Eur Arch Psychiatry Clin Neurosci (1991) 241:57–60

European Archives of Psychiatry and Clinical Neuroscience

Superficial Siderosis of the Central Nervous System

A 37-year follow-up of a case and review of the literature

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Received November 28, 1990

Summary. The course of a patient suffering from superficial siderosis of the central nervous system for 37 years is presented and diagnostic and therapeutic approaches are evaluated. The syndrome is clinically defined by slowly progressing deafness, cerebellar ataxia, myelopathy and neuropsychological deficits in combination with recurrent xanthochromia of the cerebrospinal fluid with siderophages. The diagnosis may be confirmed by computed tomography, which shows degeneration of the cerebellar vermis, and by magnetic resonance imaging, demonstrating iron deposits on the surface of brain, brain stem and spinal cord. Therapy should seek to identify and remove the source of bleeding, since pharmacotherapy with iron-depleting drugs is of limited effectiveness.

Key words: Superficial siderosis – Chronic subarachnoid haemorrhage – Triethylenetetramine – Magnetic resonance imaging

Introduction

Superficial siderosis of the central nervous system (SSCN) is known to be the result of recurrent subarachnoid haemorrhage or persistent oozing of blood into the subarachnoid space, first described by Noetzel (1940) in a case of meningiosis carcinomatosa due to stomach carcinoma. Among other findings slowly progressive deafness was reported. Histopathologically there was ependymitis granularis of the ventricular system and the special vulnerability of the cerebellar folia with loss of Purkinje cells and proliferation of iron-loaded Bergmann glia (most pronounced in the vermis) was pointed out. In the following years a number of possible causes of SSCN were described: ependymoma (McGee et al. 1962; Tomlinson and Walton 1964; Gomori et al. 1985; Koeppen and Dentinger 1988); oligodendroglioma (Rosenthal 1958; Koeppen and Dentinger 1988); malignant glioma (Braham and Wolman 1965); pinealoma (Dastur and Sinh 1962); paraventricular haemangioblastic meningioma (Sherwin and Toll 1972); tumours at the roof of the fourth ventricle (Neumann 1948); aneurysms of cerebral arteries (Cammermeyer 1947; Hughes and Oppenheimer 1969); arteriovenous malformations (McGee et al. 1962; Pinkston et al. 1983; Koeppen and Dentinger 1988); subdural haematoma (Hughes and Oppenheimer 1969; Koeppen and Dentinger 1988); neonatal intraventricular bleeding (Gomori et al. 1987; Hughes and Oppenheimer 1969); and post-hemispherectomy (Ulrich et al. 1965; Hughes and Oppenheimer 1969).

To our knowledge, 40 cases of SSCN have been reported. A bleeding source was ascertained in 26 of them, the most common being brain tumours (mostly ependymoma), followed by hemispherectomy, aneurysms and arteriovenous malformations. Several authors failed to identify the possible cause of recurrent bleeding (Noetzel 1940; Lewey and Govons 1942; Neumann 1956; Garcin and Lapresle 1957; Braham and Wolman 1965; Castaigne et al. 1967; Hughes and Oppenheimer 1969; Katsuragi et al. 1988). The aetiology of SSCN was still uncertain in 1942 and was for the first time clearly distinguished from cerebral manifestations of haemochromatoses in 1963 by Noetzel and Ohlmeier. More recently immunocytochemical, chemical and electron-microscopic investigations of the underlying neuropathological process leading to special vulnerability of the eighth cranial nerve and the cerebellum were reported by Koeppen and Dentinger (1988). According to their findings cerebellar Bergmann glia and the eighth nerve's astrocytes are able to synthesize ferritin when stimulated by constant contact with iron in the cerebrospinal fluid (CSF). The authors discuss the possibility of ferritin incorporation into intermediate filaments (glial fibrillary acidic protein, vimentin).

We report the 37-year follow-up of a 56-year-old woman with SSCN. The diagnosis was established during lifetime by repeated xanthochromic CSF samples, typical clinical course and by magnetic resonance imaging

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(MRI). The patient suffered from slowly progressing deafness, anosmia, ageusia, cerebellar ataxia, myelopathy, spastic paraparesis and, finally, deficits of memory for recent events. The main findings of MRI in SSCN were signal extinctions on T2-weighted images, predominantly in the basal cisterns, around the fourth ventricle and on the surface of the brain stem. A source of bleeding was not found, despite extensive neuroradiological studies: repeated computed tomography (CT) and MRI of head and spine, cerebral angiography, cisternography and myelography. Therapy with the iron-depleting drugs desferrioxamine and triethylenetetramine (TETA) was instituted and continued for, so far, 2.5 years.

Case report

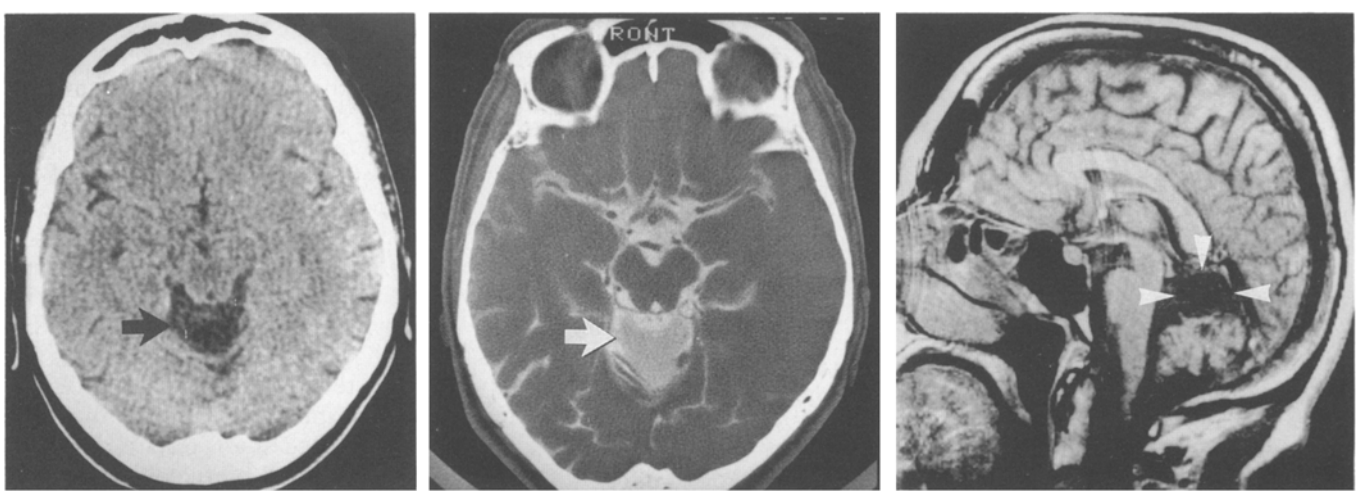
In 1952, at the age of 28 years, the patient was first admitted to our hospital. The presenting symptoms were acute severe headache, vomiting, vertigo and stiffness of neck. The general physical examination was unremarkable. Neurological findings were impaired hearing on the right side, increased tendon reflexes of the right leg and slight intention tremor on the left. There was no record of previous illness except for recurrent lower back pain suspected of being lumbago. Family history was unremarkable. Laboratory findings were inconclusive. A lumbar puncture showed xanthochromic CSF. Ventriculography was normal. A few month later recurrent episodes of severe headache led to renewed hospitalization. The posterior fossa was explored by a burr hole through the occipitoatlantic membrane, but neither an aneurysm, nor a tumour or any other source of bleeding could be ascertained. The CSF was again xanthochromic. During the following years the headaches improved.

Readmission was necessary in 1979 because of slowly progressive spastic paraparesis, cerebellar ataxia, sensory impairment in both legs and increased headache and vertigo. Smooth pursuit was slightly impaired and there was anosmia and ageusia. Babinsky's sign was positive on the right. While touch and pinprick sensation were unimpaired, vibration and positional sense were diminished. ENT examination revealed deafness of the right and impaired hearing of the left ear. While caloric testing of the left vestibular organ was normal, there was complete failure on the right. Visual evoked potentials (VEPs) were normal, but tibial sensory evoked potentials (SEPs) were delayed bilaterally. Lumbar puncture again revealed xanthochromic CSF without signs of inflammatory changes. Brachial angiography was unremarkable, as was an ascending myelography. CT revealed shallow periventricular hypodensities within the white matter around the posterior horn of the lateral ventricles and early atrophy of the upper vermis.

In 1983 the patient complained of progressive impairment of gait, hearing and memory. In auditory evoked potentials (AEPs) no response was evoked on the right side and on the left only peak 1.

In 1985 the patient was re-admitted with almost complete deafness and rapid progression of spastic paraparesis. CSF again was xanthochromic and showed siderophages and erythrophages. VEPs were still normal. As in 1979, CT showed bilateral occipital and frontal hypodensities in the white matter, which now were more pronounced. These findings were confirmed by MRI, which demonstrated numerous dot-like signal enhancements in the white matter, a cystic lesion of approximately 20 mm diameter in the upper cerebellar vermis and superficial signal extinctions along the basal cisternae on T2-weighted images. Up to this time no diagnosis had been established and no treatment besides antispastic medication was instituted.

In June 1988 paraparesis had deteriorated considerably and the patient suffered from spinal automatisms. Impairment of memory and concentration was present.



a b c

Fig. 1a–c. Vermian atrophy documented on (**a**) axial precontrast CT, (**b**) axial CT cisternography and (**c**) midsagittal T1-weighted MR image (SE 0.6/15). The vermian cistern appears dilated without compression of the fourth ventricle. Its density (CT) and signal intensity (MR) is equal to CSF (**a, c**). On CT cisternography (**b**) there is less enhancement of the vermian cistern than of the surrounding CSF spaces, suggesting CSF loculi and excluding a solid, hypodense tumour

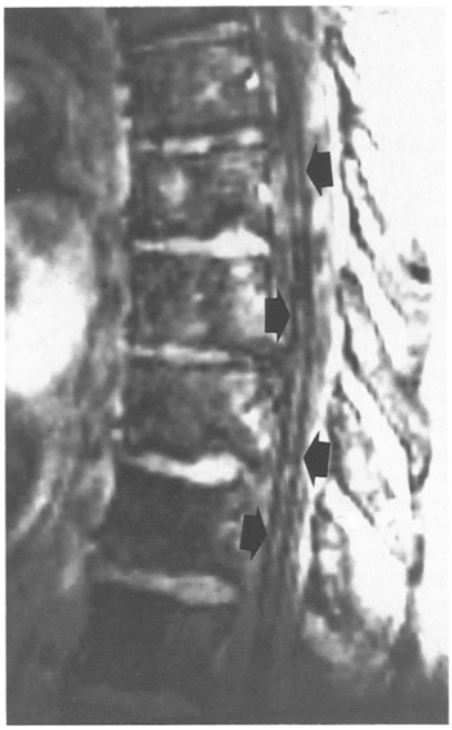


Fig. 2. Sagittal T2*-weighted MR image, acquired with a gradient-echo sequence (FLASH), demonstrates the entire spinal cord to be covered by haemosiderin, causing marked superficial signal extinctions *(arrows)*

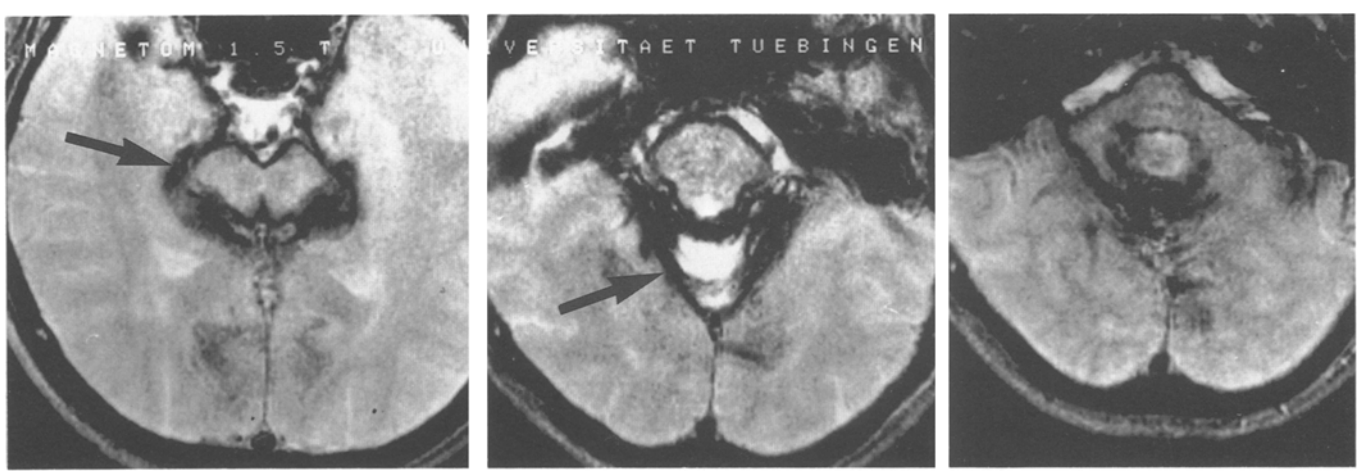
Beside deafness, anosmia and ageusia, impairment of trigeminal sensory functions and slight hypoglossal paresis was now noted. Vision and visual fields were normal. On both sides AEPs were lost, as were SEPs of the tibial nerves. SEP latencies of the median nerve were prolonged bilaterally and VEPs were normal. Cranial and spinal MRI showed a CSF-containing cyst (Fig. 1), replacing the markedly atrophic upper cerebellar vermis without any space-occupying effect. Compared with 1985, the cyst seemed to have enlarged (20 × 25 mm) and on T2-weighted images (1.5 T, SE, TR = 2.0 s, TE = 90 ms) there were extensive superficial signal extinctions along the basal cisterns, the fourth ventricle, the basal face of the temporal and occipital lobes, the surface of the cerebellum, brain stem, and the entire spinal cord. The signal extinctions were more pronounced on T2*-weighted images (1.5 T, FLASH 15°, TR = 0.5 s, TE = 20 ms), interpreted as susceptibility effects of haemosiderin deposits due to chronic subarachnoid haemorrhage (Figs. 2, 3) described by Gomori et al. (1985, 1987).

Repeated neuroradiological examination of head and spine did not disclose a vascular or tumorous bleeding source; cerebral angiography was normal. Myelography and post-myelography CT revealed only a communicating ventral arachnoidal pouch at the level of D7–8 without compression of the atrophic spinal cord. CT cisternography 2 h after myelography (Fig. 1) showed the cyst in the upper vermis to be homogeneously and slightly less enhanced compared with the surrounding CSF spaces. This finding ruled out the differential diagnosis of an epidermoid or other solid tumour. The cyst was interpreted as a post-haemorrhagic CSF loculation similar to the previously described spinal arachnoidal pouch.

General haemochromatosis was rendered unlikely by the clinical and laboratory findings, including a normal abdominal CT scan. Red and white blood cell counts, sedimentation rate, blood urea nitrogen and liver enzymes had always been normal.

Unfortunately the gait disturbance rapidly deteriorated, spinal automatisms increased dramatically and there was transient loss of spontaneous micturition. Within 4 months further deterioration necessitated the constant use of a wheelchair. There was also progression of the neuropsychological deficits and short-term memory was completely lost.

Assuming that the neurological symptoms were caused by the cytotoxicity of iron degradation products, especially by haemosiderin-induced lipid peroxidation, an intramuscular treatment with desferrioxamine (Desferal) was begun. As desferrioxamine has only minor CSF per-



a b c

Fig. 3a–c. Superficial siderosis of the basal cisterns *(arrows)* shown on T2-weighted MR images (FLASH 15° 0.5/20). Pathological hypointensity *(black)* on the surfaces of the midbrain and temporal lobes (**a**), pons and cerebellum (**b**), fourth ventricle and along the eighth cranial nerves (**c**)

meability (Koeppen and Barron 1971), medication was later changed to TETA (Trientine), which so far has been well tolerated at a dose of 5×300 mg for more than 2 years, and 400 mg of vitamin E as an antioxidant. Despite, 2 years of treatment with TETA and vitamin E, no significant therapeutical effect has been achieved. The myelopathy progressed, probably owing to adhesive arachnoiditis. In view of the poor condition of the patient no surgery was performed. As continuous bleeding into the CSF must be assumed, treatment with TETA was instituted to prevent further deterioration of mental abilities, visual impairment or development of occlusion hydrocephalus due to ependymitis granularis. At present, the patient is bound to the wheelchair, has a suprapubic urinary conduit and since 1989 has had neither sensory nor motor control of defaecation.

Discussion

We consider our case noteworthy as a 37-year follow up is unusual and the importance of early diagnosis and therapy has been pointed out. The characteristic clinical signs of recurrent headache, progressing deafness, cerebellar ataxia, myelopathy and neuropsychological deficits in combination with repeated xanthochromic CSF samples can be valuable hints of the diagnosis of SSCN.

Radiologically atrophy of the cerebellar vermis may be noted. Iron deposits are mainly in the cerebello-medullary cistern, on the surface of the cerebellum and brain stem. As they can be detected by MRI, this technique is essential in diagnosing SSCN when xanthochromic CSF is present. Although in our case the bleeding source could not be found, extensive diagnostic evaluation is justified, in view of the limited pharmacological approaches. Surgical removal of the bleeding source is most desirable to prevent the fatal progression of complications of SSCN.

References

Braham J, Wolman M (1965) Subpial siderosis of the central nervous system. Acta Neuropathol (Berl) 4:559–562

Cammermeyer J (1947) Deposition of iron in paraventricular areas of the human brain in haemochromatosis. J Neuropath Exp Neurol 6:111

Castaigne P, Escourolle R, Laplane D, Berger B, Augustin P (1967) Étude anatomo-clinique d'un cas de sidérose marginale du système nerveux central. Rev Neurol (Paris) 116:105–118

Dastur DK, Sinh G (1962) Toxic iron and the nervous system. Siderotic necrosis of spinal root sheaths, ganglia and nerve, and siderosis of central nervous border-zones, in a case of "pinealoma". Acta Neuropathol (Berl) 2:161–176

Garcin R, Lapresle JI (1957) Sur un cas de surcharge ferrique du système nerveux central. Rev Neurol (Paris) 97:417–432

Gomori JM, Grossman RI, Bilaniuk LT, Zimmerman RA, Goldberg HI (1985) High field MR imaging of superficial siderosis of the central nervous system. J Comput Assist Tomogr 9:972–975

Gomori JM, Grossman RI, Goldberg HI, Hackney DB, Zimmerman RA, Bilaniuk LT (1987) High-field spin-echo MR imaging of superficial and subependymal siderosis secondary to neonatal intraventricular hemorrhage. Neuroradiology 29:339–342

Hughes JT, Oppenheimer DR (1969) Superficial siderosis of the central nervous system. A report on nine cases with autopsy. Acta Neuropathol (Berl) 13:56–74

Katsuragi S, Sakai T, Watanabe T, Shimoji A, Deshimaru M, Kuramoto R, Miyamoto K, Yamashita K, Miyakawa T (1988) An autopsy case of idiopathic superficial hemosiderosis of the central nervous system: a microscopic and immunohistochemical study. Clin Neuropathol 7:87–92

Koeppen AHW, Barron KD (1971) Superficial siderosis of the central nervous system. A histological, histochemical and chemical study. J Neuropathol Exp Neurol 30:448–469

Koeppen AH, Dentinger MP (1988) Brain hemosiderin and superficial siderosis of the central nervous system. J Neuropathol Exp Neurol 47:249–270

Lewey FH, Govons SR (1942) Hemochromatotic pigmentation on the central nervous system. J Neuropathol Exp Neurol 1:129–138

McGee DA, Patter HJ van, Morotta J, Olszewski J (1962) Subpial cerebral siderosis. Neurology 12:108–113

Neumann MA (1948) Hemochromatosis of the central nervous system. J Neuropathol Exp Neurol 7:19–34

Neumann MA (1956) Hemochromatotic pigmentation of the central nervous system. Arch Neurol 76:355–368

Noetzel H (1940) Diffusion von Blutfarbstoff in der inneren Randzone und äußeren Oberfläche des Zentralnervensystems bei subarachnoidaler Blutung. Arch Psychiatr 111:129–138

Noetzel H, Ohlmeier R (1963) Zur Frage der Randzonensiderose des Zentralnervensystems (Tierexperimentelle Untersuchung). Acta Neuropathol (Berl) 13:164–183

Pinkston JW, Ballinger WE, Lotz PR, Friedman WA (1983) Superficial siderosis: a cause of leptomeningeal enhancement on computed tomography. J Comput Assist Tomogr 7:1073–1076

Rosenthal P (1958) Siderose der Randzonen des Zentralnervensystems. Dtsch Z Nervenheilkd 178:431–472

Sherwin I, Toll K (1972) Superficial hemosiderosis of the central nervous system. J Neuropathol Exp Neurol 18:413–417

Tomlinson BE, Walton JN (1964) Superficial haemosiderosis of the central nervous system. J Neurol Neurosurg Psychiatry 27:332–339

Ulrich J, Isler W, Vassalli L (1965) L'effet d'hémorragies leptoméningées répétées sur le système nerveux (la sidérose marginale du système nerveux central). Rev Neurol (Paris) 112:466–471