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Case report:

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ABSTRACT

We report two cases of superficial siderosis (SS) of the central nervous system (CNS), which is caused by chronic haemorrhaging into the subarachnoid space with haemosiderin deposition in the superficial portion of the CNS. Patient 1 had fluid collection in the spinal canal, which was reported as the source of the chronic bleeding. Patient 2 was bleeding from thickened dura at the level of the sacral vertebrae. Both of the patients had xanthochromic cerebrospinal fluid. We surgically repaired the sources of bleeding. Subsequently the cerebrospinal fluid (CSF) cleared and their symptoms were not aggravated for about one year. We measured several CSF markers of SS before and after surgery. Total tau protein (CSF-t-tau), phosphorylated tau protein (CSF-p-tau), iron (CSF-iron) and ferritin (CSF-ferritin) in the CSF were highly elevated at diagnosis. After surgery, the levels of CSF-t-tau and CSF-p-tau were markedly reduced while CSF-iron and CSF-ferritin had not decreased. It is suggested that CSF-t-tau and CSF-p-tau reflected the neural damage in SS and were useful to evaluate the effectiveness of SS therapies.

1. Introduction

Superficial siderosis (SS) of the central nervous system (CNS) is a rare disease that produces haemosiderin deposition in the subpial layers of the brain and spinal cord due to chronic and repeated haemorrhaging into the subarachnoid space, leading to progressive and irreversible cerebellar ataxia, auditory disturbance and dementia [1–8]. The causes of SS include a prior intradural surgery, carcinoma, arteriovenous malformation, amyloid angiopathy and fluid collection in the spinal canal [1–3,8].

MR T2-weighted images are characterised by hypointensity around the surfaces of the brainstem, cerebellum, cortical fissures and spinal cord, which allows the diagnosis of SS without the need for either biopsy or autopsy. Although MRI is useful for detecting haemosiderin deposition in SS, it cannot show disease activity. Several lumbar punctures are necessary to identify the bleeding in SS because some patients have intermitted bleeding sources, and 25% of SS patients do not show haemorrhagic and/or xanthochromic cerebrospinal fluid (CSF) [1].

The only effective treatment for SS is the repair of the bleeding site by surgery [1,4,5]. The slowly progressive course of SS makes it difficult to confirm the effect of treatment and requires a long follow-up period and several lumbar punctures to ensure that the surgery has successfully prevented progression of the disease. We encountered two patients with SS, whose bleeding points were repaired and who underwent CSF analysis before and after surgery. In SS, iron is released from red blood cells (RBCs) to the subarachnoid space and stored as ferritin, and CSF-t-tau and CSF-p-tau are elevated [6]. Therefore, CSF levels of CSF-t-tau, CSF-p-tau, iron (CSF-iron) and ferritin (CSF-ferritin) could be CSF markers for SS to evaluate the effects of surgery. We found CSF-t-tau and CSF-p-tau were reduced after the surgery despite high levels of CSF-iron and CSF-ferritin. Here, we report the clinical courses of two patients with SS and the utility of CSF-t-tau, CSF-p-tau, CSF-iron and CSF-ferritin as CSF markers for SS.

2. Case reports

Patient 1

A 71-year-old woman was admitted to our hospital with a 7-year history of progressive gait

difficulties and auditory disturbance. A neurological examination revealed right dominant deafness and mild truncal ataxia. Muscle tonus, motor strength, sensory examination, tendon reflexes and cognitive function were normal. She could walk without a cane despite her ataxic gait. T2-weighted MRI revealed hypointensity in the superficial areas of the CNS, suggestive of haemosiderin deposition involving the brain and spinal cord (Fig. 1 A). The initial lumbar puncture revealed a watery clear CSF and slightly elevated levels of CSF protein (47 mg/dl). We determined the levels of the four CSF markers, all of which were elevated (Table 1). The next month, she underwent CSF analysis once more, which showed xanthochromia.

Spinal MRI demonstrated an unusual fluid collection in the ventral portion of the vertebral canal ranging from C7 to T12 (Fig. 1 B and C). At surgery, a dural defect involving the arachnoid membrane at the level of T2–3 was detected (Fig. 1 D) and repaired.

One year after the surgery, the clinical manifestations were not aggravated. The CSF had become clear, and levels of CSF-t-tau and CSF-p-tau had rapidly decreased, whereas the concentrations of CSF-ferritin and CSF-iron remained high (Table 1).

Patient 2

A 67-year-old woman presented with an 8-year history of progressive gait disturbance, dysarthria and hearing loss. She had been diagnosed with spinocerebellar degeneration and medicated with protirelin tartrate since the age of 61. On admission, a neurological examination revealed mild dementia, deafness, dysarthria, severe ataxia and hyperactive tendon reflexes in all extremities. She could not walk by herself. She showed no meningeal signs, sensory impairment or orthostatic hypotension. T2-weighted MRI images of the brain demonstrated hypointensity around the surface of the brainstem, cerebellum and perisylvian areas and at the base of the cerebrum (Fig. 2 A and B). A CSF analysis revealed xanthochromia with an increase in RBC count (595/μl) and elevated levels of protein (79 mg/dl), CSF-t-tau, CSF-p-tau, CSF-iron and CSF-ferritin (Table 1).

A spinal MRI demonstrated marked thickening of the meninges with mild gadolinium

enhancement at the level of the sacral vertebrae (Fig. 2 C). At surgery, the sacral arachnoid membrane presented with tremendous thickening and bleeding (Fig. 2 D); therefore, we resected it with the surrounding dura. The pathological examination revealed no neoplasm and that the thickening of the dura was just a reaction to the bleeding.

Eight months after the surgery, a CSF analysis showed reduced levels of CSF-t-tau and CSF-p-tau without significant changes in CSF-iron or CSF-ferritin and no xanthochromia (Table 1). There was no aggravation in the clinical manifestations after surgery.

3. Discussion

We report two patients with SS who underwent surgery for the repair of the bleeding site. Patient 1 had fluid collection in the spinal canal, which was related to chronic bleeding [2]. In Patient 2, we detected the bleeding point in the thickened dura at the level of the sacral vertebrae and resected it with the surrounding dura. Chronic and repeated bleeding stopped in both patients because there were no xanthochromia or RBCs in the CSF of several lumbar punctures after surgery. We measured CSF-t-tau, CSF-p-tau, CSF-iron and CSF-ferritin as CSF markers of SS. Sandwich enzyme linked immunosorbent assays were used to determine CSF levels of total tau protein (CSF-t-tau; Innotest hTAU-Ag; Innogenetics, Gent Belgium) and phosphorylated tau protein (CSF-ptau; Innotest Phospho-tau (181p); Innogenetics) [9,10]. CSF- iron was measured using a colorimetric method, and CSF-ferritin was measured using a chemiluminescent immunoassay. Their levels were significantly elevated before surgery, and surgical treatment resulted in a significant reduction of CSF-t-tau and CSF-p-tau despite the high levels of CSF-iron and CSF-ferritin.

Kondziella et al.[6] reported a 37-year old man with SS, who had gait ataxia, mild sensory hearing loss, spastic paresis of the right arm and both legs, mild dysarthria and urge incontinence. T2-weighted MRI showed hypodense layers around the brain and spinal cord, and a lumbar puncture confirmed chronic subarachnoidal bleeding. In this patient, CSF-t-tau and CSF-p-tau were elevated (CSF-t-tau: 1070 pg/ml; CSF-p-tau: 127 pg/ml) as observed in our

patients. To our knowledge, this is the only report of an elevation in the CSF level of a tau protein in an SS patient, and none has reported a change in the CSF level of the tau protein after surgical treatment.

Tau protein is a microtubule-associated protein primarily localised in neuronal cells [11]. Elevated CSF-t-tau levels have been reported in a variety of neurodegenerative diseases, such as Alzheimer's disease, corticobasal degeneration, dementia with Lewy bodies and Creutzfeldt-Jakob disease as well as in the acute phases of stroke and encephalitis [9–13]. These reports indicate that increased CSF tau protein is associated with neuronal damage, during which intracellular tau protein is released into the extracellular space and CSF. Iron toxicity and oxidative stress in SS lead to the progressive death of neurons and provoke the high levels of CSF-t-tau and CSF-p-tau [6]. The finding that two proteins had decreased following surgery in Patients 1 and 2 indicated that the surgical treatments successfully prevented further neural damage.

In our patients, the levels of CSF-t-tau and CSF-p-tau were significantly lower after surgery, whereas the CSF-iron and CSF-ferritin levels showed little or no reduction. This discrepancy suggests that although haemostasis of the new bleeding point corrected iron exposure against the neural tissue, iron and ferritin were continuously released into the CSF from the haemosiderin deposited surface. Another possibility is that other blood components were causative agents of the neuronal damage as well as iron.

In conclusion, SS is associated with elevated CSF-t-tau, CSF-p-tau, CSF-iron and CSF-ferritin levels. Measuring CSF-t-tau and CSF-p-tau was useful for evaluating the effectiveness of SS treatment.

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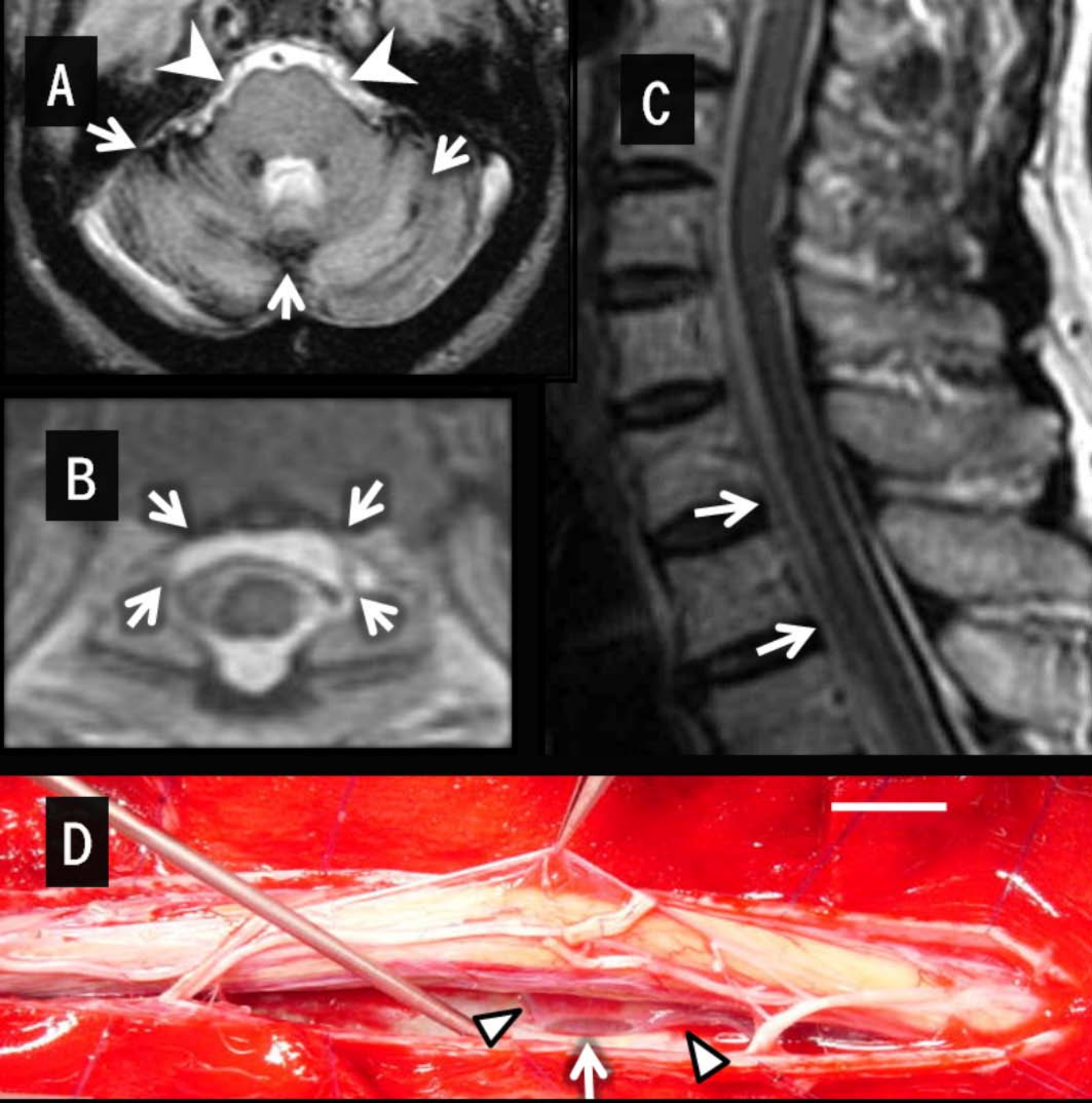
FIGURE LEGENDS

Figure 1. (A) Axial T2-weighted brain MRI in Patient 1. Signal hypointensity is observed on the surface of the cerebellum (arrows) and pons (arrowheads). (B and C) Sagittal and axial T2-weighted spine MRI in Patient 1. Surface of the spinal cord shows hypointensity, and there is fluid collection along the dorsal surface of the vertebrae (arrows). (D) Operative findings in Patient 1 (bar = 1 cm). A C2-T5 laminectomy was performed. There was a dural defect (arrow) involving the arachnoid membrane (arrowheads) at the level of T2–3.

Figure 2. (A and B) Axial T2-weighted brain MRI in Patient 2. Signal hypointensity is observed on the surface of the medulla oblongata, cerebellar hemisphere and bilateral perisylvian fissures (arrows). (C) Sagittal T1-weighted MRI of the spine with gadolinium enhancement (inset) in Patient 2. Thickening of the meninges with slight enhancement is seen at the level of the sacral vertebrae (arrow). (D) Operative findings in Patient 2 (bar = 1 cm). On L4-S3 laminectomy, a bleeding point (arrow) with thickened dura (arrowheads) was detected.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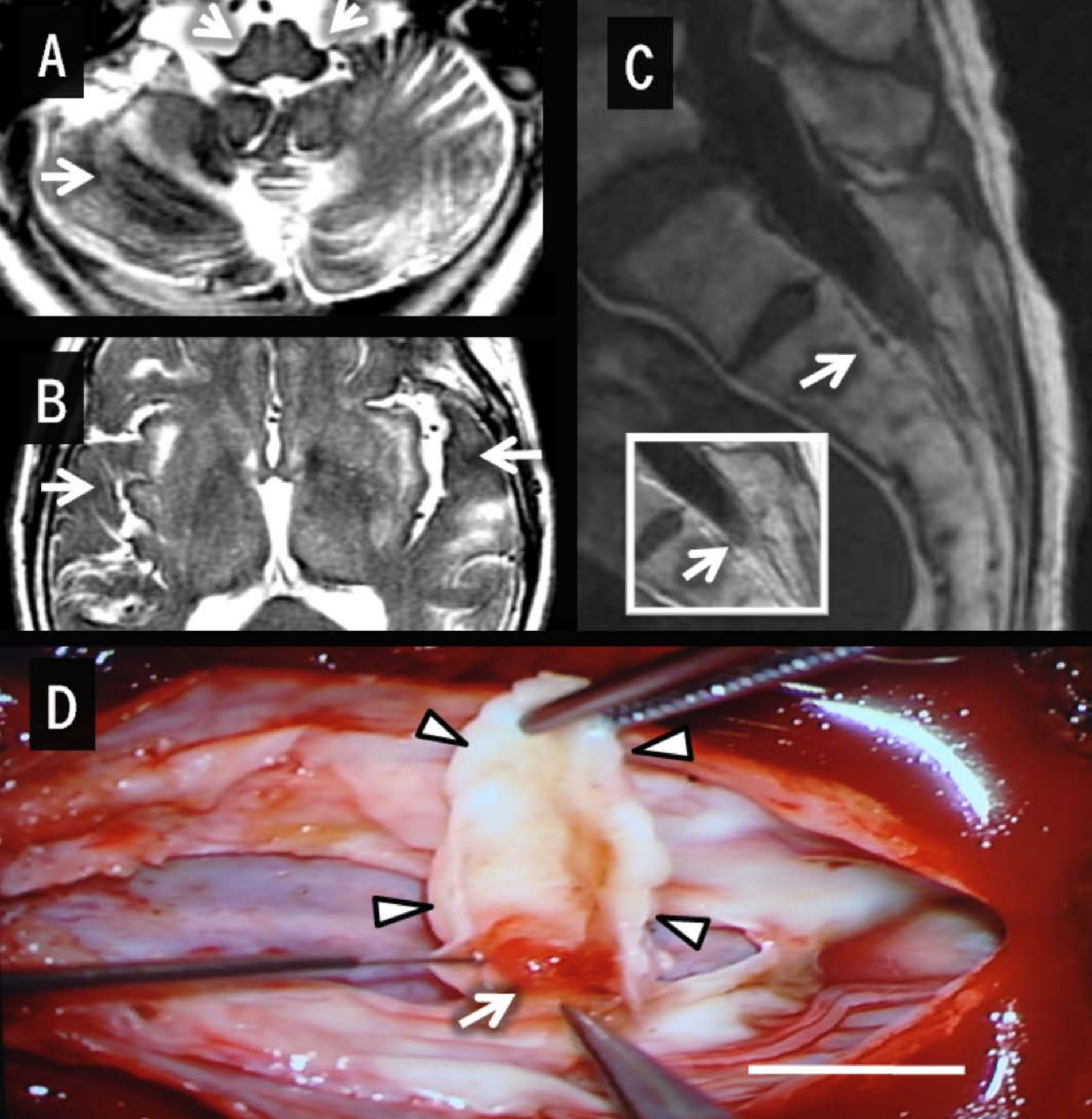
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