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Reversible leukoencephalopathy associated with cerebral amyloid angiopathy

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Abstract—The authors describe three patients with reversible leukoencephalopathy associated with cerebral amyloid angiopathy (CAA). Rapid progression of neurologic symptoms was followed by dramatic clinical and radiographic improvement. Pathologically, CAA was associated with varying degrees of inflammation ranging from none to transmural granulomatous infiltration. In the appropriate clinical context, the MRI finding of lobar white matter edema with evidence of prior hemosiderin deposition may indicate the presence of a reversible CAA leukoencephalopathy.

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Cerebral amyloid angiopathy (CAA) causes recurrent intracerebral hemorrhage in the elderly, and is defined by the deposition of amyloid in cerebral blood vessels, especially small and medium sized arteries of the leptomeninges and superficial cortex. The spectrum of clinical manifestations includes leukoencephalopathy.^{1,2} We report three cases of CAA with leukoencephalopathy. The course in all three was remarkable for dramatic reversal of clinical and radiographic abnormalities.

Cases. Patient 1. A 70-year-old man, with no prior headache or dementia, noted increasing forgetfulness for 2 weeks, followed by the sudden onset of aphasia and seizures. MRI of the brain showed increased T2 signal in the right parieto-temporal white matter. He recovered with mild residual reading difficulty and was discharged on aspirin and phenytoin. Three months later, he returned with acutely worsening aphasia, which again improved to baseline. MRI revealed nonenhancing white matter signal abnormalities involving primarily the temporo-occipital lobes bilaterally (figure 1A). The patient was given warfarin. Six months later, he returned after 4 days of lethargy and inability to speak. The erythrocyte sedimentation rate (ESR) was 66 mm/hour; CSF was unremarkable except for protein of 53 mg/dL. Biopsy of the right frontal lobe revealed abundant amyloid deposition within cortical blood vessel walls. The underlying white matter showed dilatation of perivascular spaces, but no significant demyelination or inflammation was present (figure 2). He received 2 days of perioperative corticosteroids, but was discharged without immunosuppressive therapy, and was neurologically normal 2 years later. MRI showed complete resolution of the white matter abnormalities (figure 1C). Blood pressure ranged from 110 to 130 mm Hg systolic and 65 to 80 mm Hg diastolic during his illness.

Patient 2. Over 2 weeks, an 80-year-old woman with no prior dementia or headache was confused and developed expressive aphasia. MRI revealed white matter edema in the right parieto-occipital and left frontal lobes without abnormal enhancement (figure 1D). Her symptoms abated on dexamethasone therapy, 6 mg four times a day. Repeat MRI after dexamethasone therapy showed improvement of the edema. However, symptoms recurred

2 months later, and MRI showed nonenhancing right temporo-parietal, left parieto-occipital, and left frontal white matter edema. ESR was 20 mm/hour and CSF was unremarkable. CT of the chest, abdomen, and pelvis was normal. Brain biopsy of the right parietal area revealed amyloid-laden small blood vessels with perivascular inflammation comprised of chronic inflammatory cells with well-formed multinucleated giant cells. The white matter showed marked tissue edema (see figure 2). Special staining showed relatively intact myelin network. No infarction was identified. The patient was given IV methylprednisolone 1 gram per day for 5 days and remained on oral prednisone for 8 months, when the confusion had abated and there was mild residual dysnomia; MRI showed marked improvement (figure 1E). The patient remained normotensive during her illness.

Patient 3. A 77-year-old man, with a history of multiple transient ischemic attacks, was admitted to the hospital for aphasia that developed over several hours. Examination demonstrated receptive aphasia. His blood pressure peaked at 160/95 mm Hg during his hospital stay. MRI revealed lobar white matter edema in the left temporal lobe with a small subacute hematoma, and no abnormal enhancement (figure 1F). CSF was unremarkable except for protein of 63 mg/dL. The ESR was 7 mm/hour and CT of the chest, abdomen, and pelvis was unremarkable. Ten days after onset, a stereotactic biopsy revealed marked amyloid angiopathy of cortical gray matter associated with transmural infiltration of the amyloid laden vessels by mononuclear and multinucleated cells (see figure 2). Patchy areas of edematous change were also noted in the white matter. The patient was given IV dexamethasone 100 mg twice a day for 5 days and discharged home on a 1-month taper of oral prednisone. At 6-week follow-up the aphasia had improved and MRI showed improvement of white matter edema (figure 1G).

Discussion. Reversible leukoencephalopathy, as seen in these patients, is an unusual manifestation of CAA. Focal neurologic deficits and varying degrees of encephalopathy characterized the neurologic findings. One patient had seizures. The MRI showed lobar white matter signal abnormalities extending out to subcortical U fibers, consistent with edema. Mass

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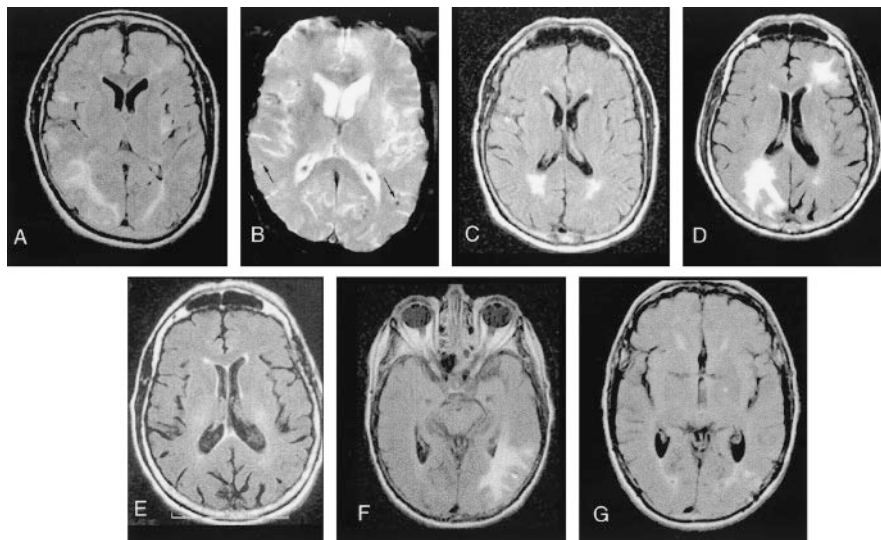


Figure 1. (A) MRI of Patient 1 at 3 months. Fluid-attenuated inversion recovery (FLAIR) sequence image at the level of basal ganglia shows white matter hyperintensity in the right temporo-occipital, right frontal, left temporo-occipital, and left subinsular regions. (B) Patient 1. Gradient-echo pulse sequence shows scattered punctate areas of low signal intensity (arrows) representing hemosiderin deposition at foci of petechial hemorrhages. (C) MRI of Patient 1 at 2 years. FLAIR sequence image shows improvement in the appearance of the white matter. (D) Initial MRI of Patient 2. FLAIR sequence image through the level of the lateral ventricle shows hyperintense signal in the left frontal and right parieto-

occipital regions. The hyperintensity extends from the periventricular white matter to the white-gray junction. (E) Patient 2 at 8 months. The abnormal white matter signal has resolved completely. (F) Initial MRI of Patient 3. FLAIR sequence image through temporal lobe shows abnormal signal in the subcortical white matter of left temporal lobe. The central punctate hyperintense focus represents subacute blood product. (G) MRI of Patient 3 at 6 weeks. The abnormality in the white matter has resolved significantly. Postoperative changes are noted at the level of biopsy site.

effect was evident but gadolinium enhancement was not seen. Two patients had small subacute hematomas, but the extent of white matter edema was out of proportion to the size of the hematomas. Gradient-echo sequences (figure 1B) showed hemosiderin deposition as evidence of prior subclinical hemorrhages in all three patients.

Pathologically, these cases showed varying degrees of inflammation associated with CAA. We found no evidence of inflammation in the first patient (although a sampling error cannot be excluded). Perivascular inflammation comprised of lymphocytes and multinucleated giant cells was found in the second. Transmural granulomatous infiltration of the

vessels was present in the third. White matter showed evidence of edema including dilatation of the perivascular spaces and splaying of the neuropil in all patients, but evidence of infarction or demyelination was absent.

The clinical course in our patients was remarkable for dramatic resolution of the leukoencephalopathy. Patient 1 showed dissemination of the white matter abnormalities to bilateral parieto-occipital lobes 3 months after presentation. Subsequent MRI showed near complete resolution of these abnormalities. The pattern mimicked the reversible posterior leukoencephalopathy (RPLE) syndrome,³ which has not before been associated with CAA. Patient 2 evolved to

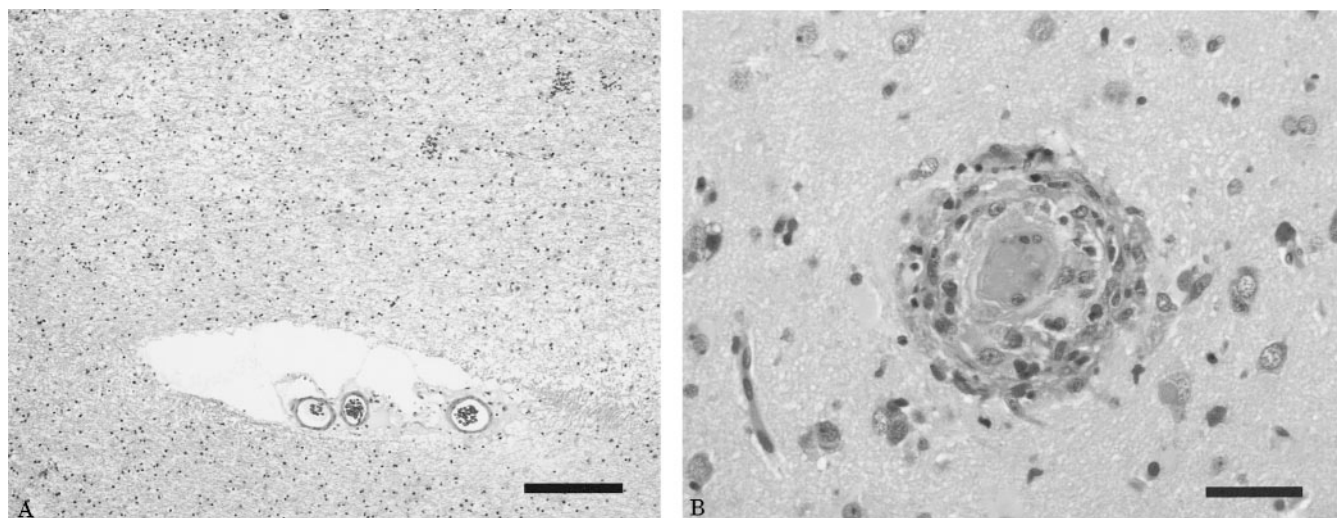


Figure 2. (A) Representative low magnification field of edematous white matter from Patient 2. A noticeably dilated perivascular space is also evident. Scale bar = 200 μ m. (B) Transmural infiltration of a gray matter blood vessel with mononuclear cells from Patient 3. Biopsy from Patient 1 showed moderate¹ cerebral amyloid angiopathy (CAA) (not shown). Patients 2 and 3 showed severe¹ CAA. Scale bar = 50 μ m. Hematoxylin-eosin stain.

Table Summary of reported patients with CAA leukoencephalopathy

Patient	Age, y/sex	MRI or CT	Treatment	Follow-up
No inflammation				
1 ¹	72/F	↑ T2 signal L frontal white matter; GRE: N/A	N/A	Profound dementia at 24 mo
2 ¹	58/M	↑ T2 signal PVWM; GRE: N/A	Carbamazepine; serial lumbar punctures	Death at 5 mo—"medical complications"
3 ⁵	59/F	↑ T2 signal R temporo-parietal white matter; GRE: N/A	Phenytoin; high-dose steroids	Death at 5 mo
4 ⁴	41/M	↑ T2 signal multilobar white matter; GRE: N/A	N/A	At 12 month f/u, MRI showed improved T2 signal on R and worsening on L
5 ⁹	74/F	↑ T2 signal R frontal & L parietal; GRE: +	Dexamethasone	Death at 12 mo
6 ⁸	71/F	↑ T2 signal multilobar white matter; GRE: N/A	AED, anti-hypertensive	Improved (clinical and radiographic resolution) at 8 mo
PVI				
7 ⁶	55/F	CT: R frontal nonenhancing hypodensity	Phenytoin	Residual left leg weakness at 4 mo
8 ⁷	7 patients, average age 68	N/A	N/A	3/5 treated with corticosteroids or cyclophosphamide improved
TGI				
9 ¹⁰	71/M	↑ T2 signal R temporo-parietal white matter; GRE: N/A	Cyclophosphamide	Asymptomatic at 22 mo

CAA = cerebral amyloid angiopathy; GRE = gradient-echo pulse sequence on MRI; N/A = not available; PVWM = periventricular white matter disease; f/u = follow-up; AED = anti-epileptic drug; PVI = perivascular inflammation; TGI = transmural granulomatous inflammation.

multilobar involvement on MRI after 2 months but subsequently showed nearly complete resolution. Patient 3 also showed remarkable resolution of the white matter abnormalities on MRI after 6 weeks. Treatment with immunosuppressive agents varied according to evidence of inflammation. Patient 1 did not receive maintenance immunosuppressive agents. Patients 2 and 3 were treated with an initial high-dose corticosteroid regimen followed by oral prednisone therapy. All patients showed improvement in neurologic deficits.

The reports on CAA leukoencephalopathy describe two distinct syndromes. The potentially reversible lobar leukoencephalopathy involving the U fibers with evidence of mass effect, as seen in our cases, should be distinguished from a symmetric periventricular leukoencephalopathy sparing the U fibers with evidence of atrophy. The reversible CAA leukoencephalopathy exemplified by our cases has rarely been described. In the few reported cases, mass effect and involvement of the U fibers invoked infiltrating glioma in the differential diagnosis.⁴⁻⁶ As in our cases, some have commented on the reversibility of imaging and clinical abnormalities.^{4,7,8} However, the course is highly variable (table).

In contrast, a symmetric periventricular CAA leukoencephalopathy that spares the U fibers is associated with a more chronic clinical picture often with a

history of lobar hemorrhage.² There have been no reports of reversibility. Serial CT showed slowly progressive enlargement of the periventricular white matter abnormalities.²

The mechanism of reversible CAA leukoencephalopathy is unknown. In the literature, CAA leukoencephalopathy is associated with varying degrees of inflammation (see the table). Analysis of the cases with respect to the presence or absence of inflammation is problematic due to differences in treatment, length of follow-up, and limitations inherent in diagnosis from single biopsy specimens. However, it seems that immunosuppressive therapy may help when inflammation is present,⁷ suggesting its role in pathogenesis.

On the other hand, the lack of inflammation and the resolution without immunosuppressive therapy in some cases suggest a central role for amyloid angiopathy in the pathogenesis of reversible CAA leukoencephalopathy. In addition to the histologic changes, amyloid angiopathy may alter vascular reactivity, leading to dysautoregulation and altered blood-brain barrier integrity. Reversible CAA leukoencephalopathy may share a similar pathogenesis with RPLE. In RPLE, an altered blood-brain barrier renders the brain susceptible to reversible edema precipitated by hypertension, fluid overload, or inflammation.³ In reversible CAA leukoencephalopa-

thy, CAA may be the underlying susceptibility upon which factors such as inflammation or perhaps hypertension⁸ might lead to progression over the threshold to clinical disease. Indeed, the recurrence of symptoms after periods of remission in Patients 1 and 2 suggest the presence of a persistent underlying susceptibility.

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