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Potential neurotoxic effects of gadopentetate dimeglumine: clinical significance.

A Alhassan and H J Weinmann

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LETTERS

Radiation-Induced Temporal Lobe Necrosis

Because nasopharyngeal carcinoma has a high frequency of intracranial spread, adequate radiation treatment inevitably results in irradiation of the temporal lobes.

A 38-year-old woman who was treated for nasopharyngeal carcinoma 30 months previously and had been given radiation therapy (70 Gy to the primary site) presented with headaches. Computed tomography (CT) showed an enhancing lesion in the right temporal lobe, with edema extending superiorly into the parietal lobe. Biopsy revealed brain necrosis and a course of corticosteroid therapy was started. Five months later, magnetic resonance (MR) showed less edema in the right temporal lobe but an extensive lesion on the contralateral side, not seen before (Fig 1A–C). Corticosteroid therapy was again given and 9 months later, the nasopharynx was reevaluated but no tumor recurrence was seen. MR showed dilatation of the temporal horns indicating cerebral atrophy (Fig 1D). Enhancing lesions in both temporal lobes were still evident, though less extensive than before.

Doses below 60 Gy at conventional 2 Gy daily appear inadequate for tumor control (1). Unfortunately, the effective dose for nasopharyngeal carcinoma (65 to 70 Gy) exceeds the quoted tolerance limits for the adjacent neural structures (2). There is, therefore, a substantial risk of radiation damage to the brain. Temporal lobe necrosis (TLN) is the most dreaded complication of radiation therapy and accounts for 65% of treatment mortality. Lee et al (1) reported a 3% cumulative incidence of TLN in a series of 4527 patients. The latent interval ranged from 1.5 to 13 years (median, 5 years). TLN is probably underdiagnosed, because in Lee et al's study 39% of patients had only vague symptoms, whereas 16% had no symptoms (3).

Although the radiation dose to the brain is approximately equal on both sides, changes in the brain are often asymmetric. Half the patients with TLN will present with unilateral abnormalities; in only 10% of these patients will bilateral lesions subsequently develop (3). The earliest sign of TLN is cerebral edema, which can be extensive. Enhancing lesions can be located in the gray or white matter. On CT, TLN appears patchy but delayed scans often show less inhomogeneity and better-defined margins. On MR, the necrotic foci show patchy enhancement but demarcation from the adjacent brain is better seen. Necrotic foci within the gray matter are often associated with minimal edema. These lesions at the skull base can be difficult to detect on CT and hence are better seen with MR.

When treated early with corticosteroids, patients can make a complete or near-complete clinical recovery with only residual cerebral atrophy. However, in patients with extensive necrosis, macrocystic encephalomalacia of varying degrees is the end result. An interesting feature among corticosteroid responders is a 12% incidence of

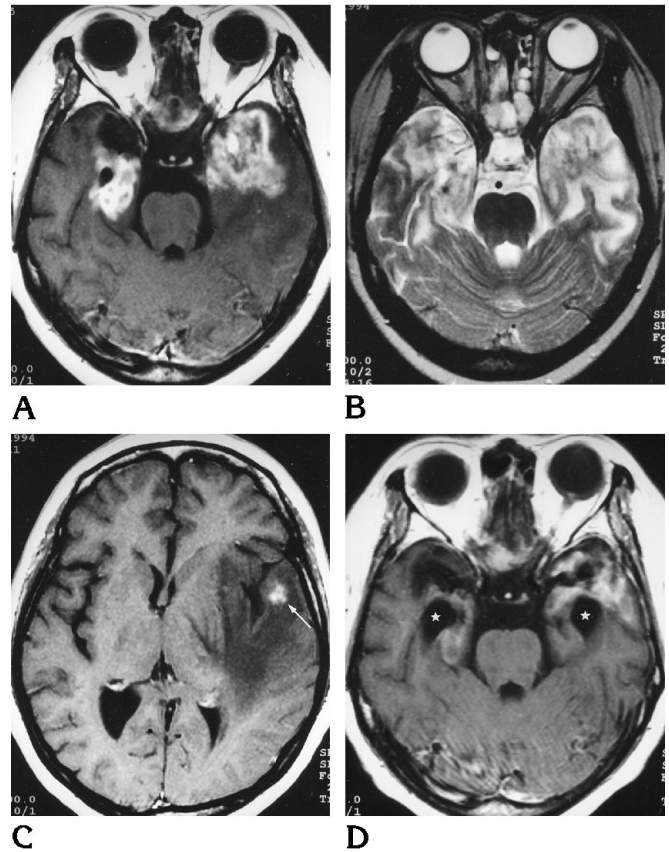


Fig 1. A, Axial contrast-enhanced MR image (600/15/2 [repetition time/echo time/excitations]) shows enhancing lesions in both temporal lobes.

B, Axial T2-weighted MR image (5000/90/1) shows bilateral temporal lobe edema. The necrotic areas appear relatively hypointense compared with the surrounding zone of edema.

C, Axial contrast-enhanced MR image (600/15/2) shows extensive edema in the left temporoparietal area not seen previously. A focus of contrast enhancement in the left parietal lobe is noted (arrow).

D, Axial contrast-enhanced MR image 9 months later (600/15/2) shows bilateral temporal horn dilatation (stars). No edema is seen but residual enhancement in both temporal lobes is noted.

necrosis on the side that initially appeared normal on CT, as was seen in our patient (3).

The disparity between clinical and radiologic findings is noteworthy and highly suggestive of TLN. Together with an appropriate history, a presumptive diagnosis can be made and pathologic proof in most cases is not required (4). Changes in the temporal lobe remain worrisome because tumor recurrence still needs to be considered. NPC with intracranial recurrence is rarely associated with cerebral edema.

Positron emission tomography (PET) with fludeoxyglucose F 18 (FDG) accumulates considerably lower levels of

FDG in areas of radiation-induced necrosis than recurrent tumor, but radiation-induced necrosis sometimes appears hypermetabolic. Single-photon emission CT (SPECT) with thallous chloride TI 201 can also be used to separate the above entities. There is, however, no significant difference in the ability of TI 201 SPECT and FDG PET to separate tumor from radiation-induced necrosis consistently (5).

In summary, one must be aware of the appearance of TLN in a patient who received previous radiation therapy to the skull base. TLN should not be mistaken for tumor recurrence or intracranial metastasis because the therapeutic approach to these are different, one requiring more radiation and the other none at all.

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Potential Neurotoxic Effects of Gadopentetate Dimeglumine: Clinical Significance

In a recent issue of the *AJNR*, Ray et al (1) reported that, in a rat model, high doses of gadopentetate dimeglumine (Magnevist) injected intrathecally cause both acute and lasting neurotoxic effects. Unfortunately, no reference standard was included in this well-conducted experimental study to enable the reader to put the findings into perspective. Results of other agents analyzed with similar techniques have not been reported in the literature.

The intrathecal dose of 5 $\mu\text{mol/g}$ brain used by Ray et al is equivalent to a dose of 5 mmol/kg body weight and so the brain shows exactly the same tolerance threshold as the whole body (intravenous median lethal dose [LD_{50}] is approximately 5 mmol/kg). Rats given high intravenous doses (>2.5 mmol/kg) daily for subacute toxicity testing showed no special neurodeficits: it seems the normal blood-brain barrier protects the brain even from extremely large concentrations circulating in the blood. Other commonly used diagnostic agents, including iodinated x-ray contrast media, have been reported to cause acute exci-

tation (2). These agents elicited strong reactions, including death, at a much lower dose of about 80 $\mu\text{mol/kg}$ administered intracisternally.

The clinical relevance of toxicologic findings after intracisternal injection is not clear. A large dose of any compound administered directly into the central nervous system is likely to elicit neurotoxic effects and the temptation to infer that similar effects could occur when clinically used doses of the same compound are administered intravenously should be resisted.

Magnevist is indicated for intravenous use at doses of up to 0.3 mmol/kg body weight in some countries. At these doses, no Magnevist-related neurotoxic effects have been reported to our knowledge. This supports experience with Magnevist at routine doses (0.1 to 0.2 mmol/kg) in more than 10 million patients (3, 4). Ray et al mentioned that the German federal health authorities advised against the use of Magnevist in infants less than 2 years of age. This recommendation (in 1993 in a "rapid alert letter") suggested that Magnevist should not be used in these children because the blood-brain barrier might not be fully developed at that age. This should be reviewed carefully, because it has been established that gadopentetate dimeglumine will not cross the blood-brain barrier even in neonates (5). Further evidence comes from the absence of neurologic adverse events in a clinical trial involving 72 infants aged 0 to 2 years (Schering Pharma Research Report No. A 650, data on file at Schering AG), and from a postmarketing surveillance study by Nelson et al (6) that included 74 patients less than 2 years of age. There was no statistically significant difference in the rate of adverse reactions among infants, neonates, and older patients.

Several European countries, including Germany, have now granted marketing licences for Magnevist to be used in patients younger than 2 years.

Ray et al have produced an interesting paper on the specific neurotoxic effects of a gadolinium-based contrast agent injected intrathecally at high doses, and we look forward to seeing data generated with other agents used in diagnostic radiology. Their speculations as to possible clinical ramifications are not supported by clinical studies in children and postmarketing experience in a very large patient population. It would be interesting to learn the neural tolerance of ionic x-ray contrast materials that are being used in much larger amounts in clinical routine without eliciting significant neural toxicity findings.

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Reply

It is difficult to model the unusual state of potential vulnerability to toxic agents presented by the human brain in conditions of abnormally increased blood-brain barrier permeability. Normal animal toxicity testing does not simulate this condition because the agent does not gain significant access to the intact brain. Our rodent intracerebroventricular injection model represents one attempt to achieve this access, to examine the nature of the toxicity, and to estimate safety margins.

MR contrast agents are commonly used in patients with such blood-brain barrier problems. We chose to begin with one agent, gadopentetate dimeglumine, because it had been previously reported to cause adverse effects, osmotic barrier disruption, in another animal model (1). In our model we found it to have a low but finite potential to produce excitation and brain lesions, some in areas not accessed by the osmotic model. Our conclusion was that these high-dose effects were unlikely to be seen in normal clinical use.

Alhassan and Weinmann point out that gadopentetate dimeglumine has proved safe in clinical practice, and we are glad to have further clinical confirmation of our own conclusions that it is safe *when used at the recommended dose and route*.

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Editor's note.—Invited comments on the article by Ray et al and the letter from Alhassan and Weinmann follow.

Comment

The article by Ray et al draws attention to the fact that intraventricular administration of high-dose gadopentetate

dimeglumine in rats produces neurotoxic effects manifest by both behavioral changes in living animals and neuropathologic changes at autopsy. Although the authors acknowledge the limitations of their study, the implications are that even conventional-dose, intravenously administered gadolinium contrast might have subtle neurobehavioral and neuropathologic effects.

The letter by Alhassan and Weinmann provides some perspective on the dose of gadolinium contrast used in these experiments in relation to whole-body doses and toxicities. Furthermore, they correctly point out that intraventricular injection of many hyperosmolar drugs and substances irritate the brain and can induce neuropathologic alterations.

What does all this mean for the practicing neuroradiologist? We neuroradiologists do not inject gadolinium contrast intrathecally into human patients. We do commonly inject iodine-based contrast intrathecally, however, and are aware of the occasional neurotoxic effects (eg, headaches, nausea, seizures) induced by these familiar drugs and dosages.

In the experiments of Ray et al, the lowest dose of intrathecal gadopentetate dimeglumine producing neurobehavioral and neuropathologic changes was 20 $\mu\text{L/g}$ brain. How does this dose compare to the intraventricular or intrathecal injection of a nonionic iodine-based contrast agent, such as iohexol or iopamidol?

Keeping in the realm of round numbers, let us assume a human brain weighs about 1500 g and that for a shunt ventriculogram patency study we might inject as much as 5 mL of iohexol or iopamidol. (This is a generous estimate, because often only 1 to 3 mL of contrast is required.) The administered dose of intraventricular iodine contrast per gram of brain in this case would be 5 mL (5000 μL) $\div$ 1500 g $\approx$ 3.3 $\mu\text{L/g}$ brain. Furthermore, because the osmolality of gadopentetate dimeglumine is approximately 3 times higher than that of iohexol or iopamidol, the equivalent osmotic dose for comparison with the toxicity experiments of Ray et al would be only one third this much, or about 1.1 $\mu\text{L/g}$ brain.

Using this comparison, the minimum neurotoxic dose of gadopentetate dimeglumine used in the experiments of Ray et al (20 $\mu\text{L/g}$ brain) is at least 20 times higher than the "osmotically adjusted" dose of iodine contrast used for intraventricular injection in humans. Because even conventional doses of intrathecally administered iohexol and iopamidol can be associated with subclinical leptomeningitis, electroencephalographic, or psychometric changes (1-3), we should not be too surprised that a significantly higher intrathecal dose of gadopentetate dimeglumine would have demonstrable behavioral and neuropathologic effects. Exceeding the conventional dosage of nearly any drug by a factor of 10 to 20 will likely result in significant biological toxicity.

Attempting to extrapolate potential neurotoxic effects of low-dose intravenous iodine or gadolinium contrast from experiments using high-dose intraventricular contrast is intriguing but treacherous. Although work of Ray et al is provocative, it is far from being immediately applica-

ble (or even relevant) to the intravenous administration of conventional-dose gadopentetate dimeglumine in humans. If you are still overly concerned about the clinical ramifications of their research, please take 20 000 mg of aspirin and call me in the morning.

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Comment

In their article, Ray et al attempt to determine the neurotoxic potential of gadopentetate dimeglumine in an animal model by showing functional effects after intraventricular administration. This article has two sets of implications. The first deals with the practicality of actual cisternography using a gadolinium contrast agent. The second concerns potential neurotoxic effects of gadolinium chelates when given intravenously in patients in whom blood-brain barrier disruption might have occurred.

With respect to intracisternal injection of gadolinium, early reports have discussed the potential of placing MR contrast agents in the subarachnoid space. For example, Di Chiro et al (1) injected varying doses (six doses of 0.5 mL, each of progressively higher concentrations ranging from 0.125 to 250 mmol) of gadopentetate dimeglumine into the cerebrospinal fluid (CSF) of eight monkeys and found correspondingly varying levels of CSF enhancement. At the doses they used, no adverse effects were seen. The authors noted that gadopentetate dimeglumine cisternography and myelography might be useful in MR imaging of central nervous system disease, for example, in tumors adjacent to CSF cavities, abnormal CSF collections (for example, arachnoid cysts), CSF rhinorrhea and otorrhea, syringohydromyelia, and studies of hydrocephalus and CSF flow dynamics.

For multiple reasons, direct intracisternal injection of gadolinium chelates has never been a topic of concentrated research. First, it is obviously an extremely invasive procedure. Second, the very basis of MR physics allows us to alter signal intensity in the CSF noninvasively, by manipulating parameters in one of several available pulse sequences. Therefore, a contrast agent is really not

needed. For example, El Gammal et al (2) recently used a heavily T2-weighted fast spin-echo technique, combined with background suppression, to perform MR cisternography. They noted that MR cisternography might be useful in evaluating CSF fistulas and suprasellar and posterior fossa masses and in differentiating intraaxial from extraaxial tumors.

One exception to the general rule that direct instillation of gadolinium into the CSF is not needed might be in the unusual patient with a history of severe iodinated contrast reactions who cannot undergo MR and needs myelography. A recent paper by Kaufman et al (3) suggests using gadolinium chelates in place of routine iodinated agents for angiography in patients with a history of severe past reactions. Such an approach might also be useful in myelography in the extreme clinical circumstance noted above.

Even if instillation of gadolinium into the CSF is considered, the intrathecal placement of gadopentetate dimeglumine, specifically, has not been seriously considered since it is an ionic contrast agent. It is well known from myelography that any contrast agent placed in the CSF should be nonionic (4). For all of the above reasons, the implications of placing gadopentetate dimeglumine in the CSF for clinical purposes are not really relevant.

Of greater concern is the implication that gadolinium chelates given in normal dose intravenously can cause neurotoxic effects in patients with an altered blood-brain barrier. There is no question that gadolinium chelates can pass through the disrupted blood-brain barrier and even enter the CSF in a concentration high enough to produce shortening of T1. For example, enhancement of the entire CSF space can be seen in patients with either severe meningitis or leptomeningeal tumor after intravenous administration of contrast because of presumed leakage of gadolinium chelate into the CSF (Fig 2). Yet even in these cases, no neurotoxic effects have been seen.

It is notable that the intrathecal doses used in this paper are equivalent to far higher doses than would generally be given intravenously in routine imaging. In fact, simple

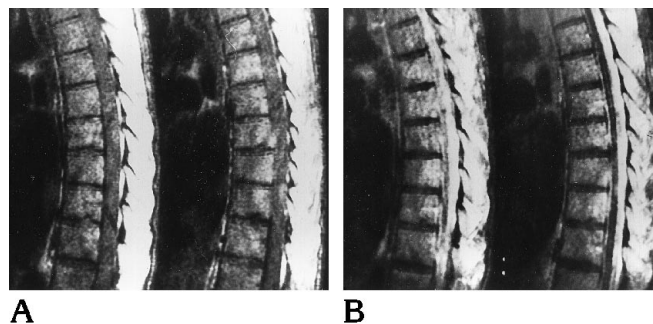


Fig 2. A, Short-repetition-time (550/12) MR image shows poor definition of the intraspinal structures. The cord cannot be identified.

B, After the administration of contrast material, short-repetition-time (550/12) MR image shows diffuse enhancement of the entire CSF space. The cord is now well delineated as a markedly hypointense structure, compared with the enhancing CSF.

calculations show that they approach the intravenous LD₅₀ of 5 mmol/kg, compared with the normal 0.1 to 0.3 mmol/kg in clinical use. The fact that neurotoxicity can be produced by intracisternal injection of such high doses seems clinically irrelevant. One wonders how the ionic iodinated contrast agents used routinely in CT would fare if a similar experiment were performed. Clearly, in patients with a mostly normal blood-brain barrier, the vast experience with gadopentetate dimeglumine shows that the neurotoxic effects reported in this paper do not occur (5, 6).

If the blood-brain barrier were disrupted diffusely, Ray et al imply that levels that approach the threshold level indicated in their paper, particularly after triple-dose administration, might be reached. This suggestion makes the significant assumption that brain tissue levels approach peak plasma levels. Such an assumption has been indicated not to be the case in prior work by Morris et al (7), who showed that peak CSF and neural tissue concentrations remain far below peak plasma concentrations. Nevertheless, caution might be indicated with new agents, such as RMP-7 (Alkermes), which are being used on an experimental basis to increase blood-brain barrier breakdown before the intraarterial administration of chemotherapy for the treatment of primary brain tumors. In cases such as this, gadopentetate dimeglumine might be avoided. For example, Roman-Goldstein et al (8) found that in a dog model, gadopentetate dimeglumine used in conjunction with osmotic blood-brain barrier disruption led to a statistically significant dose-dependent increase in the frequency of seizures. Other than in such extreme examples, however, it is unlikely that the paper by Ray et al will raise real, clinically relevant concerns.

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MR Findings in Essential Hypertension

In the provocative study concerning MR screening for neurovascular compression in essential hypertension, Watters et al (1) retrospectively studied a large group of patients who underwent MR studies for any reason. They concluded that vascular compression of the root entry zone of 9th and 10th cranial nerves does not produce hypertension.

We have a few problems with their method of evaluation and conclusion. First, they did not clarify their patients' blood pressure and duration of hypertension. Patients with transient hypertension must be excluded. Second, they used nonhypertensive patients who had undergone MR for symptomatic brain disorders as control subjects. As they mentioned, such patients would not be a suitable control group. Some disease processes such as arteriosclerosis can cause false-positive results. We believe that they should have studied younger patients to exclude arteriosclerosis and aging effect. Third, they evaluate vascular compression against the lateral medulla with routine spin-echo images probably taken for other diagnostic purposes. They used spin-echo T2-weighted sequences with 5-mm sections at 7-mm intervals. For depiction of cranial nerves other than the 5th and 8th, we would recommend a three-dimensional Fourier transform T1-weighted sequence (2). In addition, because the root entry zone of the 9th and 10th cranial nerves lies within 15 mm of the pontomedullary junction, there is only one section that is adequate for evaluation. We should use specific sequences for this delicate study.

We admit that there might be a significant number of patients with "essential hypertension" not caused by neurovascular compression of the ventrolateral medulla. We observed that 22.2% of a control group showed false-positive findings, as Tash et al (3) observed in a study of 7th nerve neurovascular compression. We must confirm our findings with larger studies with the results of neurovascular decompression for essential hypertension.

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Reply

We thank Dr Akimura and colleagues for their comments. Their study, like ours, looked at MR screening for vascular compression of the medulla in patients lacking symptomatic cranial neuralgias.

All our patients, both hypertensive (group 1) and nonhypertensive control subjects (group 2), had symptomatic brain disorders prompting MR. The primary variable was whether there was a history of chronic essential hypertension, defined in accordance with published criteria (1). Cases of transient hypertension were not included. We reviewed the same MR sequences for both groups and feel that any sampling errors due to sensitivity should affect both groups similarly. Our review was retrospective, and hence relied on standard sequences used in clinical practice. Such sequences are familiar and indeed proved sensitive enough to reveal compressions in the majority of patients in both groups. The MR sequence used for grading purposes was the axial T2-weighted spin echo, although other sequences as suggested by Dr Akimura and colleagues might improve resolution of the cranial nerves. The Akimura prospective study was not yet published at the time of completion of our study, and we felt that our spin-echo T2-weighted MR imaging would be more sensitive and less invasive than the previously published angiographic data (2). Additionally, with our sequences we were looking for contact or compression of the brain stem in the region of the root entry zone of cranial nerves IX/X, and not imaging of the cranial nerves per se. Our MR sectioning of 5-mm thickness at 7-mm intervals would allow at least 2 images through the 15-mm interval between the pontomedullary junction and the root entry zone, not a single image as suggested by Dr Akimura and colleagues.

Our hypertensive group's mean ages were 63 years (male) and 61 years (female), only slightly older than the hypertensive patients in the Akimura study (58 years). Our nonhypertensive control group, like the controls in the Akimura study, were younger (53 years for male and 50 years for female) and of similar age as the Akimura control group (50.5 years). Although we did not include these data in our published study, we do have additional data regarding the mean age (in years) and the grade of MR findings:

	Group 1 (Hypertension)	Group 2 (No Hypertension)
Grade 0	63.9	52.3
Grade I	59.7	49.8
Grade II	63.4	50.5
Grade III	65.3	68.7

Among those with MR abnormalities (grades I to III), the mean age advances as the degree of brain stem compression increases. This trend (not significant) was seen in both groups. Serial images over time would be needed to assess the effects of aging on compression and hypertension.

Unlike Akimura et al, we found similar MR abnormalities in both groups. The Akimura study found an incidence similar to ours of brain stem compression among hypertensive patients, but much less compression in their volunteer nonhypertensive control group. Our control group, like our hypertensive group, had symptomatic brain disorders prompting MR evaluation, and hence differed from our study group principally on the basis of no hypertension and slightly younger age. The lower prevalence of MR abnormalities in the Akimura study controls may be a result of using neurologically asymptomatic volunteers, and their smaller sample size ($n = 18$, compared to $n = 60$ in our study). We agree with Akimura et al that larger studies would be helpful for assessing the effect of neurovascular compression on the development of chronic systemic hypertension in patients lacking symptomatic cranial neuralgias.

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Editor's note.—Dr Akimura et al's letter was also forwarded to Robert Tash and Gordon Sze for their review. Their comments follow.

Comment

There have been discussions in the literature of MR findings in patients with hyperactive dysfunction syndromes (1, 2). Trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neuralgia have been discussed at some length, but there has been only limited discussion of brain MR findings in essential hypertension. As in the other hyperactive dysfunction syndromes, it is thought that continuous pulsatile pressure on the left ventrolateral medulla can result in "misfiring" of neurons, resulting in the symptoms in some patients with essential hypertension. This potential cause of essential hypertension has received little attention in our literature, despite the large size of the affected population.

The articles by both Akimura et al and Watters et al deal with the MR findings in patients with essential hypertension

with respect to compression of the left ventrolateral medulla by vascular structures. Despite differences in scanning techniques, both had similar results in their hypertensive groups. Akimura found 22 (69%) of 32 and Watters found 34 (57%) of 60 patients had neurovascular contact and/or compression of the left ventrolateral medulla. The major difference in their reported results is between the respective control groups. Akimura found 4 (22%) of 18 and Watters found 33 (55%) of 60 normotensive patients had neurovascular contact and/or compression of the medulla. Explaining this difference is difficult but probably multifactorial. First, methods of selection of the control group might have played a role. Second, technical factors in MR acquisition differed, as did methods of scoring the degree of impingement by the vessel on the lateral medulla. Third, in neither paper were blinded readings used. It should be noted that in both studies, the control group was younger than the hypertensive group. Clearly, a study of a larger population of control patients would yield a more realistic and reproducible figure.

Finally, one other point should be made. With age, there is elongation and tortuosity of the blood vessels at the base of the brain. This may be accentuated by underlying hypertension. The question then arises, which came first, neurovascular compression or hypertension? Finding the answer to this question would require longitudinal studies of normotensive and hypertensive patients. It certainly seems worthwhile to pursue this issue with further studies given the large number of patients with essential hypertension in our population.

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Operator Dependence of Cerebral CT Angiography in the Detection of Aneurysms

We are responding to two papers in the March 1996 *AJNR* on intracranial aneurysm detection by 3-D CT angiography by Ogawa et al (1) and Hope et al (2). It is important to point out the inherent limitations of these studies in order to place their results in perspective.

Ogawa et al, in a large study, report sensitivity for the detection of cerebral aneurysms as 67% to 70%. These results could lead many radiologists to conclude that CT angiography has an insufficient sensitivity for the critical task of aneurysm detection. The CT angiographic examinations by Ogawa et al required 2.8 minutes to image the circle of Willis. Unfortunately, this slow nonhelical CT an-

giographic acquisition technique falls short of the rapidly evolving state of the art, resulting in decreased vascular coverage and vulnerability to patient motion. Today's faster CT scanners can perform approximately one helical revolution per second (or a conventional section every 2 seconds), completing a typical circle of Willis CT angiogram in under 1 minute. Furthermore, the slower scanning speed used by Ogawa et al necessitated a decreased intravenous contrast administration rate of 1 mL/s. This may be a sufficient injection rate for CT angiographic studies in the absence of visible subarachnoid hemorrhage when maximum intensity projection (MIP) displays or source images are relied on for interpretations. It, however, is a less-than-ideal injection rate for CT angiographic studies with dense cisternal blood adjacent to the circle of Willis or for studies relying predominantly on shaded surface display for interpretation. We have found that in order to minimize vascular deletions from the 3-D model, shaded surface displays require greater levels of vascular enhancement above the background noise floor than MIP displays require. Faster CT angiographic acquisitions avoid the excessive cavernous sinus and pituitary gland enhancement that caused some diagnostic difficulty for Ogawa et al. We realize that since the original submission of their research in July 1993, Ogawa et al might have improved on some of the above limitations. Finally, it appears that only seven printed shaded surface display images per case were used in the blinded interpretation sessions and it is unclear whether source image review contributed to the data. A limited review of the complex circle of Willis may in part contribute to the relatively low sensitivity in aneurysm detection.

Hope et al likewise used conventional scanning (8.6 seconds per section with an estimated total scan time of over 7 minutes) in their CT angiograms of the circle of Willis. This slow acquisition technique has the same limitations discussed above. It is thus not surprising that four false-positive studies resulted from either high-attenuation blood clots or motion artifacts. In our experience, even dense subarachnoid hemorrhage in adjacent cisterns presents no diagnostic difficulty on MIP displays, provided that a sufficient contrast material bolus rate (for example, 3 mL/s) is used (3). While the sensitivity of Hope et al in aneurysm detection with CT angiography is close to that of other studies (3, 4) at 90.4%, the specificity of 50% is significantly lower, at least in part the result of technical limitations.

Hope et al acquired sections with 2-mm collimation while Ogawa et al used 1.5-mm beam collimation. Many institutions now have helical scanners with collimations as low as 1 mm. Use of this smaller collimation is advised to maximize CT angiography z-axis resolution.

Our CT angiography experience indicates that cerebral aneurysms as small as 2.5 mm in diameter can be detected with high sensitivity when 3-D MIP displays and source images are actively reviewed at a workstation (3). In our hands, MIP has a higher sensitivity and specificity in aneurysm detection than shaded surface display (unpublished data).

The meaning of the term *CT angiography* has been given a very wide latitude in recent radiologic publications. The term has been used to describe simple review of helical contrast-enhanced axial images. CT angiography also includes the use of 3-D models constructed from either conventional nonhelical or faster helical CT data sets. Additionally, the term is used to describe 3-D models displayed with differing algorithms, most commonly MIP or shaded surface display. To evaluate results of a study on cerebral CT angiography, it is thus important to know the precise acquisition and reformation protocols as well as whether MIP, shaded surface display, source images, or other display algorithms (or any combination of these) were used in data collection. It is also important to know whether workstation reformations were performed by the physician readers. Workstation interaction should ideally include the use of cutaway views to reduce vascular overlap in 3-D models and the use of paging through source or multiplanar reformatted images.

In conclusion, it must be emphasized that the detection of intracranial aneurysms with CT angiography is an operator-dependent task. Both sensitivity and specificity will be influenced by technical factors and the thoroughness of the chosen exam interpretation methods of the radiologist.

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Reply

We appreciate the interest of Drs Casey, Alberico, and Ozsvath in our article. They point out the disadvantages of nonhelical CT angiography compared with helical CT angiography for the evaluation of cerebral aneurysms. Moreover, they also point out that 3-D images by shaded sur-

face rendering or MIP methods should be actively reviewed at a workstation. We agree with them in all their views. In our article, we summarized the data obtained with nonhelical CT angiography. We stressed that this technique was especially useful in the preoperative evaluation of giant aneurysms, because 3-D CT angiography can simultaneously show cerebral aneurysms and bone structures. Nonhelical 3-D CT angiography was not an effective tool for searching for small aneurysms.

We have studied more than 100 patients with suspected cerebral aneurysms using helical CT angiography for the last 8 months. We could obtain higher sensitivity and specificity in aneurysm detection than those obtained with nonhelical CT angiography (unpublished data). This is mainly attributable to shorter acquisition time and better spatial resolution in the z direction of helical CT.

In routine 3-D CT angiography, we always evaluate 3-D images obtained with shaded volume rendering and MIP methods at a workstation. In the retrospective evaluation of a 3-D CT angiogram, it is not easy for two or three neuroradiologists independently to evaluate many patients at a workstation. However, in order to assess the diagnostic accuracy of 3-D CT angiography in aneurysm detection, we should perform a blinded study reviewing 3-D images using a workstation.

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Reply

We thank Casey et al for their interest in our recent paper, and the Editor of *AJNR* for the opportunity to respond to their comments. During the period of our study, we estimate only 5% to 30% of operational CT scanners either were helical models or possessed fast scanning capability and postprocessing software. Our intent therefore was to assess the efficacy of 3-D CT angiography in aneurysm detection using the currently available technology.

Casey et al have suggested that our sensitivity and specificity (90.4% and 50%) fall short of the currently expected norm using state-of-the-art helical scanning. They provide a good theoretical argument that this technology should provide both higher sensitivity and specificity in aneurysm detection than we were able to achieve. They then seek to support this argument with figures derived from their own experience and that of others.

While we accept that helical scanning will provide an incremental improvement in the detection of intracranial aneurysms, we note with interest that the sensitivity of aneurysm detection achieved, at 88% and 96%, appears little different from our own (90.4%). Had these two papers by Alberico et al and Liang et al included larger numbers of aneurysms, they would undoubtedly have run into a number that lay outside the imaged volume (3 of 94 in our

study) and this would have reduced their sensitivities further.

With regards to specificity, however, we regard claims that this can approach the 89% to 100% quoted with skepticism. Our reservations arise from two sources. Our study included 14 false-positive aneurysms. We have reexamined these in the light of comments raised by Casey et al and we would now reclassify seven of these as errors which would not likely occur with helical scanning. However, this would improve our specificity only to 71%. Allowing for the fact that 13 false positives were 3 mm or smaller, and that four were infundibula of the posterior communicating artery classified as aneurysms (a differentiation that may not be easy even with angiography), and that a further three were tight vascular loops misinterpreted as aneurysms (Figure 1 in our article), we do not believe that this figure of 71% can be significantly improved upon.

Our second and more important reservation arises from the design of the two studies quoted. In the one by Casey et al, with specificity of 89%, the numbers used (8 of 9) were small. One more or less false positive would alter that specificity to 78% or 100%. This highlights the unreliability of statistics in studies with small patient numbers, and is the reason we recruited larger numbers (94 aneurysms in 80 patients).

Alberico et al's study shows several design flaws. That study subdivided patients into true-positive (27 patients) and true-negative (41 patients) groups on the basis of CT, 3-D CT angiography, and lumbar puncture. Unfortunately, the standard of reference (angiography or MR angiography) was applied only to the true-positive group. Because four of their true positives were identified only on the basis of 3-D CT angiography, we cannot be sure that the "normal" group of 41 did not in fact harbor other aneurysms either too small to be detected, or not detected because they lay outside the scanning volume. We would suggest that it is unscientific to assess the efficacy of 3-D CT angiography in aneurysm detection when that same test has also been used as part of the standard of reference for the presence or absence of an aneurysm.

As neuroradiologists, we are aware that the presence or absence of subarachnoid hemorrhage on a CT scan, in the clinical context of possible aneurysm rupture, has a high predictive value for the presence or absence of berry aneurysm (87% and 11% in Alberico et al). For this reason, when we evaluated 3-D CT angiography, the diagnostic CT was not available to us. We felt that this would bias us toward a correct prediction of a questionable abnormality on 3-D CT angiography. Casey et al might argue that the identification of four aneurysms and an arteriovenous malformation in the absence of subarachnoid hemorrhage refuted this argument; however, two of these aneurysms were 19 and 40 mm in diameter, and the arteriovenous malformation in question was described as "large frontal," and should therefore be readily visible on CT even without subarachnoid hemorrhage.

Finally, in testing the value of 3-D CT angiography, Casey et al seem to have used only 22 of their 42 negative cases to determine the false-positive rate. Unfortunately,

the criteria used in selection of this subgroup is not specified. Can we assume that (unlike our 80 cases) all were of equal quality and that selection of these "controls" was random?

In summary then, we thank Casey et al for their comments and we acknowledge that the use of helical scanning will make an incremental but significant contribution to the noninvasive diagnosis of berry aneurysms. However, we would ask them to exercise caution when quoting specificities of 89% to 100% for 3-D CT angiography, at least until these figures can be confirmed with a larger series of patients and with studies of greater scientific rigor.

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Extrusion of Osteoconductive Biosynthetic Polymer Dowels after Cervical Fusion Surgery

Biocompatible osteoconductive polymer (BOP) is a synthetic copolymer designed to replace bone grafts in surgical procedures providing a substrate for bone growth and promoting bone fusion (1). BOP grafts have proved popular in cervical fusion procedures (Cloward's operation) because they can be "pre-prepared" at the correct size and the risks associated with bone graft harvesting can be eliminated. We have recent experience of four cases in which BOP dowels were extruded from the implantation site after cervical fusion.

Over a 2-year period, 45 patients underwent cervical fusion with BOP grafts. The group comprised 25 men and 20 women ranging from 32 to 74 years of age (mean, 48 years). Fusion was performed at multiple levels in 11 cases with a total of 56 operative levels. With a minimum of 6 months follow up, 41 of 45 patients remain well. Extrusion of the graft occurred in four cases (7%) at times ranging from 4 days to 6 months after surgery. In each case, graft extrusion was suspected because of clinical symptoms including dysphagia (four cases), the sensation of a lump in the throat (one case), pain in the throat (one case), change in voice (one case), or restriction of neck movements (one case).

In each case, plain radiographs showed widening of the prevertebral soft tissues but failed to show the position of the graft (Fig 3A). CT clearly showed extrusion of the graft in each case together with direct compression of the esophagus in three patients (Fig 3B). Removal of the BOP dowel led to immediate resolution of symptoms in all cases.

Cloward (2) described the details of an anterior approach for cervical spondylitic disease in the mid-1950s. After removal of the intervertebral disk, the spinal canal is entered through a trephine hole through the intervertebral space. Interbody fusion is accomplished by inserting a well-fitting dowel bone graft into the trephine hole. Al-

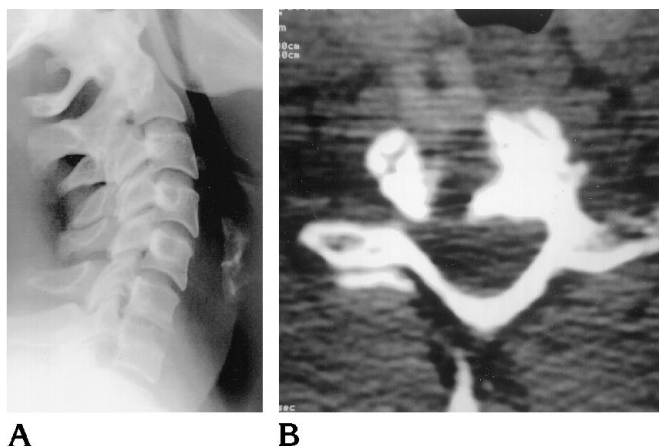


Fig 3. A, Lateral radiograph of the cervical spine. There is widening of the prevertebral soft tissue space at C6-7, the level of the previous cervical fusion and BOP insertion.

B, Axial 5-mm CT section at C6-7 shows the previous Cloward's procedure. The BOP has been extruded and lies to the right of the midline anterior to the bone defect.

though a number of alternative bone graft materials have been tried, autogenous bone, harvested from the iliac crest, is still considered the most effective agent in stimulating an osteogenic response (3). This harvesting procedure is associated with well-recognized complications of pain, blood loss, and increased surgical time and expense, which have been major limitations to its acceptability (4).

BOP is a synthetic copolymer composed of 1-vinyl-2-pyrrolidone, methylmethacrylate, calcium gluconate, and polyamide 6 fibers designed to provide a substrate for bone fusion (1). BOP grafts have been in use for 5 years and have been widely used in cervical fusion procedures because they can be prepared in advance at the correct size and eliminate the risks associated with bone graft harvesting. BOP is a radiolucent material that cannot be delineated from soft tissue on plain radiographs. This can lead to difficulty in the diagnosis of graft extrusion as was noted in two of our cases. Bone ingrowth leads to gradual opacification of the graft; however, opacities are not detectable on plain radiographs for at least 5 months. These radiographic opacities appear to enclose the implant first posteriorly and laterally, then finally anteriorly, and are good indicators of osteoneogenesis and successful spinal fusion (1).

The 7% incidence of graft extrusion in the current series is far greater than would be expected with autologous bone grafts (5). In each of the cases described here, the extrusion of the graft appeared to be a mechanical problem with no evidence of any infective procedure, and graft removal led to uncomplicated recovery in all cases. Although the present series is too small to allow conclusions as to the reasons for graft extrusion, it should be noted that in two cases symptoms did not commence until several months after surgery and that CT scans showed little or no evidence of osteoneogenesis in these cases. These observa-

tions suggest that in some cases mechanical instability of the graft is associated with failure of osseointegration and osteoneogenesis.

In each case, the symptoms were dramatic and highly localized, leading to a clear clinical suspicion of complications at the surgical site. Nevertheless, plain radiographs were unhelpful or misleading because of the radiolucency of the graft. CT clearly shows the graft position and its relationships to the surgical defect and surrounding soft tissues. We therefore recommend CT as the first-line investigation in these cases.

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On Tomatotropic Sopranos

I read with great interest the article by Chicaneria et al (1) about the MR appearance of cerebral *Drancunculus borealis* infection in the April 1996 issue of the *AJNR*. It is one of the most interesting papers of this issue. After reading this issue, which contains numerous other scientific papers, I wonder whether there is only one April Fool's Day paper. Further readings are probably necessary to answer this question.

Nevertheless, Georges Perec, French man of letters (1936-1982), remains the best author in the field of this

“scientific” literature, with his major contribution on the experimental demonstration of the tomatotopic organization in the soprano (*Cantatrix sopranica L.*) (2). I would like to give you a collection of scientific papers of Georges Perec, in which you will find the tomatotopic article. I hope that you will enjoy this paper.

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Reply

Dr Miaux’s letter is a comment on a “medical bon-bon” that appeared in the April 1996 issue of *AJNR*. One of the joys of editing is receiving letters to the Editor, most of which get published. The letter from Dr Miaux contained a copy of the book by Georges Perec, which contained a hilarious tongue-in-cheek article, complete with bibliography, about a soprano whose singing was “tomatotopic.” It is hard to reply to Dr Miaux except to say that even the most lofty of us has feet of clay and that the bulk of the humor that Dr Miaux perceives in *AJNR* is at least peer reviewed.

Michael S. Huckman
Editor