AJNR

Multifocal inflammatory leukoencephalopathy after fluorouracil and levamisole therapy for colon cancer.

C L Murray, W J Ford, K K Swenson, D Heros and P W Sperduto

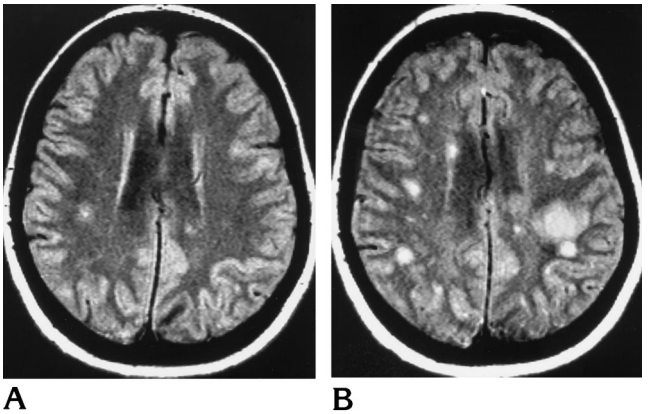
AJNR Am J Neuroradiol 1997, 18 (8) 1591-1592
http://www.ajnr.org/content/18/8/1591.citation

LETTERS

Multifocal Inflammatory Leukoencephalopathy after Fluorouracil and Levamisole Therapy for Colon Cancer

Multifocal inflammatory leukoencephalopathy, a central nervous system disorder characterized by demyelination with perivascular inflammation, has recently been reported in several patients treated with the combination of fluorouracil and levamisole chemotherapy (1–4). Symptoms include memory loss, confusion, ataxia, dysarthria, diplopia, and paresthesia.

A lower gastrointestinal hemorrhage developed in a 59-year-old woman. Colonoscopy showed a lesion in the cecum. She underwent a right hemicolectomy and was found to have infiltrating adenocarcinoma in the cecum. The tumor grossly extended through the colonic wall into the pericolonic fat. Three months after starting a combination of levamisole and fluorouracil, she noted increasing fatigability with excessive daytime drowsiness. Magnetic resonance (MR) imaging of the brain showed subtle areas of increased T2 signal in the periventricular white matter bilaterally (Fig 1A). A subtle area of enhancement was noted in the right hemisphere lateral to the body of the right lateral ventricle and a second lesion was identified in the right centrum semiovale. No mass effect or edema was present. One month later, MR showed rapid progression of the disease, with an increase in the number and size of the foci in the brain (Fig 1B). Stereotactic biopsy showed demyelinating lesions, which were sharply defined with Luxol fast blue/periodic acid–Schiff stain because of myelin loss. There was incomplete loss of myelin sheaths and only rare macrophages. One biopsy fragment showed a complete loss of myelin associated with numerous macrophages and a few lymphocytes surrounding small blood vessels. Axons were well preserved. Electron microscopy revealed nonspecific degenerative changes. Numerous macrophages, some containing apparent fragments of myelin, were identified. There was no evidence of viral infection. Within 1 month of prednisone therapy, her memory, gait, and right hand coordination improved. She received no additional chemotherapy. Twenty months later, MR showed that her disease had stabilized.



A B

Fig 1. *A*, Multiple axial MR images were obtained (September 25, 1992) using double-echo T2-weighted axial acquisition and enhanced T1 weighting, showing three small lesions in the white matter that were interpreted as possible multiple cerebral metastases (2380/20, 90/1 [repetition time/echo time/excitations]).

B, MR of the brain (October 22, 1992) shows rapid progression with increased number and size of lesions on proton density– and T2-weighted axial acquisition (2380/24,110/1).

The pathophysiology of this inflammatory demyelinating process remains unknown. Fluorouracil is known to cause acute cerebellar toxicity. Rarely, encephalopathy with confusion ensues. Atypical fluorouracil toxicity has been postulated as the underlying cause of the neurologic dysfunction in patients receiving this adjuvant chemotherapy for colon adenocarcinoma. It is important to recognize this neurologic syndrome in patients being treated with this combination of chemotherapy for adenocarcinoma of the colon. Recognition could prevent neurosurgical intervention, avoid additional toxic therapies such as radiation therapy, and prompt discontinuation of the causative chemotherapy.

Charles L. Murray
Department of Oncology Research

William J. Ford
Department of Radiology

Karen K. Swenson
Department of Oncology Research

Methodist Hospital
HealthSystem Minnesota
Minneapolis

Deborah Heros
Mt Sinai Comprehensive Cancer Center
Miami Beach, Fla

Paul W. Sperduto
Department of Radiation Therapy
Methodist Hospital
HealthSystem Minnesota
Minneapolis

References

1. Hook C, Kimmel D, Kvols L, et al. Multifocal inflammatory leukoencephalopathy with 5-fluorouracil and levamisole. *Ann Neurol* 1992;31:262–267
2. Kimmel D, Schutt A. Multifocal leukoencephalopathy: occurrence during 5-fluorouracil and levamisole therapy and resolution after discontinuation of chemotherapy. *Mayo Clin Proc* 1993;68:363–365
3. Chen TC, Hinton DR, Leichman L, Atkinson RD, Apuzzo MLJ,

Couldwell WT. Multifocal inflammatory leukoencephalopathy associated with levamisole and 5-fluorouracil: case report. *Neurosurgery* 1994;35:1138–1143
4. Savarese DM, Gordon J, Smith TW, et al. Cerebral demyelination syndrome in a patient treated with 5-fluorouracil and levamisole. *Cancer* 1996;77:387–394

Dysembryoplastic Neuroepithelial Tumors

I read with interest the paper by Ostertun et al (1) on dysembryoplastic neuroepithelial tumors (DNTs). The authors specifically state that no previous report apart from that of Daumas-Suport described a cohort of greater than eight patients. I would point out a publication in *Brain* by Raymond et al (2) which discussed the clinical, electroencephalographic, and imaging findings as well as follow-up in 16 patients with this lesion. The radiologic findings would have been of relevance to Ostertun et al since a common finding in this group of 16 patients was blurring of the gray–white matter boundary within the affected temporal lobe. In Figure 4 of Ostertun et al's paper the left temporal lobe certainly seems smaller than that on the right in coronal sections through the tumor, and I would be interested to hear whether this abnormality, which Raymond et al ascribed as being evidence of the dysembryoplastic nature of the tumor, was present in Ostertun et al's patients. Raymond et al also pointed out the presence of occasional mitoses in 12 of the 16 patients. Was this also found by Ostertun et al?

Shawn S. F. Halpin
Radiology Directorate
University Hospital of Wales
Heath Park, Cardiff
United Kingdom

References

1. Ostertun B, Wolf HK, Campos MG, et al. Dysembryoplastic neuroepithelial tumors: MR and CT evaluation. *AJNR Am J Neuroradiol* 1996;17:419–430
2. Raymond AA, Halpin SFS, Alsanjari N, et al. Dysembryoplastic neuroepithelial tumour: features in 16 patients. *Brain* 1994;117:461–475

Reply

We thank Dr Halpin for his interest in our analysis of DNTs and for his comments, especially concerning the features of ipsilateral temporal lobe atrophy, blurring of the gray–white matter junction, and the presence of tumor mitoses in our material.

The interesting phenomenon of ipsilateral atrophy was seen only in the case depicted in Figure 4 of our paper. It was not present in any other of our 15 patients. Blurred margins of DNT were described by Raymond et al in five of their 16 patients; their paper unfortunately was missed in our literature inquiry. We found unsharp tumor margins in half of our cases (8 of 16). In addition, Raymond et al describe direct involvement of white matter and an indistinct gray–white matter interface adjacent to the lesion in six patients. Subcortical white matter tumor involvement was present in 10 of our 16 cases. Six DNTs showed blurred gray–white matter junctions adjacent and even rather distant to the tumor, which was not directly attributable to tumor infiltration. Three of these cases are shown in Figures 1, 3, and 4 of our paper. Blurring is probably caused by peritumoral edema in the case in Figure 1. In Figures 3 and 4, reduced contrast between white matter adjacent to the tumor and nonaffected cortex is visible, although no typical signs of edema are present. These changes are most pronounced on T2-weighted images. Thus, our findings are very similar to those of Raymond et al. Almost half of the tumors in both papers show this feature, which may indicate a dysplastic architecture not only of the cortex, but probably also of the subcortical white matter, which shows slightly increased signal on T2-weighted and decreased signal on T1-weighted images, resulting in decreased contrast versus gray matter. Frequently, we have also seen similar changes in patients with ipsilateral hippocampal sclerosis.

Concerning the presence of mitoses in our material, all specimens have been carefully reviewed once again. Unlike Raymond et al, who found infrequent mitoses in 12 of their 16 cases, we did not identify mitotic figures in any of the tumors.

B. Ostertun
Department of Neuroradiology/Radiology
University of Bonn (Germany)

H. K. Wolf
Department of Pathology
University of Mainz (Germany)

H. H. Schild
Department of Radiology
University of Bonn (Germany)

MR of Papilledema

In their recent article "MR of Optic Papilla Protrusion in Patients with High Intracranial Pressure," Jinkins et al (1) use conventional spin-echo MR images of the optic nerve to show anterior protrusion of the optic disks in patients with presumed papilledema. However, the authors provide no data to confirm the diagnosis of papilledema. No mention is made of lumbar punctures being performed to confirm that these patients had high intracranial pressure. No clinical or neuroimaging data are provided to establish the underlying cause of the papilledema or the chronicity of signs and symptoms of elevated intracranial pressure. The finding of decreased vision in all patients casts serious doubt on the diagnosis of papilledema, which is classically associated with retention of central acuity until very late in its course. How did the authors rule out the possibility of infectious, inflammatory, or infiltrative optic neuropathies in their patients?

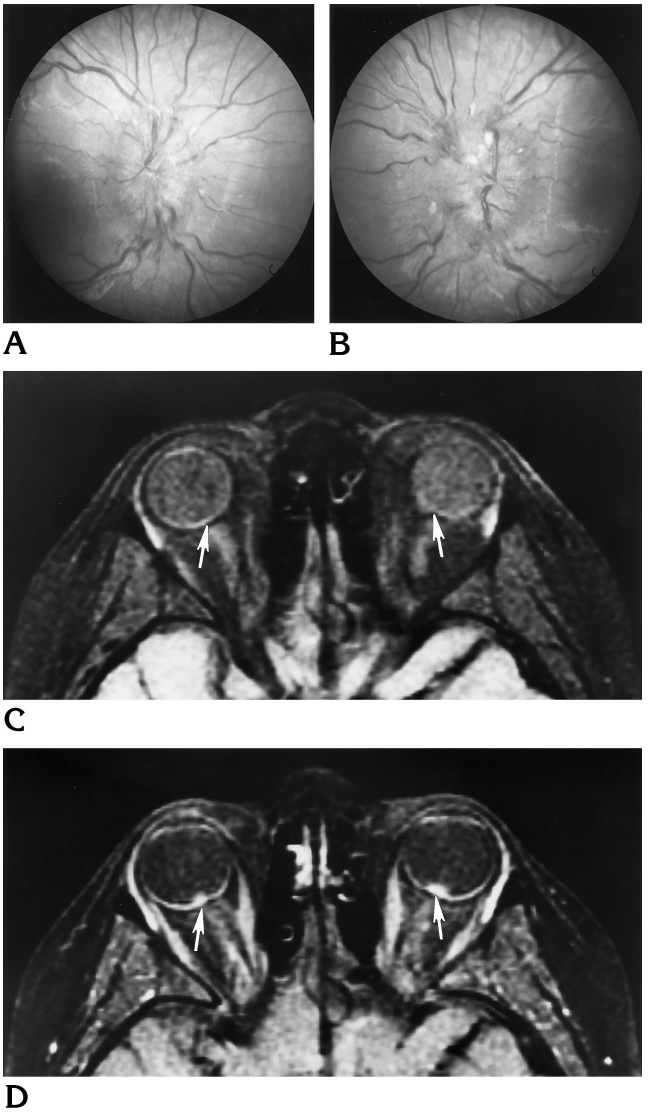


Fig 2. MR imaging of papilledema (from Brodsky and Glasier [2]).

A and *B*, Optic disk photographs show bilateral papilledema. Note optic disk elevation with distended retinal veins, and exudates overlying both optic disks.

C, Axial T1-weighted MR image (800/29/2) of the orbital optic nerves with fat suppression shows indention of the left posterior sclera at its junction with the optic nerve, with no intraocular signal abnormality. *Arrows* denote the position of the optic disks.

D, Axial contrast-enhanced MR image (800/29/2). Hyperintense foci corresponding to the swollen optic disks (*arrows*) are now visible within the vitreous cavities.

It is also important to note that axial contrast-enhanced MR imaging has previously shown enhancement of the optic disks within the globes of patients with papilledema (Fig 2) (2). Fluorescein angiography in papilledema shows dilated capillaries, microaneurysms, and flame-shaped hemorrhages in the arteriovenous phase, followed by diffuse prelaminar capillary leakage and a late staining of the optic nerve head and adjacent tissues, which persists in the chronic stages of papilledema (3, 4). Intraocular contrast enhancement of the swollen optic disk on MR imaging is analogous to leakage of fluorescein dye from the surface of the disk; both result from diffuse prelaminar capillary leakage secondary to severe venous congestion.

Despite profuse capillary leakage on the surface of the disk, histopathologic studies in animals with experimentally induced acute papilledema have shown distended prelaminar axons with little extracellular edema (5), which could explain the hypointensity of the optic papilla observed by Jinkins et al on T2-weighted images without invoking chronicity as a determining factor. If the authors could substantiate the diagnosis of papilledema in their patients (underlying cause, elevation of intracranial pressure without additional cerebrospinal fluid abnormalities), their finding of hypointensity of the optic papilla on T2-weighted images would be a useful addition to the neuroradiologist's armamentarium.

Michael C. Brodsky
Department of Ophthalmology
Arkansas Children's Hospital
Little Rock

References

1. Jinkins JR, Athale S, Xiong L, et al. MR of optic papilla protrusion in patients with high intracranial pressure. *AJNR Am J Neuroradiol* 1996;17:665–668
2. Brodsky MC, Glasier CM. Magnetic resonance visualization of the swollen optic disc in papilledema. *J Neuroophthalmol* 1995;15: 122–124
3. Hayreh SS. Optic disc edema in raised intracranial pressure, V: pathogenesis. *Arch Ophthalmol* 1977;95:1553–1565
4. Sanders MD. A classification of papilloedema based on a fluorescein angiographic study of 69 cases. *Trans Am Ophthal Soc* 1969; 89:177–192
5. Tso MOM, Hayreh SS. Optic disc edema in raised intracranial pressure, III: a pathological study of experimental papilledema. *Arch Ophthalmol* 1977;95:424–434

Reply

Our paper was not specifically clinically oriented; it was not intended to be. It was primarily a visual MR imaging study. To reiterate, the purpose of the published study was to evaluate the signal characteristics of the optic papilla on cranial MR images of patients with clinical evidence of elevation of the optic papilla. We reviewed retrospectively the routine cranial images of 15 patients who were referred for MR imaging and who had subjectively and objectively altered visual acuity and objective fundoscopic findings of optic papilla elevation. On the basis of clinical criteria and imaging findings, the patients had final diagnoses of various pathologic processes or states, including cerebral venous sinus thrombosis (n = 1), neoplasia (n = 3), and primary pseudotumor cerebri (n = 11). In the patients diagnosed with primary pseudotumor cerebri, the average duration of the clinical syndrome was approximately 2 months; their clinical syndrome invariably consisted of

chronic, persistent headache and blurred vision, sometimes accompanied by diplopia. Optic neuritis was excluded on a clinical basis.

In all 15 (100%) of the patients, the signal of the optic papillae on T2-weighted conventional spin-echo images was hypointense relative to the vitreous of the globe. The control subjects showed hypointensity of the optic papillae identical to the patient group in all cases. We feel that these results suggest that true edema of the optic papilla was not a major component of the process of chronic optic papilla elevation shown by fundoscopy in these patients. However, these findings do not preclude an element of true cellular or interstitial edema during the acute period (first days or weeks of elevated intracranial pressure) (1). Additional work needs to be done concerning the imaging findings in the acute stages of optic papilla protrusion.

The precise reason for shortening of the T2-weighted MR signal in the optic papilla in both normal and abnormal cases is not understood and perhaps requires further in vitro study. Nevertheless, because the optic papilla is largely composed of myelinated axons and because white matter is hypointense on T2-weighted images, some degree of low signal intensity is to be expected, as was shown in the control subjects.

The histologic observation that there is little interstitial fluid is contradictory to the claim of the fluorescein angiographic study, which seems erroneously to indicate otherwise. The pathologic finding that there is a distention of the prelaminar axons does not necessarily indicate that the papilla would be hypointense. In fact, swollen axons (ie, increased intracellular edema) would likely be expected to produce hyperintensity on T2-weighted MR studies.

In the future, high-resolution MR imaging of the optic globe, coupled with better clinical correlation of disease phase and pathologic condition, might clarify the difference between true swelling of the optic papilla caused by intrinsic disease (eg, optic neuritis) and disk elevation resulting from physical protrusion (as seen in cases of cranial hypertension).

J. Randy Jinkins
Neuroradiology
University of Texas Health Science Center
San Antonio

References

1. Manfre L, Lagalla R, Maniameli A, et al. Idiopathic intracranial hypertension: orbital MRI. *Neuroradiology* 1995;37:459–461

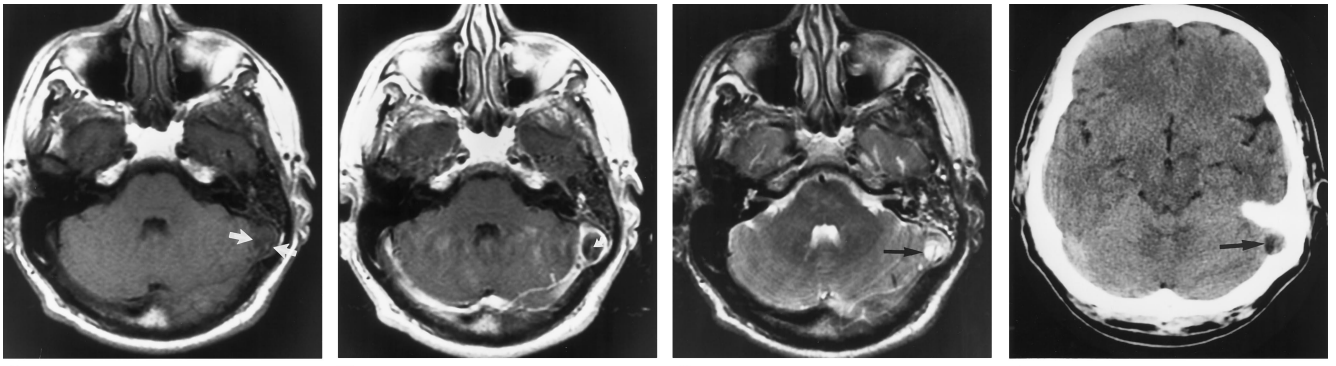
Prominent Arachnoid Granulations

I read with great interest the recent article by Leach et al (1) regarding the normal appearance of arachnoid granulations on computed tomographic (CT) and MR imaging exams. The purpose of this letter is to share the imaging features of an additional case of a presumed prominent arachnoid granulation in a patient with mastoiditis and the treatment quandary it presented.

A 52-year-old man presented with headache. An MR study showed a prominent filling defect within the left transverse sinus that was hypointense on T1- and hyperintense on T2-weighted sequences (Fig 3 A and B). T2 hyperintensity within the left mastoid air cells indicating fluid and/or mucosal edema consistent with mastoiditis was present. There was minimal central punctate enhancement (Fig 3C). MR venography confirmed a focal filling defect within the left transverse/sigmoid sinus junction (Fig 3D). The left transverse sinus was atretic and the vein of Labbé drained into the immediate vicinity of the filling defect. There was normal flow enhancement within the vein of Labbé and no evidence of venous collaterals or dural enhancement. An unenhanced CT scan showed the mass to be hypodense to brain (Fig 3E). The diagnosis of prominent arachnoid granulation was suggested; however, because of the presence of mastoiditis, which could predispose the patient to dural sinus thrombosis, and the clinician's low level of confidence with the proposed diagnosis, anticoagulation therapy was begun. Follow-up MR examinations performed 2 weeks and 5 months after initial imaging studies showed no change in size or signal intensity of the filling defect within the transverse sinus, thus excluding thrombus as the cause. The patient's anticoagulant therapy was discontinued.

This case serves to reiterate the points made by Leach et al regarding the imaging features of arachnoid granulations. Arachnoid granulations are variably iso/hypointense on T1- and hyperintense on T2-weighted MR sequences. Although acute thrombus could have similar signal intensity, hypodensity on CT scans helps to exclude this diagnosis. Little if any enhancement of arachnoid granulations on MR and CT studies is consistent with their histologic appearance. An arachnoid villus consists of a core of arachnoidal tissue and collagen fibers, within which are interstices or tubules containing cerebrospinal fluid that communicate with the subarachnoid space (2). Although tubules containing blood cells (capillaries) have been described within the arachnoid granulations of sheep, their presence within the arachnoid granulations of humans is controversial (3–5). Given the discordant findings of these researchers, it appears that blood vessels are not a prominent feature of arachnoid granulations, explaining their relative lack of enhancement. As demonstrated by Leach et al's patient population and our case, the transverse sinus is a common location, especially near entry sites of superficial veins, particularly the vein of Labbé. Finally, the origin of attachment of the filling defect can help to confirm the diagnosis. Arachnoid granulations project from the brain surface through the meningeal layer of dura into the sinus lumen, where they are covered by an endothelial cell layer. When located within the transverse sinus, arachnoid granulations should project from the brain (medial) surface into the sinus lumen. Coronal MR images (not shown here) in our patient showed a broad base of attachment to the medial sinus wall with a patent lumen laterally.

In summary, I thank Leach et al for publishing their work. I hope their article will serve to familiarize more radiologists with the characteristic imaging features that



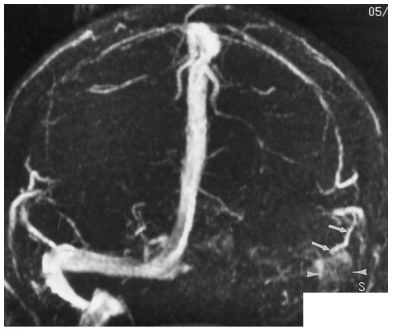


Fig 3. *A*, T1-weighted (650/11/1) MR image shows hypointense nodule in left transverse/sigmoid sinus junction (*arrows*).

B, Axial contrast-enhanced T1-weighted (650/11/1) MR image shows hypointense filling defect with minimal central punctate enhancement (*arrow*).

C, Axial T2-weighted (3500/85/1) MR image shows hyperintense nodule (*arrow*). Note mucosal thickening/fluid within left mastoid air cells.

D, Axial CT scan shows hypodense nodule (*arrow*).

E, Two-dimensional time-of-flight MR venogram (45/8.8, 60° flip angle) shows atretic left transverse sinus. Vein of Labbé (*arrows*) drains into immediate vicinity of prominent arachnoid granulation (*arrowheads*).

differentiate prominent arachnoid granulations from dural sinus thrombosis, thus preventing the unnecessary use of anticoagulant therapy.

Michael T. Zagardo
Section of Neuroradiology
Department of Diagnostic Radiology
University of Maryland Medical System
Baltimore

References

1. Leach J, Jones B, Tomsick T, Stewart C, Balko G. Normal appearance of arachnoid granulations on contrast-enhanced CT and MR of the brain: differentiation from dural sinus disease. *AJNR Am J Neuroradiol* 1996;17:1523–1532
2. Allan P, Palay S, Webster H. *The Fine Structure of the Nervous System: The Neurons and Supporting Cells*. Philadelphia, Pa: WB Saunders Co; 1976:342
3. Jayatilaka A. An electron microscopic study of sheep arachnoid granulations. *J Anat* 1965;99:635–649
4. Clark L. On the pacchionian bodies. *J Anat* 1920;55:40
5. Kiss F, Sattler J. Struktur und Funktion der pacchionischen Granulation. *Anat Anz* 1956;103:284

Reply

We appreciate Dr Zagardo's interest in our paper. His case of a large arachnoid granulation in the left transverse sinus shows the typical imaging features of this entity that allow its distinction from sinus thrombosis, namely: typical lateral transverse sinus location, focality, common adjacent entering superficial veins, typical signal intensity on MR (isointensity to hypointensity on T1-weighted images, hyperintensity on T2-weighted images), and low (near cerebrospinal fluid) density on CT. The origin of attachment of the granulations might be an additional helpful feature. Although it was not specifically evaluated in our imaging study, in the anatomic portion of our study we found granulations most commonly projecting from the inner, or subarachnoid facing surface of the dural sinuses, as in Dr Zagardo's case.

James L. Leach
Department of Radiology
University of Cincinnati (Ohio) Medical Center

Reduced Caliber of the Internal Carotid Artery

Publication of MR angiography papers unfortunately runs the risk of ignoring contrast cerebral angiography and reinventing the wheel. In a recent publication, Kane et al (1) describe reduction of the caliber of the internal carotid artery, seen on MR angiography, as a normal finding when the A1 segment of the anterior cerebral artery is absent or hypoplastic. This observation is not new, is well known to the cerebral angiographers of the old school, and in fact was reported by Harold Lehrer in 1968 (2). Kane et al begin by making the astonishing statement, "The circle of Willis, which can be seen on MR angiograms, is not visible by means of conventional angiography owing to single-

vessel injection." How did we ever diagnose cerebral aneurysms before the advent of MR angiography?

Samuel M. Wolpert
Section of Neuroradiology
New England Medical Center
Boston, Mass

References

1. Kane AG, Dillon WP, Barkovich AJ, et al. Reduced caliber of the internal carotid artery: a normal finding with ipsilateral absence or hypoplasia of the A1 segment. *AJNR Am J Neuroradiol* 1996;17: 1295–1301
2. Lehrer HZ. Relative calibre of the cervical internal carotid artery: normal variation with the circle of willis. *Brain* 1968;91:339–348

Reply

We thank Dr Wolpert for his comments and for referencing Dr Lehrer's fine paper. We apologize for inadvertently excluding it from our bibliography. We would point out that the mutual observations in both his and our paper were not new, as both Dr Lehrer's and our bibliography include earlier pathologic studies by Dr Baptista (1, 2).

We felt this observation was important to bring to the attention of the readership of *AJNR* because it is not well known among neuroradiologists. Indeed, despite its relevance, particularly now in the era of cross-sectional imaging, Dr Lehrer's observations are not included in the bibliographies or discussions in classic texts on cerebral angiography published before and after the advent of CT and MR (3–5). Furthermore, discussions of reduced carotid caliber in these and other textbooks primarily emphasize those abnormal conditions leading to it. Benign hypoplasia of the carotid artery is occasionally mentioned, but not its relationship to normal variations of the circle of Willis. On these grounds and the frequency with which we currently see this asymmetry, one might dispute whether this association is well known.

We hope that Dr Wolpert did not misinterpret our comments regarding the circle of Willis as seen on conventional angiography. Obviously, we were referring to the fact that only portions of the circle are visible on each single vessel injection, making exact comparison of carotid artery caliber difficult. Dr Lehrer overcame this problem by selecting only bilateral carotid angiograms with equivalent degrees of magnification and angulation, and in some instances injected both arteries simultaneously.

We would again like to emphasize that the asymmetry of carotid vessels in healthy subjects as seen on conventional or MR angiography is rather common (25% in Dr Lehrer's series), and has pathogenesis easily explained by variations in the anatomy of the circle of Willis. We hope that some patients are helped or procedures avoided by bringing this concept as it applies to MR angiography to the readership's attention. We again compliment Dr Wolpert for his erudite library skills and thank him for bringing Dr Lehrer's paper to our attention.

Arthur G. Kane
William P. Dillon
Department of Radiology
University of California, San Francisco

References

1. Baptista AG. Studies on the arteries of the brain, III: circle of Willis, morphologic features. *Acta Neurol Scand* 1964;40:398–414
2. Baptista AG. Studies on the arteries of the brain, II: the anterior cerebral artery: some anatomic features and their clinical implications. *Neurology* 1963;13:825
3. Dilenge D, Heon M. The internal carotid artery. In: Newton TH, Potts DG, eds. *Radiology of the Skull and Brain*. St Louis, Mo: CV Mosby; 1974:1233–1245
4. Osborne AG. The internal carotid artery: cervical and petrous portions. In: Osborne AG, ed. *Introduction to Cerebral Angiography*. Philadelphia, Pa: Harper & Row; 1980:90–108
5. Taveras J. Brain vascular disorders. In: Taveras J, ed. *Diagnostic Neuroradiology*. New York, NY: Williams & Wilkins; 1996:477