AJNR

Brain MR: Pathologic Correlation with Gross and Histopathology. 2. Hyperintense White-Matter Foci in the Elderly

Bruce H. Braffman, Robert A. Zimmerman, John Q. Trojanowski, Nicholas K. Gonatas, William F. Hickey and William W. Schlaepfer

AJNR Am J Neuroradiol 1988, 9 (4) 629-636
http://www.ajnr.org/content/9/4/629

Brain MR: Pathologic Correlation with Gross and Histopathology.
2. Hyperintense White-Matter Foci in the Elderly

Bruce H. Braffman[1, 2]
Robert A. Zimmerman[1]
John Q. Trojanowski[3]
Nicholas K. Gonatas[3]
William F. Hickey[3]
William W. Schlaepfer[3]

MR was performed on 23 formalin-fixed brain specimens of patients 60 years old or older at the time of death. In two of these subjects MR had also been performed in vivo prior to death. Fifteen hyperintense white-matter foci were found on long TR MR images in seven brains. These lesions were correlated with gross and microscopic pathology. Six lesions were infarctions, two were small foci of gliosis or noncavitated infarcts, two were plaques of demyelination, one was a minute brain cyst, and one was a congenital diverticulum of the lateral ventricle; in three foci the abnormality was not found. We identified no MR criteria to distinguish noncystic infarction from either gliosis or demyelination. However, MR was able to distinguish all these lesions from fluid-containing spaces—including cystic infarction, brain cyst, and ventricular diverticulum—since the lesions in the latter group may be isointense relative to CSF in vivo or to fluid in the subarachnoid space in the postmortem fixed state on all pulse sequences. The relationship of a ventricular diverticulum and a brain cyst to the ventricle or subarachnoid space serves as an additional differentiating feature on MR. In cases in which CT was also performed, it revealed corresponding hypodensities in two infarctions, but failed to reveal the foci of gliosis (or non cavital infarction), demyelination, or brain cyst.

These data suggest that subtle changes of gliosis and demyelination, presumably from chronic vascular insufficiency, and/or frank infarction account for the majority of hyperintense white-matter lesions seen in MR in elderly patients. Distinguishing among the various lesions is difficult, but subtle differences are present when MR is correlated with histopathology.

Confluent periventricular and punctate hemispheric foci of abnormal high signal intensity are commonly seen in elderly patients on MR images with long TR sequences. The reported frequency in patients older than 60 years of age is 30% [1–3]. The collective work of several investigators has resulted in a gamut of physiologic and pathologic entities that may result in confluent periventricular hyperintensity on MR. Sze et al. [4] described a decrease of myelin and ependymitis granularis (a localized breakdown of ependyma) in pathologically normal brain specimens anterior to the frontal horns. Zimmerman et al. [5] observed this finding on MR not only in patients with hydrocephalus, demyelinating diseases, or other pathologies, but also in otherwise normal subjects. A physiologic explanation for the finding in the latter group is the normal flow of interstitial water into the lateral ventricles from the extracellular space. Marshall et al. [6] performed MR studies on postmortem brain specimens and found infarction, gliosis, and nonspecific protein deposition corresponding to this finding.

Similar reports have described different entities that may account for the punctate hemispheric foci of abnormal high signal intensity seen on MR. Brant-Zawadzki and Kucharczyk [7] reported that most of these are likely small, clinically silent infarcts, or perhaps diffuse ischemic changes. Holland [8] stated they are probably regions of white-matter gliosis. Kirkpatrick and Hayman [9] observed that perivascular white-matter gliosis with shrinkage and atrophy of axons and myelin are the most common white-matter lesions in normal elderly subjects. Our study is the first

This article appears in the July/August 1988 issue of *AJNR* and the September 1988 issue of *AJR*.

Received September 8, 1987; accepted after revision February 24, 1988.

Presented at the annual meeting of the American Society of Neuroradiology, New York City, May 1987.

This work was supported in part by National Institutes of Health grant PO1–AG06107.

[1] Department of Radiology, Hospital of the University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104. Address reprint requests to R. A. Zimmerman.

[2] Department of Radiology, Memorial Hospital, Hollywood, FL 33021.

[3] Division of Neuropathology, Hospital of the University of Pennsylvania, Philadelphia, PA 19104.

***AJNR* 9:629–636, July/August 1988**
0195–6108/88/0904–0629

we are aware of that correlates MR features of variable punctate foci of high signal intensity on long TR sequences with the gross and microscopic pathology of these abnormalities.

Materials and Methods

Of the cases described in our companion article [10], 24 were 60 years old or older. MR scans were obtained in 23 brain specimens, 21 after formalin fixation and two both before and after death and subsequent formalin fixation. One patient was only investigated 10 weeks before death. Our companion article provides more detailed information on the methods used in this study.

CT scans were obtained in 15 of these 24 subjects before death. MR and CT examinations were correlated in all available cases.

Results

Six lesions in three subjects (cases 5, 6, and 10) were white-matter infarctions with varying amounts of cavitation (Table 1). Five were confined to the white matter of the centrum semiovale, and the sixth (case 10) extended from the white-matter into the gray matter. On MR, the lacunar infarct in case 5 was slitlike (Fig. 1), the four lacunae in case 6 were ovoid, and the infarct that extended to the cortical medullary junction in case 10 was ovoid with irregular margins (Figs. 2A–2D). These lesions were hyperintense relative to brain parenchyma on both long TR sequences (short and long TEs), slightly hyperintense relative to water mixed with dilute formalin on the long TR/short TE sequence, and approximately isointense relative to this fluid on long TR/long TE sequences. CT was performed in cases 5 and 10 and revealed both lesions. In case 5 it demonstrated a linear hypodensity. CT examination in case 10 revealed an ovoid hypodensity (Fig. 2G). On gross pathologic examination, the lesion in case 5 was a slitlike cavity, the lesion in case 10 an irregular cavity with tan brown softening (Fig. 2H), and no gross abnormality was noted in case 6. Histopathology confirmed the diagnosis of infarction in these cases (Fig. 2I). The confluent high signal intensity surrounding the slitlike infarction on MR in case 5 was gliosis.

A lesion in case 6 and one lesion in case 11 were either small foci of white-matter gliosis or minute infarctions. On MR (Fig. 3) the lesion in case 11 was round, hyperintense relative to CSF on the long TR/short TE sequence, approximately isointense relative to CSF on the long TR/long TE sequence, and hyperintense relative to brain parenchyma on both these sequences. CT was performed in this patient before death and failed to disclose this abnormality. The lesion in case 6 was irregular on MR, and demonstrated intensities identical to those seen in infarction in the postmortem fixed state. On gross pathologic evaluation the lesions were small, pale foci. These lesions were described microscopically as foci of either gliosis or infarction. Caplan and Schoene [11] described a spectrum of changes in the white matter, from diffuse loss of nerve fibers with delicate fibrillary necrosis to cavitated infarcts with dense gliosis. A state that is intermediate between the two extremes may be difficult to categorize, even histopathologically.

Two lesions in one brain (case 12) were plaques of demyelination. In this case, no neurologic symptoms were known to have existed during life. The foci probably were caused by incidental (benign) multiple sclerosis (see Discussion). On MR (Figs. 4A and 4B), one lesion was rounded and one was

TABLE 1: Supratentorial White-Matter Lesions

Case No.	Age	Gender	Cardiovascular Status			MR and Pathologic Features			
			HTN	Other	Systemic Atherosclerosis	Site	Morphology	Size (mm)	Histopathology
5	78	F	Yes (P+C)	MI	Severe	R centrum semiovale	Slitlike	4 × 2	Infarct
6	70	F	Yes (P+C)	MI, A	Severe	(1) L occipital WM (2) Bifrontal WM (four sites)	Irregular, rounded Ovoid	10 × 10 2 × 2 (all)	Gliosis vs infarct Infarcts
7	75	M	Yes (P)	No	Severe	Adjacent to temporal horn R lateral ventricle	Round	10 × 10	Congenital variant of temporal horn
10	64	M	Yes (P+C)	MI, A	Severe	(1) L frontal WM & GM	Irregular, ovoid	10 × 5	Infarct
						(2) L occipital WM	Mostly round, one side straight	6 × 6	Brain cyst
11	61	M	No	No	Mild	L centrum semiovale	Round	4 × 4	Gliosis vs infarct
12	60	M	Yes (P+C)	MI, A	Severe	(1) Splenium, corpus callosum	Round	4 × 4	Demyelination
						(2) L parietooccipital WM	Irregular	25 × 5	Demyelination
13	63	M	No	No	Mild	Bilateral centrum semiovale	Three round lesions	3 × 3 4 × 3 3 × 3	No abnormality found

Note.—HTN = hypertension; R = right; L = left; P = pathologic evidence of hypertension (concentric left ventricular hypertrophy); C = clinical evidence of hypertension during life; MI = post–myocardial infarction; A = arrythmia; WM = white matter; GM = gray matter.

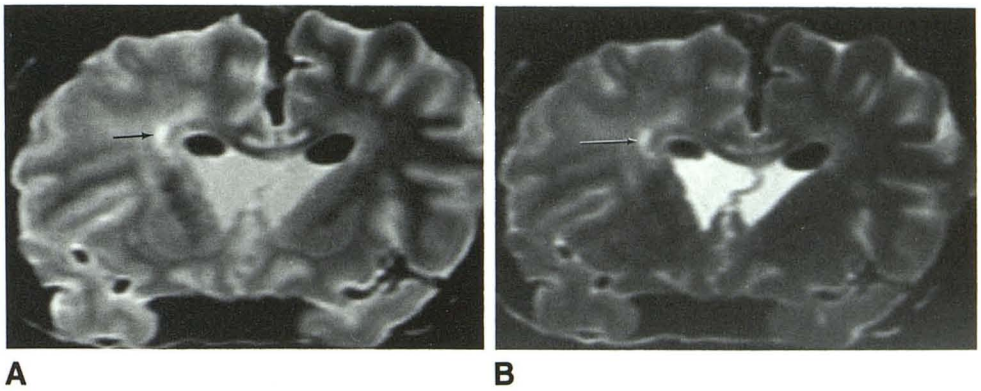


Fig. 1.—Case 5: lacunar infarct in right centrum semiovale near entrance to internal capsule with surrounding gliosis. Coronal MR images, 2500/30 (*A*) and 2500/80 (*B*), of brain specimen. Slitlike lacunar infarct (*arrows*) is hyperintense relative to brain parenchyma on both long TR sequences. Note that on long TR/short TE sequence (*A*), infarct is slightly hyperintense relative to fluid in ventricles. Surrounding hyperintensity of right centrum semiovale was gliosis.

irregular. They displayed intensities identical to those described for infarction and gliosis. CT was performed and failed to disclose either lesion. On gross pathologic examination, the larger lesion in the left parietooccipital white matter was a gray, translucent region with irregular margins, while the smaller lesion in the splenium of the corpus callosum was not seen. Histopathology (Fig. 4C) revealed two foci of demyelination, with sharp margins of demarcation between the demyelinated areas and the normal white matter. A Bodian stain (not shown) revealed preservation of axons within the affected regions. These two features (the sharp margins of demarcation and the axonal preservation) are characteristic histologic features of a primary demyelinating process.

Two foci in two brains consisted of a small intraparenchymal brain cyst (case 10) and a diverticulumlike structure arising from the temporal horn of the lateral ventricle (case 7). On MR the intraparenchymal brain cyst was smooth, with a largely rounded but partly straightened wall, and was located adjacent to a sulcus (Figs. 2A, 2B, 2E, and 2F). The origin of the diverticulumlike structure off the temporal horn of the lateral ventricle was appreciated on MR (Fig. 5A). Both these fluid-filled structures were isointense relative to fluid in the ventricles and sulci on both echoes of the long TR sequence. CT was performed in the subject with a brain cyst but it failed to reveal this lesion (Fig. 2G). On gross pathologic examination the brain cyst was a cavity with partly round, partly straight, smooth margins (Fig. 2J), and the diverticulum was a rounded extension of the temporal horn of the lateral ventricle (Fig. 5B). Histopathology showed a single cell layer lining the brain cyst (Fig. 2K) and normal ependyma lining the diverticulum, which most likely represented a congenital variant.

In case 13 (Fig. 6), MR detected three small round bilateral lesions in the white-matter. They were hyperintense relative to CSF on the long TR/short TE sequence, approximately isointense relative to CSF on the long TR/long TE sequence, and hyperintense relative to brain parenchyma on both long TR sequences. Gross pathologic evaluation did not reveal corresponding abnormalities. Microscopic sections through the regions imaged on MR also disclosed no abnormalities.

Of the 24 patients 60 years old or older in our study, six (25%) had one or more foci of abnormal high signal intensity in the supratentorial white matter, yielding a total of 15 lesions (Table 2). Six (40%) were foci of infarction, two (13%) were regions of gliosis or noncavitated infarcts, two (13%) were plaques of demyelination, one (7%) was a brain cyst, and one (7%) was a congenital diverticulum of the lateral ventricle; in three (20%) no abnormality was found.

Discussion

White-Matter Ischemia and Infarction

In a recent study by Kirkpatrick and Hayman [9], 15 brains from normal subjects older than 52 years of age were studied. Slices of whole, celloidin-embedded brain cut at 35 μm were examined. The most common lesion found in the supratentorial white-matter was atrophy and shrinkage of axons and myelin, with gliosis surrounding thickened tortuous vessels. They called this perivascular atrophic demyelination. (The entity comprises features that are similar, if not identical, to état pre-criblé [12], which is described in our companion article [10].) Kirkpatrick and Hayman postulated that these changes are from chronic, low-grade vascular insufficiency. They distinguished this chronic process from occlusive vascular disease, which results in acute tissue necrosis. The authors concluded it is likely that these lesions account for most of the punctate white-matter lesions seen on MR in the elderly.

In our series, white-matter infarction was the most common lesion responsible for a punctate hyperintense signal (Table 2). The reason for the discrepancy between our results and those of Kirkpatrick and Hayman [9] is uncertain. They included only clinically healthy subjects, while we included patients with and without known neuropathology. In addition, both series had limitations. In our study, only three cases (cases 6, 10, and 12) had more than one lesion in the supratentorial white matter, and in only one of these (case 6) did infarction account for more than one lesion. Yet it is common to see several or enumerable hyperintense white-matter foci in the elderly on MR. In addition, our study predominantly was performed on postmortem brain specimens after formalin fixation. Although certain changes on MR after fixation are well described (see our companion article [10]), some lesions (such as perivascular atrophic demyelination) may be less noticeable on postmortem MR compared with an in vivo examination. The one limitation of the series of Kirkpatrick and Hayman [9] was the lack of MR correlation.

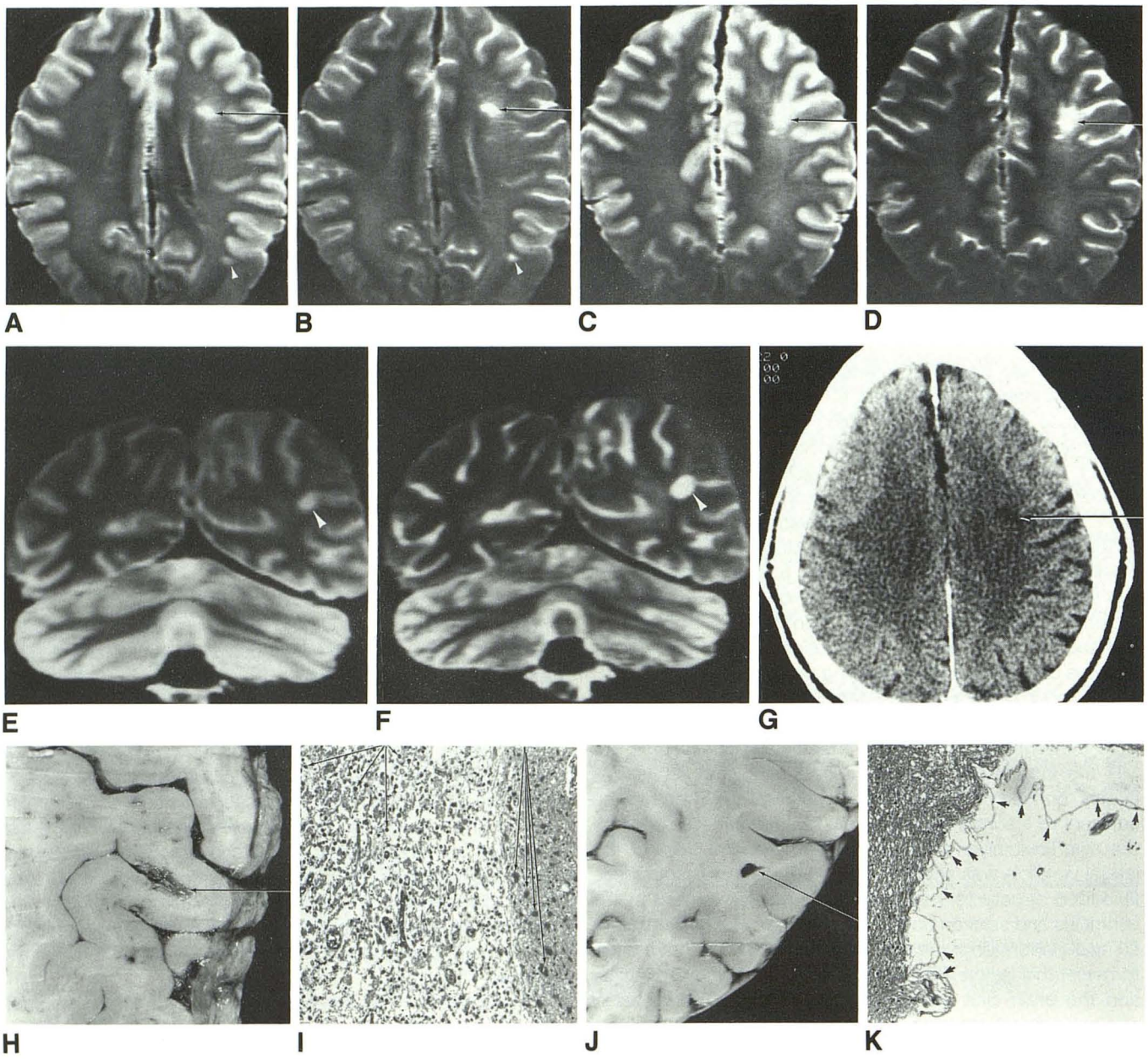


Fig. 2.—Case 10: infarct in left centrum semiovale extending to gyrus. Brain cyst in left occipital white matter.

A–F, Axial and coronal MR images, 2500/30 (*A*, *C*, and *E*) and 2500/80 (*B*, *D*, and *F*), of brain specimen. Infarct (*arrows*) has irregular borders and is hyperintense relative to brain parenchyma on both long TR sequences. Brain cyst (*arrowheads*) in contrast, has smooth borders and is approximately isointense relative to fluid in sulci on both sequences. Cyst is adjacent to sulcus. This is appreciated in coronal, but not axial, plane.

G, Axial CT scan. Infarct (*arrow*) is ovoid hypodensity in left centrum semiovale. Brain cyst was not detected on this or other CT sections.

H, Gross pathology of infarct. Cortical component of infarct (*arrow*) is discolored cavitating region at gyrus.

I, Histopathology of infarct. Macrophages (*shorter arrows*) are present in this recent infarct, which is beginning to cavitate. Infarct is bordered by reactive astrocytes (*longer arrows*). (H and E ×37.25)

J, Gross pathology of brain cyst. Cavity (*arrow*) has partly round, partly straight, smooth margins.

K, Histopathology of brain cyst. Brain cyst is cavity with single cell lining (*arrows*), and is surrounded by virtually normal white matter. Note absence of reactive astrocytes. (H and E ×37.25)

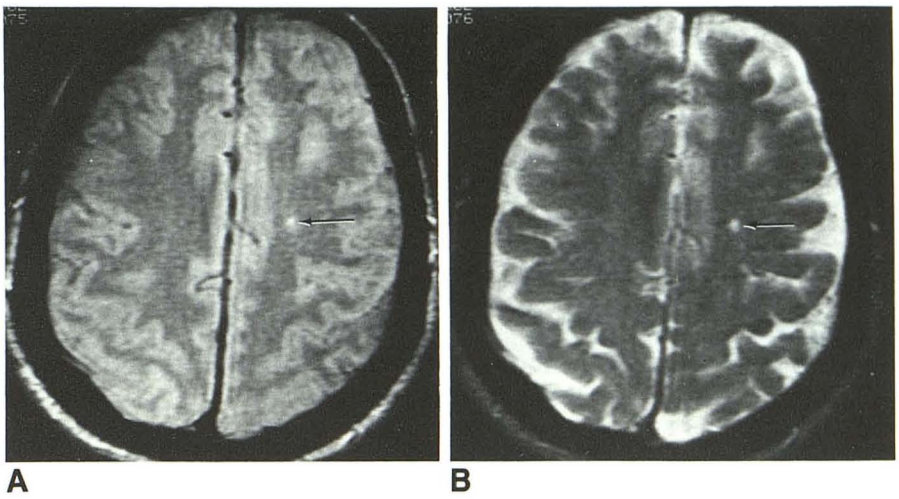


Fig. 3.—Case 11: gliosis vs infarction.
A and *B*, Axial MR images, 2500/30 (*A*) and 2500/80 (*B*), before death. Small round lesion in left centrum semiovale (*arrows*) is hyperintense relative to brain parenchyma on both long TR sequences. On long TR/short TE sequence (*A*) the lesion is hyperintense relative to CSF.

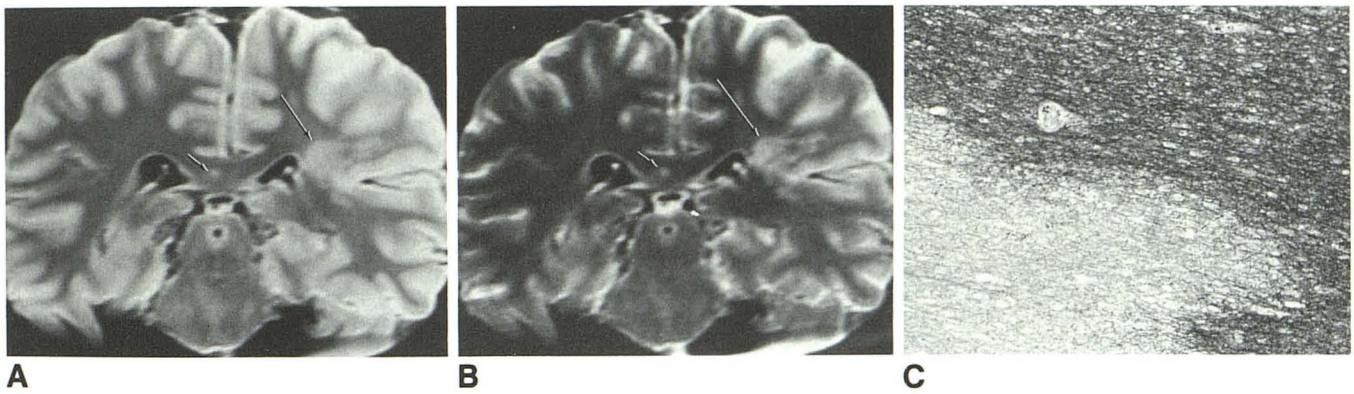


Fig. 4.—Case 12: two plaques of demyelination.
A and *B*, Coronal MR images, 2500/30 (*A*) and 2500/80 (*B*), of brain specimen. Small round lesion in splenium of corpus callosum (*short arrows*) and larger, irregular lesion in centrum semiovale of parietal lobe (*long arrows*) are hyperintense relative to brain parenchyma on both long TR sequences.
C, Histopathology. Demyelinated plaque is pale area; normal myelin is dark area. Note sharp margin of demarcation between demyelinated area and normal white matter, a characteristic histologic feature of a primary demyelinating process. (Weil ×37.25)

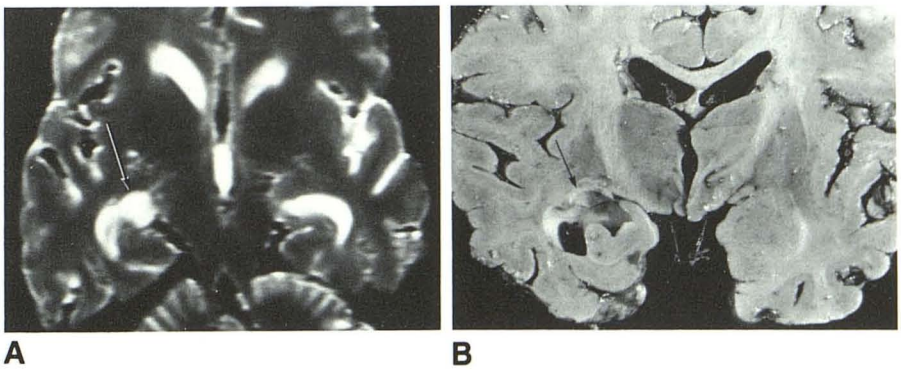
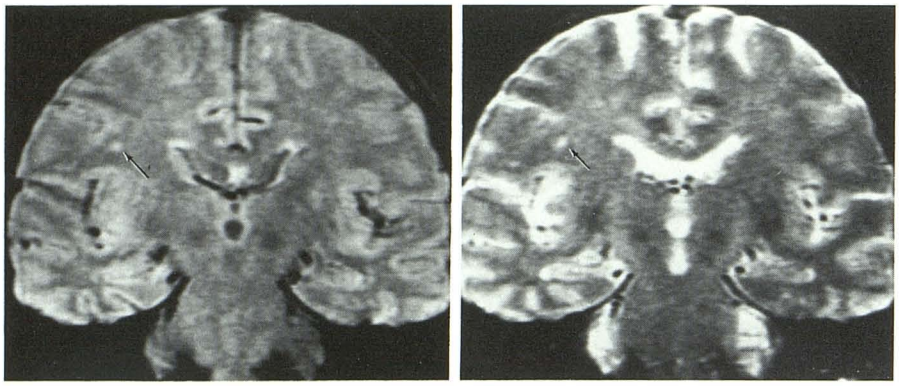


Fig. 5.—Case 7: congenital variant, diverticulumlike structure off temporal horn of right lateral ventricle (*arrows*).
A, Axial MR image, 2500/80, of brain specimen. Rounded structure adjacent to temporal horn is isointense relative to fluid in ventricles.
B, Gross pathology reveals congenital variant of temporal horn.

Nonetheless, previous neuropathologic studies also documented a high occurrence of lesions caused by vascular insufficiency and frank infarction in the elderly population. Tomlinson et al. [13] reported small or large cerebral softenings in 71% of nondemented elderly subjects. Wisniewski and Terry [14] described gross or microscopic lesions caused by vascular insufficiency in almost all brains from individuals above the age of 65 years. Peress et al. [15] reviewed necropsy data during the 16-year period 1954–1969 and reported an incidence of encephalomalacia of 20–30% in patients 60 years old and older. Tomlinson and Henderson [16] described small ischemic lesions in brains in about 50% of people over the age of 65, the majority being in the basal ganglia but not uncommonly in the white matter. Therefore, it is likely that either more subtle lesions caused by vascular insufficiency (i.e., perivascular atrophic demyelination) and/or



A B

Fig. 6.—Case 13: abnormality not found. Coronal MR images, 2500/20 (*A*) and 2500/80 (*B*), before death. Round lesion in right centrum semiovale (*arrows*) is hyperintense relative to brain parenchyma on both long TR sequences.

TABLE 2: Types of Supratentorial White-Matter Lesions

Type of Lesion	No. (%)
Infarct	6 (40)
Gliosis vs infarct	2 (13)
Plaques of demyelination	2 (13)
Brain cyst	1 (7)
Congenital ventricular diverticulum	1 (7)
Unknown	3 (20)
Total	15 (100)

frank infarction account for the majority of hyperintense punctate white-matter lesions seen on MR in the elderly.

Gerard and Weisberg [3] reported that these foci occur on MR in the geriatric population with a frequency of 7.8% in asymptomatic patients with no cardiovascular risk factors; 31% in asymptomatic patients with hypertension, diabetes mellitus, or heart disease; and 78.5% in patients with cardiovascular risk factors and a history of a completed stroke, reversible ischemic neurologic deficit, or transient ischemic attack. There are some possible reasons for perivascular atrophic demyelination and infarction in both the normal elderly without cardiovascular risk factors and the increasing prevalence of these foci in the elderly patient with cardiovascular risk factors. Gradual and progressive decreases in cerebral blood flow and atherosclerotic vascular disease occur with increasing age and are accelerated in hypertension, in diabetes, and with other cardiovascular risk factors [9, 17–21]. These processes may result in impairment of the transport of vital material (glucose and oxygen) from blood to brain parenchyma.

The clinical sequelae of the lesions is uncertain. Tomlinson and Henderson [16] reported a significantly lower frequency of intracerebral ischemic changes in a normal group compared with a demented group. However, it is usually the larger infarcts that play a greater role in the development of dementia rather than fine scattered ones. Brant-Zawadzki et al. [2] stated the likelihood of dementia may be increased if there is an increase in the number of such small lesions detected on MR. The location of these foci may also play a role in the presence or absence of clinical manifestations.

Similar, although more extensive changes of both infarction and gliosis occur in the rare entity subcortical arteriosclerotic encephalopathy (Binswanger disease). Caplan and Schoene [10] described the criteria for this entity. The pathologic features are severe thickening of small penetrating vessels and diffuse white-matter loss with gliosis, lacunar infarctions, and hydrocephalus. The clinical highlights consist of hypertension, systemic vascular disease, acute strokes, subacute accumulation of focal neurologic symptoms and signs over weeks to months, long plateau periods, lengthy clinical course, dementia, and prominent motor signs and pseudobulbar palsy. Both état lacunaire and subcortical arteriosclerotic encephalopathy are caused by disease of the small penetrating vessels. However, the former is defined pathologically only by lacunar infarctions, while the latter demonstrates both lacunae and white-matter gliosis. The majority of elderly patients who have punctate hemispheric foci of abnormal high signal intensity on long TR sequences do not meet the diagnostic criteria of subcortical arteriosclerotic encephalopathy.

Incidental Multiple Sclerosis

In a review of 2450 autopsies from 1974 through 1981, Gilbert and Sadler [22] reported five cases (0.2%) of unexpected multiple sclerosis in subjects with no or minimal neurologic symptoms during life. Clinical studies have documented a group of patients with multiple sclerosis who have no severe disability up to 25 years after their initial symptoms [23–25]. Complete conduction block need not occur if the axons in the plaque of demyelination are preserved [26]. Gilbert and Sadler [22] observed that in their cases, as well as in other autopsy cases of incidental multiple sclerosis [27–29], the majority of lesions were small in the cerebral hemispheres and absent from the brainstem and cerebellum (Fig. 4). These features may explain the subclinical nature of such cases.

Foci of demyelination are hyperintense relative to white matter on long TR/short TE sequences (Fig. 4A) and on long TR/long TE sequences (Fig. 4B) due to an increase in proton density and T2, respectively [30]. Neither plaque of demyelination in case 12 was detected on CT.

We were unable to distinguish a small focus of demyelination from either white-matter gliosis or infarction on MR (Figs.

1–4). The relative intensities and morphologic features were similar. The reported infrequent occurrence of incidental multiple sclerosis suggests it accounts for far fewer of the abnormal foci of high signal intensity on MR than does perivascular atrophic demyelination or infarction in the elderly population. However, it is possible that MR may disclose additional cases of subclinical demyelinating disorders that otherwise may have escaped clinical and pathologic detection.

Brain Cyst, Congenital Diverticulum

The origin of all intracerebral cysts may be neuroepithelial, whether or not they are related to the ventricles [31–34]. Cysts that do not communicate with the ventricle are uncommon. When they are in the cerebral hemisphere, they usually border the ventricle or subarachnoid space (Figs. 2H and 2I) [31, 34–40]. They are heterogeneous, and may be epithelial, ependymal, choroidal, or teratogenous [41].

An important feature that may allow MR to distinguish a brain cyst, congenital diverticulum, and other fluid-containing spaces from gliosis, infarction, and demyelination is the isointensity the former may display to CSF in vivo or to fluid in the subarachnoid space in the postmortem fixed state (Figs. 2A, 2B, 2H, and 2I). A chronic, cavitated infarct, however, may become cystic, and be isointense relative to CSF on all pulse sequences (see Fig. 3 in our companion article [10]) [7]. The relationships of a diverticulum to a ventricle (Fig. 5) and of a brain cyst to a ventricle or subarachnoid space (Figs. 2H and 2I) may be appreciated on MR and are additional differential features. Although a rounded configuration is more characteristic of a cyst or diverticulum, this is a less reliable distinguishing feature since infarction, gliosis, or demyelination may appear similarly round (Figs. 3 and 4).

Three lesions were seen on MR in case 13 (Fig. 6), yet no histopathologic abnormality was found. We suspect that since they were minute we were unable to localize them precisely at the time of pathologic evaluation.

Conclusions

MR imaging of the brains of elderly individuals yielded five different types of lesions, all of which appeared as hyperintense white-matter foci. Correlation of MR findings with histopathology enabled some differentiation among the lesions. In order of decreasing frequency, the lesions comprised infarction, infarction vs gliosis, demyelination, ventricular diverticulum, and a brain cyst. Prominent Virchow-Robin spaces (état criblé without surrounding parenchymal changes), which we identified in the basal ganglia in our companion article [10], may also occur in the white matter [42] and should be included in the gamut of causes of punctate hyperintense white-matter foci on MR in the elderly. A partial differentiation of these lesions is possible by their intensities on varied MR pulse sequences (Table 3). Fluid-filled spaces, such as cystic infarction, prominent Virchow-Robin spaces, ventricular diverticulum, and brain cyst, may be isointense relative to CSF in vivo or to fluid in the subarachnoid space in the postmortem state on all pulse sequences. The relationships of a diverticulum to a ventricle or of a brain cyst to a ventricle or subarachnoid space may serve as additional differentiating features. We were unable to differentiate noncystic infarction from either gliosis or demyelination on MR. The relative intensities (hyperintense relative to brain parenchyma on both long TR sequences) and morphologic features were similar. On the basis of our study and those of previous investigators it is our preliminary impression that infarction and/or perivascular atrophic demyelination account for the majority of the hyperintense white-matter foci seen on MR in elderly subjects [9, 13–16]. More definitive conclusions, however, await additional investigations.

TABLE 3: Relative Signal Intensities of Supratentorial White-Matter Lesions

Signal Intensity: Type of Lesion
Hyperintense relative to brain parenchyma on both long TR sequences:
Noncystic infarction
Gliosis
Demyelination
Isointense relative to CSF or to fluid in the subarachnoid space on all pulse sequences:
Cystic infarction
Brain cyst
Ventricular diverticulum
Prominent Virchow-Robin spaces (état criblé without surrounding parenchymal changes)

ACKNOWLEDGMENTS

We thank Peggy Kelly, Julie Talachadze, Joseph DiRienzi, Beverly Farrar, Christine Harris, Lynn Herbert, and Eileen Heatherby for their kind assistance.

REFERENCES

1. Bradley WG, Walluch V, Brant-Zawadzki M, Yadley RA, Wycoff RR. Patchy, periventricular white matter lesions in the elderly: a common observation during NMR imaging. *Noninvas Med Imaging* **1984**;1:35–41
2. Brant-Zawadzki M, Fein G, Van Dyke C, Kiernan R, Davenport L, DeGroot J. Magnetic resonance imaging of the aging brain: patchy white matter lesions and dementia. *AJNR* **1985**;6:675–682
3. Gerard G, Weisberg LA. MRI periventricular lesions in adults. *Neurology* **1986**;36:998–1001
4. Sze G, De Armond S, Brant-Zawadzki M, et al. "Abnormal" MRI foci anterior to the frontal horns: pathologic correlates of an ubiquitous finding (abstr). *AJNR* **1985**;6:467–468
5. Zimmerman RD, Fleming CA, Lee BCP, Saint-Louis LA, Deck MDF. Periventricular hyperintensity as seen by magnetic resonance: prevalence and significance. *AJNR* **1986**;7:13–20
6. Marshall VG, Bradley WG, Rhodes RH, Bhoopat T, Marshall CE. MR appearance of deep white matter infarction: correlation with histopathology. Presented at the annual meeting of the Radiologic Society of North America, Chicago, December **1986**
7. Brant-Zawadzki M, Kucharczyk W. Vascular disease: ischemia. In: Brant-Zawadzki M, Norman D, eds. *Magnetic resonance imaging of the central nervous system*. New York: Raven, **1987**:221–234
8. Holland BA. Diseases of white matter. In: Brant-Zawadzki M, Norman D, eds. *Magnetic resonance imaging of the central nervous system*. New York: Raven, **1987**:259–277
9. Kirkpatrick JB, Hayman LA. White-matter lesions in MR imaging of clinically healthy brains of elderly subjects: possible pathologic basis. *Radiology*

1987;162:509–511

10. Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer WW. Brain MR: pathologic correlation with gross and histopathology. 1. Lacunar infarction and Virchow-Robin spaces. *AJNR* **1988**;9:621–628
11. Caplan LR, Schoene WC. Clinical features of subcortical arteriosclerotic encephalopathy (Binswanger disease). *Neurology* **1978**;28:1206–1215
12. Blackwood W. Vascular diseases of the central nervous system. In: Greenfield JG, Blackwood W, McMenemey WH, Meyer A, Norman RM, eds. *Neuropathology* London: Edward Arnold, **1958**:67–131
13. Tomlinson BE, Blessed G, Roth M. Observations on the brains of non-demented old people. *J Neurol Sci* **1968**;7:331–356
14. Wisniewski HM, Terry RD. Morphology of the aging brain, human and animal. *Prog Brain Res* **1973**;40:167–186
15. Peress NS, Kane WC, Aronson SM. Central nervous system findings in a tenth decade autopsy population. *Prog Brain Res* **1973**;40:474–483
16. Tomlinson BE, Henderson G. Some quantitative cerebral findings in normal and demented old people. In: Terry RD, Gershon S, eds. *Neurobiology of aging*. New York: Raven, **1976**:183–204
17. Kety SS. Human cerebral blood flow and oxygen consumption as related to aging. *J Chronic Dis* **1956**;3:478–486
18. Naritomi H, Meyer JS, Sakai F, Yamaguchi F, Shaw T. Effects of advancing age on regional cerebral blood flow: studies in normal subjects and subjects with risk factors for atherothrombotic stroke. *Arch Neurol* **1979**;36:410–416
19. Melamed E, Lavy S, Bentin S, Cooper G, Rinot Y. Reduction in regional cerebral blood flow during normal aging in man. *Stroke* **1980**;11:31–35
20. Shaw TG, Mortel KF, Meyer JS, Rogers RL, Hardenberg J, Cutaia MM. Cerebral blood flow changes in benign aging and cerebrovascular disease. *Neurology* **1984**;34:855–862
21. Fang HCH. Observations on aging characteristics of cerebral blood vessels, macroscopic and microscopic features. In: Terry RD, Gershon S, eds. *Neurobiology of aging*. New York: Raven, **1976**:155–166
22. Gilbert JJ, Sadler M. Unsuspected multiple sclerosis. *Arch Neurol* **1983**;40:533–536
23. McAlpine D. The benign form of multiple sclerosis: results of a long-term study. *Br Med J* **1964**;2:1029–1032
24. Percy AK, Nobrega FT, Okazaki H, Glattre E, Kurland LT. Multiple sclerosis in Rochester, Minn: a 60-year appraisal. *Arch Neurol* **1971**;25:105–111
25. Confayreux C, Aimard G, Devic M. Course and prognosis of multiple sclerosis assessed by the computerized data processing of 349 patients. *Brain* **1980**;103:281–300
26. Sears TA, Bostock H. Conduction failure in demyelination: is it inevitable? *Adv Neurol* **1981**;31:357–376
27. Georgi VW. Multiple Sklerose: pathologisch-anatomische Befunde Multiplier Sklerose bei klinisch nicht diagnostizierten Krankbeiten. *Schweiz Med Wochenschr* **1966**;20:605–607
28. MacKay RP, Hirano A. Forms of benign multiple sclerosis: report of two 'clinically silent' cases discovered at autopsy. *Arch Neurol* **1967**;17:588–600
29. Morariu M, Klutzow WF. Subclinical multiple sclerosis. *J Neurol* **1976**;213:71–76
30. Wehrli FW, Breger RK, MacFall JR, et al. Quantification of contrast in clinical MR brain imaging at high magnetic field. *Invest Radiol* **1985**;20:360–369
31. Blom R, Witt N, Johnson ES. Demonstration of a symptomatic intraventricular cyst using direct intraventricular metrizamide instillation. *AJNR* **1986**;7:1093–1095
32. Shuangshoti S, Roberts MP, Netsky MG. Neuroepithelial (colloid) cysts. *Arch Pathol Lab Med* **1965**;80:214–224
33. Shuangshoti S, Netsky MG. Histogenesis of choroid plexus in man. *Am J Anat* **1966**;118:283–293
34. Friede RL, Yasargil MG. Supratentorial intracerebral epithelial (ependymal) cysts: review, case reports, and fine structure. *J Neurol Neurosurg Psychiatry* **1977**;40:127–137
35. Jakubiak P, Dunsmore RH, Beckett RS. Supratentorial brain cysts. *J Neurosurg* **1968**;28:129–136
36. Bouch DC, Mitchell I, Maloney AFJ. Ependymal lined paraventricular cerebral cysts; a report of three cases. *J Neurol Neurosurg Psychiatry* **1973**;36:611–617
37. Palma L. Supratentorial neuroepithelial cysts: report of two cases. *J Neurosurg* **1975**;42:353–357
38. MacGregor BJL, Gawler J, South JR. Intracranial epithelial cysts: report of two cases. *J Neurosurg* **1976**;44:109–114
39. Harwood-Nash DC. Congenital craniocerebral abnormalities and computed tomography. *Semin Roentgenol* **1977**;12:39–51
40. Haddad FS, Alba A, Allam C. Ependymal brain cyst. *Surg Neurol* **1982**;18:246–249
41. Koto A, Horoupian DS, Shulman K. Choroidal epithelial cyst: case report. *J Neurosurg* **1977**;47:955–960
42. Fisher CM. Lacunes: small, deep cerebral infarcts. *Neurology* **1965**;15:774–784