

Illustrated Review

Superficial siderosis of the central nervous system following cervical nerve root avulsion: the importance of early diagnosis and surgery

K. Aquilina¹, R. Kumar¹, J. Lu², and D. Rawluk¹

¹ Department of Neurosurgery, Beaumont Hospital, Dublin, Ireland

² Cleveland Clinic Spine Institute, Cleveland Clinic Foundation, Cleveland, Ohio

Published online January 27, 2005

© Springer-Verlag 2005

Summary

Superficial siderosis (SS) of the central nervous system is an insidious, progressive, irreversible and debilitating neurological disorder caused by recurrent haemorrhage within the subarachnoid space. The subsequent deposition of haemorrhagic breakdown products in the spinal cord and nervous tissues leads to the loss of neurones and myelin, and to the development of a neurological deficit. In a small number of patients, the source of haemorrhage is related to traumatic cervical nerve root avulsion occurring several years prior to the onset of symptoms. Surgical ablation of the source has been shown to halt the progression of the disease, at least in the short term. We review the literature on SS secondary to cervical nerve root avulsion and report a further case in which surgical management was successful in halting disease progression. We emphasize that early detection and recognition of the initial non-progressive symptoms related to this poorly known disease, coupled with timely surgical management, minimizes the degree of neurological disability.

Keywords: Superficial siderosis; cervical nerve root avulsion; brachial plexus injury; pseudomeningocele.

Introduction

Traumatic cervical nerve root avulsion occurs in young, active individuals, and, like other brachial plexus injuries, carries a high long-term morbidity [7]. SS is an infrequent and less well-known consequence of cervical nerve root avulsion. Symptoms begin several years after the injury and are insidious but progressive, leading to severe neurological deficits. Twelve cases of SS resulting from such injuries have been documented in the literature [3–5, 7, 13–15, 17, 22]; surgical management, including findings and outcome, has only been described in five [3, 5, 13, 22]. We review the available literature on SS and describe a further case in which surgical management led to arrest of the patient's neurological deterioration.

Literature review

A Medline search, from January 1966 to September 2004, using the key words *superficial siderosis*, yielded 124 articles. Other key words, including *cervical nerve root avulsion*, *pseudomeningocele* and *brachial plexus trauma* did not yield any further articles relevant to SS. The manuscripts were reviewed and their bibliographies scanned for further articles. Another 23 manuscripts were identified in this manner; almost all were published before January 1966. Nine articles describing cases of SS secondary to cervical nerve root avulsion were then examined in detail [3–5, 7, 13–15, 17, 22]; they form the basis of this review.

Analysis

A total of 199 cases of SS were identified. This included cases where the diagnosis was made at autopsy. In 103 cases, a source of subarachnoid bleeding was not identified despite extensive investigation. The causes of subarachnoid bleeding included spinal or cranial ependymomas (17 cases), cavernous angiomas (8 cases), cerebellar tumours (7 cases), cerebral tumours (7 cases), arteriovenous malformations (6 cases), post-hemispherectomy (5 cases), other spinal tumours (5 cases), intracranial aneurysm (4 cases), subdural haematomata (3 cases), cranial trauma (4 cases), occipital encephalocele (2 cases) and lumbar pseudomeningocele (1 case). Twelve cases of SS secondary to cervical nerve root avulsion were identified [3–5, 7, 13–15, 17, 22]. Surgical intervention was undertaken in six cases [3, 5, 13, 16, 22].

Table 1. Cases of superficial siderosis of the CNS secondary to traumatic cervical root avulsion managed surgically

Publication	Root(s) involved	Age at root avulsion (years)	Age at symptom onset (years)	Documented first symptom	Age at surgery (years)	Surgical findings	Outcome	Follow-up
Lewey <i>et al.</i> , 1942 [16]	not specified	not specified	not specified	hearing loss; ataxia	36	posterior fossa exploration; haemosiderin-stained cerebellum	not specified	not specified
Bonito <i>et al.</i> , 1994 [3]	left C8	20	30–35	temporary facial nerve paralysis; sensorineural deafness	51	hyperaemic arachnoid-medullary scar pad	normalisation of CSF; evolution of symptoms arrested	4 weeks
Tapscott <i>et al.</i> , 1996 [22]	right C5–C8	23	39	Tinnitus; sensorineural deafness	48	right C5 meningeal diverticulum; large vein on posterior wall of the cavity	initial deterioration with subsequent return to baseline condition	2.5 years
Kole <i>et al.</i> , 2004 [13]	right C8-T1	22	44	gait difficulty; hearing loss	51	slow ooze from anterior portion of pseudomeningocele, associated with epidural vein	resolution of CSF xanthochromia; no further progression of symptoms	8 months
Cohen-Gadol <i>et al.</i> , 2004 [5]	left C7-T1	21	34	ataxia; sphincter dysfunction; hearing loss	42	friable vessels in hyperaemic scar tissue	no further progression of symptoms	2 years
Case 2	left C7-T1	10	47	unsteadiness	52	pseudomeningocele; no abnormal vessels identified	resolution of CSF xanthochromia; no further progression of symptoms	15 months
Current case	left C5-T1	21	30	Tinnitus; sensorineural deafness	34	arachnoid adhesions; multiple small fragile vessels	no further neurological deterioration	3 years

All the reported cases of SS secondary to cervical nerve root avulsion were male; the mean age at presentation was 48.1 years, ranging from 36 to 69 years. The latent period from injury to development of symptoms varied between 15 and 37 years, with a mean of 20.7 years. The most commonly involved roots were the lower cervical roots, those between C8 and T1 being involved in all cases. In one case all the right-sided roots, from C5 to T1 were involved [22]. The predominant initial symptoms were gait difficulties and hearing loss; these symptoms appear to have progressed steadily until the time of surgery. The only non-progressive symptom was transient episodes of facial nerve palsy, occurring in two cases [3, 4]; tinnitus was the only symptom which did not, in itself, constitute a neuro-

logical deficit, and was reported in one case [22] as well as in the patient we present.

Surgical management was discussed in six cases (Table 1). The mean duration from onset of symptoms to surgery was 8.6 years. In one case the posterior fossa was explored; the cerebellum was noted to be haemosiderin-stained, but no direct surgical management of the dural diverticulum at the avulsed roots was undertaken [16]. In four other cases, vessels were found in association with the pseudomeningocele; these were coagulated [3, 5, 13, 22]. In two cases a piece of muscle was sutured into the diverticulum to ensure closure of the communication between the subdural and subarachnoid spaces [5, 13]. No abnormal vessels were found in one case [5]. Including our own case, post-operative

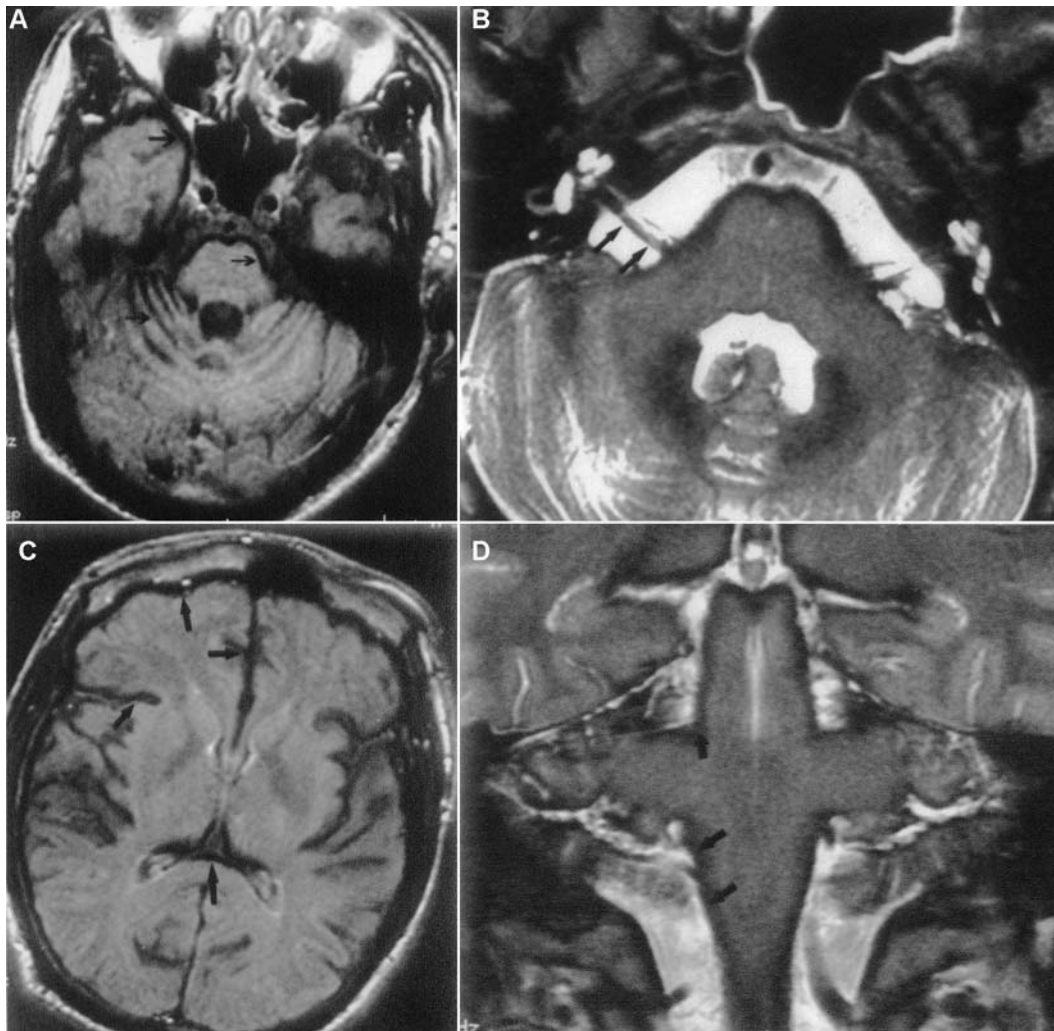


Fig. 1. (A) T2 axial brain MR image; the arrows point to the hypointense margins around the medial temporal lobe, the brainstem and the cerebellar folia; (B) T2 axial MR image of the pons and the peri-pontine cistern demonstrates the dark signal from the right vestibulocochlear nerve; (C) T2 axial brain MR image showing hypointensity over the cerebral hemispheres, sylvian fissures, anterior interhemispheric fissure and the ependymal surface of the atrium of the ventricular system; (D) T2 coronal MR image of the brainstem showing extensive superficial haemosiderin deposition

follow up ranged from four weeks to three years, with a mean of 19 months. Arrest of progression of neurological symptoms was reported in all cases. Confirmation of resolution of CSF xanthochromia was obtained in three cases [3, 5, 13].

Case illustration

In 1988, at the age of 21, our patient sustained traction injury to his neck and left upper limb in a road-traffic accident, with avulsion of the C5 to T1 nerve roots on the left side; his left arm was flail and painful after the injury. There was no improvement in his neurological deficit or pain over the subsequent years.

At the age of 30 he developed bilateral tinnitus which progressed to bilateral asymmetric sensorineural deafness over the next four years. At age 32, he developed problems with his gait as well as weakness in the right upper extremity and micturition difficulties. He sought medical care at the age of 34; by then he was unable to use the telephone.

On review in 2001 the patient had severe lower extremity spasticity, with exaggerated reflexes and extensor plantar responses. There were signs of cerebellar dysfunction in both the upper and the lower extremities. There was lower motor neurone-type weakness in the right upper extremity with extensive wasting of the intrinsic muscles of the right hand. Cranial nerve exam-

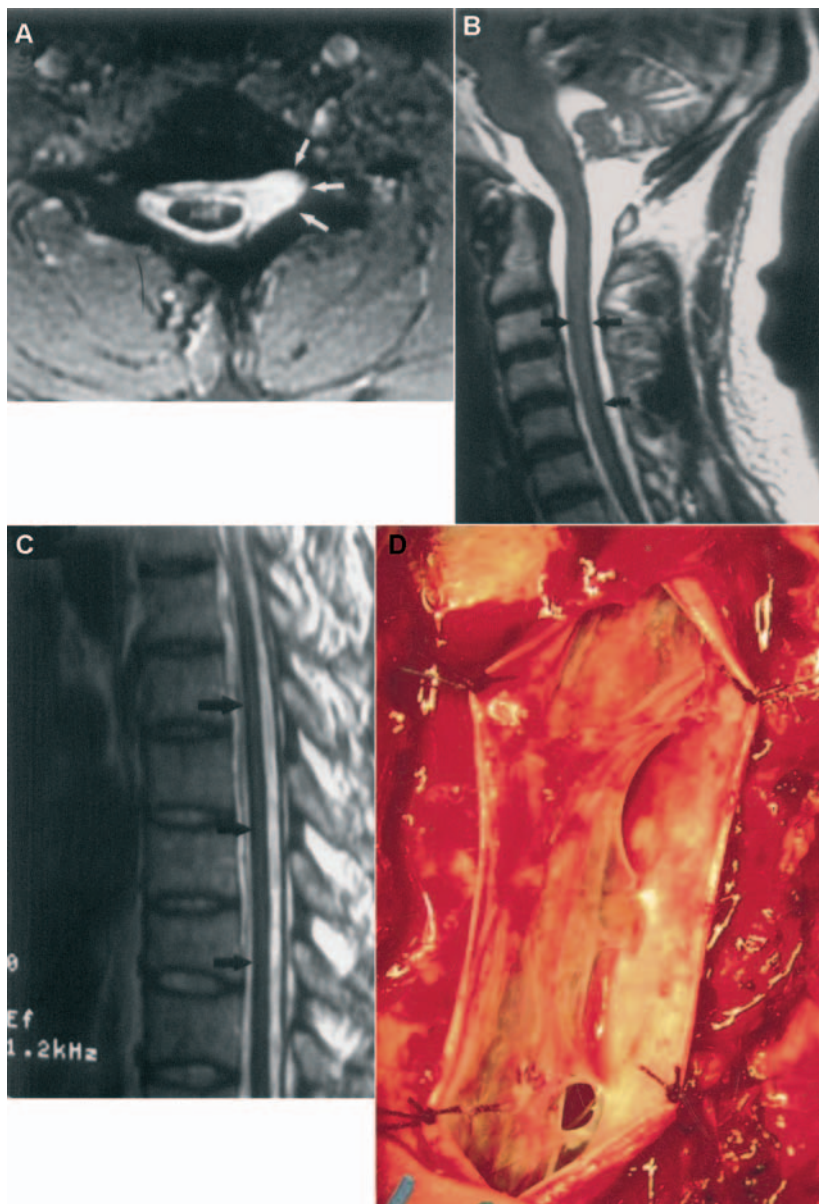


Fig. 2. (A) T2 axial cervical spine MR image showing left-sided pseudomeningocele at the point of avulsion of one of the nerve roots (white arrows); (B, C) T2 sagittal MR images of the cervical and thoracic spine; the black arrows point to the marginal hypointense rim on the cord surface; (D) intra-operative photograph showing yellowish discoloration of the arachnoid layer in the cervical spine

ination showed severe bilateral sensorineural deafness, bilateral anosmia and pupillary anisocoria. The pupillary reaction to light was poor. Audiometry confirmed bilateral high frequency sensorineural deafness.

Cerebrospinal fluid (CSF) obtained at lumbar puncture yielded a red cell count of 29 cells/ml. The protein level was elevated at 5.7 g/l. There was no xanthochromia. Four-vessel cerebral angiography was normal.

Magnetic resonance (MR) imaging of the brain and spine were performed. The T2-weighted images of the brain showed marked marginal hypointensity at the brainstem, cerebellum and cerebral cortex, particularly at the sylvian fissures. Cerebellar atrophy was maximal in the superior cerebellar vermis. The ventricular ependymal lining was also hypointense (Fig. 1a to d). Axial and sagittal T2-weighted MR imaging of the cervical spine showed prominent pseudomeningoceles at C7 and T1, on the left side (Fig. 2a) as well as a hypointense rim on the surface of the entire length of the spinal cord (Fig. 2b and c).

A C7 to T2 laminectomy was performed. The dura over these segments was divided in the midline. A yellowish-brown discoloration of the inner surface of the dura and the arachnoid was evident (Fig. 2d). The pseudomeningoceles at the points of avulsion of the nerve roots on the left side were explored. Adhesions between the arachnoid, dura, and nerve roots were divided. Abnormal and friable vessels within and around granulation tissue and scarring in the region of the avulsed roots, presumed to be the cause of recurrent haemorrhage into the subarachnoid space, were coagulated.

Three years postoperatively the patient shows no significant improvement in his neurological status. However, there has been no further progression in his symptoms.

Discussion

SS is a consequence of recurrent bleeding into the subarachnoid space and the CSF. There is deposition of haemosiderin in the leptomeninges and subpial layers of the central nervous system (CNS) extending to a depth of three millimetres [19]. The ependymal surface, in continuous contact with the circulating CSF, is also involved. The haemosiderin deposition, within macrophages in the perivascular spaces and along pial vessel walls, leads to neuronal loss, gliosis and demyelination [6]. The peripheral nervous system is spared. The clinical presentation is characterised by progressive sensorineural deafness, cerebellar ataxia, pyramidal signs

(which may be due to myelopathy or to brainstem involvement), sphincter dysfunction and dementia. These symptoms occur at a mean of fifteen years from the onset of the bleeding [6].

In SS following cervical nerve root avulsion, venous bleeding from granulation tissue or arachnoid and medullary scarring within pseudomeningoceles at the site of the avulsions is the usual source of the repeated episodes of subarachnoid bleeding. This was evident in four of the reported cases undergoing exploration of the pseudomeningocele [3, 5, 13, 22]. The radicular and medullary veins converge at the origin of the spinal nerves, particularly along the proximal posterior roots. Root avulsion damages these veins. Once they become scarred and friable, minor neck movements may be enough to induce venous oozing [6]. Surgical treatment aims to stop bleeding by coagulation of the abnormal vessels and granulation tissue.

Pathogenesis involves the sequestration of the products of haeme breakdown within glia and microglia; these cells initially accumulate ferritin, a water soluble protein in which 24 polypeptide subunits shield a central crystalline core of ferric oxyhydroxide. Haemosiderin is produced once the available iron exceeds the cell's ability to synthesise ferritin; it is an insoluble aggregation of ferric oxyhydroxide and contains far less protein than ferritin [2]. The process of ferritin and haemosiderin synthesis is probably protective, and neurotoxicity occurs only when it is exhausted, leaving the ferric ions unbound. These are thought to mediate apoptosis by free radical mechanisms [11]. It has been suggested that the preferential involvement of the cerebellar vermis is due to high iron uptake, probably directly from the CSF, by Bergmann's glia [22]. Experimental intrathecal injection of red blood cells in rabbits led to the identification of ferritin and haemosiderin deposits in the leptomeninges three to six months later. Microglia were seen to contain ferritin granules and, subsequently, haemosiderin deposits [9]. These studies identified the central role of glial cells in this process, explaining its confinement to the CNS. An abrupt cut-off in haemosiderin deposition at the CNS-PNS junction has been clearly shown on the vestibulocochlear nerve and along the spinal nerve roots [10].

Sensorineural deafness is the most common cranial nerve deficit, occurring in up to 95% of all reported SS patients [6]. Its vulnerability to haemosiderin deposition is related to its long centrally myelinated segment and to the high flow of CSF within the pontine cistern [6]. The olfactory nerve and bulb are also frequently

involved, as are the pupillary fibres in their exposed and superficial superolateral location within the oculomotor nerve.

Although initially diagnosed only at autopsy, the hypointense rim around the CNS tissues on T2-weighted MR imaging, due to the paramagnetic effect of haemosiderin at body temperature [2], is diagnostic of SS. This is maximal in the superior cerebellar vermis, crests of the cerebellar folia, brainstem, spinal cord, nerve roots and cranial nerves I, II, V, VIII and X [4, 6]. A single CSF examination is often negative for xanthochromia; this was evident in our case and at least in one other [18], where only one specimen was xanthochromic out of three lumbar punctures over a six-year period. An elevated CSF protein level is typical of the diagnosis and is due to arachnoiditis. Investigations to identify the source of bleeding are often negative; our review shows that the source of the chronic subarachnoid bleeding has not been identified in over half the reported patients. This is probably due to the slow and episodic nature of the bleeding. In three cases of cervical nerve root avulsion, 99 m-Technetium red blood cell scanning was not helpful in identifying a source of haemorrhage [3, 5, 22]. Four-vessel cerebral angiography is used to exclude an intracranial source of chronic subarachnoid haemorrhage.

Although rare in the overall SS population, two patients presenting with SS after cervical nerve root avulsion were reported to have transient and intermittent facial nerve deficits in the early symptomatic period [4, 22]. This, as well as tinnitus, evident in our patient and in one other [22], constitutes the only non-progressive symptom in the early symptomatic phase of the disease. Our patient also demonstrated lower motor neurone-type weakness in the right upper extremity, contralateral to the brachial plexus injury; this may be due to radiculopathy or to anterior horn cell involvement in the cervical spinal cord [21, 23].

Although the period from injury to symptom onset is long, with a mean of fifteen years, SS subsequently runs a chronic and progressive course. The auditory deficit progresses over one to twelve years to complete deafness and 27% of patients become bed-bound over a mean period of eleven years as a result of severe cerebellar ataxia or myelopathy, or a combination of the two [6]. One of the case reports is appended by a patient commentary outlining how very slow but progressive deficits 'took their toll' and 'dramatically altered' quality of life [22]. Eight years elapsed between the onset of his first symptom (tinnitus) and the recognition of SS.

Medical management in the form of iron chelation has been repeatedly unsuccessful [6]. Trientene, a potent copper chelator that crosses the blood-brain barrier, slowed disease progression over a two-year period in only one patient [20]. Metalloporphyrins are structural analogues of haeme and therefore potent inhibitors of haeme oxygenase, the enzyme catalyzing the rate-limiting step of haeme breakdown into iron and carbon monoxide by oxidative cleavage of the porphyrin ring [24]. The experimental injection of tin protoporphyrin with red blood cells into the cisterna magna in rabbits reduced the amount of histologically detectable parenchymal iron [12]. One case has been reported to respond to corticosteroids; this case was unique in that SS was associated with anti-Ri antibodies [1]. The use of anti-oxidants has also been proposed [15]. Surgical management by coagulation of the identified source is the only method known to halt the progression of the disease. Although the CSF was shown to have cleared post-operatively in some cases, the established neurological deficits were not reversed [3, 5, 13, 22].

Conclusion

SS is an irreversible, progressive and debilitating process, easily diagnosed on MR imaging. Symptoms begin after a long interval following cervical nerve root avulsion, and may therefore not be intuitively associated with the previous injury by patients or their doctors. Diagnosis and surgical management in the early symptomatic phase is indicated to control disease progression before severe neurological deficits develop. We suggest that in cases of brachial plexus trauma with cervical nerve root avulsions, regular neurological examination and evaluation of eighth nerve function, including clinical examination and audiometry, should be performed. Such patients should be offered CNS MR imaging upon detection of myelopathy, ataxia or early cranial nerve symptoms, particularly those involving the vestibulocochlear and facial nerves. The importance of non-progressive symptoms such as transient episodes of facial nerve weakness, and of symptoms which do not in themselves constitute a neurological deficit, such as tinnitus, within the context of remote brachial plexus injury, should not be overlooked. Upon confirmation of SS on MR imaging, surgical exploration of the pseudomeningoceles is indicated even when the source of the bleeding is not evident pre-operatively, as occult subarachnoid haemorrhage in these cases has proven difficult to detect.

References

1. Angstwurm K, Schielke E, Zimer C, Kivelitz D, Weber JR (2002) Superficial siderosis of the central nervous system: response to steroid therapy. *J Neurol* 249: 1223–1225
2. Atlas SW, Thulborn KR (2002) Intracranial haemorrhage. In: Atlas SW (ed) *Magnetic resonance imaging of the brain and spine*. Lippincott Williams and Wilkins Philadelphia, pp 773–832
3. Bonito V, Agostinis C, Ferraresi S, Defanti CA (1994) Superficial siderosis of the central nervous system after brachial plexus injury. *J Neurosurg* 80: 931–934
4. Bracchi M, Savoiaro M, Triulzi F, Daniele D, Grisoli M, Bradac GB, Agostinis C, Pelucchi D, Scotti G (1993) Superficial siderosis of the CNS: MR diagnosis and clinical findings. *AJNR* 14: 227–236
5. Cohen-Gadol AA, Krauss WE, Spinner RJ (2004) Delayed central nervous system superficial siderosis following brachial plexus avulsion injury. *Neurosurg Focus* 16(5): Article 10
6. Fearnley M, Stevens JM, Rudge P (1995) Superficial siderosis of the central nervous system. *Brain* 118: 1051–1066
7. Fishman RA (1993) Superficial siderosis. *Ann Neurol* 34: 635–636
8. Kim DH, Yong-Jun C, Tiel RL, Kline DG (2003) Outcomes of surgery in 1019 brachial plexus lesions at Louisiana State University Health Sciences Centre. *J Neurosurg* 98: 1005–1016
9. Koeppen AH, Borke RC (1991) Experimental superficial siderosis of the central nervous system. I. Morphological observations. *J Neuropathol Exp Neurol* 50: 579–594
10. Koeppen AH, Dentiger MP (1988) Brain hemosiderin and superficial siderosis of the central nervous system. *J Neuropathol Exp Neurol* 47: 429–470
11. Koeppen AH, Dickson AC, Chu RC, Thach RE (1993) The pathogenesis of superficial siderosis of the central nervous system. *Ann Neurol* 34: 646–653
12. Koeppen AH, Dickson AC (2002) Tin-protoporphyrin prevents experimental superficial siderosis in rabbits. *J Neuropathol Exp Neurol* 61(8): 689–701
13. Kole MK, Steven D, Kirk A, Lownie SP (2004) Superficial siderosis of the central nervous system from a bleeding pseudomeningocoele. Case illustration. *J Neurosurg* 100(4): 718
14. Konitsiotis S, Argyropoulou MI, Kosta P *et al* (2002) CNS siderosis after brachial plexus avulsion. *Neurology* 58: 505
15. Leussink VI, Flachenecker P, Brechtelsbauer D, Bendszus M, Sliwka U, Gold R, Becker G (2003) Superficial siderosis of the central nervous system: pathogenetic heterogeneity and therapeutic approaches. *Acta Neurol Scand* 107: 54–61
16. Lewey FH, Govons SR (1942) Hemochromatotic pigmentation of the central nervous system. *J Neuropathol Exp Neurol* 1: 129–138
17. Maggioni F, Mantovan MC, Carollo C, Chierichetti F, Zanchin G (1997) Morphological and functional study in a case of superficial siderosis of the central nervous system. *Ital J Neurol Sci* 18: 113–118
18. Offenbacher H, Fazekas F, Reisecker F, Schmidt R, Payer F, Lechner H (1991) Superficial siderosis of the spinal cord: a rare cause of myelopathy diagnosed by MRI. *Neurology* 41: 1987–1989
19. Rosenthal P (1958) Siderose der Ranzonen des Zentralnervensystems. *Dt Z Nervheilk* 178: 431–472
20. River Y, Honigman S, Gomori JM, Reches A (1994) Superficial hemosiderosis of the central nervous system. *Mov Disord* 9: 559–562
21. Savoiaro M, Grisoli M, Pareyson D (2001) Polyradiculopathy in the course of superficial siderosis of the CNS. *J Neurol* 248: 1099–1100
22. Tapscott SJ, Eskridge J, Kliot M (1996) Surgical management of superficial siderosis following cervical nerve root avulsion. *Ann Neurol* 40: 936–940
23. Turner B, Wills AJ (2002) Superficial siderosis associated with anterior horn cell dysfunction. *J Neurol Neurosurg Psychiatry* 72: 274–280
24. Wagner KR, Dwyer BE (2004) Hematoma removal, heme, and heme oxygenase following hemorrhagic stroke. *Ann NY Acad Sci* 1012: 237–251

Comment

This paper describes a single case of superficial siderosis of the brain as a very rare consequence of avulsion of cervical roots in brachial plexus injury.

The paper is well documented and has a comprehensive review of the literature and discussion on the possible causes and symptomatology of the few cases described so far. The mechanism of the entity has not been definitely determined. The proposal is that there are multiple recurrences of mild subarachnoidal bleeding of unknown origin. The common feature of the cases described in the literature are of a young age (around 20 years) at the time of cervical root avulsion, occurrence of symptoms mostly related to dysfunction of the cerebellum and brainstem only after a mean time of around 10 years. It is interesting that surgical exploration of the posterior fossa and plugging of the dural diverticulum resulting from root avulsion arrested the progress of, and reversed the symptoms of cerebellar and medullary dysfunction.

This remains a somewhat mysterious disease and further observations are needed to bring new concepts on its mechanism, diagnosis and management.

Tomasz Trojanowski
Lublin

Correspondence: Kristian Aquilina, Department of Neurosurgery, Cork University Hospital, Wilton, Cork, Ireland. e-mail: kristianaquilina@hotmail.com