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Superficial Siderosis

A Potential Diagnostic Marker of Cerebral Amyloid Angiopathy in Alzheimer Disease

Howard H. Feldman, MD; Luis F. Maia, MD; Ian R.A. Mackenzie, MD;
Bruce B. Forster, MD; Jeff Martzke, PhD; Andrew Woolfenden, MD

Background and Purpose—Superficial siderosis of the central nervous system results from chronic bleeding in the superficial layers of the cortex and spinal cord. In cerebral amyloid angiopathy (CAA), there is amyloid deposition in meningeal and meningo-cortical arteries and capillaries, predisposing them to rupture. CAA is frequently associated with Alzheimer disease (AD).

Methods and Results—We report a series of 3 AD patients with MRI evidence of superficial siderosis. Two had neuropathological examination confirming superficial siderosis, AD, and CAA.

Conclusions—Superficial siderosis should be recognized within the spectrum of AD with CAA and considered as a possible antemortem diagnostic feature. (*Stroke*. 2008;39:2894-2897.)

Key Words: Alzheimer disease ■ cerebral amyloid angiopathy ■ superficial siderosis

Superficial siderosis of the central nervous system (SS-CNS) is an uncommon condition in which hemosiderin deposits in the subpial layers of the brain, spinal cord, and cranial nerves. SS-CNS can result from repeated or chronic bleeding in the subarachnoid space because of hemorrhagic tumors, trauma, vascular malformations/aneurysms, or transthyretin meningo-vascular amyloidosis.^{1,2} It can be detected with gradient-recalled echo MRI with T2* weighting that demonstrates bleeding with low signal from deposited iron products.^{1,2} The most common clinical syndrome of SS-CNS includes sensorineural hearing loss, cerebellar ataxia, and pyramidal signs.¹ SS-CNS has not been clearly associated previously with either cerebral amyloid angiopathy (CAA) or Alzheimer disease (AD).^{1,3} CAA is defined by amyloid deposition in the media of vessels within arteries and arterioles of the cortex and leptomeninges.⁴ Although CAA can be age-related in individuals without dementia, it has an estimated prevalence of 80% to 100% in patients with AD.⁵ The in vivo diagnosis of CAA is limited, based on radiological or biopsy features.⁶ Gradient-recalled echo MRI with T2* weighting demonstrating chronic parenchymal cortical microhemorrhages supports the diagnosis of CAA.⁶ In AD-related CAA, there is usually prominent involvement of the most superficial vessels of the brain; however, subpial/subarachnoid hemorrhage or SS have not been previously reported with it.⁷

Subjects and Methods

We describe a case series of 3 patients from the University of British Columbia Clinic for Alzheimer Disease & Related Disorders. These

patients had clinical, cognitive, and neuroimaging assessments (Table, Figure 1). The neuropathology of 2 patients are presented in Figure 2.

Case 1

Case 1 is a 60-year-old right-hand-dominant man who presented with 6 months of progressive aphasia. He had mild psychobehavioral changes. The results of his neurological examination were normal, whereas cognitively he had severe nonfluent aphasia with relative sparing of episodic memory. Laboratory work-up for coagulopathy was negative and noninvasive stroke work-up (carotid duplex, echocardiogram, and Holter monitor) was normal. Cerebrospinal fluid was slightly blood-tinged with 450 red blood cells ($\times 10^6$), 2 white blood cells ($\times 10^6$), and normal protein. His condition declined progressively in the subsequent 2 years before experiencing several 20-minute episodes of right facial and arm numbness, without change in speech or language. Gradient-recalled echo MRI showed left hemispherical gyriform low-signal pattern. (Figure 1A). Cerebral angiography was normal. He died 3 years after first assessment from a left parietal cortical hemorrhage. Autopsy examination demonstrated neuritic senile plaques, neurofibrillary tangles, and neuropil threads of sufficient number and distribution to fulfill NIA/Reagan criteria for definite AD. Many cortical and leptomeningeal vessel walls were thickened by amyloid deposition (Figure 2A). There were moderate numbers of small, focal, cortical defects characterized by reactive astrocytes and hemosiderin-laden macrophages, consistent with chronic microscopic hemorrhages or hemorrhagic infarcts. There was more diffuse accumulation of hemosiderin within macrophages in the subarachnoid space and superficial cortex (Figure 2B). The neuropathological diagnosis was AD and CAA associated with SS. The number, size, and distribution of microscopic infarcts and

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From Division of Neurology (H.H.F., J.M., A.W.), Department of Medicine, Division of Neuropathology (I.R.A.M.), Department of Pathology, Department of Radiology (B.B.F.), University of British Columbia, Vancouver, British Columbia, Canada; Department of Neurology (L.F.M.), Hospital Geral Santo António, Porto, Portugal.

Correspondence to Dr Howard H. Feldman, Division of Neurology, University of British Columbia Hospital, S192-2211 Wesbrook Mall, Vancouver, British Columbia, V6T 2B5, Canada. E-mail hfeldman@interchange.ubc.ca

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Table. Clinical, Neuropsychological, and Neuroradiological Features of CAA-Related Meningeal Siderosis Patients

Patient N/Age/Sex	Presenting Features			MR T2* or T2WI	
	Cognitive Severity		Cognitive Domains	Gyriform Hyposignal, Location	Cortical Microbleeds, N
	MMS	3-MS			
1/60/M	23	83	Language* Short-term memory‡ Visuospatial processing§ Praxis§ Executive function§	Left frontal* Left parietal* Left temporal* Right frontal‡ Right parietal§ Right temporal§	2 (left and right frontal lobe)
2/59/M	21	52	Language* Short-term memory‡ Visuospatial processing‡ Praxis‡ Executive function†	Left frontal lobe* Left parietal† Left temporal‡ Right frontal§ Right parietal§ Right temporal§	NA
3/69/F	22	71	Language† Short-term memory‡ Visuospatial processing‡ Praxis§ Executive function‡	Left frontal† Left parietal* Left temporal‡ Right frontal† Right parietal§ Right temporal§	1 (right frontal lobe)

*Severely affected.
†Moderately affected.
‡Mildly affected.
§Not affected.

F indicates female; L, left; M, male; NA, not available; R, right.

hemorrhages were not sufficient enough to warrant a separate diagnosis of vascular dementia.

Case 2

Case 2 is a 65-year-old, right-hand-dominant man who presented with a 6-year history of dementia with progressive aphasia. His neurological examination results were normal, whereas cognitively he had bihemispherical impairment, with language being the most impaired (Table). MRI demonstrated a small, left, occipital cortical infarct, whereas spin-echo T2-weighted images showed gyriform left hemispherical low signal (Figure 1B). Noninvasive stroke work-up was normal. Laboratory studies excluded coagulopathy. Autoimmune serology was negative. His condition declined steeply over 18 months, with progressively disabling gait apraxia developing. Autopsy examination demonstrated severe senile plaque and neurofibrillary tangle pathology, fulfilling NIA/Reagan criteria for definite AD. Small, chronic, cortical infarcts were present in both occipital

lobes and cerebellar hemispheres. Histological definite AD was confirmed by NIA/Reagan criteria. There was severe CAA affecting cortical and leptomeningeal vessels (Figure 2C). Neocortical regions showed focal collections of hemosiderin-laden macrophages around congophilic vessels and in the subpial region (SS), most extensively over the left frontal lobe (Figure 2D). There was moderately severe arteriolosclerosis of the basal ganglia but no lacunar infarcts. Neuropathological diagnosis was AD and CAA with SS and cerebrovascular disease. The location of the chronic infarcts made it unlikely that they contributed to the patient’s dementia.

Case 3

Case 3 is a 69-year-old right-hand-dominant woman who presented with 2 years of progressive cognitive decline. Her neurological examination results were normal, whereas cognitively she demonstrated prominent aphasia and mild episodic memory impairment (Table). CT showed a 4-mm aneurysm of the right anterior cerebral artery. Medications included acetylsalicylic acid (ASA), Ginkgo biloba, and donepezil. Her

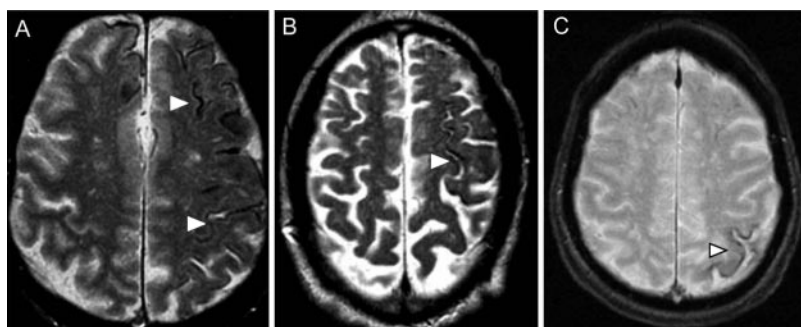


Figure 1. Gyriform low signal (arrowheads), corresponding to meningeal siderosis, in the frontal cortex bilaterally and left parietal cortex (A), gradient-recalled echo MRI (patient 1). Gyriform low signal (arrowheads) in the left frontal cortex (B), T2-MRI (patient 2). Gyriform low signal (arrowheads) in the left parietal cortex (C), gradient-recalled echo MRI (patient 3).

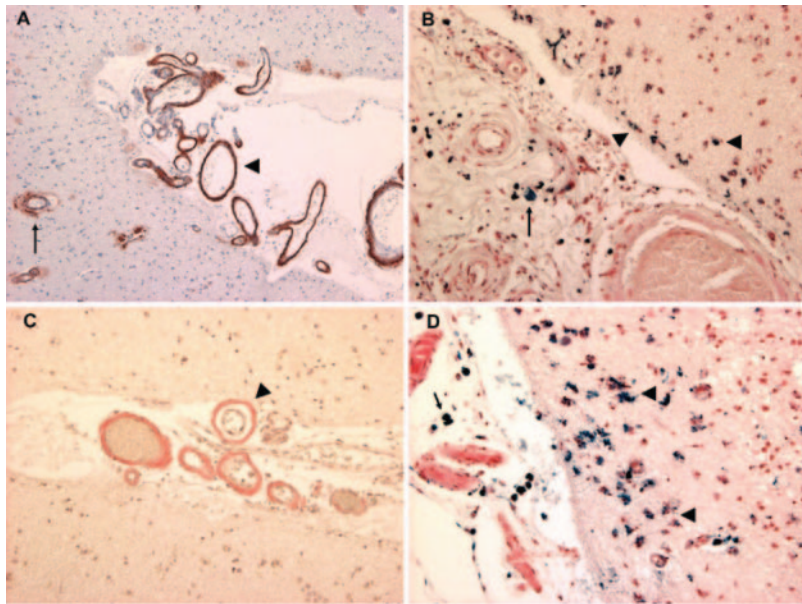


Figure 2. Leptomeningeal and cortical vessels showing severe CAA with A- β (A), immunohistochemistry staining (patient 1). Hemosiderin deposition within macrophages in the subarachnoid space (arrow) and within superficial cortex (arrowheads) (B), Pearl's blue iron staining (patient 1). Amyloid demonstrating vessel-within-vessel pattern (arrow) (C), Congo red stain (patient 2). Hemosiderin deposition (D) within leptomeningeal macrophages (arrow) and within macrophages in superficial neocortex (arrowheads), Pearl's blue iron staining (patient 2).

condition declined progressively over the next 18 months without stroke-like episodes. However, on follow-up neuroimaging, she had a new serpiginous right frontal lesion, which was confirmed by MRI to be a subacute cerebral hemorrhage. T2*-weighted gradient-recalled echo showed gyriform low signal over the left parietal lobe (Figure 1C). Her aneurysm was unchanged without low signal in the wall or adjacent interhemispheric regions. Screening for coagulopathy was negative. AD and SS, presumed to be CAA-related, were diagnosed clinically given her course and presentation without neuropathological confirmation. ASA and Ginkgo biloba were discontinued.

Discussion

We report a series of 3 AD patients with CAA-related SS. Each MRI showed SS, whereas the 2 available autopsies confirmed the diagnoses of AD, CAA, and SS. The clinical features and course of each patient had aspects that were atypical for AD. The first patient had a severe nonfluent aphasia before recurrent transient neurological spells developed. The second patient had an unusually prominent progressive aphasia for his otherwise mild-severity AD with dominant-hemisphere SS. The third patient also had prominent aphasia greater than impaired episodic memory. We postulate that these features that are atypical for AD were related to the presence of AD, CAA, and SS.⁸ Unlike patients with "classical" SS,^{1,3} these patients did not present any cerebellar or brain stem signs.

The presence of SS documents previous hemorrhage. The exact origin of the bleeding to produce this SS is not known. We suspect it either spread from superficial neocortical hemorrhage into the subarachnoid space or leaked through arteriolar/arterial vessels within the subarachnoid space, or both.¹ The remote possibility of a spinal arteriovenous malformation (AVM) in each of these 3 patients was not formally excluded. Primary subarachnoid or subpial hemorrhage related to CAA has been described concomitantly with intraparenchymal hemorrhages, whereas in a few reports sporadic

CAA cases have been associated with primary subarachnoid hemorrhage, presenting with transient neurological symptoms.^{9,10} These are the first cases to our knowledge of neuropathologically confirmed CAA in AD with SS. The relation between amyloid deposition, subarachnoid hemorrhage, and SS is not exclusive to sporadic A β -related CAA. Transthyretin meningoarteriosclerosis amyloidosis has also been reported to have transient neurological symptoms attributed to ischemia or microhemorrhage.^{2,11}

Although we might speculate about the potential clinical-radiological correlation between the prominent aphasias and the left hemispheric SS, we are limited by our small number of cases and the potential for selection bias. Further studies are needed to determine the prevalence of SS in AD and CAA and its clinical relevance in cognitive decline and focal neurological signs.

These cases illustrate that SS can be the important indicator of CAA in AD beyond the cortical microhemorrhages or lobar hemorrhages that are more readily recognized as being CAA-related. These cases reinforce the usefulness of MRI gradient-recalled echo in detecting CAA-related hemosiderin deposits, not only intraparenchymal⁶ but also at the subpial-subarachnoid level, particularly when intraparenchymal hemorrhages are not detected or observed. When present, SS may support the antemortem diagnosis of concomitant CAA in AD, and it may be associated with clinical features, including those that are atypical for AD.

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Disclosures

The authors (L.M., I.R.A.M., and H.H.F.) have previously published a review article in the *Journal of Neurological Sciences* 2007 (257):23–30 on the clinical phenotypes of cerebral amyloid angiopathy. In this previously published article, the authors included an

illustrative MRI of one of the cases discussed in more detail in this current article.

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