clinical criteria of the International Behavioral Variant FTD Criteria Consortium.¹³ These criteria require progressive deterioration of behavior and/or cognition and consist of the presence of at least 3 of the following symptoms: 1) behavioral disinhibition; 2) apathy or inertia; 3) loss of sympathy or empathy; 4) perseverative, stereotyped, or compulsive/ritualistic behavior; 5) hyperorality and dietary changes; and 6) neuropsychological profile of executive/generation deficits with relative sparing of memory and visuospatial functions.

All patients (or their family/caregivers) completed a modified Migraine Disability Assessment Score questionnaire to assess the severity of the symptoms, before and after last treatment.¹⁴ This questionnaire measures disability in 3 domains of activity (employment, household work, and nonwork activities), capturing the number of days affected over a 3-month period, with the score ranging from 0–270 (3[domains] × 3[months] × 30[days]). The modification consists of substituting “symptoms of SIH” for “headaches.” We refer to this modified questionnaire as the SIHDAS (SIH Disability Assessment Score) questionnaire. A score of 0–5 (grade I) is considered to equate to little or no disability, a score of 6–10 (grade II) is mild disability, a score of 11–20 (grade III) is moderate disability, a score of 21–40 (grade IV-A) is severe disability, and a score of more than 40 (grade IV-B) is very severe disability. The SIHDAS scale has been used previously in populations of patients with bvFTD sagging brain syndrome.^{4,7}

The imaging protocol consisted of brain MRI and MR-myelography (heavily T2-weighted spine MRI¹⁵) for all patients. Patients underwent digital subtraction myelography (DSM) in the lateral decubitus position to search for a spinal CSF leak. The DSM technique as described by Hoxworth et al¹⁶ was used with some minor modifications.¹⁷

Noninvasive imaging of the systemic venous system was performed with CT-venography or ferumoxylol (Feraheme, Covis Pharmaceuticals) venography. CT-venogram studies were performed on a dual-energy scanner with kVp: 100–120, mA: 50–500, Pitch: <1 on inspiration. Contrast used was Omnipaque 350 (GE Healthcare), 100 mL with scanning performed at 60 and 90 seconds after injection. Injection rates were 2–3 mL/s. Images were acquired at 0.625-mm thickness. Patients underwent ferumoxylol-enhanced MR venography on a 3T Vida MRI scanner (Magnetom, Siemens Healthineers) with phased array imaging coils. The participants were positioned supine in the magnet with the arms lying alongside the body. Ferumoxylol was diluted in saline and infused slowly over at least 8 minutes via an MRI compatible infusion pump to a maximum dose of 4 mg/kg. Steady-state high-spatial-resolution 3D MR venographic acquisitions were obtained during breath-holding. The process was repeated for 3 overlapping 3D volumetric slabs at different table positions, to ensure full anatomic coverage. The multistation images were subsequently combined into a single composite set to display the entire vascular anatomy of the neck, chest, abdomen, and pelvis

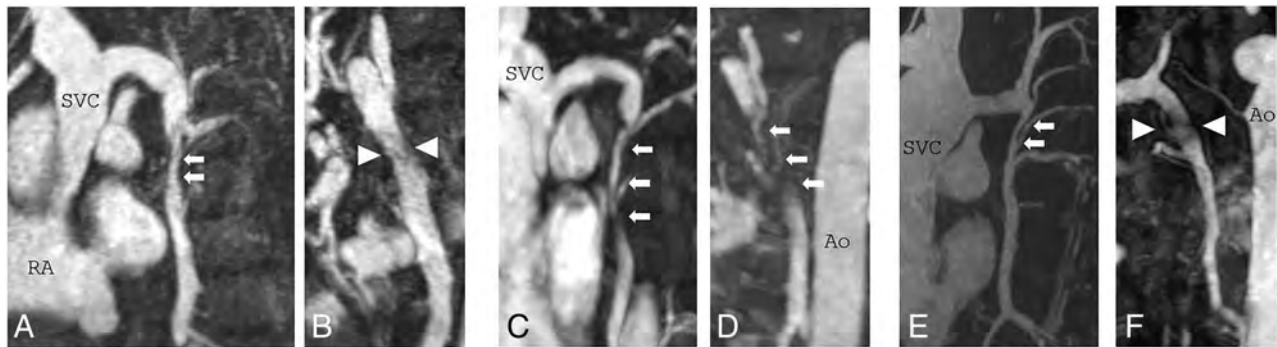


FIG 1. MR-venograms of isolated azygos vein stenosis. MRV Feraheme 2D MIP (lateral [A] and AP [B] views) of patient 1 show azygos vein stenosis (arrows). Note the decreased signal intensity due to stenosis on AP view (B, arrowheads). MRV Feraheme 2D MIP (lateral [C] and AP [D] views) of patient 2 show long segment azygos vein stenosis (arrows). MRV Feraheme 2D MIP (lateral [E] and AP [F] views) show azygos vein stenosis (arrows). Note decreased signal intensity due to stenosis on AP view (F, arrowheads). Ao = descending aorta; RA = right atrium; SVC = superior vena cava.

for easy viewing. Acquisition parameters included a TR of 2.61 ms and TE of 0.96 ms, with isotropic 0.9 mm resolution. Average scan duration was 45 minutes, and all participants were observed for a minimum of 30 minutes after termination of ferumoxytol infusion.

Imaging studies were reviewed and interpreted by 1 of 2 vascular radiologists (R.S. and H.G.L.) and 1 interventional neuroradiologist (M.M.M.). Venous luminal narrowing from 0%–50% was considered mild stenosis, 50%–70% was considered moderate stenosis, and more than 70% was considered severe stenosis.

RESULTS

The venous system was investigated in 21 patients with bvFTD sagging brain syndrome in whom no source of spinal CSF loss could be identified. The anatomic area covered with the angiographic studies included the neck, chest, abdomen, and pelvis in 18 patients and the head and neck only in 3 patients. The mean age of the 3 women and 18 men was 50 years (range, 26–68 years). All patients scored grade IV-B on the SIHDAS scale (very severe disability).

Prior treatments included epidural blood patching in 20 patients, lumbar laminectomy for dural reduction surgery in 16 patients, percutaneous fibrin glue injections targeting meningeal diverticula or calcified disc herniations in 9 patients, surgical approaches targeting calcified disc herniations in 8 patients, surgical approaches targeting meningeal diverticula in 7 patients, implantation of a wearable epidural infusion system in 4 patients, and a middle fossa craniotomy for partial resection of the tentorium cerebelli to reduce incarcerated brain sagging in 2 patients. These treatments resulted in temporary improvement of symptoms only.

The presence of venous stenosis was suggested by noninvasive imaging studies in 9 patients. The venous stenosis was confirmed with conventional angiography in 7 patients and in 2 patients the degree of stenosis had been overestimated on the noninvasive venogram. Moderate to severe stenosis involving the azygos vein was demonstrated in 3 patients (Fig 1), and mild to moderate stenosis of the inferior vena cava (IVC) or the internal jugular vein (IJV) in 2 patients each. Three patients underwent stent placement of the azygos vein, 2 patients underwent stent placement of

the IVC, 1 patient underwent stent placement of the IJV and resection of the styloid process, and 1 patient underwent resection of the styloid process only.

Azygos Vein Stent Placement

Two of the 3 patients who underwent stent placement of the azygos vein stenosis showed remarkable improvement of symptoms, starting 2 and 10 days after stent placement, respectively. One patient reported mild improvement of symptoms.

All 3 patients received preprocedure loading doses of 325 mg aspirin and 600 mg Plavix. After stent placement patients were placed on dual antiplatelets for 12 months with a daily dose of 325 mg aspirin and 75 mg Plavix.

CLINICAL CASE REPORTS

Patient 1 was a 57-year-old man who had suffered from orthostatic headaches for a few years while in his 30s and presented with a 15-year history of slowly progressive memory loss, tremors of his head and extremities, daytime hypersomnolence, bowel and bladder incontinence, gait difficulties as well as symptoms of bvFTD, namely behavioral disinhibition, apathy, perseverative behavior, and hyperphagia. At age 54 he had undergone decompression of what was thought to be a Chiari malformation. On examination, the patient was sluggish, did not speak unless spoken to, and was unable to provide a coherent account of his own history. He kept his eyes closed when seated in the chair and interacting, exhibited facial grimacing, breath-holding spells lasting at least 5 seconds, repetitive movements characterized by leaning forward at the waist with his hands in front of him, as though he was going to touch the floor, and repetitive tapping of the right foot. He did not have a cerebellar dysarthria but his speech was slow and deliberate. There was intermittent truncal and head titubation when seated. Gait was slowed and deliberate, with forward flexion at the hip and posturing of the left hand even with natural gait. The Montreal Cognitive Assessment score¹⁸ was 21 of 30. The cerebellar cognitive affective/Schmahmann syndrome scale raw score¹⁹ was 57 of 120 and 6 of 10 on the pass-fail component where a score of 3 or more is definite cerebellar cognitive affective syndrome. The SIHDAS scale score was 180 (grade IV-B, very severe disability).

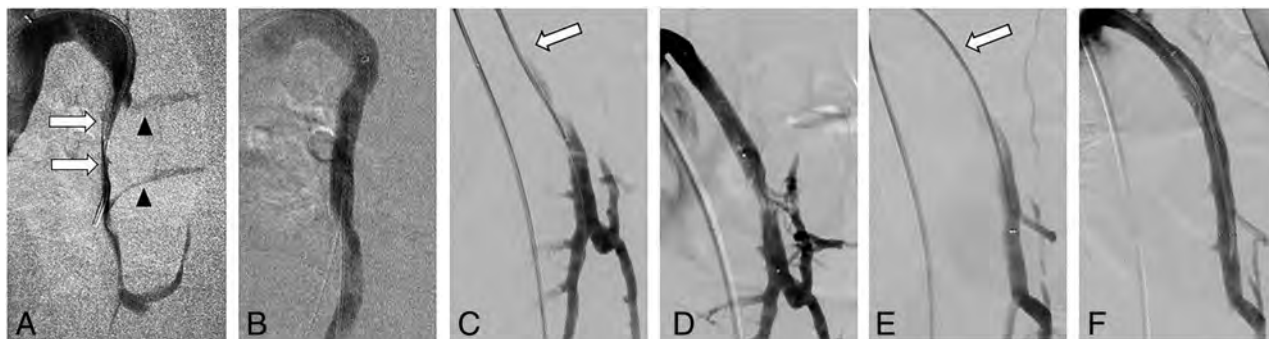


FIG 2. Venograms before and after stent placement of high-grade azygos vein stenosis. A and B, Azygos venogram of patient 1 (lateral views) shows severe stenosis (white arrows) completely relieved after stenting. Note reduced visualization of paraspinal veins (black arrows) in post stent view. C and D, Azygos venogram (AP view) of patient 2 depicts severe stenosis (arrow) with no residual stenosis after stenting. Note brisk filling of superior vena cava and right atrium (asterisk) after stenting. E and F, Azygos venogram (AP view) of patient 3 shows severe stenosis (arrow) with resolution of stenosis after stenting.

MRI showed severe brain sagging with bilateral temporal lobe herniation but no other stigmata of SIH. MR-myelography and DSM were normal. No meningeal diverticula were present. The CSF opening pressure was 20 cm CSF (normal range: 6–25 cm CSF). Post-DSM CT showed a thoracic calcified disc herniation. A thoracic laminectomy was performed but no dural defect could be identified. The ventral dura was then reinforced with an intradural dural substitute graft. The patient recovered well from surgery but there was no improvement in symptoms. Feraheme MRV suggested the presence of moderate to severe isolated azygos vein stenosis at the thoracic 5–6 level (Fig 1). Angiography showed the most stenotic segment measuring 3 mm; proximal to this, the vessel measured 14 mm and distally it measured 7 mm. A Protégé carotid stent 40 × 10 × 135 mm (Medtronic) was then deployed successfully without any residual stenosis (Fig 2). Visualization of paraspinal veins was significantly reduced after stent deployment.

On examination performed 33 days after stent placement, it was extraordinary to observe the patient's recovery to a state indistinguishable from normal. He was spontaneous in conversation, fully engaged in the interaction, asked questions of his own volition, and responded to the examiner's questions without hesitation. Voice and gait were normal. The breath-holding spells and repetitive movements had disappeared. Bowel and bladder incontinence had resolved. Neither the patient nor his family reported issues with memory, and both the patient and his family stated that his emotion was back, that he could cry and laugh appropriately, and that he was able to engage in all the activities he was previously unable to accomplish. Brain MRI showed improvement of brain sagging (Fig 3). Three months after stent placement the SIHDAS scale score was 3 (grade I, little to no disability). Four months after stent placement, partial recurrence of symptoms was noted but he has remained stable and much improved compared with before stent placement for a 19-month period of follow-up.

Patient 2 was a 33-year-old who man presented with a 6-year history of orthostatic headaches, slowly progressive memory loss, speech disturbance, daytime hypersomnolence, unsteady gait, as well as symptoms of bvFTD, namely behavioral disinhibition, apathy, perseverative behavior, and executive dysfunction. He had episodes where he would be unable to speak but could manage to

get his words out if bending over at the waist. He had undergone a craniotomy and subsequent cranioplasty for seizure surgery at age 19 that was complicated by a postoperative infection. On examination, his speech was slowed and slurred but he was able to answer simple questions. He exhibited repetitive movements at least twice a minute characterized by leaning forward at the waist with his hands touching the floor. Gait was lurching, swinging back and forth. The Montreal Cognitive Assessment score was 18 of 30. The SIHDAS scale score was 187 (grade IV-B, very severe disability).

MRI showed severe brain sagging with unilateral temporal lobe herniation but no other stigmata of SIH. MR-myelography and DSM were normal. No meningeal diverticula were present. The CSF opening pressure was 12 cm CSF. Feraheme MRV suggested the presence of severe isolated azygos vein stenosis (Fig 1). Azygos angiogram showed severe (80%) stenosis. A Protégé Everflex 8 × 60 mm stent was advanced and deployed successfully. Follow-up angiogram showed residual stenosis (50%) necessitating poststent angioplasty with a Sterling 8 mm balloon catheter (Boston Scientific) resulting in minimal residual stenosis (Fig 2). Brisk filling of the superior vena cava and right atrium was noted after stent deployment.

On examination performed 22 days after stent placement, the patient was fully engaged in the interaction, his speech was slowed but not slurred, and he was able to answer complex questions. His gait was mildly ataxic. The repetitive movements were much reduced to less than 1 per hour. Both the patient and his family stated that he was able to engage in all the activities he was previously unable to accomplish, including taking care of his children. Brain MRI showed improvement of brain sagging (Fig 3). On examination performed 42 days after stent placement, his gait was normal and the repetitive movements had abated completely. Three months after stent placement the SIHDAS scale score was 0 (grade I, little to no disability).

Patient 3 was a 63-year-old man who presented with an 8-year history of slowly progressive memory loss, daytime hypersomnolence, gait unsteadiness, left hand numbness, lower extremity paresthesias, urinary incontinence, and symptoms of bvFTD, namely behavioral disinhibition, apathy, perseverative behavior, and executive dysfunction. On examination, he exhibited frequent breath-holding spells and repetitive tapping of both

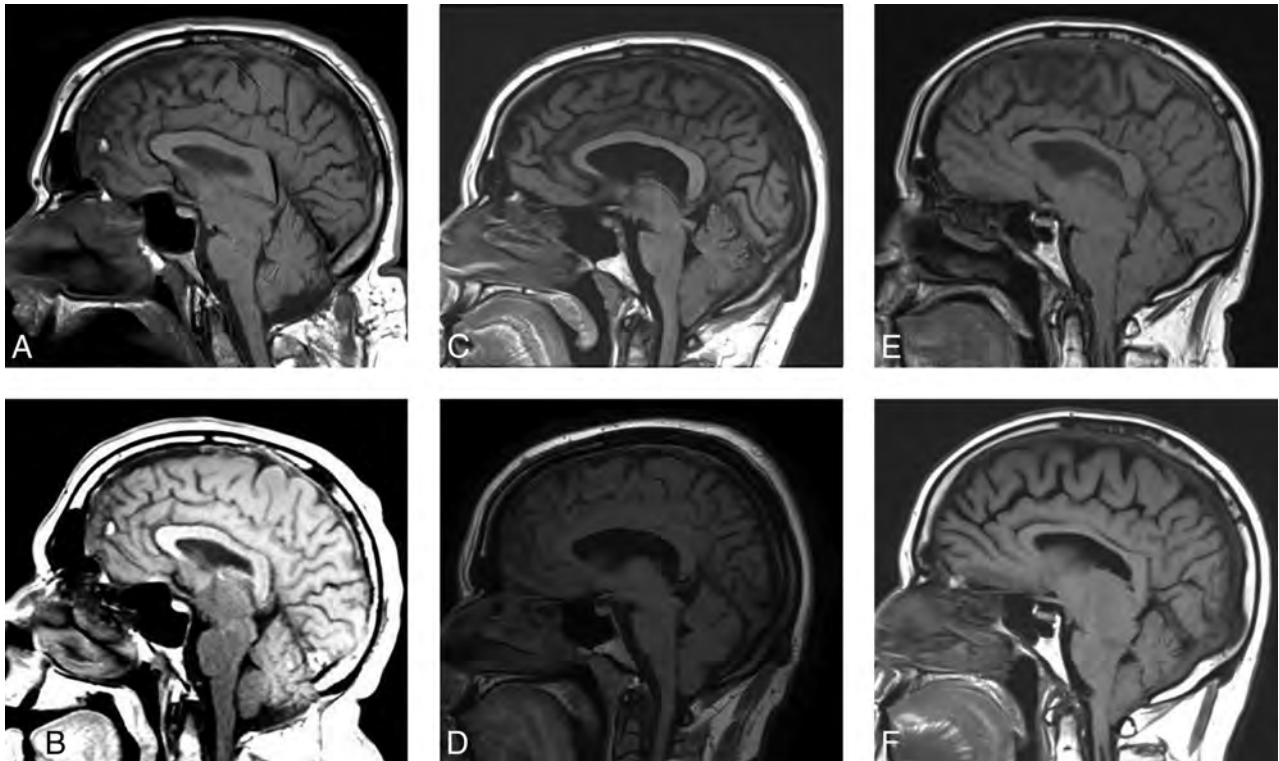


FIG 3. Brain MRIs before and after stent placement of high-grade azygos vein stenosis. Pre- (A, C, E) and post- (B, D, F) stenting sagittal T1-weighted MRIs showing mild improvement of brain sagging. Post-stenting MRIs were obtained 1 month (B), 3 weeks (D), and 24 hours (F) post-stent deployment.

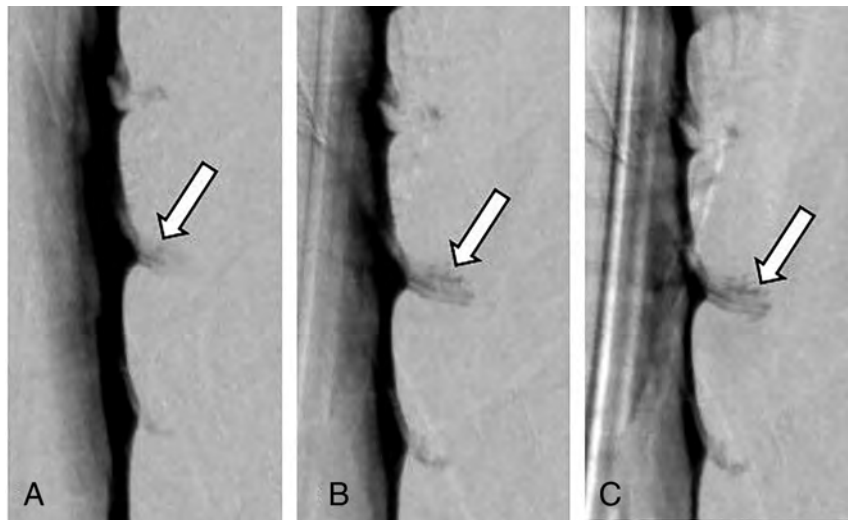


FIG 4. DSM showing possible thoracic CSF-venous fistula. Lateral decubitus DSMs showing a possible thoracic 1–2 CSF-venous fistula (A–C, arrows).

feet. His gait was unsteady. The Montreal Cognitive Assessment score was 23 of 30. The SIHDAS scale score was 70 (grade IV-B, very severe disability).

MRI showed severe brain sagging with bilateral temporal lobe herniation and cervical syringomyelia. No other stigmata of SIH were present. MR-myelography was normal. There was a 4-mm sacral meningeal diverticulum. Dynamic CT-myelograms and DSMs showed 2 possible small CSF-venous fistulas (Fig 4).

Opening pressure was 10–12 cm CSF. The fistulas were ligated surgically and there was transient improvement of left hand numbness. Dural reduction surgery did not result in any symptom improvement. Feraheme MRV suggested the presence of moderate to severe isolated azygos vein stenosis at the thoracic 5–6 level (Fig 1). Angiography confirmed the azygos vein stenosis. A Protégé GPS 10 × 60 mm stent was advanced and deployed successfully. Follow-up angiogram showed residual stenosis and an Epic Vascular 10 × 40 mm stent (Boston Scientific) was deployed resulting in minimal residual stenosis (Fig 2).

Lower extremity paresthesias improved within 24 hours of stent placement but there has been only modest improvement of other symptoms and the breath-holding spells have continued

but at a decreased frequency. MRI showed mild improvement of brain sagging and syringomyelia (Fig 3). Three months after stent placement the SIHDAS scale score was 30 (grade IV-A, severe disability).

IVC and IJV Stenosis Treatment

There was no appreciable improvement in symptom severity or brain sagging on MRI in the 4 patients who underwent treatment

of IVC or IJV stenosis. One of the patients who underwent stent placement of IVC stenosis died 49 days postprocedure from aspiration pneumonia related to severe dysphagia at age 36.

Procedures to Interrupt Venous Outflow

Procedures we utilized to, at least theoretically, reduce venous CSF absorption were performed in 7 patients. Multiple level thoracic or cervicothoracic nontargeted transvenous embolization of paraspinal veins with Onyx was performed in 5 patients and 2 patients underwent nontargeted multiple level lamino-foraminotomies for bipolar coagulation of the antero-lateral, foraminal, and dorsal epidural venous plexus. In addition, 1 patient underwent nontargeted multiple level transvenous embolization with Onyx and ventriculo-peritoneal shunt placement at another institution. There was no appreciable improvement in symptom severity or brain sagging on MRI in any of these patients. The patient who underwent multiple level nontargeted transvenous embolization with Onyx and ventriculo-peritoneal shunt placement died 109 days postprocedure from aspiration pneumonia related to severe dysphagia at age 36.

DISCUSSION

Over the years it has become increasingly apparent that the venous system plays an important role in the pathophysiology of SIH. Before the development of myelographic techniques in the 1950s with their ability to visualize spinal CSF leaks, either diminished production of CSF or increased absorption of CSF into the venous system was believed to be responsible for SIH. With the ability to visualize CSF leaks through dural tears, much of the interest in the pathophysiology of spinal leaks then focused on dural pathology. However, in 2010, Franzini et al²⁰ suggested that spontaneous spinal CSF leaks are maintained by IVC outflow to the heart and recommended performing epidural blood patching at the lumbar 1–2 level with the goal of reversing the CSF to venous gradient. Although this proposed mechanism of CSF leakage was speculative and has been called into question,²¹ it renewed interest in the spinal venous drainage system in SIH. In 2014, we reported the existence of an until then unknown type of CSF leak, the CSF-venous fistula.²² The discovery of these abnormal communications between the spinal subarachnoid space and the venous system was an important advance in the field of SIH and opened up an alternate pathway to treat CSF leaks, ie, via a transvenous route.²³ Since the report by Mokri et al²⁴ of SIH associated with Klippel-Trenaunay-Weber syndrome in 2014, an increasing number of patients with SIH and venous vascular malformations, proved or suspected to be associated with CSF-venous fistulas, have been reported.^{25–29} In 2015, Higgins et al³⁰ reported a 55-year-old man with sagging brain syndrome who was found to have bilateral high-grade stenoses of the internal jugular veins. Significant clinical and radiographic improvement was noted following angioplasty and stent placement of the internal jugular veins. In 2018, Kumar et al³¹ reported a 58-year-old man with bvFTD sagging brain syndrome who was found to have IVC obstruction causing bilateral lower extremity swelling and varicosities. A few days after IVC stent placement all symptoms resolved and brain MRI showed resolution of brain sagging. Several investigators have now observed

differences in visualization/detection of CSF venous fistulas based on the phase of the respiratory cycle. In 2020, Amrhein et al³² found increased conspicuity of CSF venous fistulas during the inspiratory cycle. In 2022, Mark et al³³ found that resisted inspiration can dramatically decrease superior vena cava venous pressure and concurrently increase CSF pressure, which has the effect of increasing the CSF-to-venous pressure gradient. They proposed that increasing this gradient will likely improve detection of a fistula. Although these studies did not include patients with bvFTD, they point to the crucial role of venous circulation in CSF venous fistula pathophysiology. Finally, we have observed a characteristic clinical sign, compulsive repetitive flexion with breath-holding in sagging brain syndrome, that is commonly seen in patients with bvFTD sagging brain syndrome and may be explained by clinical benefit derived from increasing venous pressure resulting in a decreased CSF-to-venous gradient.³⁴

The azygos vein is the main conduit between the spinal CSF space and the systemic venous circulation.^{35,36} Two of the 3 patients with bvFTD sagging brain syndrome and isolated azygos vein stenosis showed remarkable and prompt clinical improvement after successful endovascular stent placement of the area of stenosis and in 1 patient modest improvement was noted. Unlike patients with IVC stenosis in whom a significant stenosis would likely result in lower extremity symptoms, isolated azygos vein stenosis would not be expected to be associated with any systemic sequelae. However, similar to the patient with bvFTD sagging brain syndrome reported by Kumar et al,³¹ isolated azygos vein stenosis would cause abnormally low venous pressure between the stenotic azygos segment and the heart along with an increased pressure differential between spinal CSF space and the azygos vein resulting in excessive loss of CSF (Fig 5). The excessive loss of spinal CSF may have been through CSF-venous fistulas below the level of detection of current imaging techniques or, as a sump effect, through normal anatomic structures such as arachnoid granulations. Normalization of azygos vein pressure following stent placement would result in a lack of pressure gradient between CSF and venous spaces (Fig 5). The often-striking clinical improvement seen in our patients following azygos vein stent placement suggests that isolated azygos vein stenosis may accelerate spinal CSF loss and cause sagging brain syndrome.

In this study of patients with bvFTD sagging brain syndrome we also have shown the futility of our treatments directed at interrupting the spinal venous circulation either through a direct surgical or transvenous route and the futility of treatment of mild to moderate venous stenosis involving the IVC or IJV.

Disability is severe in patients with bvFTD sagging brain syndrome not only because of the devastating symptoms of bvFTD but also because of the symptoms caused by the severe sagging of the brain affecting the midbrain, brainstem, and cerebellum, including disequilibrium, dysphagia, and dysarthria. In the present study of 21 patients with bvFTD sagging brain syndrome, all patients had “very severe disability” on the SIHDAS score and 2 died at age 36 from aspiration pneumonia related to severe dysphagia. Because of this high level of morbidity and mortality we recommend considering noninvasive imaging of the systemic venous system in patients with recalcitrant bvFTD sagging brain syndrome, focusing on the azygos system, even though we

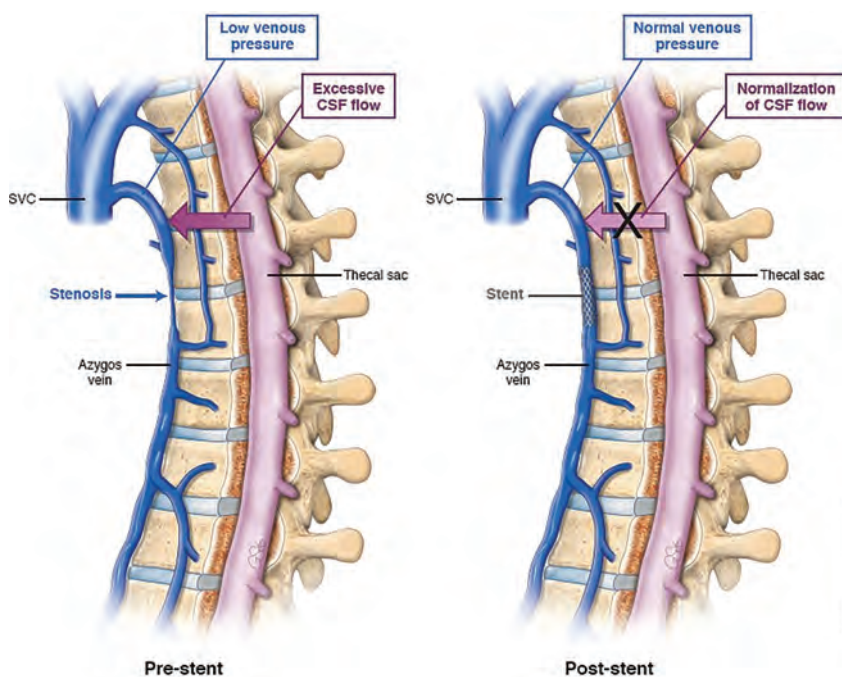


FIG 5. Illustration of proposed mechanism of stent placement of high-grade azygos vein stenosis. Illustration depicting the proposed mechanism of excessive spinal CSF loss in patients with azygos vein stenosis (after Kumar et al³¹). Low venous pressure between the area of azygos vein stenosis and the heart results in excessive CSF flow between the intrathecal CSF compartment and the venous system. This is corrected after azygos vein stent placement. Giovanna Santoni, CMI. Used by permission.

detected a clinically and radiographically significant stenosis in only 3 of the 21 patients.

It should be noted that the current study mostly represents a highly selected group of patients referred to a quaternary referral center for SIH and the generalizability of our findings is unknown. Another limitation is that the number of patients in our study is relatively small but bvFTD sagging brain syndrome is a rare disorder. Last, pretreatment neurocognitive evaluation was not standardized but patients were referred from a wide variety of medical centers.

CONCLUSIONS

Among patients with bvFTD sagging brain syndrome and no detectable spinal CSF leak, isolated azygos vein stenosis may be a cause of excessive spinal CSF loss and stent placement of the azygos vein stenosis may result in prompt and dramatic resolution of symptoms.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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β -Trace Protein as a Potential Biomarker for CSF-Venous Fistulas

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ABSTRACT

BACKGROUND AND PURPOSE: Accurately identifying patients with CSF-venous fistulas (CVF) causing spontaneous intracranial hypotension, is a diagnostic dilemma. This conundrum underscores the need for a CVF biomarker to help select who should undergo an invasive myelogram for further diagnostic work-up. β -trace protein (BTP) is the most abundant CNS-derived protein in the CSF and, therefore, is a potential venous biomarker for CVF detection. The purpose of our study was to measure venous BTP levels as a potential CVF biomarker.

MATERIALS AND METHODS: We prospectively enrolled 14 patients with CVFs and measured the BTP in venous blood samples from the paraspinal veins near the CVF and compared those levels with those in the peripheral blood. Myelograms used initially to identify the CVF were evaluated for technique, CVF laterality, CVF level, and the venous drainage pattern. Patient sex and age and symptom duration were also collected. Brain MR images were reviewed for Bern scores. We also measured the peripheral blood BTP levels in 20 healthy controls.

RESULTS: In patients with CVF, the mean BTP level near the CVF was 54.5% higher (0.760 [SD, 0.673] mg/L versus 0.492 [SD, 0.095] mg/L; $P = .069$) compared with peripheral blood. Nine (64.3%) patients with CVFs had a higher paraspinal BTP level than peripheral BTP level. The 20 control patients had a higher mean peripheral BTP level of 0.720 (SD, 0.191) mg/L compared with patients with CVF ($P < .001$).

CONCLUSIONS: We found that venous blood at the site of the CVF had higher BTP values compared with peripheral blood in most but not all patients with CVF. This finding may reflect the intermittent leaking nature of CVF. Additionally, we found that patients with CVF had a lower peripheral blood BTP level compared with healthy controls. BTP requires further evaluation as a potential CVF biomarker.

ABBREVIATIONS: BTP = β -trace protein; CTM = CT myelogram; CVF = CSF-venous fistula; DSM = digital subtraction myelography; SIH = spontaneous intracranial hypotension

Spontaneous intracranial hypotension (SIH) can present with debilitating-but-nonspecific symptoms such as headaches, dizziness, and behavioral changes overlapping with frontotemporal dementia.¹ While numerous brain MR imaging findings are associated with SIH,^{2,3} up to 20% of patients with SIH can have normal brain MR imaging findings.⁴ CSF-venous fistulas (CVFs),

abnormal connections between the spinal CSF and a paraspinal vein, are now recognized as a major cause of SIH. Unfortunately, CVFs are occult on conventional CT and MR imaging and require specialized myelography for detection.⁵⁻⁹

The absence of a reliable SIH biomarker presents 2 main diagnostic dilemmas. First, given the nonspecific symptoms and oftentimes subtle brain MR imaging findings, many patients with SIH are undiagnosed. Conversely, invasive myelography is performed in many patients who do not have a CVF or CSF leak found on the study. While myelography is a safe procedure, there is a risk of post-dural puncture headache¹⁰ and iatrogenic abnormal brain MR imaging findings.¹¹

The underlying pathophysiology of a CVF dictates that CSF, normally contained within the thecal sac or nerve sheath diverticulum, escapes across an abnormal connection into the paraspinal venous system. A potential CVF biomarker would need to have the ability to detect CSF in the venous blood. β -trace protein (BTP) is the second most common protein in the CSF after albumin and is the most abundant CNS-derived protein in the CSF.¹²

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SUMMARY

PREVIOUS LITERATURE: CVFs are occult on conventional CT and MRI and require an invasive myelogram for diagnosis. While clinical symptoms and brain MRI findings can suggest a spinal CSF leak, further development of objective data to help guide patient management is needed.

KEY FINDINGS: We found that most but not all patients with CVFs had higher BTP levels in the venous blood at the site of the CVF compared with peripheral blood. This finding may reflect the intermittent leaking nature of CVF. Additionally, we found that peripheral blood BTP levels were lower in patients with CVF compared with healthy controls.

KNOWLEDGE ADVANCEMENT: This study presents the use of BTP as a potential biomarker for CVF.

The purpose of this study was to measure venous BTP level as a potential biomarker for CVF.

MATERIALS AND METHODS

Following institutional review board approval, we prospectively enrolled (May to September, 2023) patients with CVF identified on myelography. All myelograms were obtained and read by a neuroradiologist in our spine intervention group who focuses on SIH. Each CVF was subsequently confirmed by an additional neuroradiologist who specializes in SIH (I.T.M.). Myelogram details were recorded including technique, CVF laterality, CVF level, and venous drainage pattern. The electronic health record was reviewed for the patient's sex and age and symptom duration. Pre-embolization brain MR imaging was reviewed for Bern scores.² All patients underwent transvenous catheter embolization for treatment of their CVFs (Fig 1).¹³ During the procedure, but before embolization, we attempted to obtain 2 venous blood samples (1–2 mL each) near the CVF. The first sample of venous blood was taken from a radicular vein at the level of the CVF. Given the complex paraspinal venous anatomy and CVF drainage, the azygos vein 1–2 vertebral bodies downstream from the CVF was sampled. Generally, venous blood was collected from a radicular vein first, followed by the azygos vein,

followed by the peripheral blood. The higher BTP value between the paraspinal vein and azygos vein samples was used as the CVF blood sample.

A sample of venous blood was collected from the groin access site as the peripheral blood sample. All venous samples were tested for levels of BTP using nephelometry.¹² Venous BTP gradients (BTP level of the blood near the CVF divided by the BTP level in the peripheral blood) were compared by CVF laterality (right versus left) and by level (upper cervicothoracic versus lower thoracic spine).

Peripheral venous blood samples were also tested for BTP in 20 healthy controls. In addition to BTP, age and sex were recorded for the control population. Descriptive statistics in addition to basic analysis (mean, median, SD) including *P* value cutoffs of .05 were used for analysis.

RESULTS

Fourteen patients with CVFs were enrolled and had venous blood tested for BTP. Eight (57%) were women. The mean age was 58 years (range, 40–71 years). Patient-specific data including CVF laterality and level, as well as individual Bern scores, are listed in the Table. The mean Bern score was 6 (range, 0–9; median, 8). The mean symptom duration was 29 months (range, 1–168

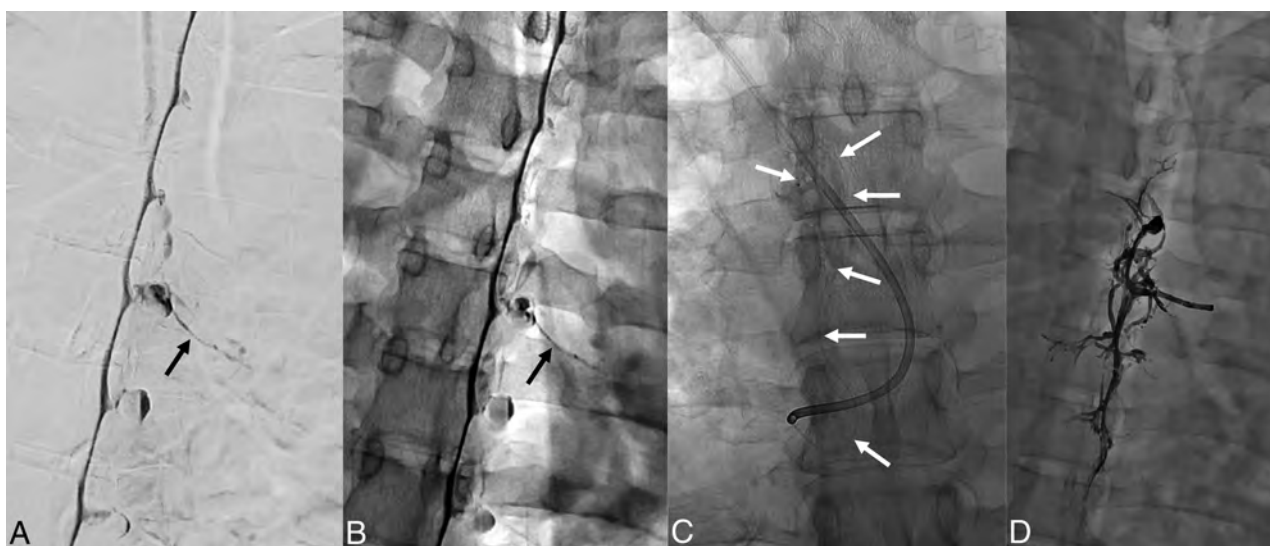


FIG 1. Patient with a right T5 CVF (black arrows) shown on DSM images (subtracted, A, and unsubtracted, B). Procedural image during transvenous embolization (C) shows a guiding catheter in the superior vena cava and azygos vein with a microcatheter (arrows) accessing the veins draining the CVF. Postembolization image (D) shows the hyperdense Onyx (Medtronic) cast.

Patient-specific data organized by ascending BTP gradients

CVF Side	CVF Level	Bern Score	Imaging Technique	CVF BTP (mg/L)	Peripheral BTP (mg/L)	BTP Gradient	Symptom Duration (mo)
L	T8	8	PCD-CTM	0.367	0.459	0.80	6
R	T6	0	DSM	0.571	0.631	0.90	4
L	T7	2	DSM/CB-CTM	0.496	0.544	0.91	24
L	T12	8	PCD-CTM	0.461	0.472	0.98	4
R	T4	4	PCD-CTM	0.397	0.397	1.00	60
R	T6	8	CB-CTM	0.534	0.503	1.06	21
R	T5	6	DSM	0.531	0.489	1.09	168
R	T7	6	EID-CTM	0.615	0.551	1.12	8
L	T9	1	PCD-CTM	0.476	0.414	1.15	36
L	C8	9	PCD-CTM	0.593	0.417	1.42	36
R	T7	9	PCD-CTM	0.480	0.291	1.65	1
R	T9	3	DSM	0.914	0.496	1.84	12
R	T8	8	DSM	1.240	0.627	1.98	8
L	T11	8	DSM/EID-CTM	2.960	0.595	4.97	12

Note:—CB indicates conebeam; PCD, photon-counting detector; EID, energy-integrating detector; L, left; R, right.

months). Excluding 1 patient who had 14 years of symptoms, the mean symptom duration was 18 months.

The mean CVF BTP level was 0.760 mg/L (SD, 0.673 mg/L), which was 54.5% higher than the mean peripheral BTP level of 0.492 mg/L (SD, 0.095 mg/L) but not a statistically significant difference ($P = .069$). Nine (64.3%) patients had a higher CVF than peripheral BTP level. We were unable to collect paraspinal venous blood in 3 patients secondary to slow flow. Azygos blood was collected in all patients. In the 11 patients with venous samples from both radicular and azygos veins, the azygos vein had a higher BTP level in 6 patients (54.5%). This likely reflects the normal complexity of the paraspinal venous drainage system. One patient with a negative BTP gradient (peripheral BTP > CVF BTP) had complex CVF drainage, including to a lateral muscular branch that was not sampled in addition to drainage to the radicular veins and azygos system. The CVF drainage patterns were predominantly the external vertebral venous plexus in 10 patients (71.4%) and predominantly the internal vertebral venous plexus in 2 patients (14.3%). Two patients (14.3%) had mixed internal vertebral venous plexus and external vertebral venous plexus drainage, one of which also involved a lateral muscular venous branch. Our sample size was too limited to draw conclusions regarding the venous drainage patterns and venous BTP levels.

There was no significant difference in BTP gradients between CVFs that occurred at T6 and above and below T6 (mean, 1.63 versus 1.35 mg/L; $P = .64$) nor was there a difference between left- and right-sided CVF (mean, 1.71 versus 1.33 mg/L; $P = .60$). Patients with low-probability brain MR imaging findings (Bern score ≤ 2) had a lower mean BTP gradient compared with high probability brain MR imaging findings (Bern score ≥ 5), 0.99 and 1.67 mg/L, respectively, but this was not statistically significant ($P = .15$).

Of the 20 control patients, 9 (45%) were men. The mean age was 47.9 years (SD, 21.4 years). The mean serum BTP level was 0.720 mg/L (SD, 0.191 mg/L). The difference between the peripheral blood samples in the patients with CVF and the control patients was statistically significant ($P < .001$).

DISCUSSION

We measured venous BTP levels in patients with CVF and found that most but not all patients had higher BTP levels in veins near

the CVF compared with the peripheral blood. Additionally, we measured peripheral venous blood in patients with CVF and found that they had lower BTP levels compared with healthy controls. BTP is the most common CNS-derived protein in the CSF and was, therefore, assessed as a biomarker for the presence of CSF in venous blood. Our work evaluated the venous BTP level as a potential biomarker for CVF.

β -2 transferrin is the most common test used in the United States to confirm the presence of CSF in nasal or ear secretions in patients suspected of having a skull base CSF leak. There are several limitations that prohibit β -2 transferrin from serving as a blood test for CVF. First, available β -2 transferrin assays are not reliable in the presence of blood.¹⁴ Additionally, the commonly used test for β -2 transferrin cannot detect low concentrations and is not quantitative.¹⁵ BTP, in contrast, is measured with nephelometry, which can assess blood samples and quantify even low levels of the target analyte and has been previously used to evaluate fluid for CSF otorrhea and rhinorrhea.^{12,15} While BTP is primarily a CNS-derived protein, other organs including the heart, testes, and prostate have also been found to produce BTP.¹⁶ Therefore, low levels of BTP in the peripheral blood are expected in patients who do not have a CVF. BTP can be systemically elevated in other conditions, including end-stage renal disease,¹⁷ which none of our patients had.

The first purpose of our study was to evaluate venous BTP levels at multiple sites. We hypothesized that BTP, originating in the CSF, should be higher near the CVF compared with the peripheral blood, where it is less concentrated. Our study found that blood near CVF had a higher BTP concentration compared with peripheral blood in 64.3% of patients. The negative BTP gradient (higher BTP in peripheral blood) in the remaining patients could be due to slow or intermittent leakage of CSF. Our group has previously studied CVF temporal characteristics and found that CVFs are intermittently seen on digital subtraction myelography (DSM).¹⁸ Callen et al¹⁹ performed a similar study using CT myelogram (CTM) and also found that CVFs are intermittently seen. Therefore, the 35.7% of patients whose CVF BTP level was lower compared with peripheral blood could be due to lack of CSF leakage at the time of venous sampling. Resisted inspiration

simultaneously increases CSF pressure while decreasing venous pressure²⁰ and has been shown to help visualize CVF on myelography,²¹ but we did not provide patients with consistent breathing instructions during our study.

The second aim of our study was to determine if peripheral venous BTP levels in patients with CVFs are different compared with those in healthy controls. We anticipated that venous BTP, a CNS-derived protein, would be elevated in patients with CVF compared with healthy controls. We found that peripheral venous BTP levels had a statistically significant difference; however, patients with CVF had lower BTP levels compared with healthy controls. The reason is unknown. Recent work by Wolf et al^{22,23} has shown that patients with SIH have altered CSF flow at the level of C2–C3, with increased downward velocities. Our recent work²⁴ has also highlighted the downward craniocaudal CSF flow in spinal CSF leaks causing SIH as a possible differentiating factor from skull base CSF leaks. The altered CSF flow in SIH could conceivably pool BTP in the dependent lumbosacral spine. The CSF escaping through the CVF, most commonly in the thoracic spine, could have lower BTP levels than normal states.

Our study had limitations, most notable being the small sample size. Our study measured BTP in only 14 patients with CVF and should be expanded in future studies. We included 20 control patients; however, our mean BTP level of 0.720 (SD 0.19) mg/L was similar to that in previous studies that measured peripheral blood BTP: 0.69 (SD, 0.33) mg/L,²⁵ 0.59 (SD, 0.23) mg/L,²⁶ and 0.59 (SD, 0.11) mg/L.²⁷ Our study had additional limitations in that the healthy controls did not have MR imaging or myelography to assess findings of SIH or CVF; however, they did not have a medical history to suggest SIH. A final limitation of the study includes the complex venous anatomy of the paraspinal veins. We cannot be certain that the radicular vein used for sampling was the primary drainage pathway for the CVF; therefore, we accounted for this uncertainty by collecting blood from the azygos vein as well. Future directions to study would not only include a larger number of patients but also assess the clinical significance of BTP levels related to patient symptoms, myelogram findings, and patient outcomes.

CONCLUSIONS

Our study measured venous blood BTP levels as a potential CVF biomarker. We found that 64.3% of patients had higher venous BTP levels near the CVF relative to the peripheral blood. The intermittent leaking nature of a CVF may explain the lack of elevated BTP in blood near the CVF in one-third of patients. Additionally, we found that patients with CVFs had lower peripheral blood BTP levels compared with healthy controls. BTP requires further evaluation as a potential CVF biomarker.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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CSF-Venous Fistulas Arising Intraosseously within Bone Remodeled by Meningeal Diverticula

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ABSTRACT

SUMMARY: CSF-venous fistulas (CVFs) are a common and increasingly recognized type of spinal CSF leak. Most of these fistulas occur in the setting of spontaneous intracranial hypotension, though nonspontaneous cases have been described as well. In most instances, CVFs arise from the dome or neck of nerve root sleeve diverticula (also called meningeal diverticula). Venous drainage typically involves some combination of the internal epidural venous plexus and external vertebral venous plexus. Not uncommonly, venous drainage into the basivertebral venous plexus or other intraosseous veins can be seen. However, the drainage is usually a secondary finding related to normal communication between intraosseous and extraosseous veins. We have recently observed unique cases in which CVFs arise directly within the vertebral elements, resulting in primarily intraosseous drainage. It is possible that this phenomenon is secondary to prominent meningeal diverticula remodeling the adjacent vertebral elements. In this clinical report, we reviewed a multi-institutional series of CVFs exhibiting primary intraosseous drainage, with the goal of illustrating the imaging findings, treatment strategies, and outcomes of the patients. Nine cases were identified demonstrating this phenomenon. We show that intraosseous CVFs can arise in virtually any part of the vertebrae and describe how this feature affects treatment.

ABBREVIATIONS: CB = conebeam; CTM = CT myelography; CVF = CSF-venous fistula; DSM = digital subtraction myelography; EID = energy-integrating detector; PCD = photon-counting detector

CSF-venous fistulas (CVFs), initially described in 2014 by Schievink et al,¹ are a common and increasingly recognized type of spinal CSF leak. CVFs represent an important cause of spontaneous intracranial hypotension, a frequently debilitating syndrome that can be potentially cured or improved with targeted treatment.^{2,3} Although most CVFs develop spontaneously, posttraumatic etiologies have also been described.⁴

The diagnosis of CVFs has increased in the past several years, largely due to improvements in myelographic techniques that are tailored to localize them. Most important, performing myelography with the patient in the decubitus position increases the yield for CVF detection.⁵ This technique was initially applied to digital subtraction myelography (DSM), and it was subsequently shown

to be beneficial for CT myelography (CTM) as well.^{6,7} Most recently, the use of photon-counting detector (PCD) CT for decubitus myelography (PCD-CTM) has been described.⁸ PCD-CTM has technologic advantages over traditional energy-integrating detector (EID) CT and has the potential to further increase the yield for CVF detection by providing superior spatial resolution, improved temporal resolution for dynamic CTM techniques, and inherent spectral sensitivity.⁹⁻¹¹ Conebeam CTM (CB-CTM) is another technique that can be performed during DSM, conferring high spatial resolution and cross-sectional detail.¹² Despite these recent improvements, techniques for CVF detection remain imperfect. Further understanding of the anatomy and pathogenesis of CVFs may be helpful to improve their detection.

Most CVFs arise from either the dome or neck of spinal meningeal diverticula (nerve root sleeve diverticula). Venous drainage is usually into the internal epidural venous plexus or external vertebral venous plexus.¹³ In some cases, intraosseous venous drainage is also observed, but this is usually related to secondary flow from extraosseous veins.⁶ In this Clinical Report, we describe cases of CVFs that arose directly within the osseous vertebral elements, which we have anecdotally observed in patients with meningeal diverticula that remodeled the adjacent bone. We report the myelographic techniques used to localize these CVFs, describe

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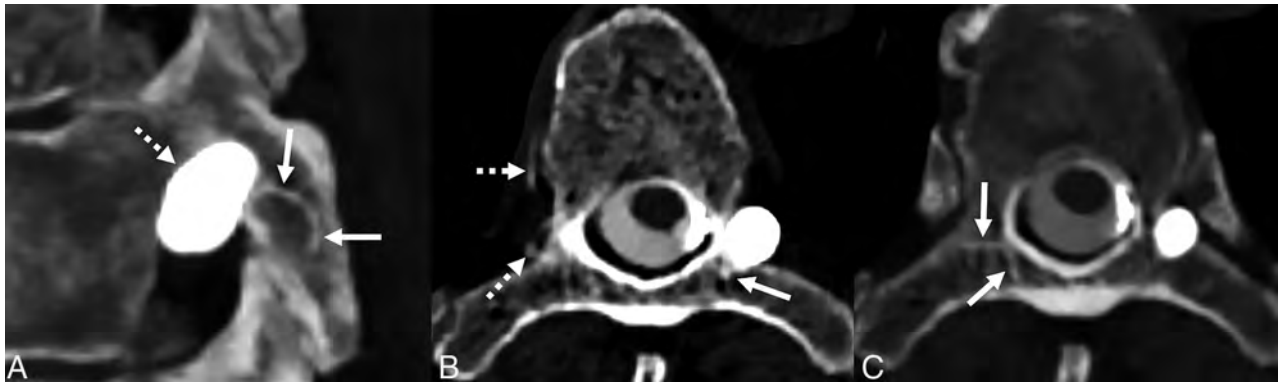


FIG 1. Sagittal (A) and axial (B and C) reconstructions from a PCD-CTM demonstrate a large left T7 meningeal diverticulum remodeling the lamina (A, *dashed arrow*). There is a CVF arising intraosseously in the left T7 lamina (A and B, *solid arrows*). The fistula crossed midline through the posterior elements (C, *arrows*), ultimately draining into the right-sided paraspinal segmental vein (B, *dashed arrows*).

imaging findings including the anatomic drainage of each CVF, and describe methods of treatment and outcomes of included patients.

CASE SERIES

Methods

This multi-institutional study was deemed exempt by our institutional review boards. We retrospectively reviewed decubitus myelograms (including DSM, CB-CTM, EID-CTM, and PCD-CTM) obtained in patients with suspected CVFs between 2019 and 2024 at 3 institutions. Imaging reports were used to identify cases demonstrating CVFs potentially originating in an intraosseous fashion, using search terms such as “intraosseous,” “CSF-venous fistula,” “pedicle,” “lamina,” and “vertebral body.” Images of cases potentially demonstrating intraosseous CVFs were reviewed independently by the neuroradiologist who performed the myelogram, as well as 1 additional neuroradiologist (the same neuroradiologist who served as the secondary reviewer for all cases). Reviewers identified cases with CVFs that arose within the osseous vertebral elements. We excluded any patients who did not have a CVF that originated intraosseously (for example, those that had secondary intraosseous contrast flow or no intraosseous involvement at all). For each patient, the neuroradiologist who performed the initial myelogram also reviewed clinical information, brain MRI findings, and spine MRI findings before myelography. Note that we did not specifically apply any radiographic scoring system to the brain MRIs, because brain MRI protocols varied among institutions. Therefore, subtle measurements on which such systems rely could not be consistently applied.

Specific techniques for specialized myelography typically used in patients with suspected CVFs, which include DSM, PCD-CTM, EID-CTM, and CB-CTM have been previously described.^{6,9,12} Briefly, a lumbar puncture is performed at L2–L3 or below. A high-density iodinated contrast agent such as Omnipaque 300 (GE Healthcare) is used, with injection volumes varying from 8 to 12 mL depending on the proceduralist’s preference. Images are obtained immediately during DSM, and within approximately 1–2 minutes of contrast injection for CTM. For CTM, one or more delayed scans were sometimes obtained to increase the yield for detection. Furthermore,

depending on the proceduralist’s preference and limitations in the total contrast dose, both right and left decubitus CTM may be performed on the same day or during 2 days. For CB-CTM, images are obtained after DSM. Before performing the CB-CTM, 3–4 mL of additional contrast (usually Omnipaque 300) is injected to maximize contrast density in the nerve root sleeve diverticula.

A standard STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist was used to assist in an appropriate design of this retrospective case series.

RESULTS

We initially identified 14 cases of CVFs with intraosseous drainage on the basis of review of radiology reports. After subsequent review of the images by the performing neuroradiologist and 1 additional neuroradiologist, 9 cases of CVFs originating in the bone were confirmed by both reviewers independently. The remaining 5 cases had CVFs originating in the internal or external vertebral venous plexus with subsequent intraosseous drainage, and these patients were excluded from the study.

The mean age of the included patients at the time of myelographic diagnosis was 72 years. Six of 9 patients were women. All patients presented with an orthostatic headache. One patient also had hearing loss and ataxia. All patients underwent brain MRI with IV contrast and spine MRI without contrast before myelography. Brain MRI showed some combination of dural enhancement, brain sagging, and/or venous distention in 6/9 patients. In 3/9 patients, brain MRI showed no findings of intracranial hypotension. One patient’s brain MRI demonstrated superficial siderosis. Spine MRI was negative for extradural CSF in all patients. There was no evidence of venous or lymphatic malformations involving the spine in any of the patients. These data are summarized in the Online Supplemental Data.

The 9 included CVFs were diagnosed on PCD-CTM ($n = 5$), EID-CTM ($n = 3$), or CB-CTM ($n = 1$). The myelograms were obtained by 1 of 3 neuroradiologists. One CB-CTM was performed in conjunction with a DSM, but the intraosseous origin of the fistula was identified only on CB-CTM and was not apparent on the DSM. CVFs were detected on decubitus myelography in 8/9 patients and on prone EID-CTM in 1/9 cases (Figs 1–6, Online Supplemental Data, 3). The patient studied with prone

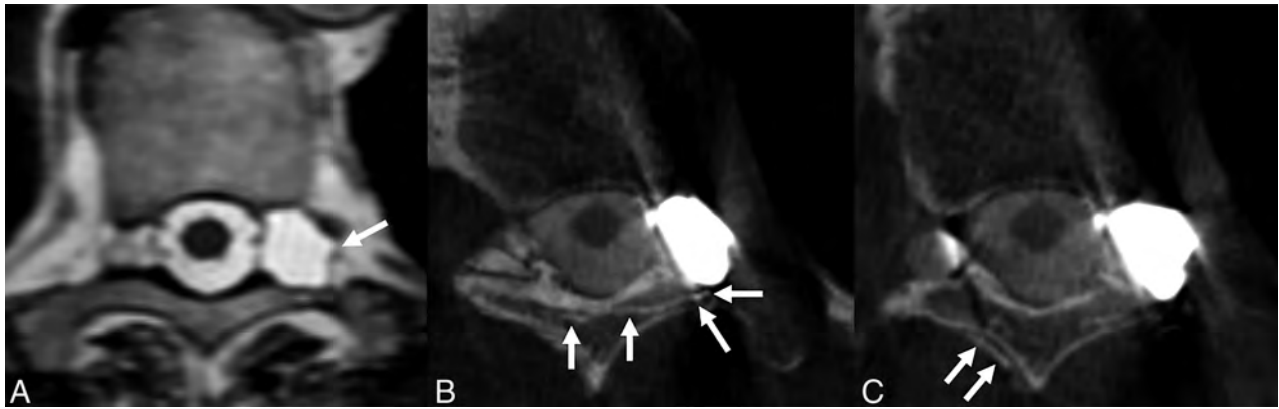


FIG 2. Axial high-resolution T2 Cube MR image (GE Healthcare) (A) demonstrates a prominent left T10 meningeal diverticulum causing remodeling of the left T10 lamina (A, arrow). A left decubitus DSM (not shown) shows subtle findings suspicious for a left T10 CVF. Cone beam CT (B and C) performed immediately after the DSM shows a CVF arising intraosseously within the left T10 lamina (B, solid arrows), ultimately crossing the midline through the lamina and exiting into right-sided posterior venous branches (C, arrows).

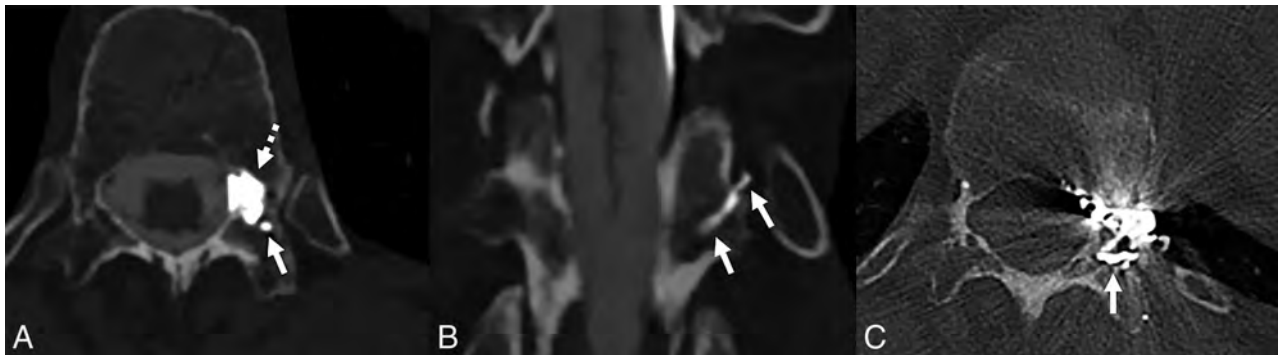


FIG 3. Axial (A) and coronal (B) images from a left decubitus PCD-CTM demonstrate a left T12 meningeal diverticulum remodeling the adjacent pedicle (A, dashed arrow). A CVF arises in an intraosseous fashion (A, solid arrow), with contrast flowing into the external vertebral venous plexus laterally (B, arrows). The patient underwent transvenous Onyx embolization of the fistula. Postembolization noncontrast CT demonstrates extension of Onyx into the intraosseous nidus of the fistula (C, arrow), confirming the desired radiographic result.

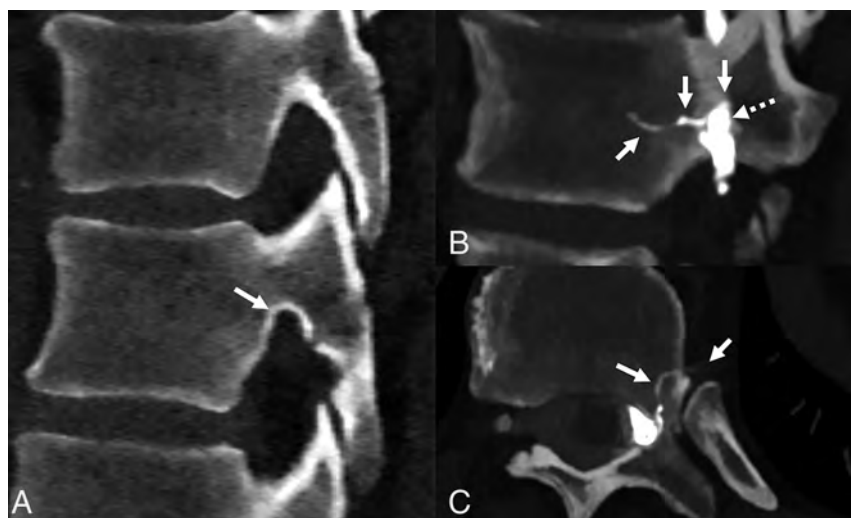


FIG 4. Sagittal image from a noncontrast CT (A) shows subtle remodeling of the inferior margin of the left T11 pedicle (A, arrow). Axial (B) and sagittal (C) MIP reconstructions from a left decubitus photon-counting CTM show a superiorly projecting left T11 meningeal diverticulum (B, dashed arrow). A CVF arises intraosseously from the superior margin of the diverticulum (B, arrows), ultimately draining into the paraspinal segmental vein (C, arrows).

EID-CTM had a ventral pseudomeningocele remodeling the vertebral body (Fig 6). The cause of the pseudomeningocele was not definitively known, but it was thought to be secondary to remote lumbar surgery for radicular symptoms. Of the 9 CVFs, 2/9 originated within the lamina (Figs 1 and 2); 4/9, in the pedicle (Figs 3 and 4, Online Supplemental Data); and 3/9, in the vertebral body (Figs 5 and 6, Online Supplemental Data). In each case, the portion of bone in which the CVF originated was being remodeled by a nerve root sleeve diverticulum ($n = 8$) or ventral pseudomeningocele ($n = 1$), and this finding was evident on both spine MRI and CTM in all patients. Specifically, in each case, there was smooth scalloping of the bone resulting in alteration of the normal expected contours. Seven of 9 CVFs occurred on

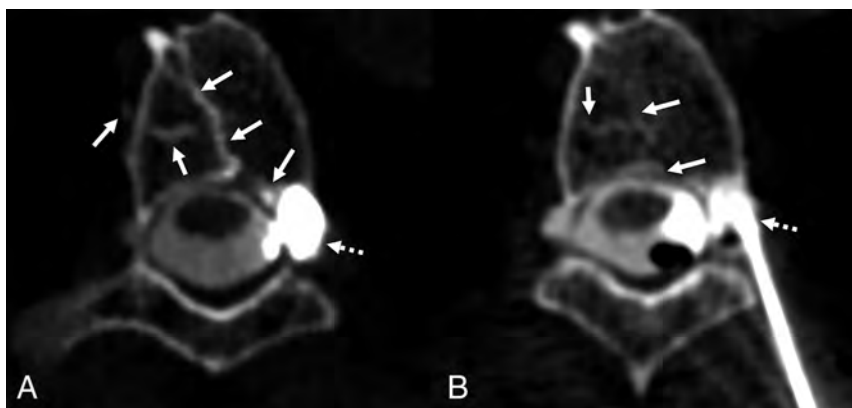


FIG 5. Axial image from a left decubitus CTM demonstrates a prominent left T4 meningeal diverticulum (A, *dashed arrow*), causing remodeling of the vertebral body. A CVF arises intraosseously within the posterior vertebral body and drains into the basivertebral venous plexus, eventually crossing the midline to the right paraspinal segmental vein (A, *arrows*). For treatment, the nerve root sleeve diverticulum was directly punctured (B, *dashed arrow*), and the fistula was occluded with fibrin glue (B, *solid arrows*).

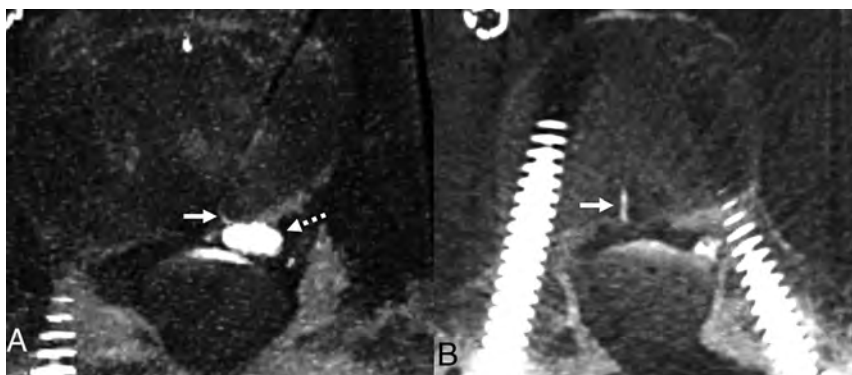


FIG 6. Axial images from a prone dynamic CTM demonstrate a ventral pseudomeningocele remodeling the posterior vertebral cortex (A, *dashed arrow*). This was thought to be secondary to remote spinal surgery for lumbar radicular symptoms. Adjacent axial images (A and B) demonstrate a CVF arising from the ventral portion of the pseudomeningocele (A, *arrow*) and draining into the basivertebral vein (B, *arrow*).

the left, 1 of 9 occurred on the right, and 1 of 9 occurred ventrally. In all cases, the fistula arose from the dome of the culprit diverticulum.

Patients were treated with transvenous Onyx embolization alone ($n = 6$), percutaneous fibrin glue injection alone ($n = 2$), or fibrin glue injection followed by Onyx embolization at a later date ($n = 1$).^{2,3,14} Clinical follow-up was available in 8/9 patients, with a mean time to follow-up of 2.9 months. Six of 8 patients reported complete symptom resolution, and 2 of 8 had partial improvement. The 2 patients with partial improvement had initially undergone fibrin glue injection. One of the 2 patients with partial improvement underwent repeat myelography, showing a persistent CVF, which was re-treated with Onyx embolization, ultimately resulting in resolved symptoms.

DISCUSSION

We have described a series of 9 patients with CVFs arising from meningeal diverticula (or a pseudomeningocele in 1 case) that remodeled the adjacent vertebral elements. In each case, the CVF

directly drained into intraosseous veins. To our knowledge, this particular variant of CVF has not previously been described in detail. Although it is relatively common for CVFs to exhibit secondary intraosseous venous drainage (Online Supplemental Data), the cases in the present series are unique insofar as the CVFs arose in an intraosseous fashion at a location of bony remodeling by meningeal diverticula. We found that decubitus myelography, including EID-CTM, PCD-CTM, and CB-CTM, was an effective means of detecting this unique variety of CVFs. Furthermore, both transvenous Onyx embolization and percutaneous fibrin glue injection provided effective treatment responses in most patients.^{2,14}

This series has important practical implications for the diagnosis and management of CVFs. First, we emphasize the need to search for opacifying veins within the vertebral elements, particularly in patients whose diverticula remodel adjacent bones. If this location is not scrutinized, subtle CVFs may be missed. High-resolution modalities such as PCD-CTM and CB-CTM may be particularly advantageous for the detection of intraosseous CVFs. Furthermore, because intraosseously-originating fistulas can cross the midline, it is important to accurately determine from which side the fistula arises so that the correct side can be treated (Figs 1 and 2). Second, although most CVFs are best detected using decubitus myelography, we did

encounter 1 intraosseous CVF that was only detected using prone dynamic CTM.⁶ In this case, the patient had a known ventral pseudomeningocele remodeling the vertebral body. Thus, one might consider deviating from standard decubitus positioning in patients with ventrally positioned diverticula or postoperative/posttraumatic pseudomeningoceles. Finally, when treating CVFs exhibiting primary intraosseous drainage, as with all CVFs, it is important to ensure that the nidus of the fistula is adequately treated.³ When percutaneous fibrin glue is used, it may be necessary to puncture the culprit diverticulum to occlude the nidus, as was done in 2 of our patients, or to inject fibrin glue intraosseously, as was done in one of our patients (Fig 6, Online Supplemental Data). When transvenous Onyx embolization is performed, posttreatment cross-sectional imaging may be helpful to ensure that the nidus is occluded (Fig 3).

These patients also provide interesting insight into the pathogenesis of CVFs whose exact cause is not yet known. It is possible that CVFs arise due to the existence of spinal arachnoid granulations, which are present in fetal development and can persist into

adulthood.¹³ It has also been suggested that minor dural trauma may potentiate CVF development in some cases.¹⁵ CVFs are also more common in patients with an elevated body mass index, a known risk factor for idiopathic intracranial hypertension, suggesting that some patients may develop CVFs as a compensatory mechanism to relieve the high CSF pressure state.¹⁶ One recent study showed that CVFs more commonly occur at levels with spinal degenerative changes.¹⁷ Regardless of the cause, CVF pathogenesis almost certainly requires diverticula to be in close proximity to spinal veins. Osseous remodeling by diverticula facilitates this process, representing a mechanistically important step in the formation of some CVFs. Most important, intraosseous CVFs can also be seen in the setting of venous or lymphatic malformations involving the bone, a very different pathology.^{18–20}

It is interesting that most of the CVFs in this series occurred on the left side. Prior studies have shown that CVFs usually have a right-sided predominance, which is generally thought to be related to the asymmetric anatomy of the azygous vein.¹⁰ Our findings could reflect a lesser degree of dependence on venous anatomy for intraosseous CVFs, though this is purely speculative. It was also notable that the mean age of the patients in our study was 72 years, which is older than the mean age of patients with CVFs in prior studies. The reason is unclear and could be related to the time required for diverticula to enlarge and remodel the vertebral elements. Regardless, it is particularly important to search for intraosseously-originating CVFs in older patients.

Our study has limitations. First, due to its retrospective and multi-institutional nature, we are unable to determine the prevalence of intraosseously originating fistulas. Nevertheless, this case series provides a framework for future study of this phenomenon. Second, our sample size was relatively small, limiting the generalizability of our conclusions. We were, however, able to identify examples of CVFs originating in all the major portions of the osseous vertebral elements, including the lamina, pedicle, and vertebral body, demonstrating the potential for intraosseous CVFs to occur ubiquitously. Future studies involving comprehensive image reviews of larger datasets may reveal additional cases of this phenomenon, better elucidating the unique characteristics of these CVFs.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Spontaneous Intracranial Hypotension Associated with Vascular Malformations

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ABSTRACT

SUMMARY: Spinal CSF leaks from dural tears or CSF-venous fistulas are the most common causes of spontaneous intracranial hypotension. Rarely, CSF leaks have also been associated with vascular malformations, which have primarily been discussed in case reports or small series. In this clinical report, we report the clinical features, imaging findings, and treatment of 6 children and adults with CSF leaks associated with vascular malformations in the spine and skull base depicted on CT myelography and cisternography.

ABBREVIATIONS: ISSVA = International Society for the Study of Vascular Anomalies; SIH = spontaneous intracranial hypotension

Spontaneous intracranial hypotension (SIH) is most commonly secondary to a spinal CSF leak either from a dural tear or CSF-venous fistula.¹ Apart from these spontaneous defects, SIH has also been described with vascular malformations, namely venous and lymphatic malformations, which are either isolated lesions or in patients with syndromes.²⁻⁷ Despite the prior reports, understanding these diseases has been hampered by incorrect nomenclature. Regarding SIH, previous publications have inappropriately reported vascular malformations associated with “Chiari I malformation,” when, in fact, the lesions were resulting in SIH.^{8,9} Vascular malformations are also often mischaracterized despite nomenclature from the International Society for the Study of Vascular Anomalies (ISSVA).¹⁰ For example, CSF leaks from underlying hemangiomas and “lymphangiomatosis” have been described,^{9,11} which now may not be appropriate nomenclature, owing to our greater understanding of the genomics of vascular malformations. Last, myelographic evidence of CSF leaking into a vascular malformation has only been briefly described in some reports. In this clinical report, we present 6 cases of SIH secondary to spinal or skull base CSF leaks from an underlying vascular malformation and discuss the proper terminology, myelographic techniques, and possible therapeutic options.

Case Series

Institutional review board (Kaiser Permanente) approval was granted, which waived the right for informed consent. The study population consisted of patients with SIH associated with a vascular malformation between 2000 and 2024. Inclusion criteria were the following: 1) diagnosis of SIH according to the International Classification of Headache Disorders, Third Edition;¹² 2) spinal or skull base CSF leak identified on CT myelography or cisternography; and 3) vascular malformation appropriately categorized according to the latest ISSVA classification after multidisciplinary review in the vascular anomalies clinic or by a radiologist experienced with vascular anomalies. Brain MRIs were assessed using the SIH Bern scoring system.¹³

Six cases of CSF leaks associated with an underlying vascular malformation were identified (Table). There were 4 females and 2 males, and the mean patient age was 20.8 years (range, 7–40 years). Three of the patients were pediatric (younger than 18 years of age). Four of the CSF leaks were in the spine, and 2 were in the skull base. There were 3 patients with CSF leaks with a venous malformation and 3 with a lymphatic malformation, and all 3 patients with a lymphatic malformation had a complex lymphatic anomaly.¹⁴ All patients had a paraspinal or skull base vascular malformation. Two of the patients were previously reported by our group and are being included to evaluate this unique cohort holistically.^{6,7}

Case 1

A 23-year-old woman presented with 8 months of positional headaches that prompted an MRI of the brain and spine, which showed severe brain sag, cerebellar tonsillar descent, and a syrinx, yielding the initial diagnosis of “Chiari I deformity.” She was being evaluated by the neurosurgery service for potential suboccipital decompression. Follow-up brain imaging was interpreted by a

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Patient demographics of CSF-vascular malformation fistulas

Case	Age (yr)	Sex	CSF Leak Location	Vascular Malformation	Syndrome	Myelographic/Cisternographic Findings	SIH Bern Score and Other Findings	Treatment and Outcome
1	23	F	T11–T12 neural foramen	Venous	None	Delayed leakage from the thecal sac to the venous malformation	6, Syrinx, large paraspinal venous malformation in right thoracolumbar spine	Fibrin glue patch with moderate relief and improved brain MRI findings
2	40	M	T1–T2	Venous	None	Right T1–T2 CSF-venous fistula	6, Syrinx, upper thoracic dorsal epidural venous malformation	Fibrin glue patch with cure
3	33	M	Temporal skull base	Venous	None	Leakage into left retromandibular venous malformation; left temporal dural ectasia	4, Syrinx, extensive left temple, facial, neck venous malformation	Targeted sclerotherapy without substantial relief
4	13	F	Petrous apex	Lymphatic	Generalized lymphatic anomaly	Brisk leakage from the left petrous apex extending to neck musculature to the C3 level	4, Syrinx, diffuse intraosseous lymphatic malformations in the skull base, spine, viscera, and right lower extremity	Surgery is planned
5	9	F	T10–T11	Lymphatic	Kaposiform lymphangiomatosis	Brisk leakage from a right T10–T11 meningeal diverticulum to a paravertebral lymphatic malformation	6, Syrinx, neck and visceral lymphatic malformations	Blood patches with transient relief; surgery with cure; improved brain MRI findings
6	7	F	L4–L5	Lymphatic	Gorham-Stout disease	Brisk leakage into the right L4–L5 paraspinal soft tissues and bones	6, Syrinx, extensive destructive intraosseous lymphatic malformations	Blood patches with transient relief; <i>n</i> -BCA liquid embolic patch with marked improvement; improved brain MRI findings

Note:—F indicates female; M, male.

member of the CSF leak team, and a diagnosis of SIH was made with a Bern score of 6 without dural enhancement (Fig 1). In a review of the spine imaging at 18 months of age, there had been an enhancing epidural lesion in the thoracolumbar spine that was thought to represent an epidural hematoma or a “hemangioma.” Twenty-one years later, she presented with headache and had a spine MRI that showed marked dural ectasia at the T12 level, with a previously undiagnosed paraspinal venous malformation. A right decubitus CT myelogram was obtained with initial scanning of the thoracolumbar spine that showed subarachnoid contrast at the T12 dural ectasia but no leakage. Delayed imaging after 3 minutes and an additional small volume of contrast showed a CSF leak in the right T11–T12 neural foramen, commencing from the thecal sac and extending to portions of the venous malformation near the pleura. A targeted fibrin glue patch was administered, with moderate relief in symptoms to date 3 months after the procedure.

Case 2

A 40-year-old man with a long-standing history of Chiari I deformity presented to our CSF leak program after suspicion of SIH by the clinical team. Brain and spine MRIs showed severe brain

sag, syrinx, and a Bern score of 6 without dural enhancement. Review of the medical records indicated that he had a suboccipital decompression at 22 years of age, which did not resolve the brain sag or syrinx. Seven years later, the patient had a T1–T3 decompression for a dorsal epidural lesion that was diagnosed radiologically and at pathology as a hemangioma. In retrospect, this lesion represented a venous malformation (Online Supplemental Data). After he presented to our CSF leak program, a right decubitus CT myelogram was obtained and showed a right T1–T2 CSF-venous fistula, which was successfully treated with targeted fibrin glue patching. Although the CSF-venous fistula did not drain into the venous malformation given its prior resection, it was thought to be related given that it was located at the same thoracic level and the intracranial SIH findings were persistent despite the prior surgery. The follow-up decubitus CT myelogram showed resolution of the CSF-venous fistula.

Case 3

A 33-year-old man with a large left scalp, facial, and neck venous malformation presented with headaches and upper and lower

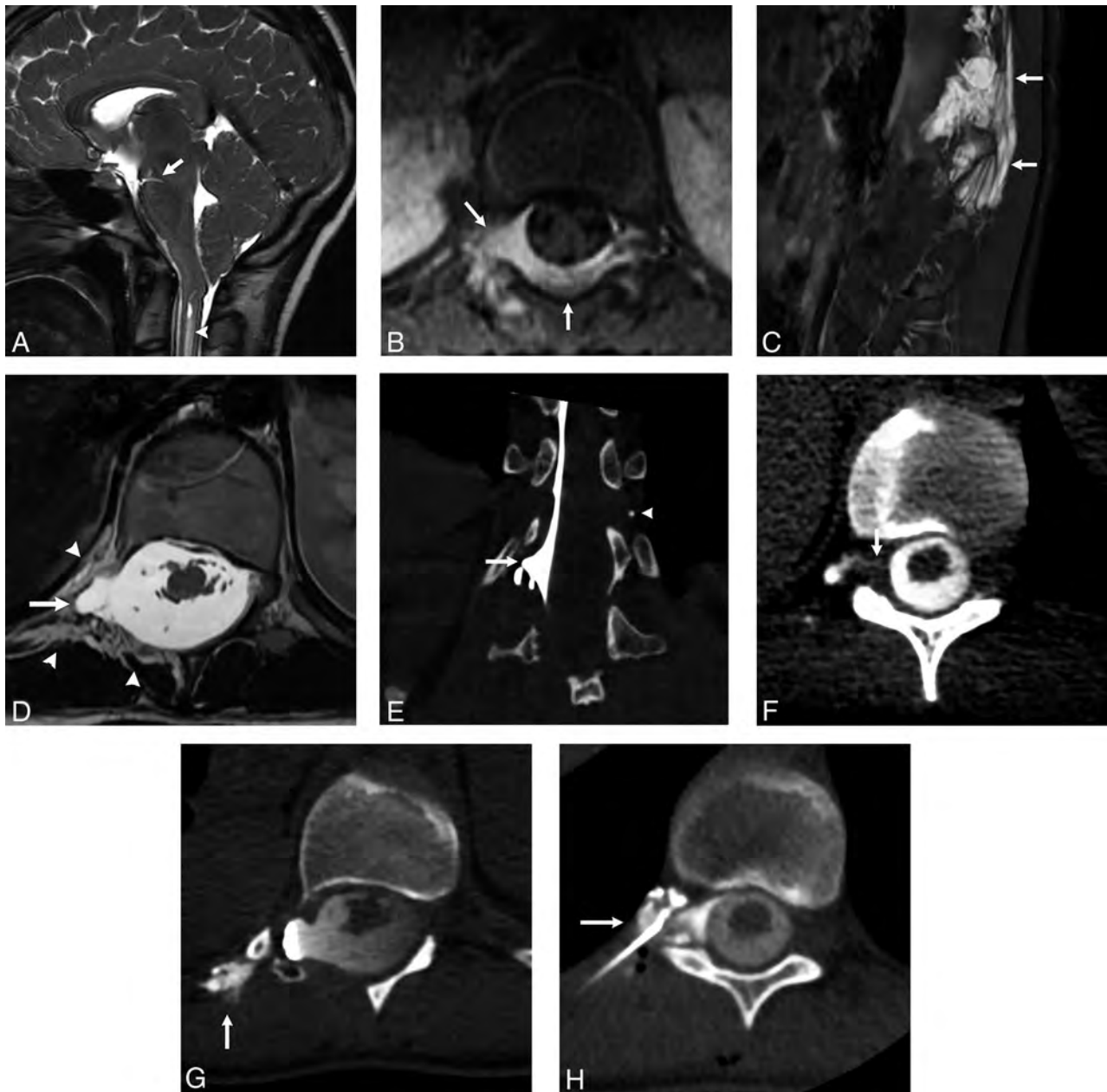


FIG 1. Patient 1. Spinal CSF-venous malformation fistula. A 23-year-old woman had a history of an “epidural hematoma” at 18 months of age. Twenty-one years later she developed postural headaches. *A*, A sagittal T2-weighted image of the brain shows severe midbrain sag (*arrow*), along with cerebellar tonsillar descent and a cervical cord syrinx (*arrowhead*). *B*, Axial contrast-enhanced fat-suppressed T1-weighted image at 18 months of age shows an enhancing lesion in the T12 epidural space (*arrows*) that extended into the right paraspinal soft tissues. *C*, Sagittal STIR obtained as an adult shows a large right paraspinal lesion (*arrows*) that was consistent with a venous malformation. *D*, Axial T2-weighted image shows the paraspinal venous malformation (*arrowheads*) and right dural ectasia at the T12 level (*arrow*). *E*, A right decubitus CT myelogram obtained in the coronal plane shows opacification of the right T12 dural ectasia (*arrow*) but no leakage. A left-sided phlebolith is noted (*arrowhead*), which is consistent with the underlying paraspinal venous malformation that extended to the left side. Delayed myelographic images 3 minutes later show a right T11–T12 fistula between the thecal sac and the venous malformation (*F*, *arrow*), with additional opacification of the venous malformation more laterally near the ribs (*G*, *arrow*). *H*, A fibrin glue patch filling the CSF-venous malformation fistula (*arrow*) provided moderate relief.

extremity numbness. MR imaging of the brain and neck (Online Supplemental Data) showed an extensive venous malformation along the left temporal scalp, erosion of the calvaria, and contiguity with the brain parenchyma. Imaging also showed severe brain sag, cerebellar tonsillar descent, and a cervical syrinx that was diagnosed as a Chiari I deformity. Scans showed a Bern score of 4 without dural enhancement. A suboccipital decompression was

performed that did not resolve the radiologic and clinical findings. Bilateral decubitus myelograms did not show a spinal CSF leak, but a CT cisternogram showed leakage into the venous malformation within the retromandibular fossa. Dural ectasia was also observed along the left temporal lobe with multiple cephaloceles. Targeted sclerotherapy has been performed for the venous malformation, but the skull base leak has not yet been repaired.

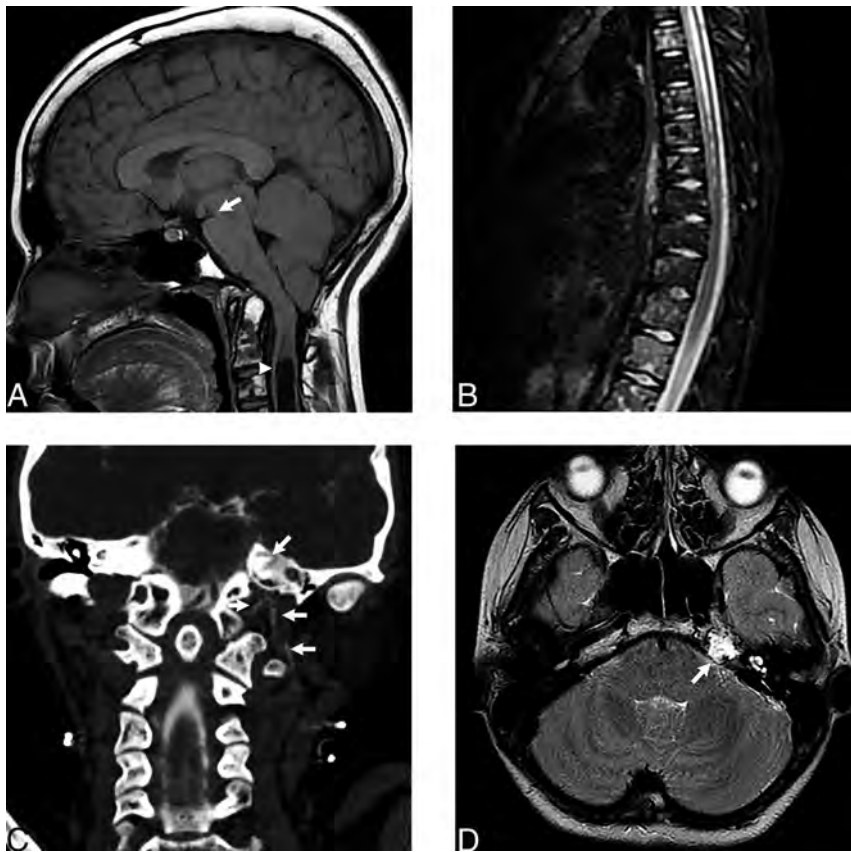


FIG 2. Patient 4. Skull base CSF-lymphatic malformation fistula in a 13-year-old girl who had a history of a generalized lymphatic anomaly for many years and presented with more recent onset of headaches. A, Sagittal T1-weighted image of the brain shows midbrain sag (arrow), along with cerebellar tonsillar descent and a syrinx (arrowhead). B, Sagittal STIR image of the thoracic spine shows diffuse intraosseous lymphatic malformations. Bilateral decubitus CT myelograms did not show a CSF fistula (not shown), but a CT cisternogram of the skull base (C) shows frank leakage from the left petrous apex into the left neck musculature (arrows) that extends to the C3 level. D, Axial T2-weighted image shows a left petrous apex lymphatic malformation (arrow) that was observed in retrospect.

Case 4

A 13-year-old girl presented with headaches and facial numbness. She was previously diagnosed with a generalized lymphatic anomaly, which was first suspected after she presented with diffuse microcystic lymphatic malformations in the right lower extremity and pelvis, with a resultant bladder fistula that caused chyluria. Multiple hematologic and electrolyte abnormalities were present on laboratory analysis, which were in keeping with a generalized lymphatic anomaly as opposed to Gorham-Stout disease, another complex lymphatic anomaly. Her brain and spine MRI showed brain sag, cerebellar tonsillar descent, and a syrinx, yielding the initial diagnosis of Chiari I deformity (Fig 2). The case was evaluated in the Vascular Anomalies Clinic, and SIH was diagnosed with a Bern score of 4 without dural enhancement. The spine MRI showed diffuse intraosseous lymphatic malformations but no extradural collection or large meningeal diverticula. Bilateral decubitus CT myelograms were performed, which did not reveal a CSF-lymphatic malformation fistula. In the same procedural session, the skull base was imaged and revealed frank CSF leakage from the left petrous apex that extended into the left neck musculature to the C3 level. In retrospect, the CSF leak was observed in the

neck on the myelograms, but the leak site was not seen due to incomplete visualization of the skull base. The prior brain MRI was also reviewed and showed a lymphatic malformation in the left petrous apex. Skull base surgery is planned for treatment.

Case 5

A 9-year-old girl with a history of kaposiform lymphangiomatosis, which was diagnosed during infancy after she presented with Kasabach-Merritt phenomenon and diffuse lymphatic malformations throughout the body, complained of headaches for several years that were initially thought to be migraines. Brain MRI was eventually performed, and a diagnosis of SIH was made with a Bern score of 6, including severe brain sag but no dural enhancement. A spine MRI showed a syrinx and diffuse intraosseous lymphatic malformations but no extradural collection or visible meningeal diverticula. A ventral prone CT myelogram was performed that showed rapid CSF accumulation in the right T10–T11 neural foramen and paraspinal soft tissues, which opacified the thoracic duct to the level of the left innominate vein, resembling a lymphangiogram (Fig 3). In retrospect, a paraspinal lymphatic malformation on the prior MRI was visible at the right T10–T11 level. Treatment with targeted blood patches provided incomplete relief; therefore, surgical ligation of the CSF lymphatic fistula resolved symptoms after a period of rebound hypertension.

Case 6

A 7-year-old girl with Gorham-Stout disease presented with postural headaches. During infancy, she had marked irritability, and MRIs of the brain and spine showed brain sag, cerebellar tonsillar descent, and a syrinx that was initially diagnosed as a Chiari I deformity, for which a suboccipital decompression was performed. The SIH Bern score was 6, and there was no dural enhancement. At 7 years of age, spine MRI showed diffuse destructive intraosseous lymphatic malformations throughout the lumbar spine. A prone CT myelogram showed CSF leakage from the right L4 nerve root into the vertebral body and paraspinal soft-tissue lymphatic malformations (Online Supplemental Data). Targeted blood patches resulted in transient relief. Subsequently, a targeted *n*-BCA liquid embolic was percutaneously injected via a spinal needle into the fistula, which resulted in marked improvement in symptoms. During the following 15 years, the patient has intermittently had both low- and high-pressure symptoms, which have been treated

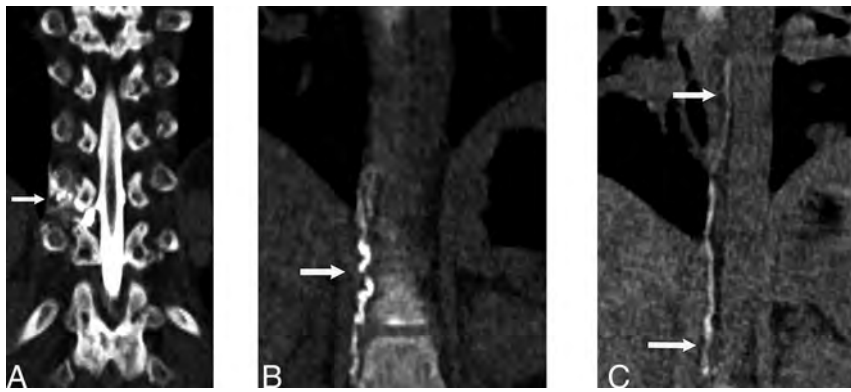


FIG 3. Patient 5. Spinal CSF-lymphatic malformation fistula in a 9-year-old girl with a history of kaposiform lymphangiomatosis who had chronic headaches. Brain and spine MRI demonstrated severe brain sag, syrinx, and intraosseous spinal lymphatic malformations (not shown). Coronal images from a prone CT myelogram show rapid egress of contrast from a right T10–T11 meningeal diverticulum to the paravertebral space (A, arrow). The thoracic duct also opacified to the level of the innominate vein (B and C, arrows), resembling a lymphangiogram procedure. In retrospect, there was a lymphatic malformation identified in the right T10–T11 paravertebral space on MRI (not shown).

with intermittent blood patches, lumbar and ventricular peritoneal shunting, and medical therapy.

DISCUSSION

Spinal CSF leaks associated with adjacent vascular malformations are uncommon. In this clinical report, we demonstrated 6 patients with CSF leaks at CT myelography or cisternography directly caused by spinal or skull base vascular malformations.

Similar to routine CSF-venous fistulas, the pathogenesis of CSF-vascular malformation fistulas has not been well-characterized, but invasion of either the dura and/or nerve root sleeve by the malformation may result in the fistulous connection. This outcome is not uncommon for vascular malformations in other parts of the body. For example, patient 4 developed chyluria from a microcystic lymphatic malformation invading the bladder wall. Similarly, patient 1 had an epidural and paraspinal venous malformation at 18 months of age but did not manifest her SIH symptoms until 2 decades later, when a fistulous connection between the thecal sac and the venous malformation was detected. Patient 2 also had an epidural venous malformation and developed a CSF-venous fistula years later. Further studies are needed to explain how these fistulas form; however, a clear observation is that the presence of an epidural or paraspinal vascular malformation is a potential risk factor for a CSF fistula.

Myelographic timing and density are complementary factors for detection of CSF-venous fistulas.¹⁵ Similarly, timing may be important for CSF-venous malformation fistulas. In patient 1, the CSF-venous malformation fistula was not visible on the early myelographic phase immediately after contrast administration but was apparent on a delayed scan 3 minutes later. We suggest that multiphase scanning may be helpful in this patient cohort. Analogously, venous malformations can often demonstrate delayed enhancement at MR imaging due to their venous nature.¹⁶

In all patients, there was a delay in the diagnosis of SIH. Five of 6 patients were incorrectly diagnosed with a Chiari I deformity, 3 patients had a suboccipital decompression as a result, and

2 patients were being evaluated for a suboccipital decompression before the correct diagnosis was established. Confusion between Chiari I and SIH occurs frequently despite criteria differentiating these 2 entities,¹⁷ particularly among pediatric patients in whom SIH is less common than in adults. One major distinction between Chiari I deformity and SIH is the mamillopontine distance. In SIH, this distance is often reduced, while in Chiari I, it is typically normal.¹⁷ Four of our 6 patients had severe brain sag, which we characterized by an absent mamillopontine distance and could be due to the severity of the hypotension. The presence of a cervical cord syrinx was another imaging feature that also likely contributed to the incorrect diagnosis of Chiari deformity. SIH can rarely result in syrinx in patients without vascular malformations,¹⁸ but it is not fully understood why a syrinx was present in all patients in this cohort with vascular malformations. Perhaps, chronic leakage into a vascular malformation results in lower CSF pressure and greater descent of the cerebellar tonsils. In pediatric patients, another theory could be due to reduced posterior fossa calvarial development. The calvaria is still developing in childhood, and this development may lead to more cerebellar tonsillar descent due to the intracranial hypotension. This rationale is the same as the one for why some studies prefer the term Chiari I deformity rather than malformation, because it is a postnatal developmental mismatch between the rates of growth of neural tissue and the osseous posterior fossa rather than a congenital finding.¹⁹ Further studies are needed to explore these potential theories of why syringes are possibly more prevalent in patients with CSF leaks from vascular malformations, but regardless, this prevalence may be a reason to search for a vascular malformation as a potential etiology for the SIH.

Dural enhancement was absent in all of our patients, which is typically the most prevalent brain MRI feature in SIH.²⁰ We speculate that this imaging sign was absent in our patient cohort due to delayed diagnosis, because it has been reported that dural enhancement can resolve with time, even without treatment.²¹

Classifying vascular anomalies can be challenging due to historical terms. For example, vascular malformations are often misclassified as hemangiomas, which are vascular tumors. In 1 study that evaluated published articles with the term “hemangioma” in 2009, >70% of hemangiomas were misclassified.²² In our case series, 2 patients had their venous malformation misclassified as a hemangioma. The ISSVA classification of vascular anomalies is subdivided into vascular tumors and malformations. Under the vascular malformation category, there are various types, but venous and lymphatic malformations are the most common. This nomenclature challenge has also been observed in patients with spinal and skull base leaks associated with vascular malformations, making it difficult to surmise the exact incidence because

correct terminology is not always used. Moreover, in patients with vascular anomaly syndromes, this nomenclature can be more challenging, given the wide variety and the greater diagnostic complexity. We suggest that patients with CSF leaks from an underlying vascular malformation be referred to a vascular anomalies clinic for care of the vascular malformation, in addition to the CSF leak treatment, if possible, because certain vascular malformations may be amenable to medical therapies, such as mammalian target of rapamycin (mTOR) inhibitors.

In 5 of the 6 patients, there was a direct fistula between the CSF and the vascular malformation, while 1 patient had a CSF-venous fistula that is typical for other patients with SIH without vascular malformations. Prior descriptions of these fistulas have also been labeled CSF-venous fistulas. While this labeling is technically true, because there is a connection between the CSF and the venous system in patients with a venous malformation, we prefer the more technically correct term of CSF-venous malformation fistula. In addition, if there is a lymphatic connection, then CSF-lymphatic malformation fistula is the suggested terminology. This more accurately characterizes the physiology and leads to better tracking for research purposes.

Two of the 6 patients had skull base leaks, specifically in the petrous apex and temporal bone. Skull base leaks do not typically result in SIH, because the spinal level in which the CSF pressure changes from negative to positive relative to the atmospheric pressure is typically in the upper cervical spine. CSF leaks occurring above this zero-pressure and hydrostatic indifference point, therefore, do not typically result in a CSF leak when the patient is upright.²³ In 1 study of 273 patients with SIH by Schievink et al,²⁴ there were no cases of skull base leaks. Subsequently, however, this same group reported a single case of a large posterior fossa CSF leak resulting in SIH.²⁵ In a more recent study, 31 patients with skull base leaks had a mean Bern score of 0.9, and the single patient who had dural enhancement had an infratentorial CSF leak.²⁶ We postulate that if a skull base leak is severe, it could possibly overcome the pressure gradient between the brain and spine and result in SIH. Further research is needed to validate this theory.

There are various treatment options for CSF-vascular malformation fistulas. In 3 cases, the fistula was targeted with blood or fibrin glue patches with some relief. In our 1 patient with a more typical CSF-venous fistula, fibrin glue patching was curative. In patient 5 with a CSF-lymphatic malformation fistula, surgery was successfully performed. Surgical treatment is not without risks, however, because 1 reported case of surgery for a spinal CSF-venous malformation fistula was complicated by extensive blood loss.² In certain cases, transvenous Onyx (Medtronic) embolization may be an option if there is a venous pathway to the fistula. Further studies are needed to determine the treatment efficacy for CSF-vascular malformation fistulas.

CONCLUSIONS

CSF-vascular malformation fistulas are a rare cause of SIH. It had been proposed previously that a CSF leak should be suspected in patients with epidural venous malformations—either syndromic or isolated—if they present with clinical symptoms of SIH.³ We agree with this recommendation but further suggest that any

person presenting with headache or other SIH symptoms in whom an underlying vascular malformation syndrome or an isolated paraspinous or skull base vascular malformation is present, should undergo a CT myelogram and/or cisternogram to identify a possible CSF leak into that entity.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Performance of the CT-Guided C1–C2 Facet (Lateral Atlantoaxial Joint) Injection

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ABSTRACT

CT-guided C1–C2 facet joint injections are a valuable tool for managing cervicogenic headaches caused by degenerative and inflammatory conditions of the atlantoaxial joint. This video article presents the procedural technique for a CT-guided C1–C2 facet joint injection in a patient with left-sided cervicogenic headache. Despite concerns regarding potential complications such as vascular injury to the vertebral artery and nerve injury to the C2 dorsal root ganglion, careful anatomic planning and imaging guidance allows safe and effective treatment. The injection involves pre-

cise needle placement between the vertebral artery and the C2 dorsal root ganglion, followed by contrast injection to confirm positioning and administration of a steroid-anesthetic mixture. Preprocedural imaging and safety precautions such as reviewing the international normalized ratio and platelet levels are essential. While rare adverse events have been reported, this technique remains a valuable option for pain relief in patients unresponsive to conservative therapies.

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CT-Guided C2 Dorsal Root Ganglion Injection and Radiofrequency Ablation for Cervicogenic Headache

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ABSTRACT

CT-guided injection and radiofrequency ablation (RFA) of the C2 dorsal root ganglion (DRG) is a safe and effective treatment for cervicogenic headache arising from C1–C2 joint arthritis. The C2 nerve root is unique in that it lacks a motor component; RFA can be performed with pain relief in exchange for occipital numbness. This video article outlines the imaging anatomy and technical considerations of this procedure.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Quantitative Susceptibility Mapping in Adults with Persistent Postconcussion Symptoms after Mild Traumatic Brain Injury: An Exploratory Study

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ABSTRACT

BACKGROUND AND PURPOSE: It is estimated that 18%–30% of patients with concussion experience symptoms lasting more than 1 month, known as persistent post-concussion symptoms (PPCS). Symptoms can be debilitating, and include headache, dizziness, nausea, problems with memory and concentration, sleep and mood disruption, and exercise intolerance. Previous studies have used quantitative susceptibility mapping (QSM) to show altered tissue susceptibility levels in adults acutely following concussion, however this finding has yet to be investigated in participants with PPCS.

MATERIALS AND METHODS: In this exploratory case-controlled study, we measured tissue susceptibility using QSM in 24 participants with PPCS after mild traumatic brain injury (mTBI) and 23 healthy controls with no history of concussion. We compute tissue susceptibility for 7 white matter tracts and 3 deep gray matter regions and compare tissue susceptibility between groups using ANCOVA models controlling for age and sex. We also assess the relationship between regional tissue susceptibility and symptoms.

RESULTS: There were no significant differences between tissue susceptibility in participants with PPCS compared with control subjects in any of the evaluated regions. However, we show lower tissue susceptibility across 4 white matter tracts was generally associated with worse symptoms in the PPCS group. Specifically, we saw relationships between white matter susceptibility and headache ($p = .006$), time since injury ($p = .03$), depressive symptoms ($p = .021$), and daytime fatigue ($p = .01$) in participants with PPCS.

CONCLUSIONS: These results provide evidence in support of persistent changes in the brain months to years after injury and highlight the need to further understand the pathophysiology of PPCS, to determine effective prevention and treatment options.

ABBREVIATIONS: ACTBI = Aerobic Exercise for Chronic Symptoms following mild Traumatic Brain Injury; ATR = anterior thalamic radiation; CCB = corpus callosum body; CCG = corpus callosum genu; CCS = corpus callosum splenium; DHI = Dizziness Handicap Inventory; ESS = Epworth Sleepiness Scale; GAD = Generalized Anxiety Disorder; FA = fractional anisotropy; FM = forceps minor; FSS = Fatigue Severity Scale; HIT-6 = Headache Impact Test 6; IFOF = inferior fronto-occipital fasciculus; mTBI = mild traumatic brain injury; RPQ = Rivermead Post Concussion Symptoms Questionnaire; PCSC = Post-Concussion Syndrome Checklist; PHQ = Patient Health Questionnaire; PPCS = persistent post-concussion symptoms; QSM = quantitative susceptibility mapping; SLF = superior longitudinal fasciculus; SE = standard error

Mild traumatic brain injury (mTBI, also known as concussion, the terms will be used interchangeably in this article,

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consistent with most recent terminology) is the most common form of brain injury, estimated to affect approximately 1.6% of Canadians.¹ Though most people recover within 10–14 days, roughly 18%–31% of adults still have symptoms months to years afterward, known as persistent post-concussion symptoms (PPCS).² Symptoms include headache, dizziness, exercise intolerance, nausea, memory deficits, difficulty concentrating, sleep difficulties, and mood disruption.³ Symptoms can be debilitating, severely impacting quality of life. Treatment options are limited, in part due to poor understanding of PPCS pathophysiology.

mTBI results from a rapid acceleration and deceleration of the brain within the skull. It can cause diffuse axonal injury from shearing of axons, shown by loss of white matter tract integrity on diffusion imaging.⁴ mTBI also leads to cascades of neurometabolic events, known as secondary injury processes. This includes stretching of membranes resulting in a flux of ions, followed by

SUMMARY

PREVIOUS LITERATURE: It is estimated that 18%–31% of adults who experience concussion continue to have symptoms months to years after injury, known as persistent post-concussion symptoms (PPCS). These symptoms can be debilitating and severely affect quality of life; however treatment options are limited due to a lack of understanding of PPCS pathophysiology. Concussion can cause cascades of neurometabolic events, which can result in prolonged pathological processes. Quantitative susceptibility mapping (QSM) can potentially quantify changes in tissue susceptibility related to concussion associated pathological processes. Previous studies using QSM have shown altered tissue susceptibility in acute concussion. Here we investigate QSM measured tissue susceptibility in participants with PPCS.

KEY FINDINGS: Lower tissue susceptibility across 4 white matter tracts was generally associated with worse symptoms in the PPCS group. Specifically, there were significant relationships between white matter susceptibility and headache, time since injury, depressive symptoms, and daytime fatigue in participants with PPCS.

KNOWLEDGE ADVANCEMENT: We interpret this to reflect increased inflammation in participants with PPCS, providing evidence for persistent changes in the brain months to years after injury, and highlighting the need to further understand PPCS pathophysiology, to determine effective prevention and treatment options.

widespread release of several neurotransmitters, particularly excitatory neurotransmitters such as glutamate.⁵ This can lead to mitochondrial calcium overload, inducing changes in membrane permeability resulting in production of reactive oxygen species and mitochondrial swelling and dysfunction. As the mitochondria fail, energy production is reduced, resulting in decreased brain metabolism. The excitatory neurotransmitters also activate microglia (gliosis) that release inflammatory cytokines.^{3,6} Additionally, mTBI can cause accumulation of iron, particularly in deep gray matter structures, which has been linked with cognitive dysfunction. Iron dysregulation may also lead to further generation of reactive oxygen species, triggering additional inflammatory processes.⁶

It is possible that prolonged pathologic processes associated with secondary injury may be linked to the development of PPCS. However, these secondary injury processes cannot be typically seen using conventional neuroimaging. Quantitative susceptibility mapping (QSM) is an application of MRI that exploits changes in the magnetic properties of tissue to measure differences in tissue susceptibility. QSM can therefore potentially quantify changes in tissue susceptibility related to mTBI-associated pathological processes, such as demyelination, accumulation of iron and calcium, and gliosis.⁷ Using QSM, previous studies have shown that, compared with controls, participants 8 days post-concussion have altered global white matter susceptibility,^{8,9} as well as altered tissue susceptibility in multiple white matter tracts.⁸ Additionally, tissue susceptibility in frontal white matter 10 days post-injury was shown to predict persistent symptoms 4 weeks post-injury.¹⁰

QSM-measured tissue susceptibility may provide new insight into the role of sustained pathological processes in PPCS. To our knowledge, there have been no studies using QSM to investigate tissue susceptibility in PPCS. This exploratory study compared tissue susceptibility from select gray matter regions and white matter tracts between participants with PPCS following mTBI and healthy controls, as well as assessing the relationship between tissue susceptibility and symptom severity. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

checklist guided reporting of this article and has been included in the Online Supplemental Data.

MATERIALS AND METHODS

Study Design

This cross-sectional case-controlled study was nested within the Aerobic Exercise for Chronic Symptoms following Mild Traumatic Brain Injury (ACTBI) trial, registered at clinicaltrials.gov (NCT03895450). The study protocol was approved by the Conjoint Health Research Ethics Board at the University of Calgary (REB18-1329). All participants provided written, informed consent. ACTBI trial methods are detailed in Mercier et al,¹³ with the relevant details described below.

Participant Population

Participants with PPCS were recruited from the Calgary Brain Injury Program and Calgary Pain Center between May 2019 and December 2023. Recruitment was paused between March 2020 and June 2021 due to the COVID-19 pandemic. Eligibility criteria for the PPCS cohort included: 1) aged 18–65 years, 2) diagnosis of mTBI based on the American Congress of Rehabilitative Medicine criteria,¹¹ 3) diagnosis of PPCS based on the International Classification of Diseases-10 post-concussional syndrome criteria,¹² 4) at least 3 months to no more than 5 years since most recent mTBI, 5) exercise intolerance defined as acute exacerbation of post-concussive symptoms with exercise, evaluated by using the Buffalo Concussion Treadmill Test,^{13,14} and 6) maintenance of a stable pharmacologic regimen for at least 1 month before study participation. Participants with PPCS had no sustained loss of consciousness greater than 30 minutes post-injury, a Glasgow Coma Scale score less than 13, and post-traumatic amnesia for less than 24 hours post-injury, as per the American Congress of Rehabilitative Medicine criteria for mTBI.¹¹ Participants with PPCS were excluded if they had a history of moderate to severe traumatic brain injury, cardiopulmonary, or musculoskeletal condition.

Age (± 3 years) and sex-matched controls without any history of concussion were recruited from the community using posters and word of mouth advertising. All control participants were

screened to rule out any neurologic conditions, including history of suspected concussion/traumatic brain injury or major psychiatric history. All participants were screened to rule out contraindications to MRI.

As stated above, this study was part of a larger trial. Participants with PPCS were age and sex matched to healthy control participants at recruitment. Participants were only included in the present study if they completed a T1-weighted structural scan and a QSM scan during the MRI portion of the trial. QSM data were collected in 33 participants with PPCS and 30 age- and sex-matched controls with no lifetime history of brain injury.

Questionnaires

Demographic and injury characteristic data were collected in the form of self-reports. Participants with PPCS completed the following questionnaires: Rivermead Post Concussion Symptoms Questionnaire (RPQ, mTBI symptom burden), Post-Concussion Syndrome Checklist (PCSC, mTBI symptom frequency, intensity, and duration), Headache Impact Test-6 (HIT-6, functional impact of headache), and the Dizziness Handicap Inventory (DHI, dizziness handicap).

Additionally, all participants (participants with PPCS and control participants) completed the following clinical questionnaires: Patient Health Questionnaire-9 (PHQ-9, depressive symptoms), Generalized Anxiety Disorder-7 Scale (GAD-7, anxiety symptoms), Fatigue Severity Scale (FSS, fatigue), and Epworth Sleepiness Scale (ESS, daytime sleepiness). Detailed description and citations for all questionnaires can be found in Mercier et al.¹³

Data Acquisition

QSM data were obtained on a 3 T MR scanner (GE Healthcare 750w) by using a 32-channel head coil. A T1-weighted structural image was acquired using a BRAVO sequence (TR/TE/TI = 7.30/2.70/600 ms, matrix size = 256 × 256, FOV = 252 × 278 mm², slice thickness = 1 mm, flip angle = 10°). QSM data were acquired with a multiecho gradient-echo sequence using the following parameters: TR = 56.7 ms, 10 echoes with echo spacing 5.3 ms with TE ranging from 4.5–52.2 ms, matrix size = 256 × 256, FOV = 240 × 240 mm², 1.9 mm slice thickness, unipolar readout gradient, and acceleration factor of 2.5. Complex-value QSM images were reconstructed and saved.

Data Processing

QSM data were processed using a customized, well-validated, and robust QSM processing pipeline¹⁵ that has been used extensively.^{10,16–18} Processing included brain extraction on the magnitude and phase images using FSL BET (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET>),¹⁹ phase unwrapping using BESTPATH,²⁰ weighted least squares calculation of the field from the phase, background field removal with RESHARP,²¹ and dipole inversion with Total Variation (TV) TV regularization.²² QSM data were registered to Montreal Neurological Institute space using FSL FLIRT (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FLIRT>).²³

White matter masks were generated using the Harvard-Oxford²⁴ and Johns Hopkins²⁵ atlases for the following regions: global white matter, anterior thalamic radiation (ATR), cingulum (CH), forceps minor (FM), inferior fronto-occipital fasciculus

(IFOF), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), corpus callosum (separated into the corpus callosum body [CCB], corpus callosum genu [CCG], and corpus callosum splenium [CCS]); several of these regions have shown altered susceptibility after concussion.⁸ We also evaluated the 3 subcortical gray matter regions: caudate, putamen, and pallidum. Masks for these regions were generated using the Harvard-Oxford Subcortical Atlas.²⁴ Mean tissue susceptibility values were computed from each region for each subject. See Online Supplemental Data for masks.

Statistical Analysis

Statistical analyses were conducted using R (Version 4.1.2, R Core Team 2020 <https://www.R-project.org/>). Age was compared between groups using a *t* test and sex was compared using a χ^2 test. ANCOVA tests were used to compare tissue susceptibility for each region between groups (PPCS versus control) while controlling for age and sex. Partial correlations were used to assess the relationship between tissue susceptibility in each region and PPCS burden, while also controlling for age and sex (in participants with PPCS only). Linear models were used to assess the relationship between tissue susceptibility and clinical questionnaire scores in the full sample, including a group by symptom score interaction. Age and sex were included as fixed factors (notation for full model using the *lm* function in R: QSM~questionnaire*group + age + sex). Due to the lack of previous research in this area and the exploratory nature of this study, we did not correct for multiple comparisons.²⁶

RESULTS

Sample Characteristics

Nine participants from the PPCS group and 7 participants from the control group were excluded due to poor quality QSM data, for example presence of streaking artifacts.

See Table 1 for demographic information of the entire sample and Table 2 for injury characteristics of the PPCS group.

Group Comparisons

There were no significant differences between groups (PPCS versus control) in tissue susceptibility values from any of the evaluated regions (Fig 1).

QSM and PPCS Burden

There were no significant relationships between tissue susceptibility in the subcortical gray matter regions and PPCS burden. Participants with PPCS with higher functional burden of headache were found to have lower susceptibility in the CCB ($R_p = -0.57, p = .006$) (Fig 2A). Participants with PPCS with a longer time since injury had lower tissue susceptibility measures in the SLF ($R_p = -0.47, p = .03$) (Fig 2B). There were no other significant relationships between white matter tract susceptibility and PPCS burden.

QSM and Clinical Questionnaires

Depressive Symptoms. There was a significant group by depressive symptom score interaction on susceptibility in the CCS ($b = 0.001$, standard error [SE] = 0.0005, $p = .02$; Online Supplemental Data). Depressive symptoms were related to susceptibility in participants with PPCS only, with no significant relationship seen

Table 1: Demographic characteristics of participants in the PPCS and control groups

Demographics	PPCS Group (<i>n</i> = 24)	Control Group (<i>n</i> = 23)	<i>p</i> Value
Age, mean (SD)	43.00 (12.12)	41.76 (11.10)	.72
Sex, M/F	5/19	4/17	.88
Education, <i>n</i> (%)			
PhD/medical doctorate	2 (8%)	1 (4%)	
Masters degree	6 (25%)	2 (9%)	
Bachelors degree	11 (46%)	9 (39%)	
Trade school/vocational education	3 (13%)	8 (34%)	
Grade 12	2 (8%)	1 (4%)	
Other	0 (0%)	2 (9%)	.21
Current work status, <i>n</i> (%)			
Full-time (employed or student)	11 (46%)	18 (78%)	
Part-time (employed or student)	4 (17%)	3 (13%)	
Not currently working (employed or student before accident)	7 (29%)	0 (0%)	
Not employed or student	1 (4%)	1 (4%)	.03
Questionnaires, mean (SD)			
Depressive symptoms, PHQ-9 [scoring range: 0–27]	11.58 (5.83)	3.81 (4.13)	<.001
Anxiety symptoms, GAD-7 [scoring range: 0–21]	6.42 (4.73)	2.86 (2.99)	.006
Fatigue, FSS [scoring range: 9–63]	43.08 (14.93)	23.81 (11.10)	<.001
Daytime sleepiness, ESS [scoring range: 0–24]	9.79 (4.54)	3.95 (2.60)	<.001

Note:—ESS indicates Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; GAD-7, Generalized Anxiety Disorder 7; PHQ-9, Patient Health Questionnaire-9; SD, standard deviation.

in the control group (Fig 3A). Depressive symptoms were significantly associated with susceptibility levels in the FM in the full sample ($b = -0.0009$, $SE = 0.0004$, $p = .02$; Online Supplemental Data), with no significant group by depressive symptom interaction ($b = -0.0007$, $SE = 0.0004$, $p = .09$; Fig 3B).

Anxiety Symptoms. Anxiety symptoms were significantly associated with susceptibility levels in the ATR in the full sample ($b = -0.0007$, $SE = 0.0003$, $p = .04$; Online Supplemental Data), with no significant group by anxiety score interaction ($b = 0.0004$, $SE = 0.0004$, $p = .3$; Fig 4A). There was a significant group by anxiety symptom score interaction on susceptibility in the FM ($b = -0.001$, $SE = 0.0005$, $p = .05$; Online Supplemental Data). Anxiety symptoms were related to susceptibility in the FM in the control group only, with no significant relationship seen in participants with PPCS (Fig 4B).

Table 2: Summary of patient injury characteristics and symptom scores

Injury Characteristics and Symptom Questionnaires	
Months since injury, mean (range)	27.13 (4–58)
Mechanism of injury, <i>n</i> (%)	
Sports/recreational play	5 (21%)
Motor vehicle collision	11 (46%)
Fall	6 (25%)
Assault	0 (0%)
Work related	1 (4%)
Other	1 (4%)
Loss of consciousness, <i>n</i> (%)	
Yes	8 (33%)
No	13 (54%)
Unknown	3 (13%)
Number of lifetime mTBIs, mode (range)	1 (1–5+)
Medications, <i>n</i> (%)	
Antidepressant/antipsychotic/neurostimulant	15 (63%)
Antiepileptic	3 (13%)
Antinausea/gastrointestinal	6 (25%)
Cardiovascular	1 (4%)
Endocrine	2 (8%)
Headache	8 (33%)
Hormone replacement therapy	1 (4%)
Metabolic	2 (8%)
Pain	6 (25%)
Respiratory/antihistamine	3 (13%)
Sleep	7 (29%)
Questionnaires, mean (SD)	
RPQ [scoring range: 0–64]	33.00 (10.08)
PCSC [scoring range: 30–150]	91.92 (19.46)
HIT-6 [scoring range: 36–78]	62.29 (6.23)
DHI [scoring range: 0–100]	31.17 (23.39)

Note:—DHI indicates Dizziness Handicap Inventory; HIT-6, Headache Impact Test; PCSC, Post-concussional Syndrome Checklist; RPQ, Rivermead Post Concussion Symptoms Questionnaire; SD, standard deviation.

Daytime Fatigue. Daytime fatigue symptoms were significantly associated with susceptibility levels in the CCG in the full sample ($b = 0.0002$, $SE = 0.0001$, $p = .04$; Online Supplemental Data). There was no significant group by fatigue symptom score interaction ($b = -0.0002$, $SE = 0.0001$, $p = .08$; Fig 5A). There was a significant group by fatigue symptom score interaction on susceptibility in the CCS ($b = -0.0005$, $SE = 0.0002$, $p = .01$; Online Supplemental Data). Fatigue symptoms were related to susceptibility in participants with PPCS only, with no significant relationship seen in the control group (Fig 5B). There was also a significant group by fatigue symptom score interaction on susceptibility in the IFOF ($b = -0.0001$, $SE = 0.00007$, $p = .04$; Online Supplemental Data). Fatigue symptoms were related to susceptibility in the control group only, with no significant relationship seen in participants with PPCS (Fig 5C).

Daytime Sleepiness. There were no significant relationships between daytime sleepiness and susceptibility in any evaluated region.

DISCUSSION

This exploratory study quantified tissue susceptibility in selected subcortical gray matter regions and white matter tracts in participants with PPCS following mTBI and a healthy control group (without history of diagnosed/suspected brain injury). We show susceptibility in the CCB and SLF tracts of participants with PPCS was associated with functional impact of headache and time since injury, respectively. Susceptibility in white matter tracts was also associated with clinical characteristics across both groups, specifically depression, anxiety, and fatigue.

Tissue susceptibility describes the response of an object when placed in a magnetic field. QSM generates images based on

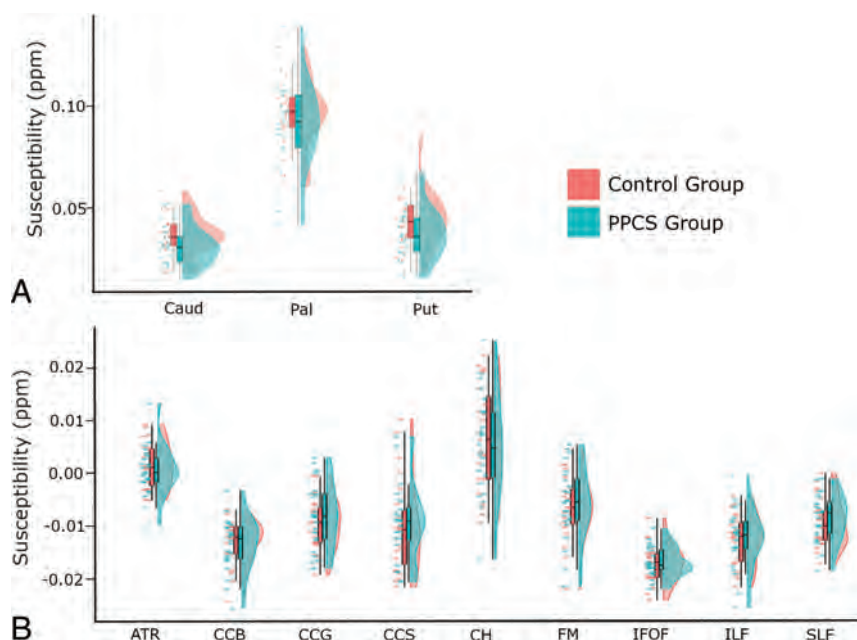


FIG 1. A, Comparison between groups (PPCS versus control) of susceptibility values from individual gray matter regions. B, Comparison between groups of susceptibility values from individual white matter tracts. There were no significant differences between groups in any gray matter region or white matter tract. Caud = caudate; Pal = pallidum; Put = putamen.

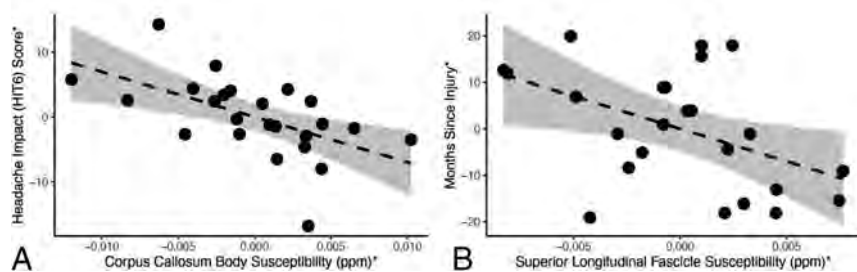


FIG 2. A, Significant relationship between susceptibility in the CCB and the headache impact score, measured by using the HIT-6 ($R_p = -0.57$, $p = .006$). B, Significant relationships between susceptibility in the SLF and months since injury ($R_p = -0.47$, $p = .03$). *For visualization of partial correlations, the residuals from a regression against age and sex are plotted, to remove variability from these factors.

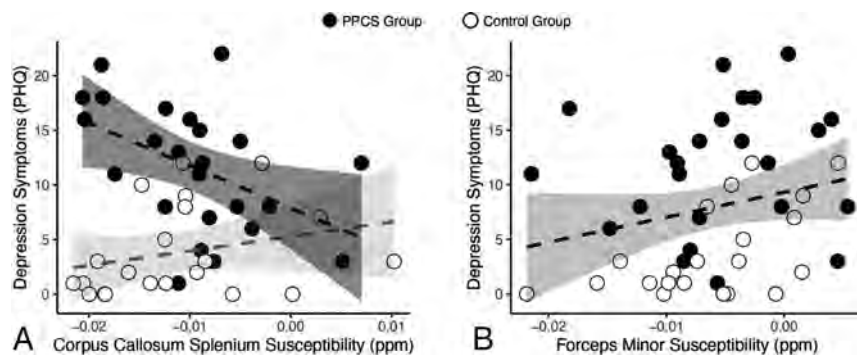


FIG 3. A, Relationship between depressive symptoms and susceptibility in the CCS in both the patient and control groups. There was a significant group by depressive symptom interaction on susceptibility in the CCS ($b = 0.001$, $SE = 0.0005$, $p = .02$). Depressive symptoms were related to CCS susceptibility in participants with PPCS only. B, Significant relationship between depressive symptoms and susceptibility in the FM in the full sample (PPCS plus control group) ($b = -0.0009$, $SE = 0.0004$, $p = .02$). PHQ = Patient Health Questionnaire.

magnetic field variations in the tissue when placed in the MRI scanner. For example, positive tissue susceptibility can be a marker of iron deposition, hemorrhage, edema, or loosening of the myelin sheath, and negative tissue susceptibility can be a marker of calcium accumulation/calcification, or an increase in myelin.⁶

We found relationships between tissue susceptibility in the PPCS group and symptom burden, with lower tissue susceptibility across multiple white matter tracts generally associated with worse symptoms. The directionality of this finding is in line with animal models of brain injury. Chary et al⁷ showed a decrease in tissue susceptibility in the corpus callosum in rodent models 6 months after injury. In the same area they found increased cell density, attributed to gliosis, and an increase in the density of myelinated axons.⁷ Gliosis can help regulate the inflammatory response but can also release free radicals and proinflammatory cytokines. A sustained inflammatory state is a significant contributor to secondary damage and neurologic impairments.²⁷ Participants with PPCS with more severe symptoms may therefore be experiencing higher levels of sustained inflammation. Indeed, previous literature shows participants with PPCS have higher levels of inflammatory markers in CSF²⁸ and blood samples.²⁹

Higher functional impact of headache was associated with lower CCB susceptibility. The corpus callosum is the largest white matter structure in the brain and serves as the primary inter-hemispheric bridge.³⁰ Computer simulations of concussion show that the greatest shear and strain forces occur in this region,³¹ and damage to this area is one of the most commonly reported pathologic changes after brain injury.⁴ Previous research shows decreased fractional anisotropy (FA) of the corpus callosum after concussion is correlated with prolonged symptomology, in line with our findings. Participants with lower FA in the CCG and CCB recovered significantly more slowly from cognitive symptoms, and participants with lower FA in the CCS recovered more slowly from depressive

symptoms.³⁰ Participants with increased FA in the CCG and decreased FA in the CCS were also more likely to have post-traumatic headache after concussion.³²

A longer time since injury was associated with lower SLF susceptibility. The SLF is the largest associative fiber bundle system in the brain,³³ with many tracts that connect most parietal regions to the frontal lobe.³⁴ Along with the corpus callosum, the SLF is another tract frequently reported to distinguish participants with PPCS from controls.⁴ The relationship between SLF tissue susceptibility and time since injury may reflect sustained inflammation that continuously increases as the brain attempts to heal.

Participants with PPCS with lower CCS susceptibility had higher depressive symptoms. Changes in CCS microstructure have been shown to be related to persistent depression after concussion.³⁰ The CCS connects parietal, inferior, and medial temporal cortices.³⁵ This includes the posterior cingulate cortex, an area involved in emotional processing, and a key region of the default mode network. Alterations here can result in an inability

to regulate the balance of internal versus external attention, and has been linked with excessive rumination in depression.³⁶

Across the full sample, higher FM susceptibility was associated with higher depressive symptoms. FM integrity has been previously linked with depression in patients with MS.³⁷ The FM connects the dorsolateral prefrontal cortices, which have been frequently linked to depression.³⁷ Additionally, higher FM susceptibility was associated with higher anxiety symptoms in the control group only. Higher anxiety symptoms were also associated with lower ATR susceptibility. Both regions have been linked to anxiety in healthy individuals. For example, Lu et al³⁸ found healthy adults who had higher trait anxiety scores had lower white matter integrity in these regions. The ATR connects the prefrontal lobe to the thalamus, and thalamocortical connectivity plays a key role in many aspects of anxiety such as threat bias, hyperarousal, and avoidance.³⁹

In the control group, higher IFOF susceptibility was associated with higher daytime fatigue symptoms. T1-weighted intensity of the IFOF has previously been associated with sleep quality in patients with chronic fatigue syndrome,⁴⁰ suggesting it has a role in sleep/fatigue. Higher fatigue scores were also associated with higher CCG susceptibility in the full sample, and lower CCS susceptibility in the PPCS group. Atrophy of the corpus callosum⁴¹ and a higher lesion load in this area⁴² has been associated with fatigue in MS. The authors postulate that impaired communication between brain regions resulting from white matter atrophy results in an increased cortical load to compensate, contributing to fatigue.⁴²

In contrast to the previous 2 papers by Koch et al^{8,9} measuring tissue susceptibility in acute concussion, we found no

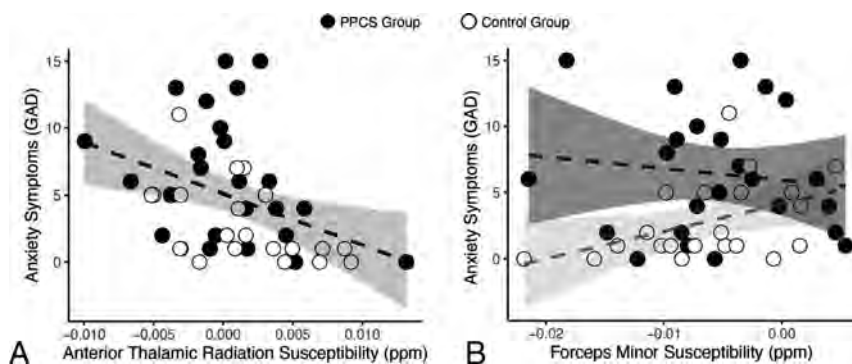


FIG 4. A, Significant relationship between anxiety symptoms and susceptibility in the ATR in the full sample (PPCS plus control group) ($b = -0.0007$, $SE = 0.0003$, $p = .04$). B, Relationship between anxiety symptoms and susceptibility in the FM in both the patient and control groups. There was a significant group by anxiety symptom score interaction ($b = -0.001$, $SE = 0.0005$, $p = .05$) on susceptibility in the FM. Anxiety symptoms were related to FM susceptibility in the control group only. GAD = Generalized Anxiety Disorder.

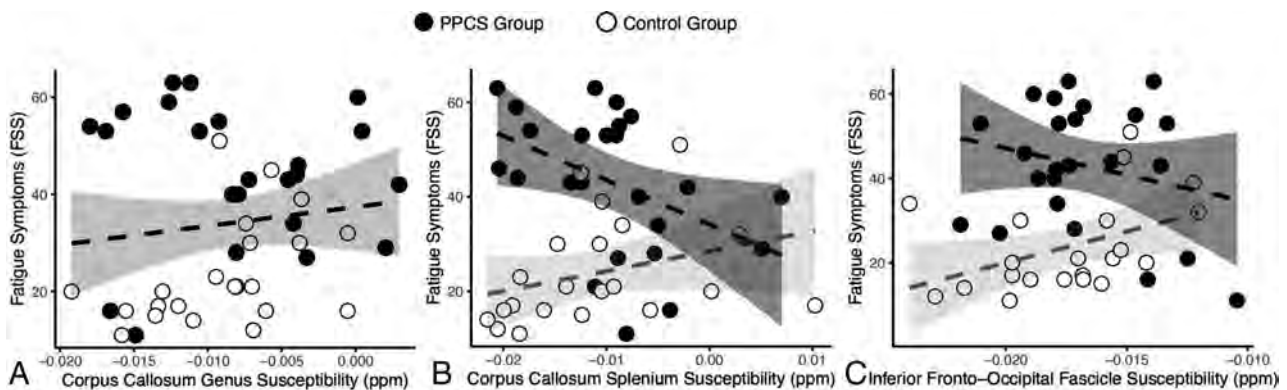


FIG 5. A, Significant relationship between daytime fatigue symptoms and susceptibility in the CCG in the full sample (PPCS plus control group) ($b = 0.0002$, $SE = 0.0001$, $p = .04$). B, Relationship between fatigue symptoms and susceptibility in the CCS in both the patient and control groups. There was a significant group by fatigue symptom score interaction ($b = -0.0005$, $SE = 0.0002$, $p = .01$) on susceptibility in the CCS. Fatigue symptoms were related to CCS susceptibility in participants with PPCS only. C, Relationship between fatigue symptoms and susceptibility in the IFOF in both the patient and controls groups. There was a significant group by fatigue symptom score interaction ($b = -0.0001$, $SE = 0.00007$, $p = .04$) on susceptibility in the IFOF. Fatigue symptoms were related to IFOF susceptibility in the control group only. FSS = Fatigue Severity Scale.

group differences in susceptibility between patients with PPCS and controls. Koch et al⁸ imaged participants 24 hours, 8 days, and 6 months after injury, and Koch et al⁹ imaged participants 48 hours after injury. The sample in our study was imaged on average 2 years after injury, therefore, it is possible that any changes have resolved at this point. A second potential reason is due to differences in recruited populations. The average age of participants in the previous studies was 18 years, substantially younger than our population, which had a mean age of 43 years. Furthermore, Koch et al⁸ compared 28 controls to 28 injured athletes, and Koch et al⁹ compared 78 controls to 78 injured athletes. Though not much smaller than the Koch et al⁸ group (24 patients with PPCS versus 23 controls), it is possible that effect sizes of group differences may decrease over time, and our study may be underpowered to detect them. Given $\alpha = 0.05\%$ and 80% power, this study is powered to detect an effect size of 0.42. This is similar to the effect sizes seen at earlier time points in Koch et al in 2018,⁸ however future studies should aim to include a larger sample size to ensure adequate power. Larger sample sizes will also be able to probe more specific relationships, such as the impact of medication. Furthermore, most of our sample obtained their injury from a motor vehicle collision, which may result in different injury processes than sport-related concussion.

Additionally, interpreting tissue susceptibility differences is challenging because these measures are influenced by multiple processes in the brain. Therefore, both higher and lower tissue susceptibility can reflect pathological processes (such as calcification, inflammation, iron deposition) as well as normal brain structures (such as myelin density). Future studies can include other imaging measures to complement QSM findings, such as diffusion imaging or T2 mapping, to aid in interpretation.

A limitation of this study is that we did not correct for multiple comparisons; this was due to the exploratory nature of our study. Because this is the first study to investigate the relationship between PPCS following mTBI and QSM-measured tissue susceptibility, we included multiple white matter tracts and gray matter regions in our comparisons, as well as multiple questionnaires, resulting in many comparisons. Due to the small number of subjects in our sample, this study is not powered to control for the large number of comparisons conducted. Subsequently, some of these results may be spurious effects, and replication is needed to strengthen confidence in these findings. Future studies can use our findings to guide their studies to probe for specific relationships. Additionally, the use of multiple questionnaires in this study can be used to inform design of future mechanistic studies examining PPCS symptom pathophysiology.

CONCLUSIONS

We provide evidence for alterations in white matter tissue susceptibility in participants with PPCS following mTBI compared with healthy controls. We show that tissue susceptibility levels in white matter tracts are correlated with specific postconcussive symptoms, providing evidence for persistent changes in the brain months to years after injury, and highlighting the need to further understand PPCS pathophysiology to determine effective prevention and treatment options.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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Dynamic Expansion and Contraction of Multiple Sclerosis T2-Weighted Hyperintense Lesions Are Present below the Threshold of Visual Perception

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ABSTRACT

BACKGROUND AND PURPOSE: The study of T2-weighted hyperintense lesions resulting from autoimmune inflammatory injury and associated volumes within the CNS remains fundamental to the diagnosis and disease surveillance of MS. We investigated the dynamic changes of individual T2-weighted hyperintense MS lesions on MRI and hypothesized that variations may be present below the threshold of visual perception when evaluating longitudinal data.

MATERIALS AND METHODS: A retrospective study was performed of people with MS, incorporating data from 3 consecutive MRI time points acquired within a single academic center. All included MRI studies lacked formal imaging interpretations of newly enlarging or contracting T2-weighted hyperintensities. Well-defined, noncoalescing, individual T2-weighted hyperintense lesions were targeted. A total of 8–12 lesions were randomly selected in a blinded fashion at MRI time point 1 and 3D lesion volumes were followed over MRI time points 2 and 3. The impact of treatment on lesion expansion and relationship to brain MRI advancement, patient-reported progression of disease, and physician-identified progression was also studied.

RESULTS: The study cohort comprised 115 people (81 (70.4%) women; mean disease duration of 9.36 years [standard deviation: 7.72 years]) who were primarily White (79.1%). A total of 1426 focal T2-weighted hyperintense MS lesions were identified on MRI time point 1 and longitudinally followed over MRI time points 2 and 3. In the evaluation of raw changes in individual T2-weighted hyperintense lesion volumes from MRI time point 1 to MRI time point 2, a similar number of individuals were observed with predominantly expanding (49/115; 42.6%) or contracting (51/115; 44.3%) lesions. However, most lesions expanded in volume (48/115; 41.7%) versus those that contracted (45/115; 39.1%) when evaluating MRI time point 3 to time point 1. Those individuals not on active treatment had a 67.15% reduction in the odds of more individual lesions predominantly contracting in volume relative to those on low-efficacy disease modifying therapy treatment (95% CI = [−83.89% to −33.01%], $P = .0008$) and 74.02% reduction relative to high-efficacy treatment individuals (95% CI = [−87.37% to −46.56%], $P < .0001$).

CONCLUSIONS: Dynamic changes in T2-weighted hyperintense lesions are abundant, occurring below the threshold of visual perception and are present more frequently in untreated individuals.

ABBREVIATIONS: BMI = body mass index; DMT = disease-modifying therapy; LMS = λ , μ , and σ ; SD = standard deviation; UTSW = The University of Texas Southwestern

MS is a complex condition with a wide disease spectrum that may result in permanent neurologic injury in susceptible individuals.¹ Fundamental to the diagnosis and disease surveillance of MS is the evaluation of distinct T2-weighted hyperintensities on MRI studies of the brain and spinal cord, features that are reflective of CNS autoimmune inflammatory injury.² Disease-

modifying therapies (DMTs) are prescribed to prevent the development of new gadolinium-enhancing lesions, new T2-weighted hyperintense lesions, and to reduce the risk of future disability. As MRI relapses commonly outnumber clinical relapses by a substantial amount, longitudinal imaging studies are performed to monitor for disease advancement.³ These data are also used to evaluate the recrudescence of disease activity in the absence of

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SUMMARY

PREVIOUS LITERATURE: The study of newly enlarging T2-weighted hyperintense lesions has been a cornerstone in MS clinical trials and routine clinical practice for disease surveillance. The appreciation of such changes on longitudinal imaging are dependent upon the review of data in gray-scale and perceptions of luminance gradients supported by visual processing within lateral inhibitory optic neurons. As a result, the expansion or contraction of T2-weighted hyperintense lesions over time may occur, however, these changes may remain below the resolution of human perception. The recognition of such changes has substantial implications for clinical management.

KEY FINDINGS: Most T2-weighted hyperintense lesions expanded in volume in people (41.7%) versus contracted (39.1%) from MRI time point 3 to 1. Nonactively treated individuals had a 67%–74% reduction in odds of more individual lesions predominantly contracting in volume based on treatment exposure to low-efficacy or high-efficacy disease-modifying therapies.

KNOWLEDGE ADVANCEMENT: Dynamic changes in T2-weighted hyperintense lesions associated with MS occur with expanding and contracting characteristics. These transformations appear to be more frequent in untreated individuals and occur below our visual perception, limiting our ability to effectively discern gray-scale differences.

immunomodulatory or immunosuppressive treatment, but more commonly to assess the DMT treatment response.

In clinical practice, repeat MRI studies are commonly performed, and clinicians rely on both the formal interpretation of the findings coupled with their direct impressions of any change. The appreciation of the interval development of a gadolinium-enhancing lesion or new T2-weighted focus is straightforward. More difficult is recognizing subtle changes that may remain below the resolution of the human perception.⁴ These changes may inform on a subgroup of focal white matter lesions pathologically corresponding to slowly expanding lesions and chronic active inflammation⁵ or even improvement. However, techniques capable of detecting such characteristics are technically complex and often unavailable. These results would be of great value not only to the health care team in providing direction for the most ideal treatment plan but, more importantly, to the patient.

Although incorporated as an essential metric within randomized clinical trials in MS, the definitions of “enlarging” T2 foci used within these studies are not always readily disclosed.^{6–9} Moreover, uniform definitions are lacking, and typically, a percent change in volume is applied as a threshold (eg, 20%–40% volume increase), which may vary considerably from study to study. Interestingly, as all DMTs have a mechanism of action that is principally anti-inflammatory, the inverse definition of “shrinking” is not applied. Instead, measures involving the observation of a new T2-weighted hyperintense lesion or change in T2-weighted lesion volume is determined.

The ability to deliver accurate imaging results when longitudinal MRI data are acquired is essential as findings may reveal disease advancement, stability, or even improvement at the individual lesion level. Identifying if lesion size, location, or treatment influences individual lesion behavior is also important. In this retrospective study, we evaluated the dynamic changes of T2-weighted hyperintense lesions over 3 MRI time points in the context of formal imaging reports by neuroradiologists. The study of lesion dynamics by location within the CNS and the relationship to future radiologic and clinical measures of disease progression was also explored.

MATERIALS AND METHODS

Research Participants

In this retrospective study, all research participants were obtained from The University of Texas Southwestern (UTSW) Medical Center and were seen in the Multiple Sclerosis and Neuroimmunology Clinic. Inclusion criteria comprised 1) male or female patients ≥ 18 years of age; 2) an established diagnosis of relapsing-remitting MS after a comprehensive medical evaluation by fellowship-trained MS specialists; 3) 3 MRI time points containing a 3D T2-FLAIR sequence; 4) formal neuroradiology interpretation of MRI studies lacking the description of ≥ 1 enlarging/contracting T2-weighted hyperintense lesions or the presence of gadolinium-enhancing lesions at baseline or during follow-up; 5) no change in DMT or treatment course within the prior 6 months to each MRI; and 6) no exposure to oral or intravenous glucocorticosteroid treatment within the past 30 days of each MRI. Exclusion criteria included 1) MRI scans with low image quality due to motion artifacts or other causes that hindered effective registration or lesion segmentation or 2) incomplete medical records. The methodology proposed in the Strengthening the Reporting of Observational Studies in Epidemiology Checklist was followed for this study (Online Supplemental Data).

The protocol was approved by the UTSW institutional review board who granted a waiver for consent.

Clinical Relapses, MRI Advancement, Physician-/Patient-Reported Progression

A clinical relapse was defined as a new neurologic symptom consistent with CNS demyelination or worsening of a prior symptom, persisting for >24 hours, that occurred in the absence of fever or acute illness. MRI advancement was defined as the development of a new T2-weighted hyperintense lesion described within the formal neuroradiology reports. Physician-reported disease progression was based on findings documented on neurologic examination. Patient-reported disease progression included personal opinions about changes in mobility, physical functioning, sensory experiences, challenges with memory, fatigue, and quality of life.

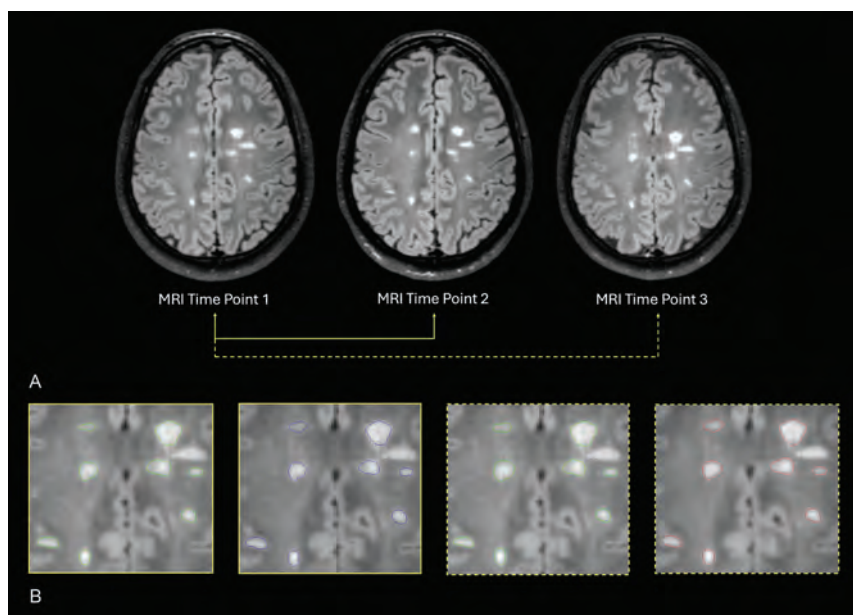


FIG 1. A, Axial T2-FLAIR brain images from 3 MRI time points. MRI time point 1 was registered to MRI time point 2 and MRI time point 1 was registered to MRI time point 3 before lesion segmentations. B, Example of T2-weighted hyperintense lesion segmentations by time point. Boxes in solid yellow demonstrate lesion selections at MRI time point 1 (left, circled in green) and MRI time point 2 (right, circled in blue). Dashed yellow line boxes show selections from MRI time point 1 (left, circled in green) and MRI time point 3 (right, circled in red).

MS DMTs

High-efficacy DMTs included alemtuzumab, natalizumab, ocrelizumab, ofatumumab, and oral cladribine. Low-efficacy DMTs comprised weekly or thrice-weekly interferon β -1 α , dimethyl fumarate, fingolimod, glatiramer acetate, monomethyl fumarate, ozanimod, and teriflunomide.

Image Acquisition

All imaging studies were performed on an Ingenia 3T MRI scanner (Philips Medical Systems) by using a 32-channel phased-array coil for reception and body coil for transmission at UTSW. Uniformity corrections were applied for all included scans during the acquisition phase. A 3D T2-FLAIR sequence ($1.1 \times 1.1 \times 1.1$ mm³, TE/TR/TI = 350/4800/1600 ms, flip angle 90°, $250 \times 250 \times 180$ mm³ FOV, NEX = 1163 slices, duration: 5:02 minutes) was used for the analysis.

The formal neuroradiologic impressions for each study were reviewed to ensure that included subjects lacked descriptors of enlarging/contracting T2-weighted hyperintense lesions.

Lesion Segmentation

Quality assurance measures were incorporated, including the evaluation of movement along with the presence of artifacts at each MRI time point. Individual lesions were selected if they had well-defined borders and measured at least 3 mm². Single lesions that coalesced with others were excluded. Of the lesions fulfilling these criteria, approximately 8–12 T2-weighted hyperintense lesions were randomly selected on MRI time point 1 by a single reviewer (D.T.O.) with additional details captured, including location, lobe, and hemisphere. The reviewer was blinded to baseline demographic and clinical information. The range of lesions

targeted in each individual allowed for proper sampling across different CNS locations and enabled the reasonable study of a meaningful number of lesions across many individuals. This facilitated an adequate comparison of changes in lesion dynamics based on their spatial dissemination characteristics. Targeted lesions were segmented by using an in-house fully automated platform utilizing expert supervision implemented in prior studies, MedIP.^{4,10–15} The MRIs for the 3 time points were initially registered based on structural positioning and intensity in which the second and third MRI time points were registered to the first time point (Fig 1). MRI studies were aligned by using the Insight Toolkit (Version 5.1.1; Kitware) multiresolution rigid registration with Mattes Mutual Information Metric.¹⁶ To ensure proper intensity alignment, histogram matching of intensities involving regions of interest was incorporated through linear transforms and ordered correspondence on a set of match points computed from the quantiles of each

histogram. After positional and local intensity alignment, segmentations were performed by implementing geodesic active contouring methodology (Fig 1).¹⁷

Lesion Threshold Determination

A centile curve was fit by using a λ , μ , and σ (LMS) method to estimate the standard deviation (SD) of the rate of volume change per year as a function of the lesion volume at the prior time point.^{18,19} The centile curve specifies a time-dependent variance so that at time t_j , the SD is estimated to be σ_j . Lesion expansion was defined to be an increase in the rate of volume change greater than $c \times \sigma_j$, a reduction if the rate of volume change was less than $-c \times \sigma_j$, and stable otherwise, such that c serves as a scalar value controlling the magnitude of the threshold.

Statistical Analysis

Baseline demographic and clinical data were summarized as the mean and SD when continuous and count and percentage when categorical. Linear regression was used to estimate the average T2-weighted hyperintense lesion volume at MRI time point 1 by lesion location. Tukey pair-wise comparisons were used to estimate differences in the average T2-weighted hyperintense lesion volumes between lesion locations within the CNS. The P values obtained from Tukey pair-wise comparisons were adjusted by using the single-step approach.²⁰

To classify lesions as expanding or contracting, a 1 SD threshold ($c = 1$) was determined based on the LMS curve such that if the rate of change in T2-weighted hyperintense lesion volume was greater than σ_j , it was classified as expanding. Similarly, if the rate of change in T2-weighted hyperintense

lesion volume was less than $-\sigma_j$, a lesion was classified as contracting. Then, for the i -th subject, let $n_{i,expand}$, $n_{i,contract}$, and $n_{i,stable}$ denote the number of lesions expanding, contracting, and stable (within $\pm\sigma_j$), respectively. A subject was then designated as improving overall if $n_{i,contract} > n_{i,expand}$, progressing overall if $n_{i,contract} < n_{i,expand}$, and stable otherwise. Logistic regression was then used to determine if there was a change in likelihood of overall improvement ($n_{i,contract} > n_{i,expand}$) for those receiving high-efficacy therapy or no therapy relative to those

receiving low-efficacy therapy, controlling for time from first symptoms and body mass index (BMI). Last, logistic regression was performed to test for differences in the odds of brain MRI advancement, patient-reported progression of disease, and physician-identified progression when an enlarging lesion is present in a particular region.

All analyses were performed in R (Version 4.3.2). A P value $< .05$ was considered significant.

RESULTS

The study cohort comprised 115 people with relapsing-remitting MS, with a mean age of 41.3 years (SD: 10.4 years) and mean disease duration of 9.36 years (SD: 7.72 years). The median time between MRI time point 1 and 2 was 1.2 years (range: 0.6–4.7 years), and from MRI time points 2 to 3, 1.1 years (0.6–4.1 years). Most people studied were treated with low-efficacy treatments (49.6%), followed by high-efficacy (27.8%), or no treatment (22.6%) (Table 1). A total of 1426 focal T2-weighted hyperintense MS lesions were identified on MRI time point 1 and longitudinally followed over MRI time points 2 and 3.

In the evaluation of raw changes in T2-weighted hyperintense lesion volumes within an individual from MRI time point 1 to MRI time point 2, a similar number of individuals were observed with predominantly expanding lesions (49/115; 42.6%) as compared with contracting (51/115; 44.3%). Only 15 individuals (13.0%) were identified with an equal number of expanding and contracting lesions within this period. When evaluating MRI time point 3 changes relative to MRI time point 1, more individuals were identified as having a majority of lesions that expanded

in volume (48/115; 41.7%) versus those that contracted (45/115; 39.1%) with 22 individuals (19.1%) having an equal number of expanding and contracting lesions.

The average periventricular T2-weighted hyperintense lesion volume at the initial scan was significantly greater than lesions located in juxtacortical/cortical ($P < .0001$), subcortical ($P < .0001$), deep white matter ($P < .0001$), paraventricular ($P < .0001$), and thalamic/deep gray matter ($P = .0001$) structures. Table 2 summarizes the observed differences in volume by location within the brain from MRI time point 1.

Fig 2 demonstrates the results from the LMS curve, estimating the standard deviation of the volume change rate per year as a function of the lesion volume at the prior MRI time point. Data points above the shaded region represent T2-weighted hyperintense lesion expansion, while data points below signify contraction, with those falling within the shaded region remaining stable based on the defined threshold.

Table 1: Baseline demographic and clinical data for the study cohort

N	115
Mean (SD) age (years)	41.3 (10.4)
Race (%)	
White	91 (79.1)
Black or African American	22 (19.1)
Native American	2 (1.7)
Sex at birth (%)	
Woman	81 (70.4)
Man	34 (29.6)
Mean (SD) height (inches)	66.4 (4.07)
Mean (SD) weight (kilograms)	80.1 (20.9)
Mean (SD) time from first symptom(s) (years)	9.36 (7.72)
Mean (SD) time from diagnosis (years)	6.62 (6.68)
Median (range) time: MRI time point 1 to 2 (years)	1.2 (0.6–4.7)
Median (range) time: MRI time point 2 to 3 (years)	1.1 (0.6–4.1)
Treatment (%)	
Low-efficacy	57 (49.6)
High-efficacy	32 (27.8)
None	26 (22.6)
Mean (SD) treatment duration (years)	2.1 (2.3)

Table 2: Differences in T2-weighted hyperintense lesion volumes (mm³) from MRI time point 1 between lesion locations within the brain

Comparison	Estimate	P Value
Infratentorial – deep white matter	–28.01	1.00
Juxtacortical/cortical – deep white matter	–2.50	1.00
Paraventricular – deep white matter	–30.64	.21
Periventricular – deep white matter	105.10	<.0001
Subcortical – deep white matter	–3.65	1.00
Thalamic/deep white matter – deep white matter	–9.71	1.00
Juxtacortical/cortical – infratentorial	25.50	1.00
Paraventricular – infratentorial	–2.64	1.00
Periventricular – infratentorial	133.11	.33
Subcortical – infratentorial	24.36	1.00
Thalamic/deep gray matter – infratentorial	18.30	1.00
Paraventricular – juxtacortical/cortical	–28.14	.47
Periventricular – juxtacortical/cortical	107.61	<.0001
Subcortical – juxtacortical/cortical	–1.15	1.00
Thalamic/deep gray matter – juxtacortical/cortical	–7.20	1.00
Periventricular – paraventricular	135.75	<.0001
Subcortical – paraventricular	26.99	.40
Thalamic/deep gray matter – paraventricular	20.94	.97
Subcortical – periventricular	–108.75	<.0001
Thalamic/deep gray matter – periventricular	–114.81	.0001
Thalamic/deep gray matter – subcortical	–6.06	1.00

Note:—All T2-weighted hyperintense lesions measured at least 3 mm² having an MRI appearance highly suggestive of multiple sclerosis. Lesion location definitions were as follows. Juxtacortical/cortical lesions were defined as T2-weighted hyperintense lesions having physical contact with the cortex with subcortical lesions defined as having a position below the cortex without apparent physical contact. Deep white matter lesions involved deeper regions of the white matter within the brain, away from the cortical/subcortical and periventricular/paraventricular regions. Periventricular lesions had direct contact with the ventricle and paraventricular lesions were positioned near the ventricle without physical connection. Thalamic/deep gray matter lesions had direct contact with the thalamus or basal ganglia. Infratentorial lesions involved structures below the tentorium cerebelli.

Utilizing this threshold for T2-weighted hyperintense lesion volume change and when evaluating MRI time point 1 to MRI time point 2, 27.8% and 13.0% of individuals were classified as having predominantly expanding and contracting lesions, respectively. Between these 2 time points, most (59.1%) were observed with equal numbers of expanding and contracting lesions or no expanding or contracting lesions. When evaluating MRI time point 1 to MRI time point 3, more people (76.5%) had equal or no expanding and contracting lesions, while 12.2% and 11.3% had a majority of expanding lesions or contracting lesions, respectively. The number and frequency of expanding, contracting, and stable lesions by location within the brain are provided in Table 3.

Regarding the impact of treatment on individual T2-weighted hyperintense lesion volume changes over the study period, no significant differences were observed between individuals exposed to high-efficacy DMTs versus low-efficacy DMTs ($P = .35$). Individuals not on active treatment had 67.15% reduction in the odds of more lesions contracting than expanding relative to those on low-efficacy treatment (95% CI = $[-83.89\%$ to -33.01%], $P = .0008$) and a 74.02% reduction in the odds of more lesions

contracting than expanding relative to those on high-efficacy treatment (95% CI = $[-87.37\%$ to -46.56%], $P < .0001$) after controlling for disease duration and BMI. There was also no significant impact of enlarging lesions on MRI advancement, patient-reported progression of disease, and physician-identified progression.

DISCUSSION

In this study, we demonstrated that MS lesions on MRI undergo dynamic change with more than 40% of individuals having predominantly enlarging or contracting T2-weighted hyperintense lesion characteristics. Importantly, these dynamic changes remained below the threshold of visual perception and therefore were not recognized or described within formal neuroradiology reports. Our findings appear to be consistent with dynamic changes in lesion behavior observed previously.^{4,13,21} The extent of lesion contraction was influenced by low- and high-efficacy DMT use compared with no treatment. The location of lesions within the CNS, disease duration, and BMI did not appear to influence volume change and the expansion of lesions and were not associated with clinical or MRI relapses or self-reported progression, findings that may have been influenced by the timeframe that individuals were followed.

The use of total T2-weighted lesion volumes, or burden of disease has been a key metric in clinical trials. The importance of the time course of T2-weighted lesion volume accumulation has been shown to impact disability measures at 20 years.²² Prior imaging techniques involving T2 subtraction demonstrated the ability to recognize occult changes from non-3D imaging sequences.²³ More recently, 3D conformational efforts have revealed the dynamic characteristics of MS lesions in orthographic view with lesions exhibiting deformation, or changes in shape, and displacement, changes in the original location, over time.⁴ Quantitative susceptibility mapping, myelin water fraction, and neurite attenuation index maps have also provided insights into lesion age.²⁴ Slowly expanding and non-expanding T2-weighted hyperintense lesions may also exhibit specific directional patterns and 85% of enlarging lesions have been associated with increases in T1-hypointense lesion volume.¹³ Stable lesions were also recognized in this work, however,

the absence of reporting changes in lesion volume when truly present may create a misleading impression of disease stability.

If distinct regions of the brain were associated with greater lesion dynamics, these data may be of value in the clinical monitoring of individuals or the study of molecules aimed at altering the biology and subsequent imaging properties of lesions. In the evaluation of raw changes in individual T2-weighted hyperintense lesion volume, periventricular lesions were found to increase in volume more than those within the juxtacortical/cortical, subcortical, deep white matter, and paraventricular regions, along with thalamic/deep gray matter.

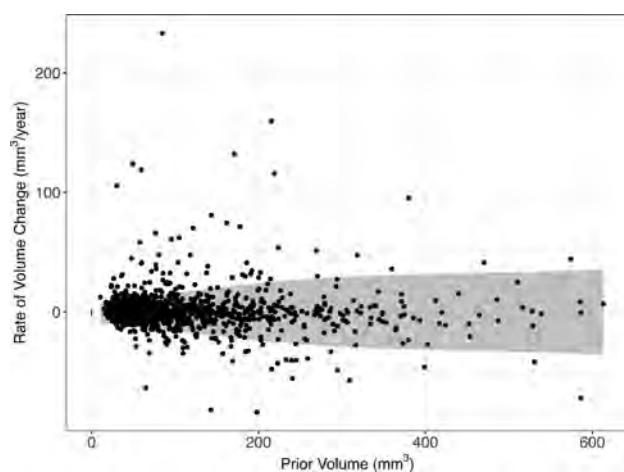


FIG 2. Estimated LMS curve for the rate of volume change per year, with shaded region representing ± 1 SD change.

Table 3: Number of expanding, contracting, or stable T2-weighted hyperintense lesions by location within the brain based on a defined threshold in volume change from the prior MRI time point

Location	N	Expansion (%)	Contraction (%)	Stable (%)
All	1426	103 (7.22)	62 (4.35)	1261 (88.43)
Juxtacortical/cortical	184	14 (7.61)	10 (5.43)	160 (86.96)
Subcortical	410	36 (8.78)	19 (4.63)	355 (86.59)
Deep white matter	630	47 (7.46)	21 (3.33)	562 (89.21)
Periventricular	68	4 (5.88)	7 (10.29)	57 (83.82)
Paraventricular	96	0 (0.00)	1 (1.04)	95 (98.96)
Thalamic/deep gray matter	34	2 (5.88)	4 (11.76)	28 (82.35)
Infratentorial	4	0 (0.00)	0 (0.00)	4 (100.00)

Note:—All T2-weighted hyperintense lesions measured at least 3 mm² having an MRI appearance highly suggestive of multiple sclerosis. Lesion location definitions were as follows: Juxtacortical/cortical lesions were defined as T2-weighted hyperintense lesions having physical contact with the cortex with subcortical lesions defined as having a position below the cortex without apparent physical contact. Deep white matter lesions involved deeper regions of the white matter within the brain, away from the cortical/subcortical and periventricular/paraventricular regions. Periventricular lesions had direct contact with the ventricle and paraventricular lesions were positioned near the ventricle without physical connection. Thalamic/deep gray matter lesions had direct contact with the thalamus or basal ganglia. Infratentorial lesions involved structures below the tentorium cerebelli.

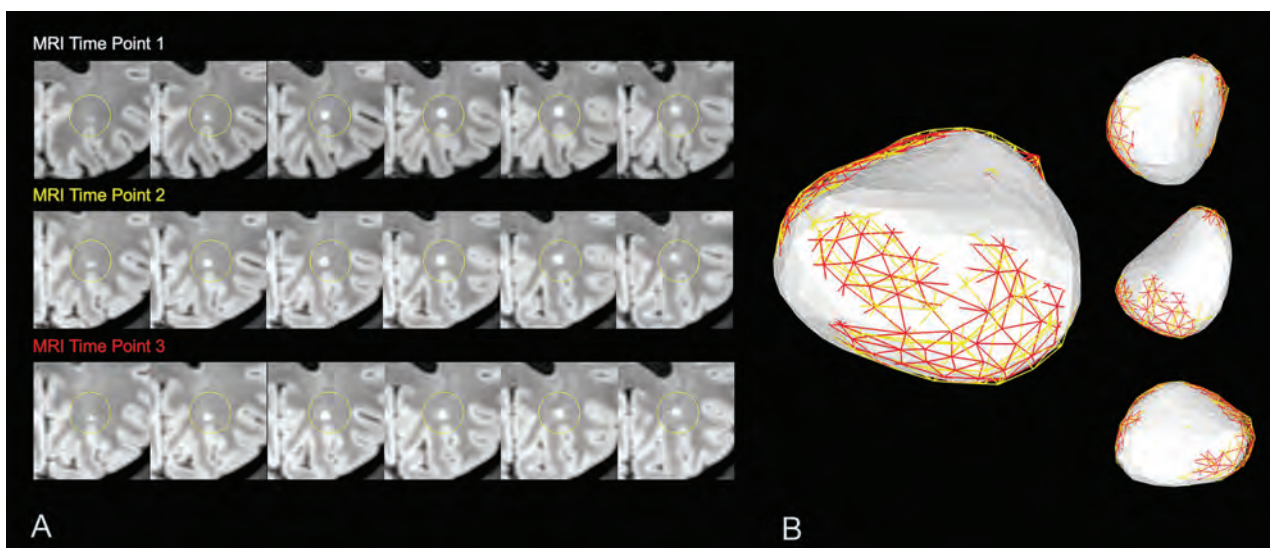


FIG 3. A, 2D MR axial T2-FLAIR images of a single MS lesion (yellow circle) from 3 MRI time points each performed a year apart. Observe the presence of the lesion throughout all slices within the MRI sequence. The T2-weighted lesion volumes were identified to be consistent between MRI time points: MRI time point 1, 41.8 mm³, MRI time point 2, 41.1 mm³, and MRI time point 3, 41.3 mm³. B, Visual models represented in 3D space depicting stable volumes over all 3 MRI time points (time point 1: solid white, time point 2: yellow mesh, time point 3: red mesh).

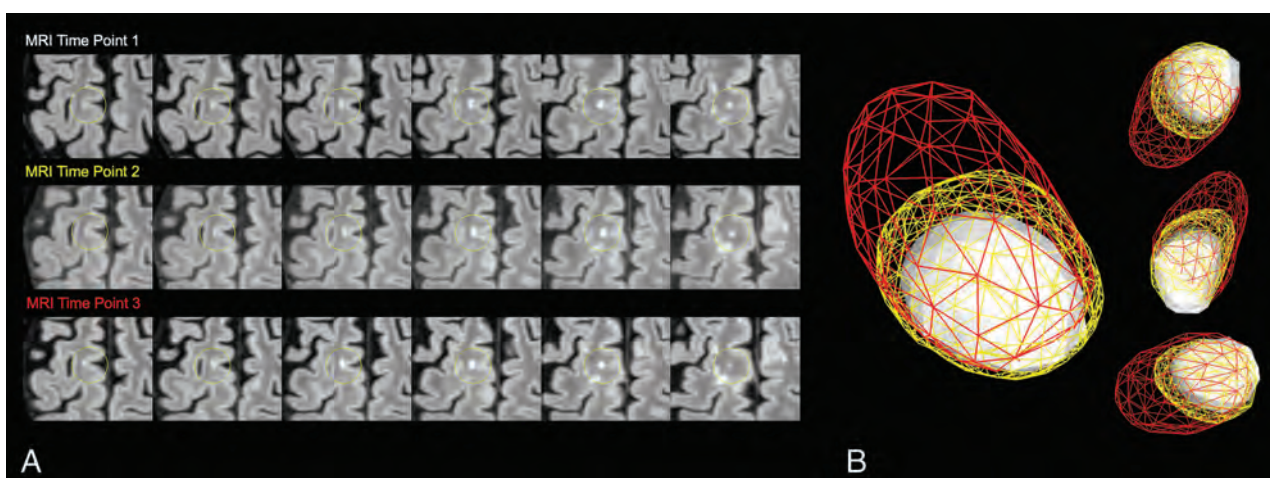


FIG 4. A, Axial 2D T2-FLAIR MR images of a single MS lesion (yellow circle) from 3 MRI time points (1 year between each time point). Note the presence of the lesion throughout all slices within the MRI sequence. Despite the similar appearance of the lesion on MRI, a volume difference of 58.2% was observed when comparing MRI time point 1 to 2, and a 51.3% volume difference when comparing MRI time point 2 to 3. B, Visual models represented in 3D space illustrating the dynamic expansion of the lesion between MRI time point 1 (solid white), MRI time point 2 (yellow mesh), and MRI time point 3 (red mesh) that is not appreciated on the 2D axial MRI view.

This may be due to the location of the lesions, having direct contact with the ependymal surface of the ventricle, along with the choroid plexus volume that may influence periventricular lesion volume.²⁵ Therefore, the characteristics of lesion dynamics in specific brain regions may be more effective for monitoring disease progression.

For the segmentation platform utilized in this study, we identified measures that deviated by a maximum of 0.82% when the same lesion is resampled up to 20 times. Similarly, when individuals were scanned and rescanned, repeat measures only deviated maximally by 1.2%. The findings reported here are of importance as the formal interpretation of brain MRI studies in untreated individuals described “stable” features without the report of newly enlarging T2-weighted hyperintense features. Comparing

T2-weighted characteristics between MRI time points may truly reveal stable findings (Fig 3). However, remarkable lesion expansions (Fig 4) may also be observed even when T2-weighted findings appeared unchanged. The reason for this may relate to our perception of the intricate spectrum of subtle gradations between black and white on MRI, altering our perspective of size estimation and change.²⁶⁻²⁸ Skewed perceptions of brightness peaks (maxima) and valleys (minima) at edges of luminance gradients occur due to the relative nature of visual processing in lateral inhibitory optic neurons,²⁹ which are responsible for contrast enhancement edge sharpening of visual stimuli and have been known to cause misinterpretation in other radiologic mediums.³⁰ In the primitive visual cortex, the brightness of surfaces is similarly

responsive to contrast cues in surrounding scenery.^{31,32} The brain is also designed to “fill-in” missing information (perceptual interpolation) to make sense of the 3D world on a 2D plane. As a result, certain changes may only be appreciated in a 3D configuration.³³ The combination of these limiting factors in 2D imaging comprehension by humans suggests that focusing on the dynamic properties of lesions in 3D without strictly adhering to 2D properties may offer a more accurate approach toward better characterization of lesion dynamics.

The use of high-efficacy DMTs did not significantly reduce individual T2-weighted hyperintense lesion volumes over time as compared with lower efficacy alternatives. Within key MS pivotal trials, even classic lower efficacy DMTs were found to be effective in suppressing the development of new and or newly enlarging T2-weighted hyperintense lesions.^{34–37} All participants in this study had a history of continued use of higher efficacy treatments beyond 6 months of the first MRI time point. In routine clinical practice, repeat MRI studies are performed 6 months after the start of a new treatment, representing new baseline MRI data. This time period allows for the prescribed treatment to achieve a full therapeutic effect. Therefore, the window for detecting any remarkable radiologic treatment benefit may have already elapsed. Alternatively, the observation of no difference between groups may have been due to different pathologic mechanisms not influenced by the anti-inflammatory nature of the treatments being used—whether high- or low-efficacy—or compartmentalized inflammation, because CNS penetrance is modest among the available treatments in comparison to the recently studied Bruton tyrosine kinase inhibitors.^{38,39} The lack of change over time may have also resulted from lesion age.^{40,41} In addition, observed expansion may reflect continued microglia activity at the lesion edge, at times yielding a hypointense rim that has been observed on susceptibility-sensitive imaging techniques.⁴² Fluctuations in T2-weighted hyperintense lesion volume may also have been influenced by self-repair or remyelination mechanisms, aspects not impacted by DMTs.^{43–45}

The study of randomly selected individual T2-weighted hyperintense lesions has benefits over assessing total T2-lesion volume. First, the study of individual lesions offers a higher level of precision for care as the study of total volumes may encompass the inclusion of nonspecific white matter lesions. Second, the use of total T2-weighted lesion volumes may mischaracterize the extent of disease. Advancing disease may lead to new and enlarging T2-weighted lesions coupled with contraction of prior lesions within the same individual, resulting in a net result of minimal change. Third, greater insights into the biology of disease may be identified. For example, how do we interpret the findings of 1 T2-weighted hyperintense lesion expanding in size in the setting of 6 that have contracted, as the former is an established metric for disease advancement in current MS clinical trials? Conversely, recent ¹⁸F-DPA-714 PET revealed the presence of an unexpectedly high proportion of MS lesions with a smoldering component.⁴⁶ Lastly, the approach may reflect simpler methods of studying disease burden across sites and may be of value within clinical trials, especially if future studies are able to demonstrate an association with future clinical/radiologic attacks or disability outcomes.

The provided work should be viewed in the context of limitations. First, not all lesions within the MRI studies were included in the analysis, which may have affected outcomes and only a single reviewer was used for the selection of T2-weighted hyperintense lesions. However, the sampling of a meaningful number of lesions across many people and the inclusion of 3 MRI time points per subject enhanced this work. Second, the threshold for an expanding, contracting, or stable lesion was defined based on the volume fluctuations for all the lesions studied. This threshold may be different if a much larger sample set is used within the analysis. Third, the study of an equal number of lesions by location was not performed. Therefore, a study involving a larger number of lesions may identify a propensity for T2-weighted hyperintense lesions to change more actively than described. Fourth, most people studied were White and including a more diverse group of individuals may reveal lesion dynamic patterns that differ from the results presented here. Fifth, the findings reported here were generated from retrospective data and a prospective study may yield different findings. Lastly, all individuals included in this study were acquired from a tertiary care center and the included subjects based on the MRI study criteria may not be generalizable to a larger group of people with MS.

CONCLUSIONS

Dynamic changes in T2-weighted hyperintense lesions are abundant, occurring below our visual perception of effectively discerning between shades of gray on MRI, and are present more frequently in untreated individuals. Our findings suggest that provided counseling involving results from surveillance MRI studies may be inaccurate and incomplete, failing to properly notify individuals of the benefit or inadequacies of their current DMT. Whether greater changes can be appreciated in those with progressive clinical courses is currently unclear. For now, recognizing these dynamic characteristics may offer a new perspective into the effective surveillance and subsequent management for those with MS.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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In the article “Partial (SAVE) versus Complete (Solumbra) Stent Retriever Retraction Technique for Mechanical Thrombectomy: A Randomized In Vitro Study” published in the October 2023 issue of *AJNR* (44:1165–70; 10.3174/ajnr.A7996), the authors regret that Santiago Ortega-Gutierrez’s name was published as Santiago Ortega.

In the December 2024 issue, credit for the cover art was omitted. The original art was created by Ann Mary John. Also in this issue, the credit line for the art on the third cover should read, “*A Look Within, The Brain of a Radiologist*” by Bar Neeman, and the credit line on the back cover should read, “*Yestermorrow*” by Andria M. Powers. The journal regrets these errors.

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Nidus of Brain AVMs: What If We Hadn't Understood Anything?

Brain arteriovenous malformations (bAVMs) are complex and aggressive vascular malformations that were, until recently, thought to be congenital. More data on the genetics and biology of these malformations support them being acquired lesions that develop on a predisposing background (the so-called “response to injury” theory) rather than congenital malformations. Additionally, there has been a major breakthrough in understanding AVM pathophysiology with the identification of somatic activation mutations in the *KRAS* proto-oncogene, specifically in the endothelial cells of AVMs.

The nidus is composed of dysplastic vessels with an ambiguous nature, sharing the pathologic characteristics of arteries and veins. These vessels do not supply the normal brain parenchyma.

Geibprasert et al¹ define the nidus as “The transition between artery and vein can take place via a so-called nidus (i.e., a tangle of abnormal vessels located in the brain parenchyma) or can be direct (i.e., fistulous) without any intervening network.” In Forsting and Wanke,² *Intracranial Vascular Malformations and Aneurysms*, Cognard and Pierot,³ in the chapter focused on brain AVMs (chapter 3), describe the nidus, “Anatomically speaking, they are constituted by a complex, tangled web of afferent arteries and draining veins linked by an abnormal intervening capillary bed—the so-called nidus—which may or not harbor direct arteriovenous shunts.” Most interesting, Newton and Potts,⁴ *Radiology of the Skull and Brain: Angiography*, in chapter 83 by Newton and Troost, focused on brain AVMs; the meaning of the term “nidus” is nowhere detailed.

The nidus (from the Latin language *nidus* = nest) is the center of gravity of the bAVM. Indeed, the shunt points of the bAVM are located in the nidal component of the bAVM. The nidus is, thus, the target of the exclusion treatment, whatever treatment technique is chosen.

The nidus is often represented in books and articles as a tangled web of dysplastic vessels, which can be more or less compact. In most drawings available in the literature and books, the nidus is displayed as a coherent vascular net fed by arterial feeders from one side, which exit one or several draining veins from the other side (Fig 1).

According to our experience in analyzing the angioarchitecture of bAVMs with new imaging tools like segmentation or anamorphosis

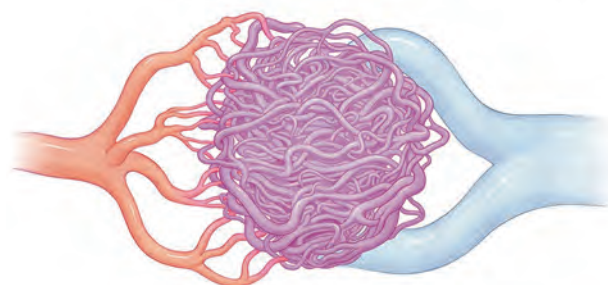


FIG 1. Classic representation of the nidus in most articles and books focused on brain AVMs.

algorithms, and to the recent advances of the transvenous approach for bAVM embolization that offered a reappraisal of the relationship between the nidus and the draining veins, the usual representation of the nidus in the literature appears to be more an intellectual construct than a faithful representation of the real details.

A very different understanding of the nidus has appeared since AVMs have been treated by transvenous embolization. The retrograde filling of the main vein of the AVM and later the primary veins has been playing a key role in redefining the angioarchitecture of the nidus.

The epicenter of the bAVM is the draining veins. The nidus may present as a “ball of yarn” and is called “plexiform” in such a configuration. Conversely, it may present a purely fistulous aspect. Some nidi may have a mixed pattern (Fig 2A). When the nidus is plexiform, it may present a spectrum of configurations depending on the compactness of the nidus, ranging from a very compact nidus to a widespread nidus. The nidus may drain directly into a main draining vein (Fig 2A), or it may drain in primary draining veins, draining themselves in a secondary draining vein (Fig 2B). The ball of yarn aspect of the nidus is because the main draining vein is usually rolled up on itself.

This more precise understanding of the organization of the nidus helps to better appreciate and anticipate the behavior of liquid embolic agents, especially ethylene-vinyl alcohol (EVOH) copolymer when injected via the arterial side and the pathomechanism of delayed hemorrhagic complications. Indeed, according to our experience, the different compartments of the nidus do not communicate with one another, except marginally via pial anastomoses. The main means (and almost the only one, without

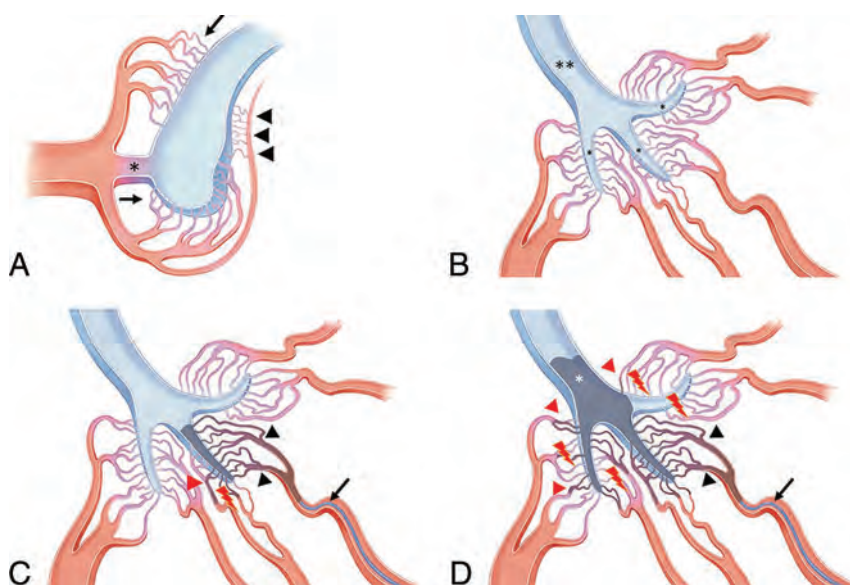


FIG 2. A, Drawing summarizing the different connection patterns of the arterial feeders with the draining vein through the nidus: via terminal branches (arrows), via “en passage” branches (arrowheads), or directly through the arteriovenous fistula (*). B, Drawing showing the connection of the vessels belonging to the nidus to the primary veins (*), which are draining themselves in a main secondary vein (**). C, An example of a liquid embolic agent (LEA) injection pattern at risk of secondary bleeding. The LEA is injected through a dimethyl-sulfoxide-compatible microcatheter (black arrow) feeding the target compartment of the nidus (black arrowheads). The LEA has filled the primary vein draining the target compartment, but the embolic agent has also refluxed in nidus vessels belonging to another adjacent compartment (red arrowhead). Because all the nidus vessels of this adjacent compartment are not occluded and the primary draining vein is compromised, the remaining nidus vessels of this second compartment are at high risk of bleeding (red lightning). D, Second, an example of an LEA injection pattern at risk of secondary bleeding. The LEA is injected through a dimethyl-sulfoxide-compatible microcatheter (black arrow) feeding the target compartment of the nidus (black arrowheads). All the nidus vessels of the target compartment are occluded, as well as the primary draining vein and all the nidus vessels of the adjacent nidus compartment. Inopportune progression of the LEA has occluded the secondary draining vein (*), as well as some nidus vessels from other compartments (red arrowheads). Because their venous outflow is compromised, these other compartments are at high risk of bleeding (red lightning).

considering the pial anastomoses) to occlude some portions of the nidus distant from the EVOH injection site while performing arterial side embolization is to penetrate via the draining vein and to retrogradely fill other portions of the nidus (in the same fashion as in embolization of intracranial dural arteriovenous fistulas treated with nonadhesive liquid embolic agents). No complication will be observed if all the nidus vessels communicating with the draining vein are occluded, even if this primary draining vein is occluded by the liquid embolic agent. If the secondary draining vein is occluded or slowed down, no bleeding will occur only if all vessels belonging to the nidus are occluded. Conversely, bleeding events may be observed in 2 scenarios: when the primary vein is occluded (or dramatically slowed down) and all the nidus vessels communicating with this vein are not occluded (Fig 2C) and when the secondary vein is occluded (or dramatically slowed down), while all the nidus vessels (ie, nidus vessels of all the compartments) are not occluded (Fig 2D).

In conclusion, the representation of the nidus of brain AVMs for many years in drawings may have negatively influenced our understanding of the angioarchitecture of bAVMs. Additionally, it may have led to a misunderstanding of the causes of embolization-

related hemorrhagic complications, while contaminating the draining veins with liquid embolic agents.

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Letter to the Editor regarding “Automated Volumetric Software in Dementia: Help or Hindrance to the Neuroradiologist?”

I would like to thank Tanabe et al¹ for their very relevant work in assessing the added value of image quantification in supporting the diagnosis of neurodegenerative disease, in particular Alzheimer disease and frontotemporal lobe dementia. Such studies help to better understand the possible value of brain volumetric reports in clinical practice.

The presented method for evaluating the impact of the brain volumetric report is a multireader multicase (MRMC) design, which plays a key role in translating novel imaging tools to clinical practice.^{2,3} However, MRMC studies can provide misleading results.²

In this letter, I would like to discuss the impact of 2 design limitations on the conclusions. The main limitation, which the authors mention, is the limited sample size of 80 cases and 4 readers (240 reads). MRMC studies that have shown improved reader performance for artificial intelligence–based devices used in clinical practice have sample sizes reported from 540 to 13,500 reads (FDA database, see Table). The average number of cases and readers are 315 and 17, respectively, indicating the study is likely underpowered to conclude that brain volumetric reports are improving radiologic reader performance. Hence, an underpowered study cannot conclude there is no improvement in reader performance, but only that reader improvement could not be proved (as the null hypothesis could not be rejected). This is further illustrated with the generalized linear mixed model that showed a positive but nonsignificant effect on reader performance by using brain volumetric reports (OR: 1.37, $P = .17$).

A second limitation relates to the control cohort that was selected of patients who reported subjective memory symptoms without abnormal findings on neurocognitive testing or a dementia clinical diagnosis. Although neoplasm, cerebral infarction, and intracranial injury are listed as exclusion criteria, this selection method could not exclude the presence of neurodegenerative disease. On the contrary, epidemiologic data provide evidence that the risk for mild cognitive impairment and dementia is increased in individuals with subjective cognitive decline (SCD),⁴ and that

Number of cases and readers of reader studies of FDA cleared devices

Device	# Cases	# Readers	# Reads
Thyroid	650	15	9750
Virtual node clinic	300	12	3600
Saige-Dx	240	18	4320
QuantX	111	19	2109
Insight	240	12	2880
Osteodetect	200	24	4800
Rayvolve	186	24	4464
ProstatID	130	9	1170
Fracturedetect	175	24	4200
BU-CAD	628	16	10,048
DS for breast	900	15	13,500
Genius AI Detection	390	17	6630
Mammoscreen	240	20	4800
360 e-ASPECTS	54	10	540
Transpara	240	14	3360
Boneview	480	24	11,520
icobrain aria	199	16	3184
Mean	315	17	5346
Median	240	16	4320

hippocampal atrophy in this population has been demonstrated to be associated with future cognitive decline.^{5–7}

Hence, we hypothesize that the poorer reported performance of assisted reading could reflect the improved detection of subclinical disease, thus assisted reading may improve prediction of decline in the population with SCD.

If the control cohort is excluded from the analysis, the “exact” and “rough” reader accuracies increase from 35% to 51%, and from 51% to 62%, respectively.

Based on my read of the results, I would conclude that this limited sample MRMC study could not prove that the reader accuracy is improved when the readers are using brain volumetric reports. However, the results show potential for improving the detection of Alzheimer disease, frontotemporal lobe dementia, and possible patients at risk for cognitive decline in the SCD cohort. A larger sample study is needed with more cases and more readers.

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REPLY:

We thank Dirk Smeets for his interest in our article and *AJNR* for the opportunity to respond. Regarding sample size, our study is in line with previous work comparing the effect of a report with no report on accuracy among clinical readers. Our study had the same or more cognitively healthy (CN) participants as in similar prior studies.¹⁻³ Most interesting, it was the CN group in which the report was associated with lower accuracy. These prior studies had 3–9 readers, including trainees and non-neuroradiologists. To mirror actual practice, we had 4 neuroradiology attendings. Smeets cited an FDA database as the basis for the total number of examinations and readers necessary to demonstrate improved performance, presumably for FDA approval; however, it is not clear whether the FDA measure consists of a comparison of radiologists' diagnoses with-versus-without a report. Still, we agree that a larger sample is needed. The reality as noted in the article cited by Smeets is that MRMC studies "are quite expensive to conduct, requiring a good deal of readers' time for image interpretation."⁴

Regarding the validity of a control cohort of patients with subjective memory symptoms, it is exactly this group that must be differentiated from patients with neurodegenerative disease. Second, volumetric analysis showed that the hippocampal, temporal lobe, parietal lobe, and whole-brain volume normalized volumes

were higher in CN relative to patients with AD and FTD, suggesting that they were CN. Last, although it is possible that the CN group might develop AD in the future, it is conjecture at this time.

While our study did not demonstrate a change in the accuracy of neuroradiologists' diagnoses with the report, we believe that quantitative volumetrics is superior to visual assessment in estimating brain volumes and advocate its use as an adjunct to clinical interpretation.

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