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Superficial Siderosis of the CNS Associated with Multiple Cavernous Malformations

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Summary: Superficial siderosis of the CNS due to chronic, recurrent subarachnoid hemorrhage is an uncommon and potentially debilitating disorder. The classic clinical manifestation is progressive bilateral sensorineural hearing loss (SNHL), although ataxia and pyramidal signs also are observed frequently. Cavernous malformations rarely present with subarachnoid hemorrhage. We describe an unusual case of a young patient who presented with progressive, bilateral SNHL who was found to have superficial CNS siderosis associated with multiple cavernous malformations.

Superficial siderosis of the CNS is an unusual cause of progressive sensorineural hearing loss; however, bilateral SNHL is the most common clinical presentation of CNS siderosis. Hemosiderin deposition along the leptomeninges, subpial tissues, and subependyma of the ventricles as a result of chronic, recurrent subarachnoid hemorrhage induces intracellular uptake of iron, leading to damage of neural tissue (1–3). Traumatic cervical nerve root avulsion, neoplasms, and vascular abnormalities are causes of siderosis. Nevertheless, in as many as 46% of the patients, no source for the siderosis is identified (3–6).

We present a report of a patient with a 15-year history of progressive, bilateral hearing loss whose MR imaging evaluation revealed CNS siderosis associated with multiple intracranial cavernous malformations. Although intra- and perilesional hemorrhages may occur with cavernous malformations, resulting in seizures or focal neurologic deficits, subarachnoid hemorrhage is an unusual sequela of these lesions. Rare cases of subarachnoid hemorrhage associated with optic nerve or spinal cord cavernous malformations have been reported (7). Several of the cavernous malformations in the patient we present are superficial, and we speculate that recurrent bleeding into the subarachnoid space

resulted in the siderosis responsible for his hearing loss.

Case Report

A 32-year-old man presented with a 15-year history of progressive, bilateral hearing loss. No physician had ever evaluated extensively his hearing loss before this visit. He denied vertigo and tinnitus. On occasion, he noted episodic twitching of the fingers of his right hand, which lasted up to several days. His medical history was significant for mild headaches and surgery at 3 years of age to correct esotropia. His family history was noncontributory. The results of a neurologic examination were notable for bilateral hearing loss and were otherwise unremarkable, with normal motor strength, symmetric reflexes, intact sensation, and steady gait without ataxia. Audiometric testing revealed bilateral, high-frequency sensorineural hearing loss, which was symmetrical.

MR imaging of the brain was performed to determine the presence of retrocochlear disease. The results of an evaluation of the cerebellopontine cistern and internal auditory canals were unremarkable. Nonetheless, MR imaging revealed multiple cavernous malformations in the cerebrum, cerebellum, brain stem (midbrain, pons, and cerebral peduncles), right periventricular and subependymal region, and the deep gray matter (Fig 1). These were not associated with edema or mass effect. Several of the cavernous malformations were superficial, including lesions in the left parietal and temporal lobes as well as in the pons. Gradient-echo MR imaging showed hypointensity consistent with siderosis along the pial surface of the brain stem and along the folia of the cerebellar vermis (Fig 1). The patient's history of finger twitching was interpreted as myoclonus owing to the focal effect of a cavernous malformation in his left motor cortex. The patient was fitted for hearing aids and will return for regular follow-up with a neurologist and otorhinolaryngologist.

Discussion

Superficial CNS siderosis is a relatively uncommon but underdiagnosed cause of progressive bilateral SNHL. The largest review of the literature to date (published in 1995), reported that patients with superficial siderosis most often present with progressive, bilateral sensorineural hearing loss (95%), ataxia (88%), and pyramidal signs (76%) (4). Other manifestations may include dementia, bladder incontinence, anosmia, anisocoria, and sensory deficits. The disorder has been identified in patients of all ages, with men affected more often than women at a ratio of approximately 3:1 (4). Close questioning of patients often reveals that their symptoms began years before they sought medical attention. Analysis of CSF intermittently may yield xanthochromia, elevated red blood cell

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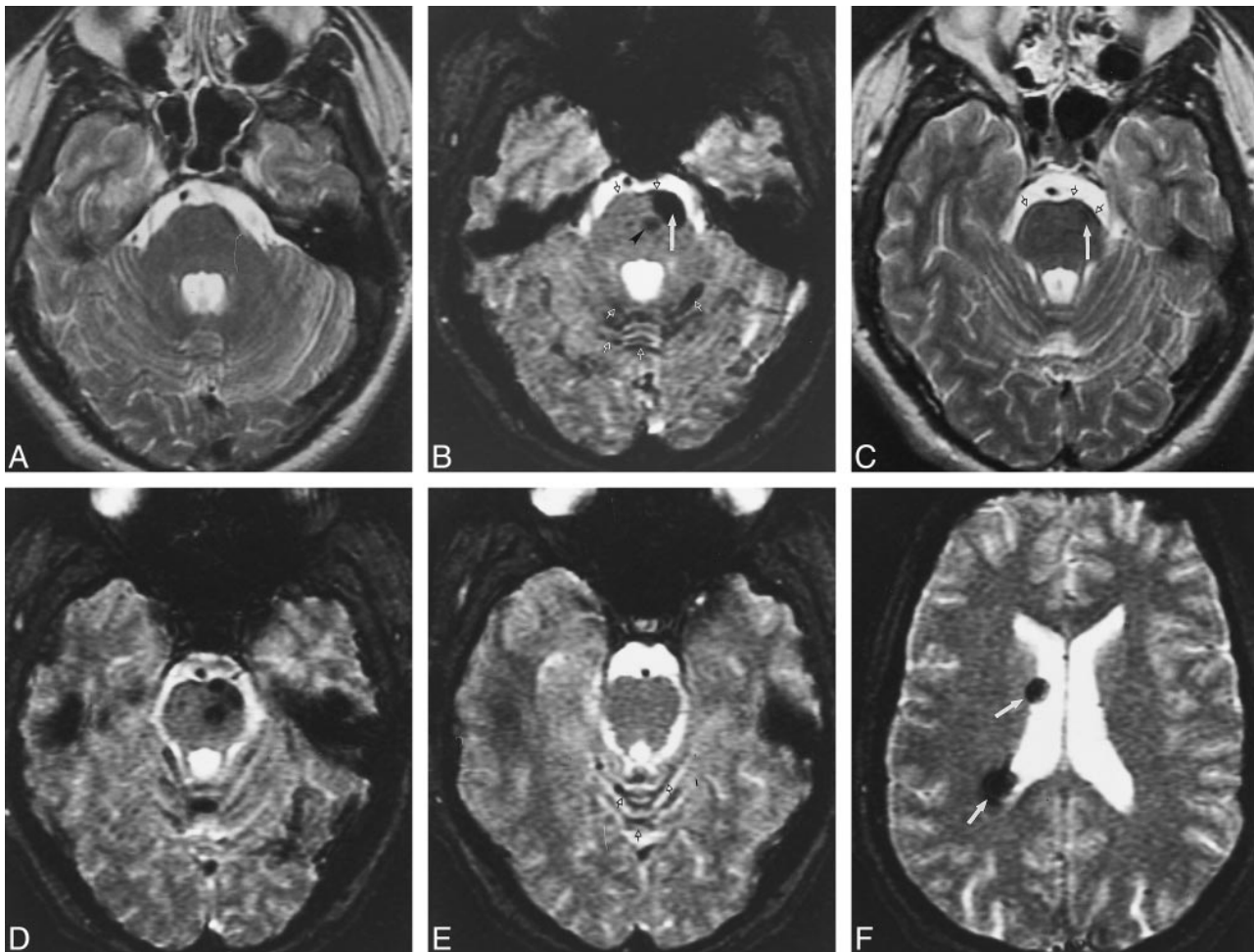


FIG. 1. Images of a 32-year-old male patient with CNS siderosis associated with multiple cavernous malformations.

A, Axial spin-echo 3500/98/1 (TR/TE/excitations) T2-weighted MR image, centered at the level of the pons, suggests mild hypointensity along the ventral surface of the pons, particularly on the left.

B, Axial gradient-echo 750/40/2 susceptibility MR image with a flip angle of 10° , obtained at the same level as that shown in A, shows focal regions of hypointensity in the ventral left pons (solid arrow) as well as the central pons (arrowhead), consistent with cavernous malformations. In addition, hypointensity along the ventral surface of the pons is better appreciated, as is hypointensity along the folia of the vermis of the cerebellum (open arrows).

C, Axial spin-echo 3500/98/1 T2-weighted MR image, obtained at the level of the upper pons, raises the possibility of mild hypointensity along the surface of the brain stem (open arrows), as well as a small focal region of hypointensity within the left upper pons (solid arrow).

D, Axial gradient-echo 750/40/2 susceptibility MR image with a flip angle of 10° , acquired at the identical level as that shown in C, shows "blooming" of the hypointensity within the left side of the brain stem, consistent with cavernous malformations that are superficial, as well as markedly improved visualization of hypointensity consistent with siderosis along the cerebellar folia and surface of the brain stem, as compared with the T2-weighted image shown in C.

E, Axial gradient-echo 750/40/2 susceptibility MR image with a flip angle of 10° , obtained at a more cephalad level, shows hypointensity consistent with siderosis along the folia of the superior vermis (open arrows).

F, Axial gradient-echo 750/40/2 susceptibility MR image with a flip angle of 10° , obtained at the level of the lateral ventricles, shows cavernous malformations along the ependymal/subependymal region (solid arrows) but no hemosiderin staining of the ependyma.

count, and elevated iron and ferritin levels (4, 6). Nevertheless, normal CSF findings are occasionally encountered.

The pathologic changes of superficial siderosis are characterized well (1–3). Macroscopically, there is dark brown discoloration of the leptomeninges and superficial CNS parenchyma as well as the subependymal lining throughout the neuroaxis. Often, there is associated hydrocephalus. Microscopically, there is extensive hemosiderin deposition in the leptomeninges and subpial and subependymal regions. The leptomeninges are thickened,

and there are varying degrees of neuronal loss, reactive gliosis, and demyelination. The superficial folia of the cerebellum almost always are involved with loss of Purkinje cells and Bergmann gliosis. In addition, cranial nerve VIII and, to a lesser extent, cranial nerves I and II exhibit dense accumulation of hemosiderin, which is often associated with demyelination and atrophy.

Animal models of superficial siderosis have shown that recurrent subarachnoid hemorrhage resulting in the prolonged contact of these tissues with iron is crucial to the development of the dis-

order (1). Within the cerebellum, microglia as well as Bergmann glia are uniquely sensitive to iron-mediated cell damage. The terminal processes of Bergmann glia that interface with the subarachnoid space mediate iron uptake from the CSF, inducing the synthesis of ferritin within these cells. Because ferritin sequesters iron and is thus thought to play a role in iron detoxification, intracellular iron may not cause toxicity until ferritin biosynthesis is overwhelmed by a large iron load. Excess free iron may then stimulate lipid peroxidation, leading to localized tissue necrosis (1).

The preferential involvement of cranial nerve VIII is partly because of its extensive lining with central myelin, which is supported by siderosis-susceptible microglia. In addition, its course through the pontine cistern exposes the nerve to an abundance of iron. Cranial nerve I also is affected similarly for the same reasons; therefore, it is speculated that anosmia is underreported in association with siderosis because this symptom often is not sought or documented clinically. It is not clear why symptoms of optic nerve involvement also are not found as often as hearing loss, but it is speculated that cranial nerve II comes into contact with significant CSF volumes over only a short distance in its course (4).

In the past, superficial siderosis was diagnosed almost exclusively at autopsy (2, 3). With the advent of MR imaging, the diagnosis has been made increasingly premortem. MR imaging has identified siderosis in reportedly asymptomatic patients. In one series, which examined 8843 consecutive MR studies, 0.15% of patients had MR findings consistent with superficial siderosis. Eighty-five percent of these patients reported no symptoms (5). This supports the theory of a presymptomatic phase (4). There are studies now in progress that will follow asymptomatic patients to determine whether and when they develop symptoms (5).

MR imaging findings of siderosis are pathognomonic. T2-weighted and, in particular, gradient-echo susceptibility imaging reveals characteristic hypointensity along the pial surface/subarachnoid space of the brain (Fig 1) and spinal cord as well as the ependyma of the ventricles (8). This finding is detected classically along the surface of the brain stem and cerebellar vermis. Frequently, there is associated cerebellar atrophy. Although a pathologic examination reveals that the cranial nerves are coated with hemosiderin, this is detected by MR imaging in only 25% of cases (4). The extent or distribution of siderosis does not necessarily correlate with the severity of clinical disease (4, 5). Some patients with diffuse findings revealed by imaging have minimal symptoms, whereas others with less severe findings may be debilitated significantly. Management of superficial siderosis is aimed at eliminating the cause of recurrent subarachnoid hemorrhage either by surgical or endovascular treatment. Iron chelators and antioxidants have been used to treat idiopathic CNS siderosis;

however, there is little evidence to support their effectiveness (3, 6).

Superficial siderosis has been associated with a spectrum of lesions, including trauma (such as cervical nerve root avulsions), neoplasms (ependymomas, oligodendrogliomas, and astrocytomas), and vascular abnormalities (arteriovenous malformations, aneurysms, and fragile capillary regrowth after brain surgery) (4). When superficial siderosis is diagnosed using imaging, efforts must be directed at identifying a source of recurrent subarachnoid hemorrhage. In the absence of an intracranial abnormality, further evaluation should include MR imaging of the spine to look for a spinal cord lesion. If no source is identified, further evaluation with conventional catheter angiography may be warranted to exclude a vascular lesion. In 25% to 46% of the patients, a source of siderosis is not identified (3–6).

Cavernous malformations are well-demarcated vascular lesions consisting of a honeycomb array of compact vessels lined by a single endothelial layer and separated by a collagenized or fibrous stroma. The vessels characteristically lack smooth muscle and elastic lamellae. In addition, there is typically no intervening neural tissue. Cavernous malformations are estimated to occur in approximately 0.5% to 0.9% of the population, with men and women affected equally (9, 10). Multiple lesions may be the result of genetic predisposition or they may occur sporadically. They also have been associated with radiation therapy and stereotactic biopsy (11). Most are asymptomatic. Clinical manifestations may include seizures with lesions located in the cortex or focal neurologic deficits in lesions associated with acute hemorrhage or both. Rare cases of subarachnoid hemorrhage have been reported with cavernous malformations of the optic nerve or spinal cord (7). In one case, a periventricular cavernous malformation was associated with siderosis and intraventricular hemorrhage (12).

MR imaging is sensitive and specific for diagnosing occult vascular malformations (13). Uncomplicated lesions are circumscribed with a complete hemosiderin ring, which is hypointense on T2-weighted images. Gradient-echo images reveal marked "blooming" of these lesions (Fig 1). The central sinusoids may be hyperintense on unenhanced T1- and T2-weighted images and may enhance after the administration of contrast material. Mass effect and edema in the surrounding parenchyma are unusual. Variable signal intensity indicating recurrent subclinical bleeds of different ages may be present with some malformations.

Superficial CNS siderosis and cavernous malformations are not common causes of SNHL. For the patient who presents with bilaterally symmetric SNHL, workup includes audiologic testing that may be followed by cross-sectional imaging if the SNHL does not fit a pattern typical for age-induced SNHL. In cases of suspected retrocochlear lesions, MR imaging is the technique of choice in patients

of all ages (14). Retrocochlear SNHL may result from lesions in the internal auditory canal, cerebellopontine angle cistern, or brain parenchyma. In the cerebellopontine angle cistern, lesions include neoplasms, especially acoustic neuromas and meningiomas, as well as arachnoid and epidermoid cysts. Bilateral acoustic neuromas are diagnostic of neurofibromatosis type 2. Leptomeningeal neoplasms (lymphoma and metastatic disease), inflammatory processes (sarcoidosis and meningitis), vascular loops, and siderosis may cause SNHL (14). In the intra-axial pathway, SNHL may be due to ischemia, neoplasms, trauma, or demyelinating diseases (14). Intra-axial lesions are usually associated with other neurologic sequelae, such as cranial nerve palsies, weakness, and respiratory symptoms. Vascular malformations strategically located may also cause SNHL.

In our case, we attribute the patient's progressive bilateral sensorineural hearing loss to siderosis caused by recurrent chronic subarachnoid hemorrhage from multiple intracranial cavernous malformations, many of which were superficial. Our case is unusual not only because siderosis is uncommon but also because cavernous malformations infrequently present with subarachnoid hemorrhage and their association with siderosis is virtually unreported. In a patient with multiple cavernous malformations, it may be difficult to determine which lesion(s) is responsible for the siderosis. The absence of subependymal staining on images of our patient (Fig 1) suggests that intraventricular hemorrhage was not responsible but rather that one or more of the superficial brain stem and parenchymal lesions were the source of subarachnoid hemorrhage.

Because siderosis is a clinically debilitating and potentially irreversible complication of superficially positioned cavernous malformations, clinicians should maintain a high level of suspicion for siderosis with cavernous malformations that abut a

CSF interface. In particular, gradient-echo imaging should be performed in search of CNS siderosis in such patients because T2-weighted imaging is much less sensitive for detecting this complication. Neurosurgical intervention in the management of cavernous malformations is aimed at treating only those lesions that are in clinically significant operable locations.

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