

Superficial Hemosiderosis of the Central Nervous System

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Summary: Superficial hemosiderosis (SH) of the CNS is a rare disease caused by repeated subarachnoid hemorrhage, with progressive superficial siderosis of the CNS. We report a patient with SH whose clinical picture was marked by progressive gait ataxia, hearing loss, dysarthria, and recurrent episodes of hemifacial spasm. Iron and ferritin levels in the CSF were significantly higher than in a control group of patients. Six month's treatment with the iron-chelating agent trientine dihydrochloride led to clinical improvement, with a concomitant reduction of CSF iron level. We suggest that, in addition to magnetic resonance imaging findings, CSF levels of iron and ferritin should be used as diagnostic criteria for SH, as well as to estimate the efficacy of iron chelation treatment. **Key Words:** Superficial hemosiderosis of CNS—Gait ataxia—Hemifacial spasm—CSF iron—CSF ferritin—Iron chelation.

Superficial hemosiderosis (SH) of the CNS is a rare condition, with only 49 cases reported in the literature (1–5). The clinical manifestations of SH are remarkably consistent and include cerebellar signs, hearing loss, and spastic quadriparesis (6,7), at times accompanied by dementia and sphincter disturbances (7–9). In about half of the reported cases, the etiology was recurrent subarachnoid hemorrhage secondary to a vascular malformation, tumor, or posthemispherectomy (1–9). However, in some patients the cause is unknown.

Most of the reported cases were diagnosed at autopsy. Extensive deposition of hemosiderin was found in the leptomeninges, subpial tissue, cerebellum, cranial nerves, and spinal cord (1,3,6,7). An animal model of SH was induced by repeated subarachnoid injections of iron-containing salts or blood (10,11). In both human and experimental SH, the CSF is typically xanthochromic and rich in protein (1,6,10). MRI findings in patients with SH were published (2,5,12). T2-weighted images consistently showed marginal hypointensity involving several

parts of the CNS. In this article, we describe a patient with SH who presented with a progressive movement disorder.

CASE REPORT

A 47-year-old man presented with a 5-year history of progressive speech disturbance and unsteadiness of gait with recurrent falls. The patient complained of occasional involuntary closure of his left eye, which was frequently followed within 5–20 s by spasm of the mouth and cheek on the left side of his face. This phenomenon began after the patient tried to open his mouth or close his eyes, and then repeated itself several times an hour, each time lasting a few minutes. Physical effort or stress aggravated and sometimes precipitated the contractions. In addition, the patient suffered from hearing loss and deterioration of memory.

At the age of 13, he had undergone complete resection of a tumor that occupied the right cerebellar hemisphere and part of the vermis. The tumor was identified as an "astroblastoma." The patient had received an unknown dose of irradiation to the posterior fossa. According to the medical records, he was free of symptoms and had had no neurological deficits for 28 years.

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On examination, recurrent episodes of left hemifacial spasm were observed. Such episodes involved either sequential or simultaneous contractions of the orbicularis oculi, procerus, zygomatic, and mentalis muscles. These lasted a few minutes and remitted spontaneously.

Cranial nerve examination disclosed bilateral horizontal nystagmus, decreased hearing on both sides, and dysarthria. Tendon reflexes were hyperactive, and the Babinski sign was elicited on the right. The gait was markedly ataxic, with a tendency to fall backwards and to the left. Finger-to-nose and heel-to-shin tests were also significantly disturbed bilaterally. Cognitive examination and the Florida Mental Status Examination showed impaired short-term verbal recall and recognition. Right eye inferior quadrantanopsia was detected.

Routine blood tests (CBC, SMAC-12) were normal. Endocrine function tests, and levels of vitamin E, vitamin B₁₂, folic acid, and thiamine were all within normal limits. Tests for antinuclear factor, HIV, and VDRL were negative. Serum iron was 15.7 $\mu\text{mol/L}$ (normal, 14–29 $\mu\text{mol/L}$), iron binding capacity 46.5 $\mu\text{mol/L}$ (normal, 44–62 $\mu\text{mol/L}$), and serum ferritin levels 71 $\mu\text{g/L}$ (normal, 15–300 $\mu\text{g/L}$). Lumbar puncture showed acellular xanthochromic fluid under normal pressure. CSF protein content was 95 mg/dL (normal, 15–60 mg/dL), and CSF glucose was 3.2 mmol/L (blood glucose, 5.1 mmol/L). CSF protein electrophoresis revealed a monoclonal IgG band that was not detected in the serum.

Iron levels in CSF were 6.9 $\mu\text{mol/L}$. The average level of iron in a control group of 20 patients was 1.6 ± 1.2 $\mu\text{mol/L}$. CSF ferritin levels were 62 $\mu\text{g/L}$ (control, 3 ± 1.56 $\mu\text{g/L}$). CSF and blood ferritin levels were measured by an enzyme-linked immunosorbent assay (13). CSF and blood iron levels were measured according to accepted recommendations (14).

Audiometry demonstrated bilateral sensory neural hearing loss, with an increased hearing threshold to 35 dB between 2,000 and 8,000 Hz. EEG was normal, and visual evoked potentials showed a normal latency of P100 wave. Brain stem auditory evoked potentials were bilaterally abnormal, with a prolongation of the first to sixth interwave latency of >5.4 ms (normal, <5 ms). CT scan revealed symmetric atrophy of the cerebellum. An MRI scan performed before and after intravenous administration of gadolinium showed on T1- and T2-weighted images severe atrophy of the cerebellum (Fig. 1). The T2 images were remarkable for the marginal hy-

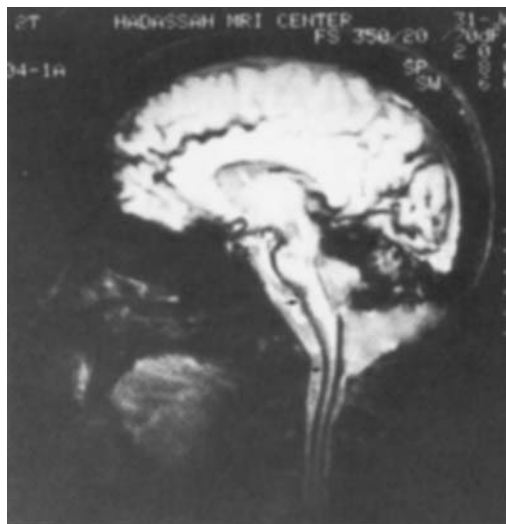


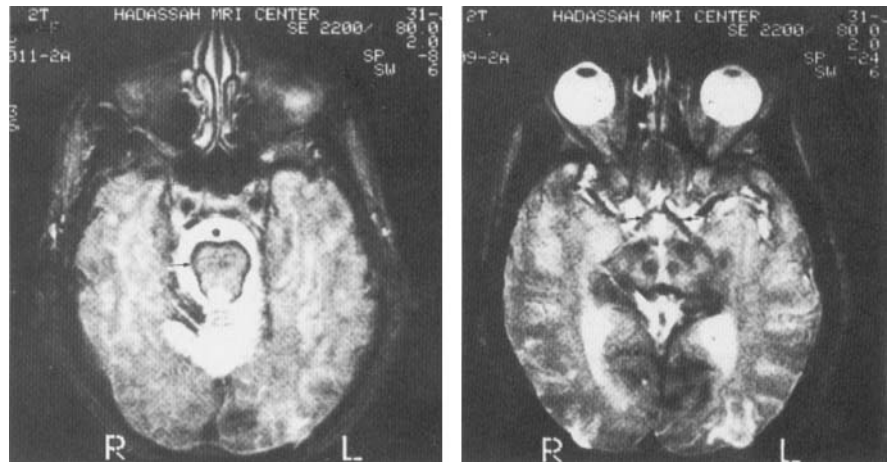
FIG. 1. Sagittal gradient echo 350/20/70 (TR/TE/Flipangle) scan showing marked cerebellar and vermian atrophy with tonsillar preservation. The T2 sensitivity of the gradient echo scan shows hemosiderin deposits as a black coating of the cerebellum, brain stem, and cervical cord (arrows).

pointensity involving the cerebellum, spinal cord, optic tracts, and brain stem (Fig. 2). A vertebral angiography demonstrated the absence of both posterior inferior cerebellar arteries, but was otherwise normal.

The patient was treated with an iron-chelating agent, trientine dihydrochloride, 2 g/day. Other than a very mild iron deficiency anemia, there were no adverse effects. Within 6 months of therapy, the troubling episodes of hemifacial spasm disappeared completely. During a follow-up period of 2 years, there was no further deterioration in his neurological condition. Although repeated MRI and brain stem auditory evoked potentials continued to show the original pathology, CSF examination showed a marked improvement, with a reduction of iron levels to 3 $\mu\text{mol/L}$ and ferritin levels to 55 $\mu\text{mol/L}$.

DISCUSSION

Our patient is noteworthy for his unique movement disorder, which consisted of progressive ataxia and recurrent attacks of hemifacial spasm. Ataxia is the salient feature of the gait disturbance in patients with SH, probably because the cerebellum is severely affected. To the best of our knowledge, previous reports have not described an association between SH and facial nerve palsy or hemifacial spasm that was possibly the result of hemosiderin deposition around the proximal part of the facial nerve. It is significant that this spasm



A,B

FIG. 2. T2-weighted axial spin echo scan (TR 2,200 ms/TE 80 ms) showing hemosiderin deposits as a hypointense coating of the brain stem (A, arrow) and optic tracts (B, arrows).

completely resolved after the initiation of chelation treatment.

When presented with a patient with SH, a thorough search to locate the intracranial or spinal source of bleeding must be made, because failure to detect the bleeding source and eradicate it is associated with a poor prognosis (1,6). In order to arrest the progression of the disease in patients without a bleeding source, several treatments have been proposed, including iron chelation, CSF shunting, and heme oxygenase inhibitors (3,15). The iron-chelating agent chosen was trientine dihydrochloride, which was previously suggested by Koeppen and Dentinger (3). This drug is known for its strong affinity to both iron and copper, and its lack of serious side effects (16). It probably reaches the CSF through the source of subarachnoid bleeding or through a disrupted blood-brain barrier.

Although the efficacy of chelation treatment is disputed (15), our preliminary impression is that the drug has had a beneficial effect in stabilizing the patient's condition and reversing some of the symptoms over a relatively short period of time.

Until recently, the diagnosis of SH was confirmed at autopsy. In the past few years, MRI was used in the differential diagnosis of SH patients (2,12). In the current report, MRI scan showed marginal hypointensity of the cerebellum, spinal cord, optic tracts, and brain stem. We also measured iron concentrations in the CSF to further support the diagnosis. Following our preliminary report (17), Willeit et al. (18) described high CSF levels of iron and ferritin in three SH patients. Their results concur with our observations that a beneficial clinical response to treatment is associated with a significant reduction of CSF iron and ferritin. However,

this is a controversial issue, and recently Koeppen et al. (15) suggested that changes in CSF constituents need not occur during the development of SH.

High CSF levels of iron or ferritin are not unique to SH; they were also described in patients with neuronal ceroid—lipofuscinosis (19) and in both malignant and inflammatory involvement of the CNS (20). Human CSF contains small amounts of low molecular weight iron, which serves as a catalyst in the formation of free radicals (21). Because part of the iron in CSF is bound to transferrin, the potential for hydroxyl radical production is much reduced (22).

It has been suggested that high iron and ferritin levels in CSF have a central role in the pathogenesis of SH (10). It is plausible that the destruction of the superficial layers of the cortex is caused by the activation of lipid peroxidation, catalyzed by high levels of iron (23). Other toxic effects to the brain might be the result of heme split products (15).

The sites most severely affected in SH are the cerebellum, eighth cranial nerve, spinal cord, and cerebral cortex (2,3,26). Koeppen et al. (3,25) suggested that the selective vulnerability of cerebellar cortex and the eighth cranial nerve stems from their unique ability to biosynthesize ferritin in response to increased iron or heme concentrations.

By binding to iron, ferritin usually serves to minimize the amount of free iron within cells and the extracellular space. However, under oxidative stress, ferritin can release iron (24) and potentially aggravate damage to the nervous tissue.

Under normal conditions ferritin, iron and transferrin are specifically located in oligodendroglia. These cells apparently mediate iron mobilization and storage in the human brain (27,28). In contrast,

most of the iron in the brains of patients with SH is stored as hemosiderin in Bergmann glia cells and microglia (3,25); this may cause some of the damage to the nervous tissue.

Our observation suggests that CSF iron and ferritin levels may be useful as an additional diagnostic criterion for SH and as a possible method to evaluate the efficacy of different treatment approaches. We believe that a further trial with chelation treatment is warranted in a selected group of patients.

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