Diagnostic and therapeutic challenges in superficial CNS siderosis

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ABSTRACT

INTRODUCTION: Superficial CNS siderosis was previously almost unknown but is now diagnosed with increasing frequency owing to magnetic resonance imaging. Patients may present with sensory deafness, gait ataxia, various sensorimotor signs and, eventually, cognitive decline. They typically have a history of traumatic brain or spinal cord injury or previous neurosurgery, or may harbour congenital malformations. However, knowledge about treatment outcomes remains scarce.

METHODS: We present a series of nine consecutive patients from a large tertiary neuroscience centre in order to highlight the challenges related to the diagnosis and treatment of superficial siderosis.

RESULTS: A potential bleeding aetiology was identified in all patients, but removal of the offending bleeding source was achieved only in three (33%). Symptom progression was halted in just one patient (11%), which suggests that neurodegeneration due to haemosiderin-associated iron toxicity becomes irreversible with time.

CONCLUSION: Surgical therapy in superficial CNS siderosis is rarely achieved. We suggest that prospective, large-scale multicentre studies are needed to search for non-surgical therapies that reverse (or prevent) ongoing neurotoxicity due to accumulating iron toxicity.

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In the "classic" or "infratentorial" type of superficial CNS siderosis, subpial haemosiderin deposits of the brain and spinal cord accumulate due to chronic subarachnoid haemorrhage, often causing progressive ataxia, deafness, dementia and sometimes a bed-ridden helpless state (**Figure 1** and **Figure 2**) [1-9]. Many different conditions can lead to this form of superficial CNS siderosis, including congenital malformations such as fluid-filled collections in the spinal canal, CNS tumours, post-neurosurgery, head or back trauma, arteriovenous malformations and brachial plexus/root injuries [4, 5]. Surgical removal of the bleeding source remains the only causative treatment option. However, knowledge about treatment outcomes is scarce and typically derived from single case reports [1, 3, 5-9]. We therefore present a consecutive case series from a tertiary neuroscience centre in order to stress the challenges related to diagnosing and treating patients with superficial CNS siderosis.

METHODS

We report on nine consecutive patients with superficial CNS siderosis (one female, eight male; median age = 49.5 years, range: 29-74 years) who came to our attention in the 2008-2013 period. The diagnosis was based on clinical symptoms suggestive of the disease, characteristic superficial hemosiderin deposits with predilection for the brainstem, cerebellum and spinal cord as revealed by magnetic resonance imaging (MRI), as well as subarachnoid haemorrhage confirmed by lumbar puncture, revealing bloody cerebrospinal fluid (CSF) (without clearance in subsequent CSF tubes) and elevated bleeding metabolites as revealed by spectrophotometry. Spectrophotometric measurement of xanthochromia showed bilirubin (broad peak around 455 nm) with or without oxyhaemoglobin (415 nm), consistent with subarachnoidal bleeding. Patients were assessed for a bleeding source using MRI, including T2-weighted and gradient-echo sequences, at 1.5 or 3 T of the brain and spinal cord. Following surgery, patients were re-assessed by lumbar puncture for clearance of bleeding derivatives.

Trial registration: not applicable. Informed patient consent for publication was obtained.

RESULTS

The complete triad of deafness, ataxia and dementia was seen in seven patients (78%; **Table 1**). Urinary incontinence occurred in four patients (44%). Four patients (44%) presented with diplopia and/or decreased visual acuity. One patient complained of monosymptomatic tinnitus (suggestive of haemosiderin damage to the vestibulocochlear nerves). The median modified Rankin Scale score was 4 (range: 1-5). MRI showed leptomeningeal haemosiderin deposits with a predilection for the posterior fossa (n = 9). Additional haemosiderin was noticed around the spinal cord, ranging from extensive and involving most of the spinal canal (n = 4) to minor deposits predominantly affecting the cervical medulla (n = 5) as well as on the cerebral cortex (n = 9), mainly localised to the Sylvian fissures (n = 7). CSF analysis revealed elevated erythrocyte counts (mean = 5,340 cells/µl, range: 199-

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FIGURE 1

With the advent of magnetic resonance imaging (MRI) sequences that are sensitive to blood products, superficial haemosiderin deposits on the brain surface are detected with increasing frequency. The "infratentorial" form of superficial CNS siderosis (**A**) is a clinical entity defined by slowly progressive neurological deficits encompassing sensory deafness, cerebellar ataxia, cranial nerve deficits, sensorimotor signs and cognitive decline, associated with a congenital or aquired chronic venous subarachnoid bleeding source and a typical MRI appearance with haemosiderin deposits mainly (but not exclusively) in the posterior fossa. This should not be confused with "supratentorial" superficial siderosis due to non-traumatic convexal subarachnoid haemorrhage (**B**) which is typically secondary to cerebral amyloid angiopathy in patients over 60 years and due to reversible cerebral vasoconsctriction syndrome in patients below 60 years [10]. To make matters even more complicated, both infratentorial and supratentorial superficial haemosiderin deposits may occur following singular, acute aneurysmal haemorrhage [11], but this is almost never associated with progressive neurodegeneration as in the classical "infratentorial" form of superficial CNS siderosis.

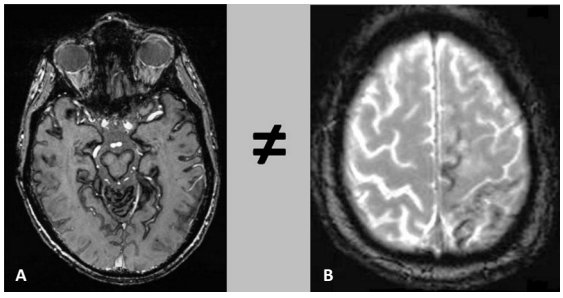
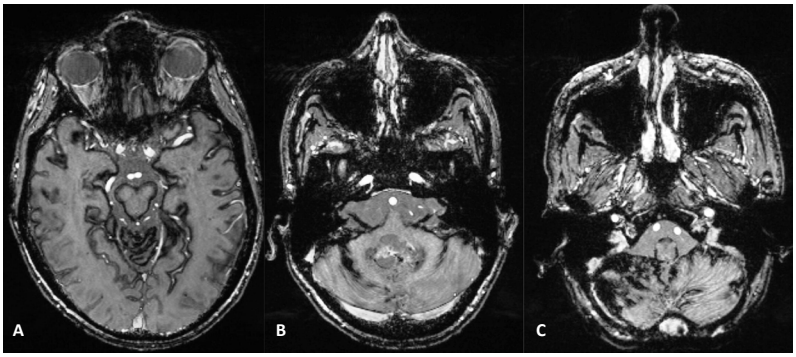


FIGURE 2

Figure 2
A 33-year-old male (patient 6) presented with a five-year history of slowly progressive gait ataxia, bilateral sensory hearing loss, spastic paresis of both legs, dysarthria, and urge incontinence. He had been treated surgically for a medulloblastoma more than 20 years previously. Magnetic resonance imaging (MRI) of the brain (T2* weighted imaging) showed excessive leptomeningeal haemosiderin deposits at the level of the midbrain (**A**), vestibulocochlear nerves (CN VIII) (**B**), and the cerebellum (**C**), consistent with a diagnosis of superficial CNS siderosis. Although the chronic subarachnoidal haemorrhage most likely was associated with the previous neurosurgical procedure, no bleeding source was found that could have been subject to surgical repair. He subsequently became bedridden and required assistance 24 hours a day (modified Rankin Scale 5).
Figure reprinted with permission from: Kondziella D, Waldemar G. Neurology at the bedside. London, UK: Springer, 2014.



12,700). Bilirubin levels were increased in all patients, but oxyhaemoglobin levels in only five. CSF protein levels (range: 0.63-2.76 g/l; normal: 0.15-0.50) and white blood cell counts (range: 5-866 cells/µl, normal < 5) were increased in all patents. CSF neurofilament light, total tau and phosphorylated tau protein levels were measured, and they were increased in three patients.

A potential bleeding aetiology was identified in all patients. Five patients (56%) had an acquired bleeding; three patients had road traffic accidents leading to brachial plexus (n = 1), respectively, cervicothoracic nerve root avulsions (n = 2), one patient had an odontoid fracture during childhood, and another patient had been operated upon for a medulloblastoma. The mean delay from injury to first symptoms was 17.5 ± 12.5 years. Three patients (33%) had congenital bleeding sources, including spinal arachnoid cysts (n = 2) and brain malformations (n = 1). One patient (11%) had both a possible congenital (thoracic arachnoid cyst) and an acquired bleeding source (previous neurosurgery for a medulloblastoma).

Neuroimaging revealed potentially excisable lesions in five patients (56%). One patient declined surgery and another was surgically explored but no bleeding source was detected. Definite surgical excision with post-operative clearance of CSF bleeding derivatives was thus achieved in three out of five patients. However, symptom progression was halted in only one patient (11%). Medical therapy was attempted in two patients (iron chelation, oral prednisolone, and/or hyperbaric oxygen) but was unsuccessful, as expected.

DISCUSSION

Establishing a potential bleeding aetiology seems possible in most patients with superficial CNS siderosis. All our patients had acquired or congenital bleeding aetiologies, the significance of which is well-established in previous reports [1, 3-5, 7, 9]. It is believed that slow and chronic venous leakage of blood products into the subarachnoid space is the cause of superficial haemosiderin deposits [2, 4, 5]. Given that all patients were referred to our tertiary neuroscience centre, there is a high likelihood of referral bias, which suggests that the present patients were affected by a rather high degree of morbidity. Indeed, the incidence of asymptomatic superficial CNS siderosis is unknown since intra vitam diagnosis of haemosiderin deposits requires MRI which is typically performed because of neurological complaints. Of note, one patient in the present case series (patient 1) was monosymptomatic, and superficial CNS siderosis was a rather unexpected finding during MRI. Although sensorineuronal deafness and tinnitus due to haemosiderin damage to the vestibulocochlear nerves are well-recognised features of the disease [2, 4], to the authors' knowledge, monosymptomatic tinnitus due to superficial CNS siderosis has not been reported previously.

As our data show, identifying a potential bleeding

TABLE 1

Clinical findings in nine patients with superficial CNS siderosis.

Patient no.	Age, yrs	Sex	Possible cause	Clinical symptoms	Interval from injury to clinical symptoms/last follow-up, yrs	Treatment	Effect of treatment
1	29	M	Motorbike accident with left-sided C7/Th1 root avulsion	Headache, tinnitus (mRS 1; remaining weakness and atrophy left arm)	5/7	None (bleeding source not identified)	–
2	71	M	Accident with cervical medullary contusion (C6-level) with Brown-Séquard syndrome and left-sided brachial plexus avulsion	Gait ataxia (wheel chair bound), neck dystonia, bilateral deafness, dementia, incontinence (mRS 5)	9/11	Removal of cervical arachnoid cyst; chelate therapy (deferiprone)	Progression despite CSF clearance
3	74	F	Cervical spinal dysraphism, thoracic arachnoidal cyst	Gait ataxia (walking distance 20 m), bilateral deafness, diplopia, mild cognitive dysfunction (mRS 4)	Congenital, progression over 7 yrs	Surgery with removal of a thoracic arachnoid cyst	Progression despite CSF clearance
4	50	M	Motorbike accident at age 16 yrs with left-sided C7/Th1 root avulsion	Tetraparesis, ambulatory with walking aid, bilateral hearing impairment, diplopia, memory disturbance (mRS 4)	27/34	Surgical exploration (negative); prednisolone, hyperbaric oxygen	Progression
5	71	M	Lumbosacral spinal dysraphism, arachnoidal cyst	Severe gait ataxia, deafness, dementia, incontinence (mRS 4)	Congenital, progression over 4 yrs	None (patient declined surgery)	–
6	33	M	Surgery, craniospinal radiation and chemotherapy for medulloblastoma at age 8 yrs, shunt revisions	Bedridden, cerebellar ataxia, deafness, cognitive dysfunction, urge incontinence (mRS 5)	14/26	None (bleeding source not identified)	–
7	49	M	Congenital brain malformation with right-sided porencephalic cyst, aqueductal stenosis, schizencephaly	Severe mental retardation, cerebellar ataxia deafness, mutism, wheel chair bound, epilepsy, visual impairment, incontinence (mRS 5)	Congenital, progression, unable to use electrical wheel chair within 2 yrs	None (bleeding source not identified)	–
8[a]	37	M	Odontoid fracture with temporary right-sided hemiparesis at 1 yr, normal motor development	Gait ataxia, mild hearing impairment, mild cognitive deficits, spastic paresis of the right arm and both legs, dysarthria, urge incontinence (mRS 4)	30/35	None (bleeding source not identified)	–
9	33	M	Surgery, craniospinal radiation and chemotherapy for medulloblastoma at age 13 yrs, congenital thoracic arachnoid cyst	Bilateral deafness, gait ataxia, diplopia (mRS 3)	9/20	Surgical excision of a thoracic arachnoid cyst	Clinical stabilization, CSF clearance

CSF = cerebrospinal fluid; F = female; M = male; MRS = modified Rankin Scale.
a) Details have been published previorsly [3].

aetiology (e.g. a previous traffic accident) does not necessarily mean that an active bleeding can be found, and definitive surgical removal of the culprit bleeding source is achieved only rarely. Nevertheless, patients may deteriorate, probably because neurodegeneration induced by haemosiderin-associated iron toxicity becomes irreversible [2, 3]. Important mechanisms, akin to those seen in other neurodegenerative disorders such as Alzheimer's disease, include hyperphosphorylation of tau protein and oxidative stress [3]. Despite post-surgical decrease of CSF bleeding derivatives in all three patients in whom a bleeding source was removed, two patients (66%) continued to deteriorate. This suggests a point-of-no-return when critical amounts of haemosiderin have accumulated [2, 3]. It remains unknown why some patients apparently tolerate larger amounts of haemosiderin deposits than others, but genetic factors may play a role [6]. Furthermore, some patients with superficial CNS siderosis clearly suffer from concurrent brain pathologies, which contribute to their neurological decline, e.g. patients 6 and 9 with a history of radiation and chemotherapy for a medulloblastoma. However, the point-of-no-return hypothesis of haemosiderin accumulation is supported by e.g. patient 4 who progressed clinically despite serial MRI showing unchanged amounts of haemosiderin during a period of 11 years.

CONCLUSION

Neurosurgeons and neurologists must become familiar with the diagnosis of superficial CNS siderosis in order to quickly establish the bleeding aetiology, identify the source of haemorrhage using high-resolution MRI of the brain and spinal cord, and, if possible, schedule patients for timely surgery. However, definite removal of a culprit bleeding source is achieved only occasionally and

even then further clinical progression is possible. With the increasing use of MRI and better knowledge of the disease among physicians, the reported incidence is expected to rise in the future. This may allow for prospective large-scale multicentre studies searching for non-surgical therapies that reverse (or prevent) ongoing neurotoxicity due to accumulating iron toxicity.

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