

Superficial siderosis: a case report and review of the literature

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SUMMARY

Background A 48-year-old man with a past history of a car-accident-induced coma at the age of 3 years and spontaneous bilateral subdural hematomas at the age of 34 years presented with a 2-year history of worsening gait difficulties, clumsiness and dysarthria. CT scans of the brain taken during the 6 months leading up to his presentation had revealed chronic subarachnoid hemorrhage, but angiograms had not been able to identify the source of bleeding.

Investigations Neurological examination, brain MRI scan, lumbar puncture, four-vessel cerebral angiogram and spinal angiogram.

Diagnosis Superficial siderosis; a complete review of the current literature on the condition is provided.

Management Iron chelating agents.

KEYWORDS diagnosis, hemosiderin, iron chelating agents, MRI, subarachnoid hemorrhage

CME

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

THE CASE

A 48-year-old man with hypertension was admitted to hospital from a neurology clinic with a 2-year history of worsening gait difficulties, clumsiness and dysarthria. At the age of 3 years he had been involved in a car accident resulting in a coma, and hospitalization that lasted 2 weeks. At the age of 34 years, he was then admitted to hospital with what he described as the worst headache of his life. He was found to have spontaneous small bilateral subdural hematomas of unknown etiology, from which he recovered completely over the following year without surgical intervention. At this time a lumbar puncture was performed that ruled out the presence of subarachnoid blood, and brain MRI scans showed no other abnormalities. Two years before his current presentation to the neurology clinic, he began to notice that his legs would stiffen after he went on long walks. During the 6 months leading up to his presentation he reported rapidly worsening gait difficulty, cramping in the legs, clumsiness, difficulty speaking and memory impairment. During this time, hospital CT scans of his brain revealed chronic subarachnoid hemorrhage. The hemorrhage was confirmed with lumbar puncture, but repeated angiograms could not localize an aneurysm or other source of bleeding.

On presentation to the neurology clinic, physical examination revealed that the patient was in no acute distress. His general medical examination was normal, and he had no relevant family history. His neurological examination was notable for normal mental status apart from marked memory impairment, normal language and comprehension, but moderate dysarthria. His cranial nerves were intact except for lateral end-gaze nystagmus. His motor strength was 5/5 throughout, but tone was markedly increased in the lower extremities. Sensory examination was

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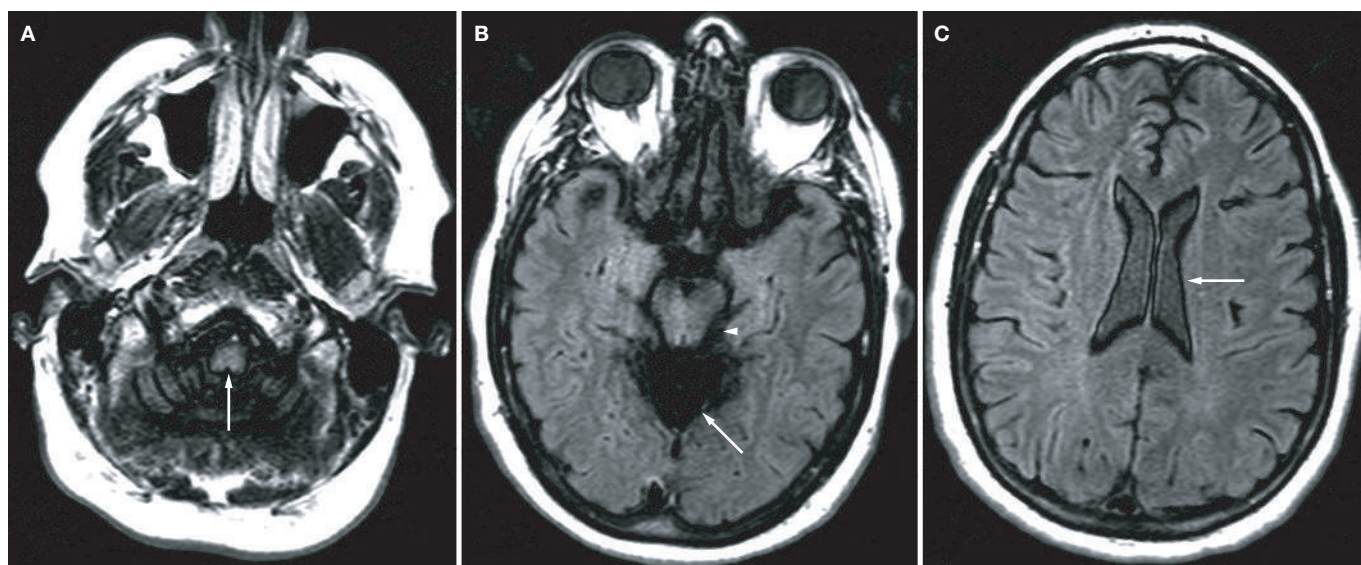


Figure 1 MRI brain images of the patient showing features characteristic of superficial siderosis. (A) A T2-weighted inversion recovery image of the patient's brainstem outlined by a rim of hypointensity (arrow) where hemosiderin has deposited. (B) The rim of hypointensity around the cerebellar vermis (arrow) and midbrain (arrowhead). (C) The same rim of hypointensity around the lateral ventricles (arrow).

largely normal. Reflexes were brisk in the lower extremities, with upgoing toes bilaterally. His coordination was bilaterally impaired in finger-to-nose testing, and his gait was notably spastic and ataxic.

An MRI scan of the brain showed extensive hypointensities on fluid-attenuated inversion recovery throughout the leptomeninges—most prominent in the posterior fossa—in addition to cerebellar atrophy and diffuse dural enhancement that was consistent with a radiological diagnosis of superficial siderosis (Figure 1). No other abnormalities were noted. A lumbar puncture was positive, revealing 19,000 red blood cells/cm³, but a repeat four-vessel cerebral angiogram and spinal angiogram again failed to locate an aneurysm or the source of the bleeding. The patient was discharged from hospital with the chelating agent trientine at a dose of 750 mg every morning and 1,000 mg every night in an attempt to reduce the symptoms caused by iron deposition from chronic subarachnoid hemorrhage.

At a follow-up visit 6 months later, the patient reported mild bilateral hearing loss, worsening ataxia and spasticity, and mild cognitive impairment—particularly with respect to his short-term memory. Despite continued treatment with trientine over the next 2 years, his neurological condition continued to decline.

DISCUSSION OF DIAGNOSIS

Superficial siderosis is a radiological or pathological condition in which hemosiderin—a product of the breakdown of blood—is deposited in the subpial layer of the CNS, which typically leads to progressive and irreversible neurological dysfunction. The condition is characterized by a classic triad of symptoms consisting of sensorineural hearing loss, cerebellar ataxia, and myelopathy. Superficial siderosis was first described almost 100 years ago, but only a handful of cases appeared in the literature before the widespread use of MRI enabled physicians to make the diagnosis without a biopsy, and to discover incidental asymptomatic cases.

In addition to greatly improving the chances of an early diagnosis of superficial siderosis, the wide availability of MRI has revolutionized our understanding of the etiology of the condition. Based on the first 69 published reports of superficial siderosis, it was calculated that 50% of cases are caused by an idiopathic chronic subarachnoid hemorrhage originating from an occult source, while the other 50% of cases are secondary to a known cause of subarachnoid hemorrhage such as a CNS tumor, arteriovenous malformation, or trauma.⁸

Using the results of 270 cases of superficial siderosis worldwide published during the period 1908–2006 (see Supplementary Table 1 online),

Table 1 Data regarding the etiologies of 270 published cases of superficial siderosis.^a

Etiology	Number of reported cases (percentage of total)	Male:female ratio	Average age at presentation (years)	Average duration ^b (years)
Idiopathic	95 (35%)	51:38	57	9
Head/back trauma	35 (13%)	27:6	51	22
Arteriovenous malformations	25 (9%)	17:8	53	12
Current CNS tumor	40 (15%)	24:13	45	6
Previously resected CNS tumor	16 (6%)	9:7	48	16
CNS post-surgical (non-tumor)	18 (7%)	10:6	38	16
Amyloid angiopathy	7 (3%)	3:4	62	5
Brachial plexus/root injury	17 (6%)	16:0	48	21
Other causes of subarachnoid hemorrhage	17 (6%)	NA	NA	NA

^aSee Supplementary Table 1 online for a full list of references. ^bAverage durations of idiopathic causes, current CNS tumors, arteriovenous malformations and amyloid angiopathy are calculated as the number of years of symptoms until presentation. For head/back trauma, previously resected tumors, post-surgical and brachial plexus injuries, the average duration is calculated as the number of years from the surgery or injury until presentation. These calculations are intended to estimate the number of years of chronic bleeding in the subarachnoid space. Abbreviation: NA, not applicable.

we have recalculated the etiologies (summarized in Table 1). In interpreting these data, it is important to note that a review of published case reports of superficial siderosis does not substitute for an actual epidemiologic study on this topic. Nevertheless, on the basis of the available data in the literature to date, the percentage of cases described as idiopathic or of unknown cause has been found to be 35%, and this figure is likely to decrease further as imaging technology improves. Among reported cases of secondary superficial siderosis for which a source of bleeding is identified, current or previous CNS tumors are the most common cause (21%), followed by head or back trauma (13%), and arteriovenous malformations/aneurysms (9%). Other less common causes of chronic subarachnoid hemorrhage leading to superficial siderosis are post-surgical changes related to neurosurgeries (7%), brachial plexus injury (6%), amyloid angiopathy (3%), and chronic subdural hematomas. For reasons that are unclear, males appear to be affected more than females by a ratio of approximately 2:1 across all etiologies. The average age of presentation is in the fifth and sixth decades, but ranges from birth to the ninth decade depending on the etiology.

It is accepted that superficial siderosis is caused by chronic bleeding into the subarachnoid space

and deposition of blood breakdown products into the subpial layer of the brain and spinal cord. Early case reports noted selective deposition of hemosiderin in the nervous system, most notably in the cerebellum, brainstem, lining of the ventricles, and spinal cord.^{1–4} These observations led to elegant animal experiments^{5,6} that were able to demonstrate that repeated injections of blood into the subarachnoid space cause cerebellar Bergmann cells, microglia, and superficial astrocytes in this brain region to take up heme and release free iron according to the following conversion catalyzed by heme oxygenase: heme → free iron + biliverdin.

Intracellular free iron inactivates iron regulatory protein, which allows upregulation of ferritin production for the chelation of the excess free iron.⁷ Initially, the heavy subunit of ferritin predominates, but after persistent free iron exposure the light subunit of ferritin is preferentially produced. The light ferritin subunits are thought to be designed for long-term storage, and they are the primary component of hemosiderin deposits. Free iron is toxic to cells because it catalyzes the breakdown of hydrogen peroxide to superoxide—a reactive oxygen species that can cause lipid peroxidation, membrane dysfunction, and ultimately cell death. For this reason, it is critical for the CNS to rapidly sequester free

iron with ferritin as described above. In the short term this process is protective, but the persistence of hemosiderin deposits containing light ferritin subunits can also be toxic to cells.

Localization of specialized cells within the cerebellum, brainstem, and spinal cord to sequester heme explains the predisposition of these CNS structures to be most adversely affected in cases of superficial siderosis. Interestingly, cranial nerves I and VIII are the most compromised cranial nerves, because they remain within the CNS for a relatively long distance outside of the brain. In comparison with the remaining cranial nerves that depart from the CNS within 1–2 mm of the brainstem, cranial nerve VIII remains in the subarachnoid space until it enters the internal acoustic canal, making it more vulnerable to the damaging effects of chronic subarachnoid hemorrhage within the CNS. The optic nerves (cranial nerve II) remain wholly within the CNS, but they are somehow spared from the damaging effects of heme, possibly because of the absence of heme-absorbing glia along their tract.

Subarachnoid hemorrhaging must persist for at least several months in order to overwhelm the body's clearance mechanisms and cause symptoms. Depending on the volume and location of bleeding, this process can take considerably longer. As in the present case, many cases involve bleeding that occurs over a period of decades before the onset of symptoms, and the ability of an individual to clear the toxic heme products over time will also vary.

Across all etiologies, unilateral or bilateral hearing loss is present in 81% of cases, as are descriptions of cerebellar ataxia; myelopathy (such as extremity weakness or spasticity) is present in 53% of cases. Only 39% of patients, however, have all three of these symptoms. The incidences of all symptoms recorded in cases of superficial siderosis are listed in Table 2. There appears to be no correlation between the specific etiology of the superficial siderosis and its associated symptoms, which supports the prevailing model that subarachnoid hemorrhage from any cause will affect the same vulnerable areas of the brain including the cerebellum, brainstem, and spinal cord.

The MRI scans of patients with superficial siderosis are unmistakable and pathognomonic. As in the present patient, T2-weighted fluid-attenuated inversion recovery sequences show rims of hypointensity around the spinal cord, cerebellum—especially the vermis of the

Table 2 Reported symptoms in 270 published cases of superficial siderosis.^a

Symptom	Percentage of total symptomatic cases
Hearing loss	81
Ataxia	81
Myelopathy	53
Urinary problems	14
Headaches	14
Anosmia	14
Diplopia	4
Bowel problems	3
Ageusia	2
Cranial nerve palsies	2

^aSee Supplementary Table 1 online for a full list of references.

cerebellum—brainstem and lining of the lateral ventricles (Figure 1). In cases in which the iron burden is heavy, CT can be used to diagnose superficial siderosis, but it fails to reveal more-subtle cases.¹¹ In cases for which there is a longitudinal fluid-filled collection in the spinal canal visible on MRI scan, dynamic CT myelogram can sometimes help localize the site of the defect when angiography fails to localize the bleeding source.¹² Cerebrospinal fluid (CSF) analysis can show xanthochromia, an elevated red blood cell count as in the present patient, and a high protein level, but in many cases the CSF appears normal because the chronic subarachnoid hemorrhaging can occur intermittently.

TREATMENT AND MANAGEMENT

Superficial siderosis is a progressively deteriorating neurological condition that must be recognized early in order to be effectively treated. The accumulated data on patients with the condition show that in more than 97% of cases the calculated duration of subarachnoid hemorrhage from date of injury to date of presentation of first symptom is at least 6 months. Once symptoms have appeared, the goal of therapy should be to prevent progression of the condition by ablating the source of subarachnoid hemorrhage when it can be identified and corrected. In the rare instance that superficial siderosis is diagnosed by MRI in an asymptomatic person, a work-up should be pursued for the source of bleeding—which should be ablated if possible.

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Competing interests

The authors declared they have no competing interests.

Unfortunately, there is no therapy to reverse the damaging effects of hemosiderin deposition in the brain. The most commonly attempted therapy is iron chelation using a medication such as desferrioxamine; however, only a single case report has described an improvement in symptoms or halting of the progression of the disease with the use of iron chelators. Trientine, a copper and iron chelator, was reported to improve one patient's symptoms and to lead to decreased CSF iron concentration.¹³ A case report was also recently reported in which lumbar CSF shunting was found to improve the patient's symptoms, which included hearing loss.¹⁴ Steroids were used successfully in one patient with an anti-Ri autoimmune disease, but there are no other reports or published studies of the role of steroids in treating noninflammatory causes of superficial siderosis.¹⁵

In a recent study by Koeppen and Dickson,¹⁶ a rabbit model of superficial siderosis was used to test the hypothesis that tin protoporphyrin, an inhibitor of heme oxygenase, could prevent the production of free oxygen radicals and improve outcome. Although microglial activation was unchanged, the amount of hemosiderin deposition in the brain was dramatically decreased. This evidence suggests that tin protoporphyrin might influence the pathogenesis of superficial siderosis. Tin protoporphyrin, trientine and CSF shunting are promising therapies that merit long-term randomized trials in humans, which would also allow a study of the natural course of the disease in the placebo arm.

CONCLUSION

Superficial siderosis is a radiological or pathological diagnosis of hemosiderin deposition in the brain and spinal cord that is caused by chronic subarachnoid hemorrhage. The classic triad of symptoms is bilateral sensorineural hearing loss, ataxia, and myelopathy, and the T2 MRI pathognomonic findings are rims of hypointensity around the brainstem, cerebellum and spinal cord. The most common causes of the chronic subarachnoid hemorrhage that lead to superficial siderosis include CNS tumors, head and neck trauma, and arteriovenous malformations, although an occult source is unidentified in

over a third of cases. When discovered early the condition can potentially be treated by ablating the source of bleeding, but the natural course of superficial siderosis is a progressive neurological decline. Iron chelators have not proven beneficial, and ongoing studies are needed to determine the role of agents targeting the production of reactive oxygen species in the treatment of superficial siderosis.

Supplementary information is available on the *Nature Clinical Practice Neurology* website.

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