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LETTERS

A Spurious Description of Hyperfixation of HMPAO

In a recent issue of *AJNR*, Shintani and colleagues (1) report a patient who suddenly had an embolic stroke. X-ray computed tomography (CT) was performed at 2, 6.5, and 24 hours after onset, single-photon emission CT (SPECT) with hexamethylpropyleneamine oxime (HMPAO) was performed at 4 hours, and intravenous administration of alteplase (tissue plasminogen activator) started at 4 hours and completed 1 hour later. CT at 2 hours was normal, at 6.5 hours revealed faint low-density lesions, and the next day showed marked low-density lesions. Eleven days later, magnetic resonance (MR) revealed a marked reduction in the size of the infarct. The SPECT scan showed a high activity in the region corresponding to the area of infarction on CT. Clinically, the patient's history was consistent with embolic stroke followed by reperfusion, and at 6½ hours no neurologic sequelae were observed.

The authors, while recognizing that reperfusion has undoubtedly taken place, admit that they do not know whether this was the result of collateralization or recanalization, and if recanalization, whether spontaneous or caused by the alteplase. Therefore, they do not know whether reperfusion occurred before or after the administration of HMPAO. If reperfusion did indeed occur before HMPAO administration, the SPECT scan is therefore consistent with reperfusion hyperemia, which has been demonstrated previously in acute strokes using positron emission tomography and xenon blood flow techniques (2–4). The authors chose not to accept this seemingly logical tenet and instead describe the high uptake of HMPAO in the region of the infarct as unexpected and as "spurious hyperfixation." It is unclear how the authors have arrived at this controversial conclusion.

The inference in the paper is that the *amount* of uptake of HMPAO is spuriously high, yet the authors do not state how high it is and, more important, have no idea how high it should be. The term *hyperfixation* was coined by Sperling and Lassen (5, 6) and has been quite clearly explained and reiterated by them. It relates to a comparison between the side-to-side cerebral blood flow asymmetry measured with xenon-133 and HMPAO. From 10 to 28 days after stroke onset, they found that HMPAO uptake relative to the normal hemisphere can be higher than the equivalent measure using xenon-133. Shintani et al had no other measure of cerebral blood flow on which to base such a comparison.

The assumption of hyperfixation is likened to the findings of Sperling and Lassen in subacute stroke, without an acknowledgment that this is entirely inconsistent with the same authors' findings in acute stroke (6, 7), where they have no evidence for hyperfixation: "acute, or early subacute increased uptake of HMPAO most likely represents hyperemia and does not overestimate blood flow" (7).

This paper presents no evidence that would call into question the use of SPECT with HMPAO in acute stroke. The scan presented is consistent with previous reports describing reperfusion hyperemia in an area of brain damaged by ischemia. SPECT with HMPAO remains a reliable, but probably underused, indicator of early reperfusion in acute stroke (8).

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Reply

We would like to thank Dr Patterson et al for their careful review of our manuscript. In the present case, SPECT unexpectedly showed marked hyperfixation of HMPAO in the ischemic region in the acute stage of embolic stroke (4 hours after onset). This area of HMPAO hyperfixation corresponded exactly to the area of infarction seen on CT and MR studies. We think that spontaneous or alteplase-induced recanalization or reperfusion of the middle cerebral artery occurred in the right hemisphere. We emphasize that the hyperfixation of HMPAO

associated with reperfusion hyperemia was *extremely marked* in our patient, more so than in the patients described in the previous reports. The hyperfixation was more strongly enhanced than that of natural reperfusion hyperemia. We did not perform xenon-133 dynamic SPECT or other SPECT studies, and therefore we can not comment on the discrepancy between our HMPAO tomogram and other SPECT studies.

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Editor's note.—*The letter from Patterson et al was also referred to Drs Yuh, Quets, Rezai, and Crosby, who provide the following comments.*

Comment

As we have come to a better understanding of the underlying pathophysiology of ischemic stroke, we have discovered a vast array of events that can occur after the initial ischemic insult (1–8). These include loss of autoregulation, vasodilation, breakdown of the blood-brain barrier, neovascularization (subacute), and secondary toxic effects from free radicals, calcium ions, and excitatory amino acids. In addition, the nature of the vascular injury and preexisting collateral circulation also play important roles with regard to the evolution and outcome of the ischemic injury (9–11). Further complicating the issue, all these elements may be involved to various degrees at different times after the onset of the initial ischemic insult.

With the advent of modern imaging techniques, including xenon CT, SPECT, positron emission tomography, MR diffusion imaging (12–14), MR perfusion imaging (11, 15) (Crosby DL, Yuh WTC, Magnotta VA, Simonson TM, Zheng J, Ehrhardt JC, "Comparison of Echo-Planar Perfusion Imaging with Cerebral Angiography and T2-Weighted MR in the Evaluation of Transient Ischemic Attack," *Proceedings of the 33rd Annual Meeting of the American Society of Neuroradiology*, Chicago, Ill, April 23–27, 1995:19) (Simonson TM, Yuh WTC, Crosby DL, et al, "Echo-Planar Diffusion and Perfusion Imaging of Ischemia in Patients without Significant Carotid Disease," *Proceedings of the 33rd Annual Meeting of the American Society of Neuroradiology*, Chicago, Ill, April 23–27, 1995: 23), and MR spectroscopy (16, 17), we can now look more deeply into the complex underlying events and mechanisms contributing to the pathophysiology of stroke. These techniques offer us a view of stroke from different vantage points and at almost any given time after the ischemic injury. Each offers different but complementary information. Xenon CT, $C^{15}O_2$ positron emission tomography, and ^{99m}Tc HMPAO SPECT provide valuable information about regional cerebral blood flow (rCBF). Uptake of ^{99m}Tc HMPAO is governed by rCBF and also by how well the tracer is extracted and retained in brain tissue. Diffusion images show abnormal water movement presumably caused by failure of the sodium–adenosine triphosphate (Na-ATP) pump. MR spectroscopy directly measures lactic acid accumulation caused by anaerobic glycolysis and indirectly evaluates the status of neuronal elements through measurement of *N*-acetyl-aspartate. MR perfusion imaging estimates the relative rCBF and cerebral blood volume of regions of ischemic and normal tissue. These bits and pieces of information, which could not be readily obtained in the past, now offer potential benefits in the optimal management of stroke, a common disease ranked number one in the cost of health care. However, the information obtained by any given modality reflects only a single piece of an intricate puzzle that may not be sufficient to define the complex events of the underlying process. We are challenged to use all available modalities to reconstruct the full spectrum of pathophysiologic events occurring as each patient's stroke evolves.

Shintani et al reported a single case of a stroke event characterized by the dramatic uptake of ^{99m}Tc HMPAO in the acute phase, evidence of early thrombolysis with clinical resolution, and minimal defect on late imaging studies. They concluded that the marked HMPAO uptake was *spurious hyperfixation*. Patterson et al take issue with the use of this term, correctly pointing out that without documentation of rCBF measurements, Shintani et al provide no evidence that HMPAO fixation was increased beyond rCBF. Although it is possible that hyperfixation did indeed occur, Shintani et al did not provide sufficient evidence to permit such a conclusion. We agree with Patterson et al that reperfusion hyperemia of a resolving acute embolic stroke is a likely explanation of the imaging findings and the clinical outcome of this patient. With MR, we have seen similar cases of acute embolic stroke followed by complete recovery with exaggerated and intense cortical enhancement without any T2-weighted signal changes (indicating intact blood-brain barrier) (18, 19). Imaging evidence of the breakdown of the blood-brain barrier usually does not occur until 6 hours after the onset of ischemia (18–21). We believe that early parenchymal enhancement on MR represents a pathophysiology similar to the HMPAO SPECT findings reported by Shintani et al, and therefore most likely represents loss of autoregulation and hyperemia after a transient ischemic insult (21). The case study provided by Shintani et al remains valuable as a demonstration of one of the complex changes that may occur after an ischemic injury to the brain.

Finally, the article by Shintani et al and the letter by Patterson et al highlight important issues that will continue to challenge neuro-related clinicians and scientists as advances in imaging capabilities continue. The availability of

many modern imaging techniques can help us to obtain important information about the complex evolution of stroke from different vantage points. However, each modality has its limitations and *great caution must be taken when drawing conclusions based on information obtained by any single modality*. In this specific case, without an independent measure of rCBF, it is not possible to know whether spurious hyperfixation did or did not occur in coexistence with regional hyperperfusion.

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False-Negative Single-Photon Emission CT in AIDS Lymphoma: Lack of Effect of Steroids

SPECT with thallous chloride Tl 201 has recently been reported to allow the differentiation between central nervous system (CNS) lymphoma and toxoplasmosis in patients with acquired immunodeficiency syndrome (AIDS) (1, 2, 3). This is a significant advance, because these two entities are the most common intracranial mass lesions in AIDS patients and are often indistinguishable by their CT and MR appearance (4, 5). The sensitivity of Tl-201 SPECT in this population in these three series is 100% (n = 70) (1, 2, 3). We report a false-negative result of Tl-201 SPECT in an AIDS patient with biopsy-proved CNS lymphoma.

A 31-year-old woman with AIDS and a recent CD4 count of 54 presented with confusion, lethargy, incontinence and possible seizure. Her medications included trimethoprim-sulfamethoxazole in doses demonstrated to provide prophylaxis for toxoplasmic encephalitis in AIDS (6). CT of the brain showed a solitary mass lesion in the left frontal cortex with rim enhancement and associated vasogenic edema in the left hemisphere (Fig 1A). Because of the brain edema, corticosteroids were started (6 mg dexamethasone intravenously every 6 hours). MR of the brain showed a left frontal mass that was heterogeneous with a slightly hyperintense rim on T1-weighted images, was hypointense and isointense on proton density– and T2-weighted images, and showed multilocular rim enhancement after gadolinium administration (Fig 1B). The patient was started on empiric treatment for toxoplasmosis with pyrimethamine, sulfadiazine, and leucovorin. Tl-201 SPECT performed 7 days after admission was unremarkable (Fig 1C); an uptake ratio using the method of O'Malley et al (2) was 1.05. Serum antitoxoplasma IgG

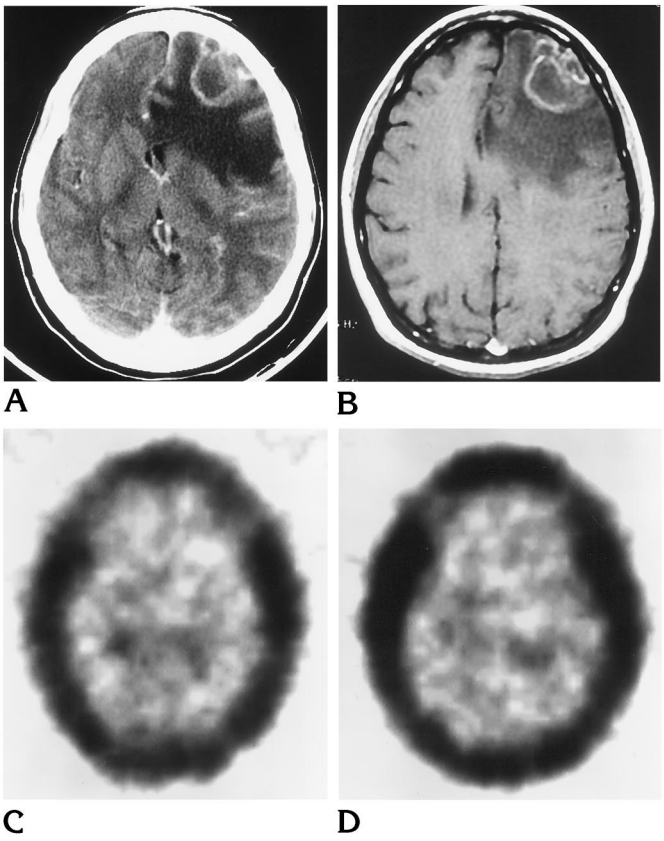

Fig 1. *A*, Postcontrast CT shows a rim-enhancing left frontal mass with extensive left hemispheric vasogenic edema at the time of admission.

B, Axial T1-weighted contrast-enhanced MR image (600/16/2 [repetition time/echo time/excitations]) shows rim-enhancing left frontal mass, vasogenic edema, and mild subfalcine herniation at the time of admission. The region of enhancement measures 3.2 cm in greatest dimension.

C, Axial Tl-201 SPECT shows no increase in uptake in the region of the left frontal mass; the patient was on corticosteroids and antitoxoplasmosis therapy for 1 week before the scan.

D, Axial Tl-201 SPECT shows no increase in uptake in the region of the left frontal mass; the patient had been off steroid therapy for 10 days at the time of the scan.

antibody titers were negative, and the patient did not improve.

The concern was raised that steroid therapy may diminish the uptake of Tl-201, because isolated reports have shown steroid therapy to result in improvement in the imaging abnormalities of CNS lymphoma in patients with AIDS (5, 7). We could find no published reports addressing the effect of steroids on the sensitivity of Tl-201 SPECT for CNS lymphoma (1, 2, 3). The steroids were stopped, and 10 days later there was no change in the CT or MR findings or in Tl-201 SPECT imaging (Fig 1D); the uptake ratio was 1.09. Stereotactic biopsy of the lesion yielded large necrotic B-cells with an immunophenotypic profile consistent with a B-cell non-Hodgkin lymphoma. The patient responded to radiation therapy and was discharged.

Potential causes of a false-negative Tl-201 SPECT scan, including lesions smaller than the resolution of the SPECT gamma camera and lesions obscured by normal high uptake in scalp or skull base (1), were not present in this case. The uptake ratios (1.05, 1.09) were notably smaller than those reported for true-positive studies (mean, 3.65; range, 2.95 to 4.30 [2]). The administration of steroids in this case did not affect the false-negative result on Tl-201 SPECT.

In the present case, although the appearance of the lesion on imaging was nonspecific, there was a strong clinical suspicion of lymphoma because of the history of appropriate antitoxoplasmosis prophylaxis, the absence of antitoxoplasma antibodies, and the failure to respond to antitoxoplasmosis therapy; these clinical features make toxoplasmosis unlikely (6, 8). A negative result on Tl-201 SPECT under circumstances of high clinical suspicion should not obviate prompt diagnostic biopsy.

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Reply

Currently, we are reviewing our own experience with Tl-201 brain SPECT in more than 300 patients with AIDS and CNS masses during the past 3 years. Like Dr Campbell et al, we have encountered very few false-negative and false-positive Tl-201 brain SPECT studies in this population. We are currently analyzing the factors that may be

involved in these results. We hope to develop some useful guidelines to avoid potential errors in diagnosis.

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Helical CT Angiography for the Detection of Intracranial Aneurysms

We presented a prospective series of 68 patients with three-dimensional CT angiograms of the circle of Willis in suspected acute subarachnoid hemorrhage in the September issue of *AJNR* (1). In the paper we state limitations of CT angiography to include range of reconstruction (4 cm in superior/inferior extent), and operator dependence of 3-D modeling. Subsequent alterations in our technique have resolved these limitations.

We now routinely scan patients with a 1-mm beam collimation with a 2 mm/s table speed (2:1 pitch). The images are then retroreconstructed to a 1-mm spacing. The total coverage with this technique is 12 cm, which is adequate to evaluate the circle of Willis and the vertebral arteries to the level of the posterior inferior cerebellar artery. More important, we have modified our 3-D modeling technique to a form of "graded subtraction" (2). First we duplicate our data set, and then isolate the unwanted structures (in this case the bone) in the duplicate model, thus creating a subtraction mask. This mask is then removed from the original data set in stages by alternating subtraction and single-pixel dilation of the mask. Dilation is a way of adding a specified number of pixels around each pixel in an existing model independent of Hounsfield units. The original data set is viewed in maximum intensity projection during this process until a clear view of the vessels is obtained (usually in 2 or 3 steps). With this method, a detailed vascular model can be made without thresholding the vessels. The risk of accidental vascular deletion from improper thresholding is eliminated, and more vascular detail is preserved (Fig 2). The reconstruction process does not require user manipulation of the areas of interest, and thus quality of the final image is less user dependent. Reconstruction time remains 10 to 15 minutes.

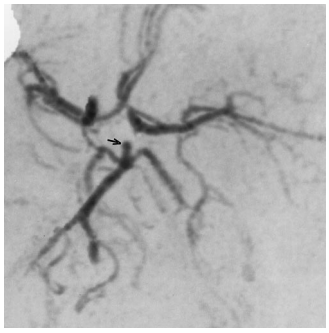

Fig 2. This maximum intensity projection image is a CT angiogram that extends 12 cm in inferior-to-superior extent. Note the inclusion of the posterior inferior cerebellar arteries, and the basilar tip aneurysm (*arrow*).

We have applied this technique to the original 68 cases and an additional 17 cases. Thirty-five cases had angiographic correlation, including 4 true negatives, 2 arteriovenous malformations, and 29 aneurysms. Review by a radiologist blinded to the data revealed 96% sensitivity and 100% specificity for the detection of aneurysms.

The expanded range of coverage and improved 3-D modeling technique has increased our confidence in the ability of CT angiography to enable detection or exclusion of presence of intracranial aneurysms in patients with suspected acute subarachnoid hemorrhage.

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Comment

The results reported in the letter from Alberico et al (96% sensitivity, 100% specificity) are very impressive. Because numerous factors can affect the accuracy of CT angiography in this setting, however, some comments are in order.

Concerning the spiral technique, the authors state that they have gone to a 2:1 pitch (2-mm table travel/rotation, 1-mm section collimation) for acquisition in order to improve axial coverage. It is important to emphasize that, in order to maintain unchanged good axial resolution with 2:1 pitch, interpolation from 180° opposite views with cubic spline interpolation or its equivalent must be used (1); interpolation from 360° opposite views, or the use of linear interpolation, causes significant blurring along the z-axis. Because the size of aneurysms and of important vessels near the circle of Willis may be only 1 to 2 mm (particularly the anterior and posterior communicating arteries), main-

tenance of axial resolution is critical. We have also noted, and have confirmed with General Electric, that image noise increases noticeably whenever the pitch is greater than about 1.4:1. Finally, adequate technique (at least 200 mA at 120 kV[p]) is essential for control of image noise.

Some differences in reader performance are visible in Table 1 of the original article by Alberico et al, and we are not told how experienced the reader mentioned in their letter was. It would also be of interest to know in what fraction of cases the images were considered adequate for surgical planning (presence of collateral vessels, location of neck), but this may require a separate study.

Finally, the authors describe the use of advanced image-processing techniques to prepare the raw data for viewing with the maximum intensity projection technique. The techniques of mathematical morphology have become popular in the image-processing and medical imaging research community in recent years (2, 3), although they are just starting to appear in commercial software, such as the CTSoft package on the General Electric Advantage Windows workstation used by Alberico et al. In typical applications, mathematical morphology is combined with more traditional operations, such as thresholding, to achieve superior foreground/background segmentation. For example, as described in Alberico et al's letter, thresholding can be used for a first, crude isolation of vessels and bone; the morphologic technique of dilation can then be used to draw a series of progressively thicker borders around the first approximation to the bony structures until only the vessels are left. Other morphologic techniques can be used to clean up salt-and-pepper noise in images or to perform various types of texture analysis. As these techniques become more familiar to radiologists, their use is likely to increase. Although the techniques themselves are fully automated, they are often most useful in an interactive setting where their application can be tailored by the radiologist. Consequently, some radiologist learning is necessary before interactive processing times can be brought down to 15 to 30 minutes per case, with preservation of optimal image quality.

In summary, we applaud the results of Alberico et al, and emphasize the necessity for attention to procedural details to optimize outcome. In CT angiography, as in most other aspects of radiology, there are no shortcuts.

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Sonography of the Ventriculus Terminalis in Newborns

We read with interest the recent *AJNR* article by Coleman et al (1) on MR of the ventriculus terminalis of the conus medullaris in children. We congratulate the authors on their study; however, similar findings can be detected in newborns with high-resolution sonography of the spinal cord. We regularly perform spinal sonography with a 7 to 10-Mhz linear array Transducer (ATL-HDI 3000) using longitudinal and transverse scans. The reasons for referral for the examination were similar to those of Coleman and coworkers: sacral dimple and pigmented skin lesions of the lumbosacral region. Meticulous sonography of 315 newborns revealed a sharply demarcated cystic lesion in 33 patients. Contrary to the findings of Coleman et al, in our patients the location of the cyst was not in the conus medullaris, but at the tip of the conus at the origin of the filum terminale (Fig 3A and B). In one patient a direct continuity between a slightly dilated central canal and this cystic structure could be demonstrated (Fig 3C). Fol-

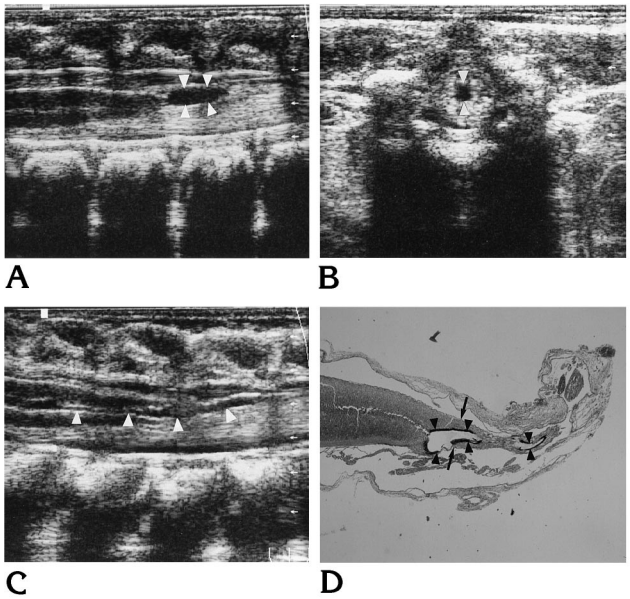

Fig 3. *A* and *B*, Longitudinal and transverse scans of the distal spinal cord at the age of 3 days. Cystic ovoid structure at the most distal end of the conus medullaris and the origin of the filum terminale corresponds to the ventriculus terminalis (*arrowheads*).

C, Longitudinal scan of the conus medullaris and the cauda equina at the age of 9 days. Dilatation of the central canal within the conus medullaris continues to the ventriculus terminalis within the origin of the filum terminale (*arrowheads*).

D, Histologic section of the fetal conus medullaris (16th week of gestation) (hematoxylin-eosin stain). Ependyma-lined ventriculus terminalis (*arrowheads*) at the most distal end of the conus medullaris are adjacent to the origin of the filum terminale (*arrows*).

low-up in all patients with spinal sonography within 1 month after the first examination demonstrated a significant reduction of cyst size. In another patient, histologic study showed similar findings regarding cyst location and morphology. Additionally, typical ependymal lining was noted (Fig 3D).

Therefore, we conclude that because of location and morphology, this cystlike structure represents the ventriculus terminalis. However, in contrast to the findings of the authors, the location of the cyst was slightly more caudal. As already described by Coleman and coworkers, this can be explained by the embryologic formation of the spinal cord: after neurulation and canalization, retrogressive differentiation leads to involution of the distal spinal cord. The evolving ventriculus terminalis within the regressive caudal cell mass can then be viewed as a remnant of a normal embryologic development of the spinal cord that can occur anywhere within the location of the former caudal cell mass.

Therefore, a spectrum of findings can be seen clinically. The ventriculus terminalis can either persist after birth and during life in the conus because of a patent communication with the central canal, or persist only after birth at the tip of the conus at the origin of the filum terminale and regress during the following months because of absent communication with the central canal. Patency of communication seems crucial for persistence of the ventriculus terminalis. Patency of the communication may be inversely proportional to distance between ventriculus terminalis and central canal.

We would also like to add that high-resolution ultrasonography of the spinal cord is an easy and inexpensive examination technique and allows one to rule out malformations of the spinal cord in newborns with cutaneous anomalies in the dorsal midline. Because of progressive ossification of the vertebrae a few months after birth, the spinal cord can then be examined only by more expensive techniques, such as CT or MR. We believe that during the first weeks of life, in children with cutaneous malformations in the dorsal midline, sonography is the method of choice for spinal cord examination.

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Reply

I am delighted that Dr Unsinn et al have found the ventriculus terminalis in the newborn at the tip of the conus medullaris extending to the origin of the filum terminale, a finding which makes sense embryologically. Evidence suggests that the ventriculus terminalis persists in patients, but that its size may make it beyond the resolution of current imaging techniques in many patients. The issue of whether or not sonography or MR is the method of choice in evaluating the neonate with a cutaneous abnormality in the dorsal midline remains to be proved by a statistically significant study that looks at all the variables.

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