

## Research Review

# Superficial Siderosis: A Potentially Important Cause of Genetic as Well as Non-Genetic Deafness

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**Superficial siderosis is an important disease that is increasingly being recognized as a cause of sensorineural hearing loss. Hemosiderin, resulting from repeated episodes of subarachnoid bleeding, is deposited preferentially on the surface of the eighth nerve, cerebellum, and brain stem as a consequence of glial catabolism of ferritin within those structures. This deposition eventually results in destruction and demyelination within the central nervous system, leading to the cardinal clinical findings of superficial siderosis: hearing loss, ataxia, and myelopathy. This mechanism may contribute to the pathogenesis of several forms of genetic deafness, and should be considered as a diagnostic possibility in cases of late onset deafness even in the absence of an overt history of subarachnoid bleeding.**

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**KEY WORDS:** deafness; superficial siderosis; genetics; Alport syndrome; macrothrombocytopenia; cerebral cavernous malformation; MYH9

### INTRODUCTION

Our awareness of the importance of superficial siderosis as a cause for deafness was prompted by the observation of a 35-year-old man who presented for evaluation of a progressive, high frequency sensorineural, non-syndromic hearing loss. At the age of 21 years, he first became aware of left-sided hearing loss, which had progressed to involve both ears. He had tried digital hearing aids with variable success and denied symptoms of imbalance, ataxia, dementia, anosmia, or bladder dysfunction.

His past medical history revealed that he had a posterior craniotomy at age 4, for a cystic lesion of the cerebellum. He suffered residual diplopia, which was reportedly corrected by ophthalmologic surgery on the left eye at age 6. His medical

history was otherwise unremarkable. The family history showed that his mother had a mild to moderate high frequency sensorineural hearing loss; his only sister was reported to have normal hearing. Physical examination revealed no abnormalities apart from his hearing loss, except for some unsteadiness on Romberg testing. However, tandem walking was well executed and he had a normal gait. A previous MRI examination demonstrated a rim of hypointensity surrounding the brain stem, consistent with superficial siderosis (Fig. 1). The pure tone audiogram showed a mild to severe sloping sensorineural hearing loss (Fig. 2).

### DISCUSSION

Until recently, superficial siderosis has been considered to be a rare pathologic entity characterized by hemosiderin deposition in the leptomeninges, which was originally described as a postmortem finding [Hamill, 1908]. Noetzel first linked superficial siderosis to subarachnoid hemorrhage in 1940, but it was not until 1964 that its syndromic association with sensorineural deafness, ataxia, dementia, and myelopathy was first recognized [Noetzel, 1940; Tomlinson and Walton, 1964]. Superficial siderosis typically results from recurrent subarachnoid bleeding. The bleeding can be clinically silent but delivers repeated doses of iron breakdown products into the cerebrospinal fluid. For many years, the prevailing view was that a defect in iron metabolism, analogous to hemochromatosis, might be required for expression of the disease; however, the syndrome was subsequently reproduced in several animal models by repeated injections of blood into the subarachnoid space [Iwanowski and Olszewski, 1960; Koeppen and Borke, 1991]. Glial cells, which actively take up and metabolize ferritin, are the most severely affected. Once their capacity to metabolize the heme degradation products is exceeded, free iron accumulates and causes lipid peroxidation and cell damage [Koeppen and Dentinger, 1988; Koeppen et al., 1993]. Prior to the advent of modern neuroradiology, superficial siderosis was seldom diagnosed in living patients. However, the paramagnetic properties of ferritin ions, which shorten the relaxation time of T2 weighted MRI, produces a characteristic a rim of hypointensity surrounding the brain stem and cerebellum [Bracchi et al., 1993; Pribitkin et al., 1994].

An astonishing feature of this syndrome is that the sensorineural hearing loss, which is present in as many as 95% of all affected patients, may not be noted until 4 months to 30 years after the first recognized episode of intracranial bleeding [Fearnley et al., 1995]. The 8th cranial nerve is especially vulnerable to hemosiderin deposition, because only a short segment of the nerve is sheathed with Schwann cells. This leaves a long residual glial segment, extending from the exit of the nerve at the cerebellopontine angle to the porus

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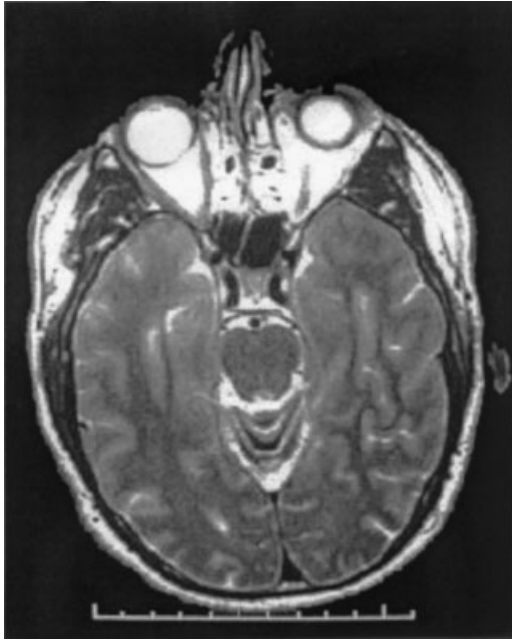


Fig. 1. T-2 weighted MR image demonstrating a rim of hypointensity outlining the brainstem and cerebellum, typical of superficial siderosis.

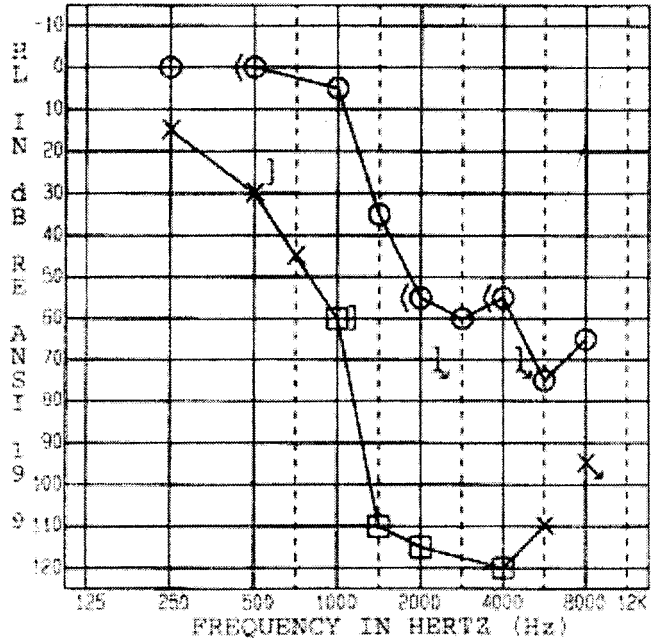


Fig. 2. Audiogram demonstrating an asymmetric, sloping sensorineural hearing loss.

acousticus, which is bathed by a high flow of cerebrospinal fluid in the pontine cistern [Koeppen and Dentinger, 1988]. The audiogram generally reveals a sloping bilateral sensorineural loss, with corresponding losses in speech discrimination and word recognition scores [Parnes and Weaver, 1992; Fearnley et al., 1995; Kale et al., 2003]. Eventually, hearing loss almost always occurs, and typically progresses to severe or profound deafness [Parnes and Weaver, 1992; Fearnley et al., 1995; Dhooge et al., 2002; Kale et al., 2003]. The high frequencies are most severely affected, and at times a small island of low tones is preserved. These patterns may well reflect the tonotopic localization of axons transmitting the high frequency sound at the surface of the auditory nerve. However, the hearing loss may initially be asymmetric and/or unilateral [Parnes and Weaver, 1992; Fearnley et al., 1995; Longridge et al., 1996; Castelli and Husband, 1997; Li et al., 2001; Kale et al., 2003]. Neurotologic testing shows a retrocochlear pattern of impairment, ranging from increased wave latencies to an undetectable Auditory Brainstem Response (ABR) [Yamana et al., 2001; Dhooge et al., 2002]. However, electrocochleography frequently reveals a lack of compound action potentials, as well as evidence for recruitment on audiometric testing [Yamana et al., 2001]. These findings suggest that some cochlear impairment may also be present [Yamana et al., 2001].

The olfactory nerves are coated by glial cells throughout their course, and are also damaged by hemosiderin deposition. However, overt anosmia is less often documented clinically [Fearnley et al., 1995]. Ataxia is the second most common presenting symptom of superficial siderosis, and generally occurs after the onset of hearing loss. Pyramidal signs, dementia, and other neurologic findings occur in order of decreasing frequency [Fearnley et al., 1995]. Depending on the cause for the recurrent hemorrhage, focal neurologic signs such as seizures or paresis may be seen.

The source of the recurrent bleeding is usually a CNS lesion such as neoplasms, most notably ependymomas, aneurysms, AV malformations, prior operations, especially of the posterior fossa and cerebellum, or neonatal intraventricular hemor-

rhage [Kumar et al., 1993; Fearnley et al., 1995; Anderson et al., 1999]. In about half of cases, no bleeding source is identified [Fearnley et al., 1995]. The precise diagnosis in our patient at the time of his craniotomy 31 years ago is unclear. It is conceivable that he had a vascular anomaly such as the hereditary cerebral cavernous malformation syndrome (CCM). Familial cerebral cavernous angiomas are abnormally large and weak vascular lesions, which are inherited as an autosomal dominant trait [Rigamonti et al., 1988; Bicknell, 1989]. Depending on the location and number of lesions, this syndrome frequently presents with focal seizures [Gil-Nagel et al., 1995]. However, recurrent hemorrhage almost always occurs, and may lead to the characteristic MRI findings of superficial siderosis [Gunel et al., 1996; Hsu et al., 1999]. In a large family reported by Gil-Nagel et al. [1995], 7 of 17 patients (41%) classified as affected or possibly affected had hearing loss, which was the second only to seizures as the most frequent clinical finding. However, the authors did not consider bilateral hearing loss to be an integral part of the syndrome, presumably because of the lack of a plausible pathogenic mechanism. Other familial and isolated cases of hearing loss have been reported with this syndrome [Bicknell et al., 1978; Hsu et al., 1999]. However, in most large surveys [Gunel et al., 1996; Labauge et al., 1998], no mention is made of hearing loss, possibly because it was considered to be an unrelated neurologic finding. Familial CCM is now known to be caused by at least three autosomal dominant genes, one of which (CCM1) has been shown to be the locus on 7q21-q22, which codes for KRIT-1, a 529 amino acid protein with an N-terminal ankyrin repeat domain that is thought to help determine the cytoskeletal structure of endothelial cells [Serebriiskii et al., 1997]. The CCM2 gene has not yet been identified but maps to 7p15-p13, a region that includes DFNA5, a gene coding for a 496 amino acid protein of unknown physiologic function. Mutations involving this gene cause a dominant, progressive high frequency hearing loss in humans but not the mouse [Van Laer et al., 1998]. Similarly, CCM3 maps to 3q25.2-q27, a region that includes the locus for DFNB15 [Van Camp et al.,

1997]. MRI and autopsy studies suggest that the prevalence of CCA may be as high as 0.5%, and the trait appears to be especially common among Mexican Americans where a founder effect has been documented [Gunel et al., 1996]. In family members who have had recognized or unrecognized subarachnoid hemorrhage without seizures, hearing loss could be an early sign of the disease.

Hereditary transthyretin amyloidosis is another genetic condition in which familial superficial siderosis has been documented. Recurrent subarachnoid bleeding in the syndrome is thought to be related to meningovascular amyloid deposition [Mascalchi et al., 1999]. Progressive sensorineural hearing loss is an integral part of the Muckle–Wells syndrome, another form of dominantly inherited amyloidosis that could share a common pathogenic mechanism [Gerbig et al., 1998]. Isolated examples of superficial siderosis have also been reported in patients with coexisting neurofibromatosis Type I, and Marfan syndrome (Manfredi et al., 2000; Lin and Westesson, 2001).

Several other genetically determined vascular disorders, including the Klippel–Trenaunay syndrome and hereditary hemorrhagic telangiectasia, can be associated with either sensorineural hearing loss or subarachnoid hemorrhage, and may represent additional examples of this pathogenic mechanism [Roman et al., 1978; Ishimoto et al., 2002]. In Alport syndrome, progressive nephritis and late onset hearing loss result from mutations involving one of three subunits of Type IV collagen. The resulting weakness in the basement membranes of the renal glomerular capillaries leads to chronic hematuria and ultimately renal failure. A similar involvement of the cerebral arteries has been invoked to explain the association of cerebral aneurysm with Alport syndrome [Vaicys et al., 2000]. It seems possible that the involvement of small vessels on the surface of the brain could lead to the chronic extravasation of red cells into the subarachnoid space. Alternatively, localized hemorrhage involving the capillaries of the stria vascularis could lead to hearing loss. Epstein syndrome (ES), Fechtner syndrome (FS), Sebastian syndrome (SS), the May–Hegglin anomaly (MH), and DFNA17 are all caused by allelic mutations of MYH9, a non-muscle myosin, on 22q11.2 [Lalwani et al., 2000; Seri et al., 2003]. In ES and FS, features of Alport syndrome, including progressive hearing loss, hematuria, and nephritis occur in association with macrothrombocytopenia, a prolonged bleeding time, epistaxis and ecchymoses. Leukocyte inclusions are also seen in FS but not ES. In SS and MH, only the hematologic features are seen, but the leukocyte inclusions differ in their morphology [Brodie et al., 1992]. Similar to the proposed pathogenesis of Alport syndrome, a different cause for either localized or subarachnoid hemorrhage could account for the hearing loss in these syndromes. Thrombocytopenia is also one of the best predictors of hearing loss in children with congenital cytomegalovirus infection, suggesting that prenatal subarachnoid hemorrhage might well be considered as a possible explanation for a delayed onset of hearing loss in these infants [Rivera et al., 2002]. Finally, several distinct forms of non-syndromic, late onset high frequency hearing loss have been identified, including DFN 6, DFNA 5, DFNA 17, and DFNA 20, in which nothing is known about the pathogenesis.

In our case, audiologic studies revealed a mild high frequency loss in the mother of the proband. In a similar case seen at Baylor, a family history of hearing loss was also noted [Reddy, 1995]. Clinical geneticists should consider superficial siderosis as a possible cause for late onset progressive hearing loss even in the absence of recognized intracranial bleeding. The diagnosis can readily be confirmed or excluded with a T2 weighted MRI.

Current treatment for superficial siderosis involves identification and correction of the source of subarachnoid bleeding.

When a specific bleeding site can be found, surgical intervention may be indicated. Avoidance of anticoagulants and antiplatelet medications, including aspirin, may also be indicated. Therapy with metal chelating agents, such as trientine, has been described but its efficacy remains to be established [River et al., 1994; Fearnley et al., 1995; Kale et al., 2003]. Cochlear implantation has also been reported to be beneficial in select cases [Irving and Graham, 1996; Dhooge et al., 2002].

## CONCLUSION

Superficial siderosis is an increasingly recognized entity, which may be responsible for many cases of genetic as well as non-genetic deafness. It should be considered in any patient with risk factors for chronic subarachnoid bleeding, including but not limited to a personal or family history of vascular malformations, thrombocytopenia, or prior CNS surgery. We recognize the possibility that intracranial hemorrhage may contribute to the hearing loss seen in Alport syndrome, ES, FS, DFNA17, and the Muckle–Wells syndrome is highly speculative. However, speculation is always justified if it leads to new knowledge. Our reading of the literature suggests that the lack of a plausible explanation for bilateral hearing loss resulting from focal intracranial hemorrhage has contributed to the failure to recognize hearing loss as an integral part of the CCM syndrome, and possibly the etiologic role of intracranial hemorrhage in other genetic deafness syndromes that can plausibly be linked to a bleeding diathesis. If our hypothesis is correct, it seems clear that some forms of progressive, bilateral hearing loss could be caused by genes that are not even expressed in the cochlea! If the positional candidate genes selected for mutation screening were limited to those that are specifically expressed in the cochlea, the identification of genes causing deafness of this type might well be delayed.

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