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Superficial siderosis of the central nervous system: a case with an unruptured intracranial aneurysm

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Abstract
We present a case of superficial siderosis (SS) of the central nervous system (CNS) with an unruptured intracranial aneurysm to illustrate that the commonly encountered unexplainable progressive sensorineural hearing loss (SNHL) can be an important sign for the early awareness of this rare disorder. The literature on SS is reviewed and the pathogenesis of SS is discussed.

Key words: Siderosis, superficial; Haemosiderin; Hearing loss, sensorineural; Magnetic resonance imaging

Introduction

The rarely encountered superficial siderosis (SS) was first described by Noetzel (1940), and characterized by deposition of haemosiderin on the surface of the brain, cerebellum, brain stem, cranial nerves and spinal cord. Superficial siderosis may manifest itself as a progressive sensorineural hearing loss (SNHL), cerebellar dysfunction, pyramidal tract signs, or mental retardation (Hughes and Oppenheimer, 1969; Koeppen and Barron, 1971; Revesz *et al.*, 1988; Willeit *et al.*, 1992). The marked hypointensity, caused by the magnetic susceptibility effect of the iron of haemosiderin deposits in the pial and arachnoid membranes, on the T_2-weighted magnetic resonance imaging (MRI) makes diagnosis of SS noninvasively (Gomori *et al.*, 1985; Gomori *et al.*, 1987). Since the VIIIth cranial nerve (CNVIII) is vulnerable to the toxic effects of the haemosiderin (Koeppen and Dentinger, 1988), an unexplainable progressive SNHL can be one of the signs for early awareness of SS. Besides eliminating the causative bleeding source, the use of iron chelating agents in SS patients with no evident bleeding source may be another choice for the management of this condition.

Case report

A 63-year-old woman was referred to our department in January 1993 complaining of bilateral progressive hearing loss of about four years duration. She had suffered from unsteadiness of gait for about seven years. As time passed, numbness appeared in the lower legs, dizziness, bilateral tinnitus, and bilateral hearing loss. During the last three years there had also appeared progressively disorders of taste and smell, constipation, and a neurogenic bladder. A feeling of nausea and dizziness, but without true vertigo also developed. No history of previous head injury could be obtained. Physical examination revealed spastic paraparesis, sensation disorder, positive Babinski sign, and increased deep tendon reflex in both lower extremities. Romberg's test was positive and Mann's test was abnormal. Bilateral gaze nystagmus, enhanced with ocular fixation and reduced by eye closure, was observed. Electronystagmography (ENG) demonstrated left eye beating nystagmus when the patient was in her left lateral position. Tracking test revealed a wandering, inaccurate tracking movement. Optokinetic test showed decreased response intensity in both fast and slow phases. Caloric test gave no response bilaterally. The tympanic membranes appeared normal, but the pure tone audiometric examination showed bilateral moderate to severe SNHL (Figure 1) with good speech discrimination. Laboratory data showed no specific disorder, except a trace of red blood cells (RBC) found on repeated cerebrospinal fluid (CSF) examinations. Atrophy of cerebrum and cerebellum was

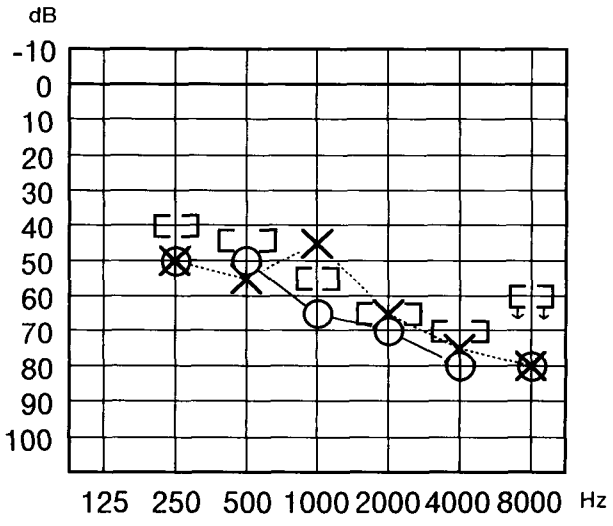

FIG. 1
Pure tone audiogram.

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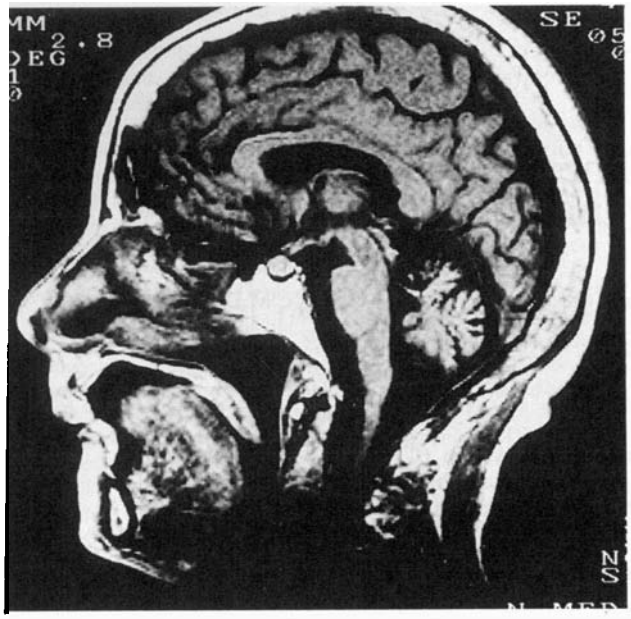

FIG. 2
Saggital MRI showing atrophic changes of the cerebrum and cerebellum.

found on CT scan and MRI (Figure 2). T_2-weighted MRI showed diffused hypointensity around the surface of cerebrum, brain stem, cerebellum, and spinal cord (Figure 3). The diagnosis was made by this specific T_2-weighted MRI finding. An aneurysm from the left internal carotid artery located just posterior to the ophthalmic artery was found on cranial angiography (Figure 4). The patient underwent an intracranial surgical exploration for the aneurysm. During the operation, the brain surface was found to be a brownish colour, but the aneurysm was found to be unruptured. Since the aneurysm remained unruptured, it was not considered to be directly concerned with the cause of haemosiderin deposition in this patient. For this so-called 'idiopathic superficial siderosis', no effective treatment was obtained as yet but the patient was followed-up.

Discussion

Superficial siderosis of the CNS is rare, and is usually diagnosed at necropsy or during an operation. This disease is characterized by the deposition of haemosiderin on the leptomeninges and subpial tissue secondary to repeated haemorrhages from intracranial tumours (especially ependymoma), cerebral trauma, intracranial haematoma, vascular malformation, meningitis haemorrhagica, and secondary to hemispherectomy (Willeit *et al.*, 1992). But in nearly one quarter of the patients, the bleeding source is

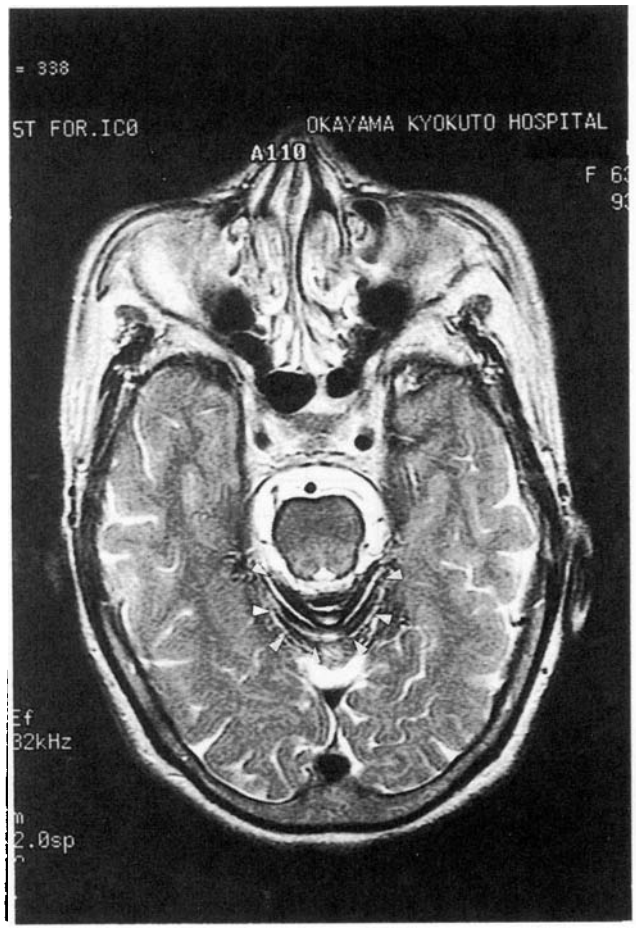

FIG. 3
Axial T_2-weighted MRI showing diffused hypointensity around the surface of the CNS, especially on the surface of the cerebellum (arrowheads).

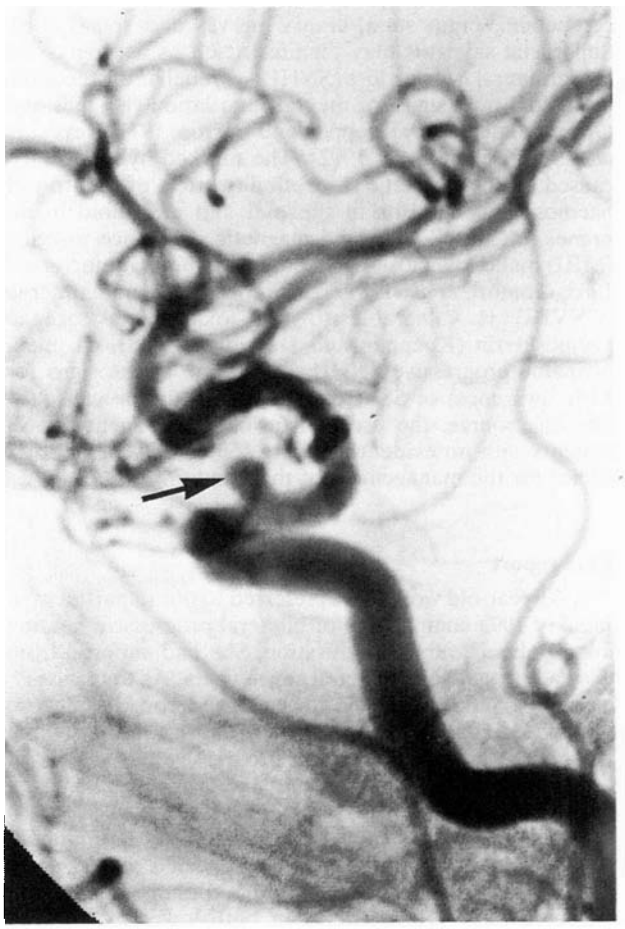

FIG. 4
Digital subtraction angiography of the left common carotid artery showing an aneurysm from the left internal carotid artery (arrowed).

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unknown (Hughes and Oppenheimer, 1969; Katsuragi *et al.*, 1988).

In our case, although there was a vascular aneurysm and a trace of red blood cells could be found in the CSF, since the aneurysm remained unruptured, the actual bleeding source still could not be well defined. For this so-called 'idiopathic superficial siderosis', the increased permeability of the meningeal arteries with passage of red blood cells into the CSF may be a reasonable hypothesis (Bracchi *et al.*, 1993). Some authors (Fukiyama *et al.*, 1993) suggested the possibility of an hereditary factor in this disease, but we did not find any evidence of a possible hereditary family history in this patient. In advanced cases, the progressive cerebellar ataxia, SNHL, and myelopathy are very characteristic clinical manifestations (Koeppen and Dentinger, 1988). But with its progressive character and the combined CNS dysfunctions superficial siderosis may mimic senile dementia. Also the progressive SNHL may just be considered as presbycusis, especially in aged patients. Hughes and Oppenheimer (1969) and Willeit *et al.* (1992) have mentioned xanthochromic viscous CSF rich in protein as the cardinal sign of SS. But in our patient the trace of red blood cells in the CSF was of no specific diagnostic value. In the pathogenesis of the tissue destruction which accompanies SS of the CNS, haemosiderin may be less important than iron-catalysed lipid peroxidation (Koeppen *et al.*, 1992). To investigate the by-products of the iron-catalysed lipid peroxidation and the changes in the associated enzyme proteins may be another way in which to approach this disease.

The pathogenesis of SS in the nervous system has been elucidated by Koeppen and Dentinger (1988), and by Koeppen and Borke (1991) using immunocytochemistry. Due to the tightness of the blood-brain barrier for iron, systemic iron overloaded conditions do not regularly lead to iron excess in the CNS (Koeppen *et al.*, 1992). However the free iron from persistent haemorrhagic CSF can stimulate microglia cells in the subpial parenchyma inducing an accelerated ferritin biosynthesis by depressing ferritin messenger ribonucleic acid (mRNA) (Zahringer *et al.*, 1976). Free iron and iron-containing haem pigments are taken up from CSF by Bergmann glia and stored in glial cells and macrophages in the form of iron-ferritin and this is later transformed to haemosiderin, which will cause the brown staining of the brain surface (Koeppen and Borke, 1991). This brownish stain was characteristic in our case as seen during the operation for the intracranial aneurysm. The T_2-weighted MRI findings in our case were also proved by this specific staining. When the iron-binding capacity is exceeded, the free iron will induce an iron-catalysed lipid peroxidation leading to the death of neuronal cells and parenchymal damage (Zahringer *et al.*, 1976; Schaefer and Theil, 1981; Shull and Theil, 1982; Nakano, 1993). Since most of the intracranial iron can be cleared from the CSF, true haemosiderin encrustation requires more than six months to be induced (Koeppen *et al.*, 1992). The real disorder causing SS to occur should be able to be anticipated early i.e. before the symptoms and signs of SS occur. History taking, especially about previous head injury, is very important in evaluating the SS patient. If there is no evidence of previous head injury, such as in our case, possible intracranial vascular disorders should be carefully checked. Intracranial angiography is an important examination procedure in this context.

The selective vulnerable areas of SS are the surface of brain stem, the superior vermis of the cerebellum, the brain tissue surrounding the sylvian cisterns, and the Ist, IInd and VIIIth cranial nerves (Koeppen and Dentinger, 1988). The resulting clinical manifestations may be various and non-specific including cerebellar ataxia, progressive SNHL, sphincter disturbances, sensory and motor deficits and dementia (Braham and Wolman, 1965; Hughes and Oppenheimer, 1969; Koeppen and Barron, 1971). In our patient, cerebellar dysfunction manifested itself as gait unsteadiness and bilateral gaze nystagmus. The abnormalities in the optokinetic test and tracking test may indicate brain stem dysfunction and/or dysfunction of oculomotor centres. The absence of response on caloric testing may be due to severe vestibular dysfunction. These manifestations depend on the areas of CNS involved. No previous report has mentioned the specific pattern of the audiogram in SS. In our case why the SNHL was more severe in the high tone remains to be investigated.

The early severely affected cerebellum in this patient can be explained by the high vascularity of this area, and by the fact that the Bergmann glia come into direct contact with haemorrhagic CSF which stimulates the uptake of iron and the biosynthesis of ferritin (Hajos *et al.*, 1982). The particular vulnerability to the blood by-products of the cerebellar glia compared to that of the cerebral glia may also be due to its specific ability to synthesize ferritin. The involvement of the VIIIth cranial nerve in our case was earlier than the involvement of the other cranial nerves. This special selective involvement of the VIIIth cranial nerve can be explained by its special histological structure. The transition from CNS to peripheral nervous system in the VIIIth cranial nerve is located near the internal acoustic canal rather than near the brain stem as for the other cranial nerves, except the Ist and IInd cranial nerves. Therefore, the VIIIth cranial nerve has the longest glial segment of any cranial nerve (Rasmussen, 1940; Koeppen and Dentinger, 1988; Kwartler *et al.*, 1991). In the cranial nerves, the distribution of SS corresponds to the extent of central myelin and glial cells, ending exactly where the Schwann cells begin (Koeppen and Dentinger, 1988). This long glial segment of the VIIIth cranial nerve is especially vulnerable to injury. The Ist and IInd cranial nerves are also enveloped by central myelin and glia for the whole extent of the nerve fibres in the cisterns (Tarlov, 1937). Therefore, their vulnerability can be understood.

Prior to the introduction of MRI, the conventional neuroradiological examinations in SS patients were almost normal (Willeit *et al.*, 1992), and the lack of awareness of this disease made the diagnosis more difficult. We reviewed the CT films of our case, and only atrophic changes in the CNS could be found. In advanced cases, plain CT could show high attenuation values compatible with the heavy haemosiderin encrusting on the surface of the CNS (Bracchi *et al.*, 1993). However in most cases CT examinations showed only non-specific CNS atrophic change or even demonstrated normal findings (Bracchi *et al.*, 1993). The magnetic susceptibility effect of iron and haemosiderin deposition in the marginal zones of CNS causes the MRI to show rims of hypointensity around the surface of the involved areas in all cases (Gomori *et al.*, 1985; Gomori *et al.*, 1987; Bracchi *et al.*, 1993). In particular the preferential T_2 proton relaxation enhancement caused by haemosiderin makes T_2-weighted images the most demonstrative images for SS (Gomori *et al.*, 1985; Bracchi *et al.*, 1993). Although, an intracranial haematoma may present the same findings on MRI as SS does, it can be differentiated by its localized feature.

Therapy for SS requires eliminating the source of bleeding. But if the bleeding source can not be well defined, as in our case, antioxidants and chelating substances, such as trientine dihydrochloride, might be the treatment of choice (Koeppen and Dentinger, 1988). Whether they will stop or slow down the course of the disease is not yet clearly known (Koeppen and Borke, 1991). An experimental study has illustrated that the

heavy-ferritin (HF) subunit can inhibit lipid peroxidation *in vitro* (Cozzi *et al.*, 1990), while the light-ferritin (LF) subunit can promote cerebral iron storage, followed by haemosiderin formation, as in the liver. Prolonged exposure to haemosiderin produces persistent shift of HF to LF (Koeppen *et al.*, 1992). The blockage or reversal of this shifting process may be another way in which to manage SS. The actual cellular damage caused by iron-catalysed lipid peroxidation in SS may be concerned with the formation of free radicals. The roles of antioxidants and free radical scavengers in changing the course of this disease may be an interesting subject for investigation.

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