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BRIEF REPORT

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Central pontine myelinolysis after liver transplantation: a case report

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Abstract A patient development deteriorating mental status, quadriparesis, and severe pseudobulbar palsy with the inability to speak or swallow following orthotopic liver transplantation (OLT). Subsequently, abnormalities were found in the pons on MRI that were consistent with central pontine myelinolysis (CPM). Marked recovery occurred following transfer to the rehabilitation medicine service. Seven months following development of CPM, a mild dysarthria has persisted, but full ambulation has returned. Although no significant fluctuations in serum sodium were seen perioperatively, multiple risk factors associated with the development of CPM were present, including end-stage liver disease, a history of alcohol abuse, malnutrition, hypoxia, and use of cyclosporin medication postoperatively. This case demonstrates that the development of CPM may occur following OLT despite meticulous attention to serum sodium concentrations. We conclude that CPM is multifactorial in nature. There can be a great variation in its clinical course.

Key words Pontine myelinolysis, liver transplantation · Liver transplantation, central pontine myelinolysis

Introduction

Multiple neurological complications surround orthotopic liver transplantation (OLT). Central pontine myelinolysis (CPM) is a demyelinating syndrome that occurs in the basis pontis and is often diagnosed postmortem. CPM is a rare neurological syndrome with a relatively high incidence following OLT [12, 26]. We present a case of CPM following OLT that demonstrates a marked recovery of function. This case also demonstrates the multifactorial of CPM following OLT.

Case report

A 38-year-old male had end-stage liver disease caused by autoimmune hepatitis and chronic alcohol abuse. On 12 January 1994 the patient was admitted with a grade 3 hepatic encephalopathy following a rapid decline in mental status. His serum sodium concentration was 127 mEq/l. Renal function was normal. A CT scan of the head was obtained in order to find any other cause for the patient's decline in mental status. This scan demonstrated only mild diffuse cerebral edema. Liver transplantation was performed the day after admission (13 January 1994). The procedure lasted 9.5 h. No attempts were made to correct the hyponatremia seen on admission either preoperatively or intraoperatively. Intraoperative transfusion requirements were 12 units of red blood cells, 16 units of fresh frozen plasma, 20 units of cryoprecipitate, 1000 ml of albumin, and 14 liters of crystalloid solution. The maximum intraoperative serum sodium was 135 mEq/l.

On the 1st postoperative day, the patient had fully regained consciousness. He initially required 100 % oxygen to maintain a PO_2 of 70. Oxygenation subsequent improved and extubation was successful 2 days later. At this time, the patient was noted to be alert, talking appropriately, and moving all four extremities without evidence of weakness. Immunosuppressive therapy, intravenous cyclosporin, was initiated at 3 mg/kg. On the 4th day, the patient's mental status began to deteriorate and his speech became slurred. Several generalized seizures were witnessed. One day later, he was not responding to commands. Speech and gag response were absent, and marked weakness had developed in all extremities. A CT scan of the head showed a mild increase in ventricular size but was essentially normal.

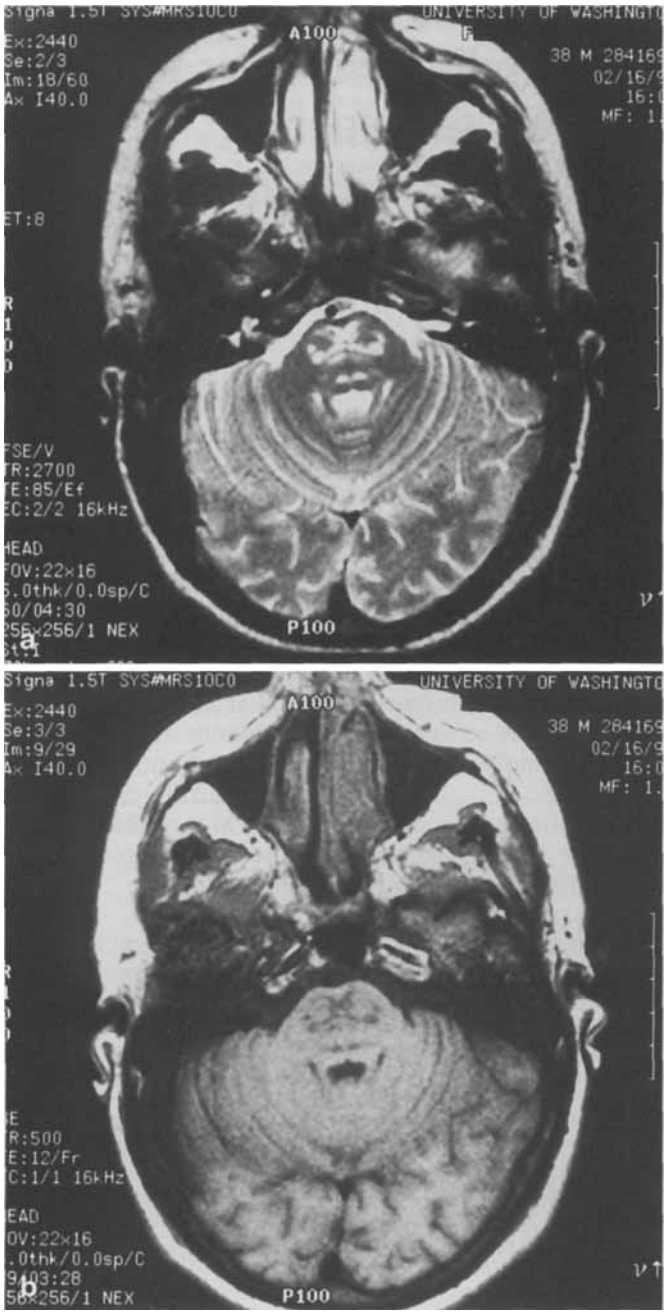

Fig. 1. **a** T2-weighted magnetic resonance image, 34 days after liver transplantation, showing areas of increasing signal intensity in the basis pontis. **b** T1-weighted magnetic resonance image showing areas of decreased signal intensity in the basis pontis

Electroencephalography demonstrated diffuse slowing, but no epileptiform activity. Cerebrospinal fluid studies were normal. Intravenous cyclosporin was given beginning on postoperative day 3. Cyclosporin was discontinued after the seizures, and a cyclosporin level of 68 ng/ml was recorded. Immunosuppressive therapy was maintained with prednisone, azathioprine, and OKT3. Oral cyclosporin was introduced after the T tube was clamped on postoperative day 11, and the patient was maintained on prednisone, azathioprine, and cyclosporin for long-term immunosuppression.

The initial MRI, on 20 January, showed only mild cerebral edema. Subsequently, on day 34 postoperatively, a repeat MRI showed lesions in the pons that produced a hypointense signal in T1 and a hyperintense signal in T2 (Fig. 1). CPM was diagnosed on the basis of clinical presentation and MRI findings.

The patient continued to make steady progress. Three weeks following surgery, he was awake and following simple commands. By week 4, moderately dysarthric speech was present, but dysphagia had subsided. At this point, the patient was transferred to rehabilitation medicine. A program of intensive physical, occupational, and speech therapy was instituted. Within 1 months of transfer, the patient was ambulating with only the aid of a single point cane. Speech similarly improved, but remained slow and mildly dysarthric at the time of discharge to home.

Recovery of function continued following return to home. Outpatient therapy continued. In the 7th month following OLT, the patient's weakness had resolved. He had returned to walking and slow running activities without balance difficulties. He had also gone back to work part-time with plans to return to full-time work when his endurance would allow. Speech was still mildly dysarthric, but this also had continued to improve.

Discussion

CPM following OLT has been well documented in the literature [1, 7–9, 12, 18, 25, 26]. The majority of cases previously reported were diagnosed on postmortem examinations [9, 12, 18, 26]. Winnock et al. [25] has reported two cases of CPM following OLT in which the patients survived but were left with severe neurological sequelae.

The onset of the disease typically occurs during the 1st week postoperatively and continues for several days without evidence of neurological impairment [11]. Clinical evidence of CPM includes a change in level of consciousness, pseudobulbar palsy including dysarthria and dysphagia, and quadriparesis [12, 19, 26].

Considerable debate remains as to the etiology of CPM. The most widely accepted theory is that CPM is due to a rapid rise in serum sodium concentration. Clinical studies have shown an association between correction of sodium greater than 25 mEq/l in the first 24–48 h and development of CPM [20]. Animal studies using rapid correction of hypoatremia with hypertonic infusion have also shown demyelinating lesions [6, 16, 23]. Others have shown that overcorrection of hyponatremia is associated with CPM [4, 5]. Lien and associates have established that rapid correction of hyponatremia in rats resulted in brain dehydration with elevation of brain sodium and chloride levels, while the reaccumulation of organic osmolytes intracellularly to protect the cell from osmotic injury was delayed [17]. It is suggested that CPM may result from ion-induced injury of brain cells that are inadequately protected by organic osmolytes.

Holt et al. [15] has demonstrated intraoperative increases in serum osmolality. The preoperative plasma so-

dium level and the number of blood products required to be transfused during surgery to correct for blood loss were the factors of importance. Patients undergoing OLT are typically hyponatremic. Transfusing hypertonic blood products in patients with liver disease and concomitant impaired renal excretion of sodium increases the risk of a rapid rise in serum sodium concentration. Careful monitoring and control of sodium input and output during surgery is, therefore, crucial. Winnock et al. [25] advocated the use of sodium-free replacement fluids and continuous venovenous hemofiltration to offset the high-sodium blood products transfused during surgery.

Factors other than the correction of hyponatremia as the cause of CPM have also been proposed. Frequently, the diagnosis of CPM is made in the setting of severe medical conditions including advanced liver disease, alcoholism, pneumonia, and malnutrition [3, 14, 22, 24] without a history of a rapid rise in sodium [8, 14]. Hypoxic brain damage has been shown to result in diffuse cerebral demyelinating lesions [2, 13, 21]. Tien et al. [22] reviewed 20 cases with the diagnosis of CPM and severe hyponatremia. They found no correlation between the rate of sodium correction and the development of CPM. Fifteen of the 20 patients had extrapontine demyelinating lesions, while only 5 had evidence of pontine demyelination. All but one of the patients had a diffuse hypoxic event prior to treatment for hyponatremia. Tien proposed that hypoxia is the most important factor in the development of cerebral demyelination following hyponatremia and that it is usually in the setting of chronic alcoholism or advanced liver disease.

Neurotoxicity from medications used post-OLT is probably another risk factor for developing CPM. Bird et al. [7] reported three cases of cyclosporine-associated akinetic mutism (lack of spontaneous motor or verbal responses) that developed on the 3rd day after cyclosporine was started. These deficits rapidly resolved following the cessation of cyclosporin. Two of the patients went on to develop a pseudobulbar palsy after the medication was withdrawn and after the akinetic mutism had improved. These two patients developed lesions in the pons, as seen on MRI, that were compatible with CPM. In neither of these patients was a significant change in serum sodium demonstrated perioperatively. De Groen et al. [10] presented the cases of three patients who developed mental status changes, cortical blindness, and weakness within 1 week of starting cyclosporin following OLT. In all cases, a cerebral CT scan showed diffuse cerebral hypodensity of the white matter. Symptoms resolved with cessation of cyclosporin and radiographic findings were reversed on subsequent examinations.

The relatively high incidence of CPM following OLT appears to be multifactorial in nature. Patients undergoing OLT may be at special risk for developing CPM due to predisposing factors such as end-stage liver disease, alcoholism, and malnutrition. These predisposing factors, in conjunction with perioperative serum sodium changes, hypoxia, and use of medications such as cyclosporin postoperatively, enhance the likelihood of developing CPM following liver transplantation.

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