

which are important in delaying or accelerating onset and duration of disease.

Supported by NIA grant AG0513C, for the University of Washington Alzheimer Disease Research Center, and grant R01-AG11762, and VA research funds.

References

1. Roses AD. Apolipoprotein E affects the rate of Alzheimer disease expression: β -amyloid burden is a secondary consequence dependent on APOE genotype and duration of disease. *J Neuropathol Exp Neurol* 1994;53:429-437
2. Goate A, Chartier-Harlin MC, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 1991;349:704-706
3. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 1995;375:754-760
4. Levy-Lahad E, Wasco W, Poorkaj P, Romano, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* 1995;269:973-977
5. Bird TD, Sumi SM, Nemens EJ, et al. Phenotypic heterogeneity in familial Alzheimer's disease: a study of 24 kindreds. *Ann Neurol* 1989;25:12-25
6. Bird TD, Lampe TH, Nemens EJ, et al. Familial Alzheimer's disease in American descendants of the Volga Germans: probable genetic founder effect. *Ann Neurol* 1988;23:23-31
7. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease. *Neurology* 1984;34:939-944
8. Van Broeckhoven C. Presenilins and Alzheimer disease. *Nature Genet* 1995;11:230-232
9. Rogaev EI, Sherrington R, Rogaev EAR, et al. Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene. *Nature* 1995;376:775-778
10. Lampe TH, Bird TD, Nochlin D, et al. Phenotype of chromosome 14-linked familial Alzheimer's disease in a large kindred. *Ann Neurol* 1994;36:368-378
11. Levy-Lahad E, Lahad A, Wijsman EM, et al. Apolipoprotein E genotypes and age of onset in early-onset familial Alzheimer's disease. *Ann Neurol* 1995;38:678-680
12. Sorbi S, Nacmias B, Forleo P, et al. Epistatic effect of APP717 mutation and apolipoprotein E genotype in familial Alzheimer's disease. *Ann Neurol* 1995;38:124-127
13. Hardy J, Houlden H, Collinge J, et al. Apolipoprotein E genotype and Alzheimer's disease. *Lancet* 1993;342:737-738
14. Van Broeckhoven C, Backhovens H, Cruts M, et al. APOE genotype does not modulate age of onset in families with chromosome 14 encoded Alzheimer's disease. *Neurosci Lett* 1994;169:179-180
15. St George-Hyslop P, McLachlan DC, Tuda T, et al. Alzheimer's disease and possible gene interaction. *Science* 1994;263:537

Surgical Management of Superficial Siderosis Following Cervical Nerve Root Avulsion

Stephen J. Tapscott, MD, PhD,* Joseph Eskridge, MD,† and Michel Kliot, MD‡

Neurosensory hearing loss, ataxia, spastic paraparesis, sphincter dysfunction, somatosensory disturbances, and cognitive effects are associated with superficial siderosis of the central nervous system caused by chronic intrathecal bleeding. We describe superficial siderosis that developed more than a decade following traumatic brachial nerve root avulsion. While cerebrospinal fluid analysis indicated chronic intrathecal bleeding, angiography did not localize a specific source. Surgical intervention that included repair of a meningeal diverticulum and venous cauterization resulted in overall reduction, but not complete elimination, of central nervous system bleeding.

Tapscott SJ, Eskridge J, Kliot M. Surgical management of superficial siderosis following cervical nerve root avulsion. *Ann Neurol* 1996;40:936-940

Chronic recurrent subarachnoid bleeding can result in the deposition of hemosiderin in the leptomeninges and subpial layers of the brain, a condition termed "superficial siderosis of the central nervous system" (CNS) [1, 2]. Associated with superficial siderosis is a clinical syndrome that includes neurosensory hearing loss, ataxia, spastic paraparesis, sphincter dysfunction, somatosensory disturbances, and cognitive effects [3-5]. Chronic exposure of the brain to hemoglobin, heme, and its products in the cerebrospinal fluid (CSF) results in sequestration of hemosiderin in glia and microglia cells, and there appears to be direct cellular toxicity, perhaps related to the accumulation of ferritin and free radical damage by ferric ions [6-8]. The ability of magnetic resonance imaging (MRI) to image ferritin deposits has significantly aided the premorbid diagnosis of superficial siderosis, and several reports have demonstrated superficial siderosis as a consequence of chronic or recurrent subarachnoid bleeding due to ruptured an-

From the *Division of Clinical Research, Fred Hutchinson Cancer Research Center and Department of Medicine; †Departments of Radiology and Neurosurgery; and ‡Department of Neurological Surgery, University of Washington, Seattle, WA.

Received Mar 20, 1996, and in revised form Jun 14. Accepted for publication Jun 19, 1996.

Address correspondence to Dr Tapscott, Fred Hutchinson Cancer Research Center, Room C3-168, 1124 Columbia Street, Seattle, WA 98104.

Date	Color	RBC #1 ^b	RBC #4 ^c	WBC	Protein (mg/dl)	Glucose
11/84	Xanochromic		260	2	75	49
12/90	Xanochromic		1,610	10	66	52
3/93	Xanochromic	3,520	2,460	0	56	52
8/93, cervical	Clear		340	5	42	54
8/93, lumbar	Clear		39	<1	64	57
1/94 ^a	Clear	22	1	1	58	60
7/94 ^a	Clear	20	64	3	65	60
11/94 ^a	Clear	170	138	1	65	64

^aSamples following surgery.

^bFirst tube of cerebrospinal fluid.

^cFourth tube of cerebrospinal fluid.

eurysms, vascular malformations, tumors (particularly spinal cord ependymomas), and nerve root avulsions [9–13]. While iron chelation therapy has been attempted experimentally, it has not been successful and there is no effective medical treatment currently available.

The surgical treatment of superficial siderosis depends on identifying and neutralizing the source of bleeding; however, in nearly half of the reported patients a specific source of bleeding could not be identified, possibly because of a relatively slow rate of bleeding or episodic bleeding. In a recently reported patient with superficial siderosis following a stretch injury to the brachial plexus, imaging studies were unable to identify a source of bleeding, yet surgical repair of an associated meningocele and electrocoagulation of a hyperemic arachnoid-medullary scar pad identified at surgery resulted in cessation of CNS bleeding as determined by CSF analysis [9]. Therefore, in the absence of an identified source of bleeding, surgery may be beneficial in patients in whom there is a presumptive region of bleeding.

We report a similar case of superficial siderosis following an avulsion injury of the brachial plexus in which imaging studies were not adequate to demonstrate a source of bleeding. Surgical intervention that included repair of a meningeal diverticulum and venous cauterization resulted in overall reduction, but not complete elimination, of CNS bleeding. Because of the debilitating and progressive nature of superficial siderosis, early surgical intervention should be considered in patients in whom a likely area of bleeding exists, even if imaging studies fail to identify a specific source.

Case History

At the age of 23 the patient was in a motor vehicle accident and sustained a traumatic injury to his right brachial plexus that resulted in occlusion of the right subclavian artery and

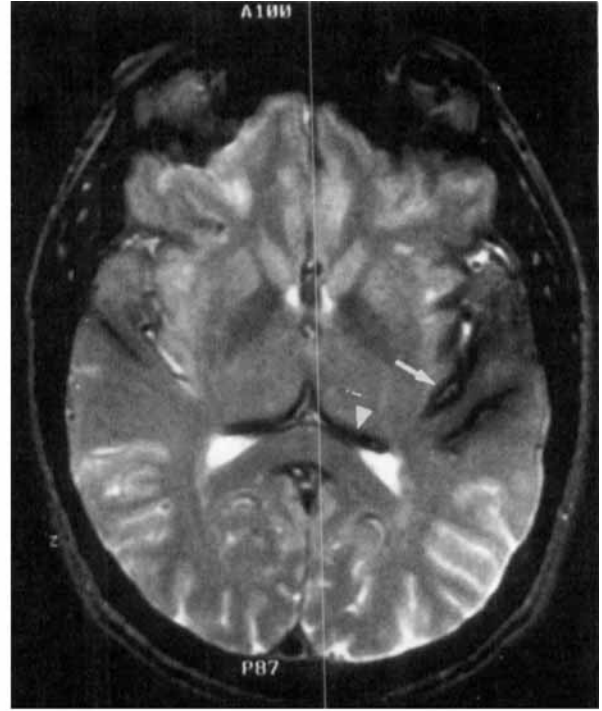
avulsion of the right C5–8 nerve roots. At age 39 he had the insidious onset of tinnitus and sensorineural hearing loss, followed by imbalance and poor fine-motor coordination. At age 41 he began to have stereotypical episodes of *déjà vu*, confusion, and lethargy that were consistent with complex partial seizures and controlled by valproic acid. An electroencephalogram (EEG) and computed tomography (CT) scan of the head were normal, but a lumbar puncture showed xanthochromic fluid with 260 red blood cells (RBCs) and a protein level of 75 mg/dl (Table). The hearing loss and coordination difficulties slowly progressed. Additional deficits of diminution of taste and smell, distal and perirectal sensory loss, urinary retention, constipation, impotence, and mild cognitive difficulties occurred over the next 4 years.

At age 46 he was referred to the Neurogenetics Clinic at the University of Washington for evaluation of presumptive spinocerebellar degeneration. At that time his cranial nerve examination was notable for pale optic discs, coarse lateral nystagmus, and dysmetric saccades. His right arm was plegic secondary to the prior brachial plexus injury. He had lower extremity spasticity with increased deep tendon reflexes, ankle clonus, and Babinski's reflexes. There were mild sensory deficits in the lower extremities and perirectal region. The left arm showed mild dysmetria and his gait was wide based and slightly ataxic.

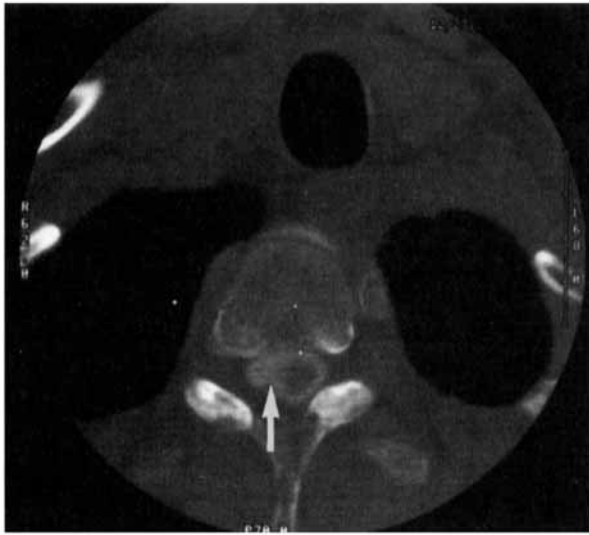
Magnetic resonance imaging (MRI) revealed superficial siderosis at the base of the brain manifested as a very-low-signal rim surrounding the midbrain, brainstem, cerebellar folia, and sylvian fissures (Figs A, B). The origin of the eighth cranial nerve at the brainstem was also involved, but the optic nerve and optic chiasm were not affected. In addition, there was volume loss of the cerebellum, medulla, and cervical and upper thoracic regions of the cord. There was moderate atrophy of the thoracic and lumbar regions of the cord with diffuse siderosis that spared the cauda equina. A CT myelogram of the spinal canal showed a meningeal diverticulum involving what are presumed to be avulsed C5–T1 right spinal nerve roots, but no evidence of a vascular malformation (Figs C, D). Spinal and cerebral arteriography showed no evidence of aneurysm or arteriovenous malformation. Baseline somatosensory-evoked response recordings used to monitor the patient during the spinal angiogram showed significant delays of the scalp responses to tibial and median



A



B



C



D

MRI and CT studies demonstrating superficial siderosis and pseudomeningocele. (A) Axial MRI through the skull base reveals classic signs of superficial siderosis. The arrow points to the black rim of hemosiderin deposition that surrounds the brainstem. (B) Axial MRI shows the black rim of hemosiderin deposition in the sylvian fissure (arrow) and around the thalamus (arrow-head). (C) CT myelogram at the C5-6 level shows the pseudomeningocele (arrow). (D) CT myelogram at the C5-6 level shows the extent of the contrast extravasation (arrow) in the region of the avulsed cervical root.

nerve stimulation, indicating a delay within the posterior columns and medial lemniscus pathways. A technetium-labeled RBC scan did not reveal any source of bleeding into the spinal canal. The potentially episodic nature of the bleeding was demonstrated by simultaneous sampling of cervical and lumbar CSF (see Table). At that time, the CSF was not xanthochromic, but did demonstrate a higher abundance of RBCs in the cervical region, consistent with an episodic source of bleeding in the cervical region. It should be noted that spectrophotometric analysis of CSF, although not utilized in this patient, is both more sensitive and accurate than visual inspection in determining hemoglobin content [14–16].

Because of the relentless progression of the patient's symptoms, at the age of 48 he underwent a C5–T2 posterior laminectomy and intradural exploration to identify the source of bleeding. The CSF was mildly xanthochromic and the cord and adjacent dura were tinged yellow, presumably from hemosiderin. The right side of the spinal cord was adherent to the dura and a meningeal diverticulum was present at the right C-5 level, with a large vein on the posterior wall of the cavity. The adhesions were released and the vein cauterized. A second large vein coursed longitudinally along the dorsal midline of the spinal cord but was left intact.

The patient's condition slightly deteriorated immediately following surgery, with increased imbalance that required use of a cane for ambulation. His gait gradually improved to the baseline condition and he was clinically stable for the subsequent 2.5 years. Subsequent to surgery, the CSF remained clear and while an abnormal increase in RBCs persisted, there was a decline from the levels seen preoperatively (see Table).

Discussion

While it has been both clinically and experimentally demonstrated that chronic intrathecal bleeding leads to hemosiderin deposits and CNS damage, the pathophysiology is only partly understood. In an experimental model of intrathecal blood injection in rabbits, relatively early responses include an increase in the number and size of the ferritin-expressing microglia in the cerebellar molecular layer [8]. Since the total number of microglia remained unchanged, this presumably reflected increased ferritin production in response to iron released from the hemoglobin. Bergmann's glia also synthesize ferritin and related iron-binding proteins and may take up iron directly from the CSF [6–8]. Chronic changes show iron deposits extending 1 to 2 mm into the brain parenchyma, largely restricted to microglia and Bergmann's astrocytes. In the cerebellum, gliosis and thinning of the molecular layer have been demonstrated in human pathology material [4]. While increased ferritin synthesis and deposits of hemosiderin correlate with the CNS damage, the mechanism of cellular damage remains unknown. It has been postulated that ionic iron induces lipid peroxidation and subsequent tissue damage [8], in a manner similar to that proposed for free radical-induced apoptotic cell death.

In superficial siderosis, the regions directly exposed to the blood are the most effected, including the eighth cranial nerve, the cerebellum, and the spinal tracts. In the current patient, the loss of taste and smell, optic atrophy, a possible complex partial seizure disorder, and cognitive loss all indicate widespread effects of the chronic exposure to intrathecal blood. While the findings occur insidiously, the common features of hearing loss, ataxia, spastic paraparesis, and sphincter disturbances are characteristic of superficial siderosis and, in cases without a confirmed etiology, should lead to evaluation that includes CSF analysis and MRI studies.

Several reports associated superficial siderosis with previous traumatic dural injury [9, 11, 17]. Currently the only available treatment for superficial siderosis is to eliminate the source of bleeding; however, in many patients, a source of bleeding cannot be identified. This is the second report of superficial siderosis following brachial plexus injury in which a bleeding source was not clearly identified, even at the time of surgery, yet reduction of the meningocele and cauterization of tortuous veins resulted in decreased amounts of bleeding. These reports indicate that the scarring and meningocele formation associated with spinal cord injuries are susceptible to small chronic venous bleeds, and that surgical intervention can potentially decrease intrathecal bleeding and retard progression of the symptoms associated with superficial siderosis. Most compelling is the need for an early diagnosis of superficial siderosis in patients showing the characteristic signs of sensorineural hearing loss, ataxia, and spasticity, particularly in the context of prior nerve root avulsion or other significant dural trauma.

The authors would like to thank Mr Leonard Kim Eliason for his help with this report.

Addendum: Patient Commentary

This commentary was written by the patient described in this report. It is published as an editorial statement regarding the implications of the diagnosis of superficial siderosis.

Robert A. Fishman, MD
Editor

My hopes are that through ongoing medical advancements in scanning, surgical procedures, and drug therapy, as well as an overall elevation of the awareness of this rare disorder among health care professionals, superficial siderosis can be detected and controlled before significant, permanent damage is sustained. In my case, 15 years elapsed from the time of the automobile accident that caused the right brachial plexus avulsion, to the point when the first symptoms of superficial

siderosis were noticed. The first impact of this slowly progressing disorder was tinnitus in the right ear, followed by a gradual loss of hearing in that ear over 3 years. At this stage, the same pattern started developing in the left ear, and it was also during this time frame that my gait became very unsteady, and falls were increasingly common. Complete anosmia and sphincter dysfunction gradually developed. Needless to say, the very slow progression of CNS damage was definitely "taking its toll," and forced many changes in activity levels, employment, and my "quality of life."

The first "speculative diagnosis" of my condition came 23 years following my nerve root injury, and 8 years after the initial symptom of tinnitus was experienced. As indicated in the primary text of this article, that *initial diagnosis of spinocerebellar degeneration* was ruled out after a thorough review of my family history. It was at this stage that the rare disorder of superficial siderosis was suspected, and later confirmed through the use of CSF analysis and MRI.

The symptoms of superficial siderosis of the CNS are extremely slow in their progression, and mirror other "natural" physical impacts of aging in their early stages. Consequently, patients and health care professionals alike often "look past" the onset of conditions such as hearing loss, ataxia, bladder dysfunction, and diminishing smell and taste sensations, and attribute the slow, insidious development to aging. This problem is compounded when results of tests for more common neurological maladies are negative. Unfortunately, with the very slow accumulation of hemosiderin deposits and the resulting nerve tissue damage, superficial siderosis usually has progressed to a stage of irreversible CNS damage by the time it is diagnosed. From a patient's perspective, I strongly agree with the recommendations of the physicians who authored the "primary" superficial siderosis article and reported the details of my history. Early diagnosis is critical and should be considered when the triad of symptoms (neurosensory hearing loss, cerebellar ataxia, and spastic paraparesis) is present, permitting early evaluation for surgical intervention, which may be warranted even in some patients who do not have a defined source of bleeding but do have a history of local dural injury.

I am very fortunate. Even though my life has been dramatically altered as a result of the very serious impact of superficial siderosis, I have been in a health care provider environment that led to prompt referrals to neurology professionals, that sought highly qualified second opinions, that included thorough testing at numerous health care facilities, and that permitted extensive neurosurgery. Unfortunately, many patients with the symptoms of superficial siderosis never get a confirming diagnosis. Further, similar health care resources to assist in the management of this serious condition are too often not available, or are not aggressively pur-

sued. My commentary is intended to amplify the serious, debilitating nature of this ailment, and to assist in raising awareness levels among health care professionals, in hopes of shortening diagnostic intervals and promoting surgical intervention at earlier stages if there is a highly likely source of bleeding.

L. Kim Eliason

References

1. Hughes JT, Oppenheimer DR. Superficial siderosis of the central nervous system. *Acta Neuropathol (Berl)* 1969;13:56-74
2. Koeppen AH, Barron KD. Superficial siderosis of the central nervous system. A histological, histochemical and chemical study. *J Neuropathol Exp Neurol* 1971;30:448-469
3. McGee DA, Van Patter HJ, Morotta J, Olszewski J. Subpial cerebral siderosis: a report of two cases. *Neurology* 1962;12:108-113
4. Koeppen AH, Dentinger MP. Brain hemosiderin and superficial siderosis of the central nervous system. *J Neuropathol Exp Neurol* 1988;47:249-270
5. Fearnley JM, Stevens JM, Rudge P. Superficial siderosis of the central nervous system. *Brain* 1995;118:1051-1066
6. Koeppen AH, Borke RC. Experimental superficial siderosis of the central nervous system. I. Morphological observations. *J Neuropathol Exp Neurol* 1991;50:579-594
7. Koeppen AH, Hurwitz CG, Dearborn RE, et al. Experimental superficial siderosis of the central nervous system: biochemical correlates. *J Neurol Sci* 1992;112:38-45
8. Koeppen AH, Dickson AC, Chu RC, Thach RE. The pathogenesis of superficial siderosis of the central nervous system. *Ann Neurol* 1993;34:646-653
9. Bonito V, Agostinis C, Ferraresi S, Defanti CA. Superficial siderosis of the central nervous system after brachial plexus injury. *J Neurosurg* 1994;80:931-934
10. Gomori JM, Grossman RI, Bilaniuk LT, et al. High-field MR imaging of superficial siderosis of the central nervous system. *J Comput Assist Tomogr* 1985;9:972-975
11. Bracchi M, Savoirdo M, Triulzi F, et al. Superficial siderosis of the CNS: MR diagnosis and clinical findings. *AJNR* 1993;14:227-236
12. Rourgouin PM, Tampieri D, Melancon D, et al. Superficial siderosis of the brain following unexplained subarachnoid hemorrhage. *Neuroradiology* 1992;34:407-410
13. Gomori JM, Grossman RI, Goldberg HI, et al. High-field spin-echo MR imaging of superficial and subependymal siderosis secondary to neonatal intraventricular hemorrhage. *Neuroradiology* 1987;29:339-342
14. Beetham R. Spectrophotometric examination of CSF for xanthochromia. *Lancet* 1992;339:1492 (Letter)
15. Wong SS, Schenkel OJ. Quantification of plasma hemoglobin in the presence of bilirubin with bilirubin oxidase. *Ann Clin Lab Sci* 1995;25:247-251
16. Trbojevic-Cepe M, Vogrinc Z, Brinar V. Diagnostic significance of methemoglobin determination in colorless cerebrospinal fluid. *Clin Chem* 1992;38:1404-1408
17. Fishman RA. Superficial siderosis. *Ann Neurol* 1993;34:635-636