

NEUROLOGICAL RARITIES

Superficial siderosis of the central nervous system

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Superficial siderosis of the central nervous system (CNS) is a rare disorder, which is the consequence of chronic subarachnoid haemorrhage. Brain MR scan (Fig. 1) shows a characteristic marginal low T₂-weighted signal of haemosiderin around the surface of the CNS, and has made antemortem diagnosis of this condition possible. Clinically, the cardinal features are progressive sensorineural deafness and cerebellar ataxia. Other features include myelopathy, polyradiculopathy, anosmia and dementia. The only effective way of treating the disorder is to identify the source of bleeding and remove it (Fearnley *et al.* 1995).

PATHOPHYSIOLOGY

Superficial siderosis of the CNS is a direct result

of chronic subarachnoid haemorrhage with free iron in the CSF causing a chain of events leading to neuronal death, gliosis and haemosiderin deposition. It is the chronicity of the bleeding that is crucial to the development of superficial siderosis and the syndrome does not occur after a single bleed. It takes six months for haemosiderin to appear in the animal model of the condition, where autologous red cells are injected weekly into the subarachnoid space (Koeppen & Borke 1991). It is thought that the presence of haeme in the CSF induces microglial synthesis of apoferritin, which acts as a sink for mopping up toxic free iron. It is likely that neuronal damage occurs once this system is saturated. Ferritin is formed from the binding of iron to apoferritin and aggregates of ferritin form haemosiderin.

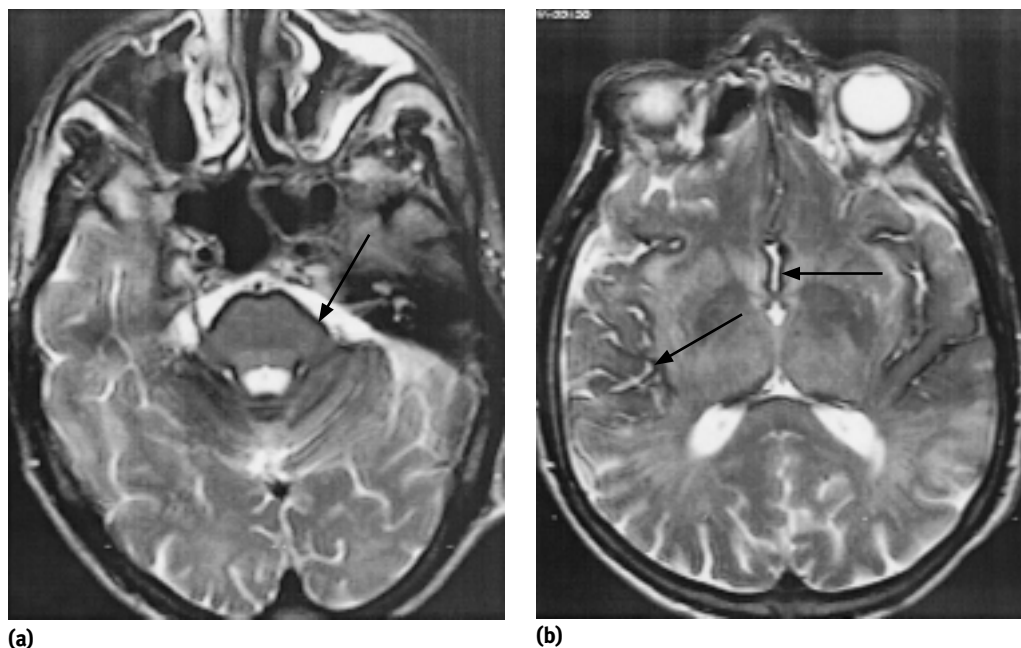


Figure 1 MR brain scan, T²-weighted image showing linear low signal (black) over (a) pons and cerebellar folia and (b) cortical surface of cerebrum due to the deposition of haemosiderin (arrows).

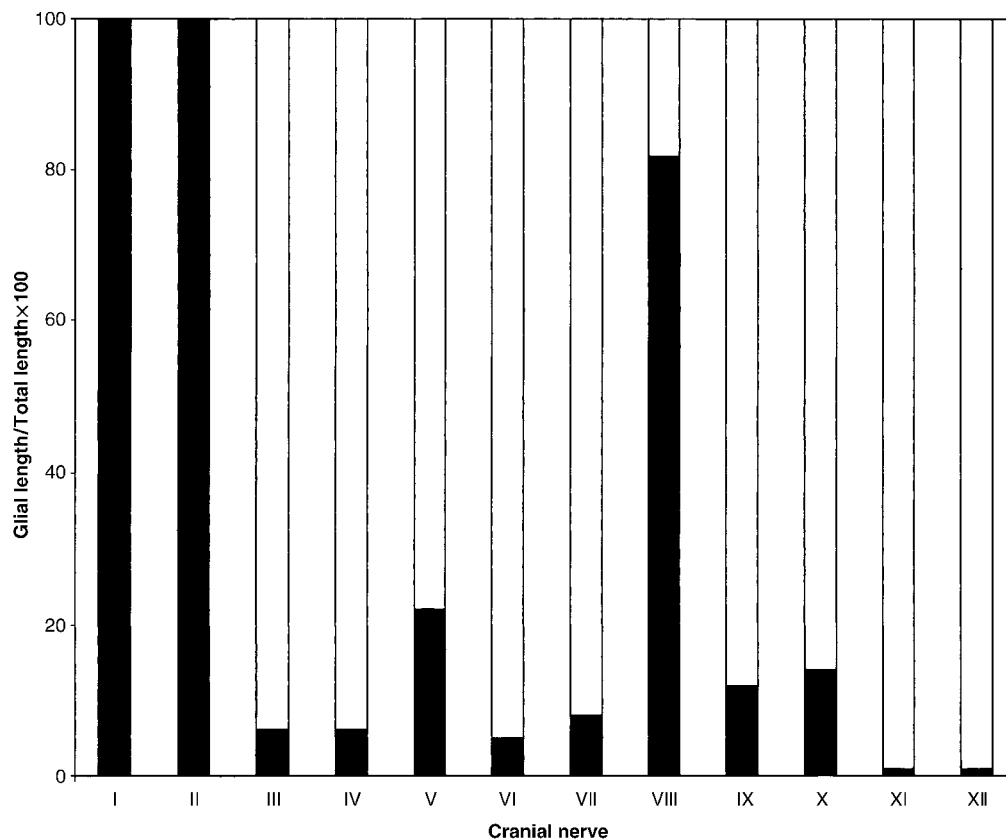
In keeping with the hypothesis that haemosiderin may be neuroprotective, is the fact that the degree of deposition does not always correlate with the amount of cell death. For instance, the deposition of haemosiderin is very high in the anterior horns of the spinal cord, but there is little loss of anterior horn cells.

Macroscopically, there is a brownish discoloration of the leptomeninges and adjacent CNS parenchyma to a depth of up to 3 mm. The parts of the central nervous system that are particularly affected are the cerebellar folia and superior vermis, basal frontal lobes, mesial temporal lobes, the cranial nerves (I, II, V, X and especially VIII), spinal cord and spinal roots. The distribution of deposition is determined by CSF exposure (proximity to the CSF and volume of CSF) and the presence of microglia thought necessary to produce apoferritin. For example, the VIIIth nerve is preferentially affected, because it has a long glial segment and it passes through the pontine cistern. The cranial nerves have a central glial portion and a peripheral component of varying proportions and it has been suggested that the length of the central component determines their vulnerability (Revesz *et al.* 1988) (Fig. 2). This appears to be contradictory if microglia and apoferritin are neuroprotective.

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The histological changes comprise haemosiderin deposition in the leptomeninges, subpial and subependymal regions. The haemosiderin is found as large granules in macrophages and macrophage casts. There is a surrounding battlefield of gliosis and the astrocytes contain intracellular ovoid bodies composed of protein and sphingomyelin.

Figure 2 Cranial nerve susceptibility in superficial siderosis of the central nervous system in relation to glial length. Relative length of the glial and peripheral segments of each cranial nerve. Open bar, peripheral nerve; closed bar, glial component. Adapted from Tarlov 1937.



THE CAUSES OF SUPERFICIAL SIDEROSIS

In most cases the causative chronic subarachnoid haemorrhage is low grade and silent, but a sizeable proportion (at the very most 40%) have a symptomatic haemorrhage with a clear-cut sudden onset of headache and meningism. The causes of superficial siderosis of the CNS are numerous and are listed in Table 1. In roughly half the patients a source of bleeding is found. The most common cause is dural pathology, in which a cavity lesion is associated with a small bleeding source such as a telangiectasia. The most striking example was seen in the operation for intractable epilepsy, hemispherectomy. The hemisphere was removed and the empty dural cavity was left in direct communication with the CSF. The dura had numerous chronic bleeding points and patients soon developed superficial siderosis of the CNS. Subsequently, the surgical technique was revised with closure and isolation of the dural cavity from the free flow of CSF. It is interesting that cervical root avulsion is a relatively frequent cause of superficial siderosis of the CNS. It is possible that trauma to the nerve root damages the fine venous plexus within the

root, or the medullary and radicular veins that run along the nerve root, resulting in a fragile vascular scar. This may then bleed following traction, as the cervical spinal cord moves on flexion and extension of the neck. Pseudomeningoceles are another potential source of bleeding, a result of trauma or surgery. There are a wide variety of dural pathologies and an example would be the report of a meningoencephalocele in a patient with neurofibromatosis type 1 secondary to sphenoidal dysplasia and herniation of the temporal lobe into the orbit. The next most common cause is the bleeding tumour and especially ependymomas. Vascular causes are far less common, although cavernomas adjacent to the subarachnoid space are increasingly reported.

CLINICAL FEATURES

There is a delay between the onset of bleeding and the appearance of the syndrome, which varies between four months and 30 years (Fearnley *et al.* 1995). In fact, some cases are diagnosed at postmortem in which there were no symptoms during life. The length of this presymptomatic phase presumably relates to whether the bleeding is continuous or intermittent, and the

amount of blood. Occasionally, superficial siderosis of the CNS can be picked up incidentally on routine brain MRI (Offenbacher *et al.* 1996). In this situation, a small proportion will be found to have early symptoms, but most will be asymptomatic. The patients with symptoms have more widely distributed haemosiderin deposition affecting the cerebral hemispheres, posterior fossa and spinal cord. It is not clear whether the asymptomatic patients are presymptomatic cases that will eventually develop the syndrome, or whether they have a static condition.

Clinically, the hallmark of superficial siderosis of the CNS is progressive sensorineural deafness with cerebellar ataxia. The absence of deafness is exceptional and should cast doubt on the diagnosis. It should be noted that sometimes the deafness is asymmetrical at the beginning. High tones are preferentially lost and the deafness progresses over a period of 1–12 years until the patient is stone deaf, or has a small island of low tone hearing. Occasionally, the patient may experience vertigo due to involvement of the vestibular component of the VIIIth nerve. Caloric and rotational testing, when performed, reveals impairment of the vestibulo-ocular reflex. The cerebellar syndrome affects gait more often than the limbs and is a major source of

disability. Some patients develop a myelopathic syndrome (17%) with a paraparesis or less frequently a quadraparesis. Pyramidal signs are frequent occurring in 75% (including myelopathy). Other features include anosmia (17%) and dementia (24%) and rarely extraocular motor palsies (IIIrd, IVth and VIth nerves). Superficial siderosis of the CNS can be complicated by hydrocephalus, but from the little experience that is available, ventricular shunting is not effective unless there is some disturbance of consciousness. The associated spinal arachnoiditis may cause troublesome backache and rarely this has been the presenting symptom. A severe cauda equina syndrome may also complicate arachnoiditis. Bladder involvement is common (24%) and may either be due to a myelopathy or polyradiculopathy.

BRAIN IMAGING

Brain MRI has revolutionized the diagnosis of superficial siderosis of the CNS. Previously, the diagnosis was usually made after death. Marginal haemosiderin deposition is shown on T₂-weighted images as a rim of hypointensity (Fig. 1), and gradient echo rather than conventional spin echo is preferable. Surface hypointensity is seen over the brainstem, anterior cerebellar

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Table 1 Causes of superficial siderosis of the central nervous system

Dural pathology
hemispherectomy
cervical root avulsion
meningocele
pseudomeningocele
Tumours
cerebral astrocytoma
oligodendroglioma
pineocytoma
medulloblastoma
ependymoma
paraganglionoma
benign meningeal melanocytoma
haemangioblastic meningioma
carcinomatous meningitis
Vascular including coagulopathy
intracranial aneurysm
arteriovenous malformation
cavernoma
subdural haematoma
transthyretin amyloid angiopathy (Mascalchi <i>et al.</i> 1999)
warfarin

hemispheres and the superior vermis and the cerebral hemispheres in the region of the basal frontal lobes, mesial temporal lobe and the Sylvian and interhemispheric fissures. As yet there is no information as to whether the pattern of haemosiderin relates to the site of the bleeding source. For example, do patients with a bleeding point in the spinal canal have greater deposition around the cord? There is usually no need to examine the CSF apart from patients presenting with symptomatic subarachnoid haemorrhage. However, it may be useful in monitoring those patients who go on to surgery for a suspected bleeding source to make sure there is no longer any further bleeding from the site. If bleeding continues then the site of bleeding may be elsewhere. In the silent bleeders, the CSF is abnormal in up to 75% with red cells (180–55 000/mm³) and/or xanthochromia. Other changes include the presence of erythrophages, siderocytes and elevated protein and ferritin and reduction of lactoferrin, an iron transport protein.

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TREATMENT

Treatment of superficial siderosis of the CNS is limited to removing the source of bleeding. All patients without an obvious bleeding source on cranio-spinal MRI must have four-vessel cerebral catheter angiography followed by spinal angiography. Disappointingly, there is no evidence that the existing deficits are reversible and the best one can hope for is to bring any further deterioration to a halt. Just half of the patients are found to have a source and this is not always amenable to surgery. In fact, there have been very few reports of successful surgical treatment. Seven cases have been described due to nerve root avulsion (Revesz *et al.* 1988), cauda equina ependymomas, benign intradural extramedullary melanocytoma, spinal pial arteriovenous malformation (AVM) and a cerebral AVM. These reports were exceptional in that they raised for the first time the thought that superficial siderosis of the CNS might be treatable and that a source of bleeding should be pursued aggressively. Unfortunately,

these reports lacked sufficient follow-up to be conclusive and there have been no epilogues. The CSF returned to normal in four cases with the disappearance of red cells, xanthochromia and/or ferritin. In a fifth case, the number of red cells fell dramatically from an average of 1400/mm³ to 100/mm³ and this patient's condition became static over a period of 2.5 years. This would suggest that the amount of iron fell below a level where it could be neutralized. Apart from this case, the clinical follow-up has been less than a year. The nerve root avulsions were associated with a hyperaemic arachnoid scar in two and a large vein in one, which was cauterized. Iron chelation so far has been unsuccessful. Trientine crosses the blood brain barrier and potentially has the ability to chelate iron in the CSF. Results have been disappointing with no hard evidence that it retards progression. Furthermore, although the CSF iron returns to normal, levels of ferritin remain elevated. No patient has been given an iron chelator via a continuous intrathecal infusion, which might be more effective.

The long-term prognosis should be guarded in the sense that patients can become very debilitated from the gait problems due to a combination of cerebellar ataxia and myelopathy. Roughly, 27% of patients become bed-bound within 1–37 years. About 10% of patients develop a severe dementia. It should be noted that these figures are skewed, because they are culled from a review of the literature that preferentially includes the worst cases (Fearnley *et al.* 1995).

REFERENCES

- Fearnley JM, Stevens JM & Rudge P (1995) Superficial siderosis of the central nervous system. *Brain*, **118**, 1051–66.
- Koeppe AH & Borke RC (1991) Experimental superficial siderosis of the central nervous system. I. Morphological observations. *Journal of Neuropathology and Experimental Neurology*, **50**, 579–94.
- Mascalchi M, Salvi F, Pirini MG *et al.* (1999) Transthyretin amyloidosis and superficial siderosis of the CNS. *Neurology*, **53**, 1498–503.
- Offenbacher H, Fazekas F, Schmidt R *et al.* (1996) Superficial siderosis of the central nervous system: MRI findings and clinical significance. *Neuroradiology*, **38**, S51–S6.
- Revesz T, Earl CJ & Barnard RO (1988) Superficial siderosis of the central nervous system presenting with longstanding deafness. *Journal of the Royal Society of Medicine*, **81**, 479–81.
- Tarlov IM (1937) Structure of the nerve root. II. Differentiation of sensory from motor roots; observations on identification of function in roots of mixed cranial nerves. *Archives of Neurology and Psychiatry*, **37**, 1338–55.