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Leukoencephalopathy in Cerebral Amyloid Angiopathy: MR Imaging in Four Cases

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We report four cases of biopsy proved cerebral amyloid angiopathy demonstrated by MR imaging. White matter signal hyperintensities on T2-weighted spin-echo pulse sequences were present in three patients. We believe the white matter lesions associated with cerebral amyloid angiopathy are not specific to this disorder but rather reflect hypoperfusion of distal white matter resulting from vascular disease.

White matter signal abnormalities on MR images are most commonly due to edema, infarction, and demyelination. Although there are numerous underlying disorders that produce white matter signal abnormalities on MR, cerebral amyloid angiopathy (CAA) has not been described in the neuroradiologic literature as a cause of leukoencephalopathy.

We describe four cases of biopsy proved CAA imaged with MR and report a spectrum of findings, including white matter signal abnormalities.

Methods and Materials

Four patients with biopsy proved CAA underwent MR imaging at our institution. Patient 1 was imaged 1 year prior to diagnosis, which was made after surgical evacuation of a lobar hemorrhage. Two patients were imaged at the time of their diagnosis: patient 2 had a right frontal brain biopsy because of a rapidly progressive confusional state, and patient 3 had a lobar hemorrhage that required surgical decompression. Patient 4 underwent MR imaging approximately 2 years after histologic diagnosis, made after surgical evacuation of a lobar hematoma. In the three patients with lobar hemorrhages, cortical biopsies were performed adjacent to the hematomas at the time of surgical evacuation.

In all four patients, histologic examination of biopsy material revealed thick-walled arteries and arterioles in the cerebral cortex that stained positive for Congo red and were birefringent under polarized light. Neuritic plaques and neurofibrillary tangles were also found scattered in the cortical mantle of patients 2, 3, and 4. The biopsy specimen of patient 2 showed astrocytic gliosis in the underlying white matter.

All patients were imaged on a superconducting magnet (Picker International, Highland Heights, OH) operating at 0.5 T. Spin-echo pulse sequences were used. T1- and T2-weighted images were obtained in all patients. Imaging parameters were 350–550/20 (TR/TE) for the T1-weighted sequences, and 2000–2350/80–100 for the T2-weighted sequences. Slice thickness was 10 mm. All patients were studied in three orthogonal planes.

The clinical records and radiographic examinations were reviewed, with particular attention paid to the presence of vascular risk factors such as hypertension, diabetes mellitus, coronary artery disease, and history of transient ischemic attacks. Unenhanced CT scans were obtained within 1 week of the MR examination in three patients.

Results

The four patients included three women and one man, ages 62, 63, 72, and 72 years, respectively. Their pertinent clinical data, vascular risk factors, and radiographic findings are summarized in Table 1.

Patient 1 had bilateral multifocal signal hyperintensities on T2-weighted images that involved primarily the centrum semiovale and deep periventricular white matter (Figs. 1A and 1B). Confluent areas of signal hyperintensity on T2-weighted images were present in the peritrigonal regions (Fig. 1C). Ventricular size was normal, and the white matter lesions spared the corpus callosum, internal capsules, and U fibers. The white matter abnormalities could not be appreciated on an unenhanced brain CT scan.

T2-weighted MR imaging in patient 2 revealed bilateral patchy and confluent signal hyperintensities involving primarily the white matter (Fig. 2). U fibers were involved as well. The white matter abnormalities were also readily apparent on T1-weighted images and on an unenhanced brain CT scan.

Patient 3 had bilateral multifocal white matter signal hyperintensities in addition to a right temporoparietal hematoma, which extended into the subarachnoid space (Fig. 3). The white matter signal abnormalities were located in the deep periventricular white matter, and spared the corpus callosum, internal capsules, and U fibers. No white matter lesions were present on the CT examination.

MR imaging in patient 4 demonstrated focal left parietooccipital white matter signal hyperintensity on T2-weighted images, with dilatation of the adjacent lateral ventricle (Fig. 4). These changes were at the site of a previous lobar hemorrhage. No other white matter signal abnormalities were found in this patient. A CT examination was not performed at the time of the MR study.

Discussion

Primary lobar intracerebral hemorrhage is a well known clinical and radiographic manifestation of CAA [1, 2]. Pathologically, CAA is characterized by deposition of homogeneous

TABLE 1: Summary of Patient Data

Patient No.	Age (years)	Sex	Clinical History	Vascular Risk Factors*	CT Findings	MR Findings
1	72	M	Declining mental status over 2 years, left frontal lobar hemorrhage 1 year later	None	Normal	Bilateral multifocal signal hyperintensities involving the centrum semiovale and deep periventricular white matter with confluent lesions in the peritrigonal region
2	72	F	Headache and progressive confusion over 2–3 weeks	HTN, CAD	Bifrontal and parietal white matter hypodensities	Bilateral patchy and confluent signal hyperintensities involving deep hemispheric white matter, centrum semiovale, and U fibers.
3	62	F	Acute-onset headaches, nausea, vomiting	HTN, CAD	Right temporoparietal lobar hematoma	Right temporoparietal lobar hematoma, bilateral centrum semiovale, and deep periventricular white matter signal hyperintensities
4	63	F	Right arm weakness from left parietal lobar hemorrhage 2 years prior to MR	None	Not obtained at the time of MR study	Focal left parietal signal hyperintensity and volume loss consistent with encephalomalacia

* Note.—Vascular risk factors include hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), and transient ischemic attacks (TIAs).

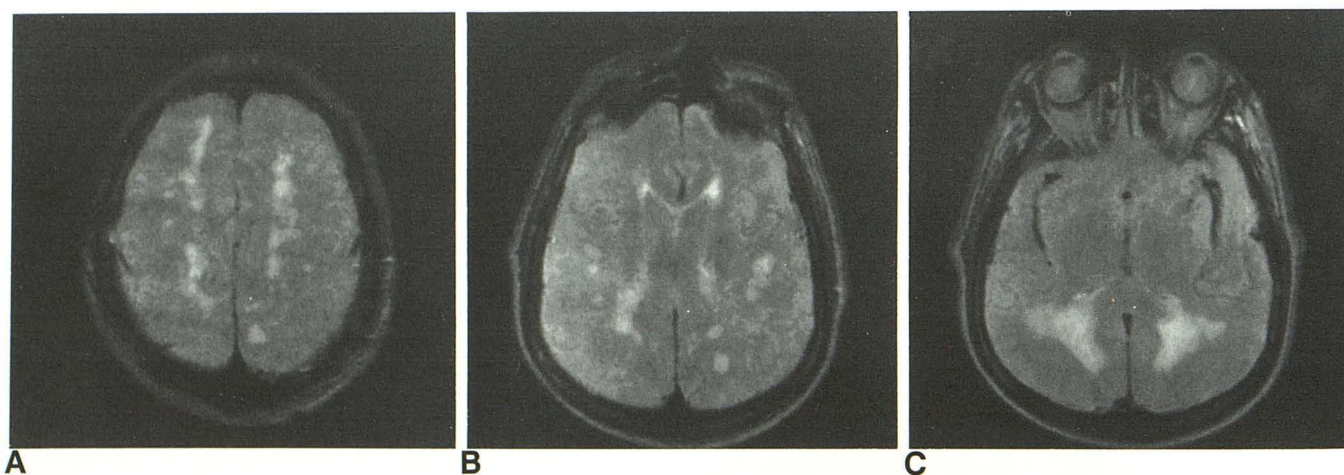

A   B   C

Fig. 1.—Patient 1.
A, Axial MR image (2350/80) shows multifocal white matter signal hyperintensities in centrum semiovale bilaterally.
B, Axial MR image (2350/80) through lateral ventricles reveals patchy signal hyperintensities in deep white matter sparing the corpus callosum, internal capsules, and U fibers. One year after this MR study, the patient developed a lobar hemorrhage in the left frontal lobe.
C, Axial MR image (2350/80) reveals bilateral symmetric confluent white matter signal hyperintensities in peritrigonal and occipital areas.
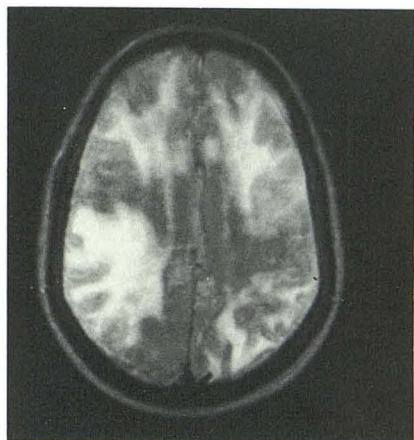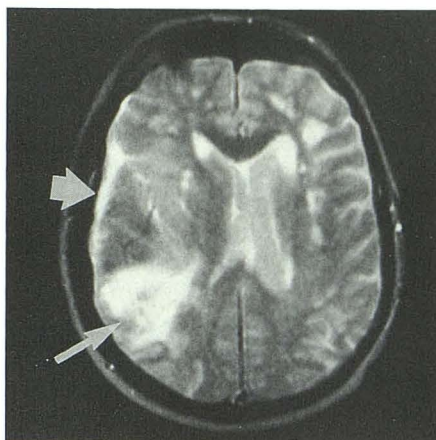
Fig. 2.—Patient 2: Axial MR image (2300/80) through lateral ventricles shows widespread confluent areas of white matter signal hyperintensity. U fiber involvement is present in this patient. Brain biopsies of both cortex and underlying white matter were performed in the posterior right frontal lobe.

Fig. 3.—Patient 3.
A, Axial MR image (2000/80) demonstrates a large focal right parietooccipital high-signal-intensity lesion (long arrow) caused by a lobar hematoma with surrounding edema and subarachnoid hemorrhage (short arrow). Multifocal white matter signal hyperintensities are present in deep periventricular regions.
B, Right parasagittal MR image (350/20) shows serpiginous area of increased signal within cortical sulci caused by paramagnetic effect of subarachnoid hemorrhage.
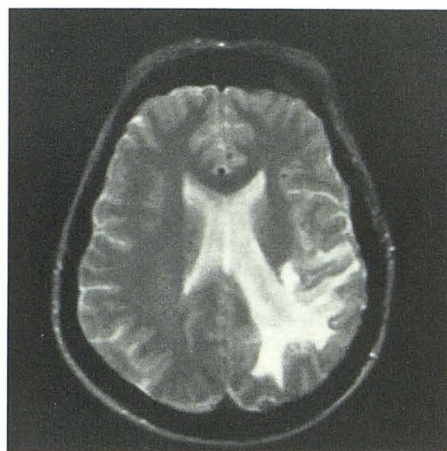

Fig. 4.—Patient 4: Axial MR image (2000/100) shows a focal area of white matter signal hyperintensity in left parietooccipital region with dilatation of adjacent lateral ventricle. These findings were at a site of previous lobar hemorrhage, and were most likely caused by encephalomalacia. No other white matter signal abnormalities were observed in this patient.

eosinophilic material in the media and adventitia of arterioles and small arteries of the cortex and leptomeninges [3]. These deposits stain red with Congo red stain and show characteristic yellow-green birefringence under polarized light [4]. Superimposed fibrinoid degeneration and microaneurysmal dilatation in involved vessels may cause these vessels to rupture and produce intracerebral hematomas [4, 5]. While any area of the brain may be involved, amyloid infiltrated vessels are rarely found in the cerebellum or white matter [2]. CAA can be quite focal and sporadic in its presentation morphologically, with some vessels heavily involved with amyloid infiltration while neighboring vessels are totally spared. In addition, serial sectioning of the brain may show amyloid deposition

along only one focal area of a vessel wall. Although various hypotheses have been proposed, the mechanism of amyloid deposition remains speculative [2].

Recently, leukoencephalopathy that was unrelated to areas of intracerebral hemorrhage was described after a histologic examination of brain tissue in 12 patients with diffuse hemorrhagic CAA [6]. Gray et al. [6] discovered both diffuse and focal areas of demyelination in the hemispheric white matter, with sparing of the U fibers, corpus callosum, and internal capsules. Microscopic examination of the white matter in these brains revealed spongiosis, swollen oligodendroglia, widening of the perivascular spaces with edema fluid and macrophages, hyalinization of the blood vessel walls, myelin loss with partial axonal degeneration, and astrocytic gliosis. Interestingly, Congophilic vessels were not found in the white matter of these patients. The authors postulated that amyloid deposits within the meningocortical vessels cause hypoperfusion of the deep white matter and subsequent ischemic demyelination.

White matter signal abnormalities, remote from areas of previous or current hemorrhage, were present in three of our four patients. While no single characteristic pattern was observed, our findings matched closely those observed by Gray et al. [6]. White matter lesions were most prevalent in the centrum semiovale and deep periventricular regions, and spared the corpus callosum and internal capsule.

White matter signal abnormalities on MR imaging in both asymptomatic and symptomatic patients have been studied in some detail. Patchy white matter lesions, which are present in 20–30% of clinically healthy subjects, have a strong correlation with advancing age and vascular risk factors such as hypertension, diabetes mellitus, coronary artery disease, and transient ischemic attacks [7–10]. A wide variety of histologically identifiable white matter lesions such as atrophic perivascular demyelination, infarcts, vascular malformations, asymptomatic zones of multiple sclerosis, and congenital

ventricular diverticula most likely account for the multifocal white matter signal abnormalities seen on MR in the neurologically asymptomatic elderly population [11].

White matter lesions on CT and MR have been associated with dementia of vascular origin [8, 12, 13]. The relationship between white matter abnormalities on CT and MR and dementia is less clear when confounding factors such as age and vascular risk factors are eliminated. George et al. [14, 15] studied patients with Alzheimer disease and normal controls with both CT and MR and found leukoencephalopathy in both groups with greater, although nonsignificant, white matter involvement in the Alzheimer group. Severity of leukoencephalopathy in this study was not related to the degree of dementia. Both Steingart et al. [16, 17] and Gupta et al. [13] found an association between white matter hypodensities on CT and mental impairment after eliminating vascular risk factors. Fazekas et al. [18] discovered a smooth extensive "halo" of periventricular signal hyperintensity on T2-weighted examinations in a significant number of patients with Alzheimer dementia when compared with age-matched controls. Erkinjuntti et al. [19] did not find any signal abnormalities in patients with Alzheimer disease. Bilateral hemispheric white matter hypodensity on CT has been reported in one patient with senile dementia of Alzheimer type (SDAT) and diffuse nonhemorrhagic CAA [20]. Brun and Englund [21] discovered a distinct white matter disorder, which they described as incomplete white matter infarction, in 60% of patients with Alzheimer disease or SDAT upon pathologic examination of their brains.

CAA is closely associated with SDAT [2]. The larger and more confluent white matter signal hyperintensities in our series were present in two patients with progressive dementia (patients 1 and 2). Patient 1 did not have any cerebrovascular risk factors; and while patient 2 did have a history of hypertension and coronary artery disease, the white matter lesions in this patient were more diffuse than the focal white matter signal hyperintensities that we often attribute to hypertensive vascular disease. Although hypertensive encephalopathy could cause diffuse white matter signal abnormalities on MR, patient 2 did not have this diagnosis clinically, as her blood pressure was normal upon admission and had been medically controlled.

The multifocal patchy white matter lesions in patient 3 could be attributed to either CAA or an unrelated vascular disease, as the patient had a history of both hypertension and coronary artery disease. White matter abnormalities, excluding an area of encephalomalacia from prior lobar hemorrhage, were not observed in patient 4. This individual had normal cognitive function and did not have any cerebrovascular risk factors.

In the absence of direct pathologic correlation, we cannot be certain that the white matter lesions seen in our patients are related to CAA. Similar white matter signal abnormalities are seen in patients with Binswanger subcortical encephalopathy. In patients with this disease, either diffuse hypoxia or ischemia from large-vessel arteriosclerosis has been incriminated as the cause of selective necrosis of the white matter in the centrum semiovale and other watershed areas. Like Gray and his colleagues, we suspect amyloid deposits along vessel walls result in hypoperfusion to vulnerable areas of white matter, as in Binswanger disease.

MR findings in patients with CAA include lobar hemorrhage and white matter signal abnormalities. The white matter lesions associated with CAA, rather than being specific to this disorder, most likely reflect vascular disease in general. We believe CAA should be considered in the broad differential diagnosis of leukoencephalopathy in the elderly patient, especially if it is found in conjunction with a lobar hematoma or in the clinical setting of progressive dementia.

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