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Pontine myelinolysis following liver transplantation: a report of two cases

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Abstract. Two cases of central pontine myelinolysis (CPM) following orthotopic liver transplantation (OLT) are reported. Several months after the onset of this neurological syndrome, the two patients are still alive but with severe neurological sequelae. Some patients undergoing emergency OLT present a high risk of CPM because of pre-existing malnutrition, encephalopathy, and hepatic insufficiency. All of these are associated with an inevitable abrupt rise in sodium serum concentration due to intraoperative compensation of blood losses with high-sodium content blood products. Whenever the renal capacity to excrete sodium is impaired by the surgical procedure, continuous intraoperative venovenous hemofiltration is recommended.

Key words: Myelinolysis, liver transplantation – Pontine myelinolysis, liver transplantation – Liver transplantation, pontine myelinolysis

Central pontine myelinolysis (CPM) is a serious, but fortunately rare, neurological syndrome, most commonly encountered in patients with advanced liver disease. Orthotopic liver transplantation (OLT) appears to be related to a relatively high incidence of this condition, which is due to an accumulation of predisposing factors in some patients. The two cases presented here highlight some of the clinical features of CPM occurring in patients undergoing liver transplantation.

Case reports

Case 1

Mrs. O., 31 years old, presented with a progressively deteriorating autoimmune hepatitis since April 1982. In early December 1988 there was a rapid onset of severe hepatocellular insufficiency with grade 3 hepatic encephalopathy (triphasic slow waves on EEG), ascites, oliguria, and coagulation disorders (thrombocytopenia, factor V activity 11%, normal values 70%–120%), an indication for emergency OLT. A preoperative hyponatremia (serum sodium concentration of 115 mmol/l, normal values 135–145 mmol/l) was corrected preoperatively within 48 h by infusion of 10% hypertonic saline (12 mmol/h). Serum sodium concentration was 135 mmol/l prior to surgery. A further increase of 10 mmol/l in sodium serum concentration was observed during surgery (Fig. 1). The operation (on 7 December 1988) lasted 10 h and the patient was transfused with an overall volume of 10.8 l, including 3.5 l of fresh frozen plasma, 3.3 l of red blood cells, 2.5 l of autotransfusion, and 1.5 l of 4% human albumin. Consciousness was regained completely 8 h later in the intensive care unit. Twenty-four hours after surgery, the patient became agitated with clonic jerks in all four limbs; she subsequently presented with a temperature of 40°C, followed by obnubilation and flaccid tetraplegia 4 days after surgery. During the following days there was extensive cranial nerve involvement with disturbances in swallowing and phonation, facial diplegia, aphemia, and loss of voluntary buccopharyngeal motoricity, despite sustained reflex activity. There was total spasticity in all four limbs and the typical "locked-in" syndrome was complete.

On day 45 postoperatively, magnetic resonance imaging (MRI) demonstrated lesions of the cerebral trunk with a hypointense appearance in T1, hyperintense in T2, in the pons and, to a lesser extent, in the superior cerebral peduncles (Fig. 2).

Considerable progress was observed over the ensuing months and the patient progressively regained normal vigilance. She was weaned from mechanical ventilation and the tracheal tube was removed. Improved buccolingual mobility enabled production of a few articulated sounds and oral feeding could be resumed. There is now some functional motor recovery and the patient is able to stand and walk several meters with assistance.

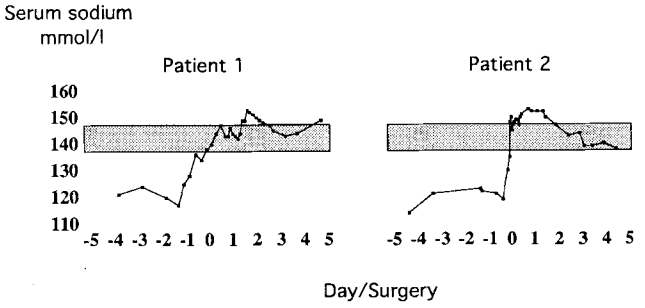

Fig. 1. Perioperative levels of serum sodium. ▭ Normal value

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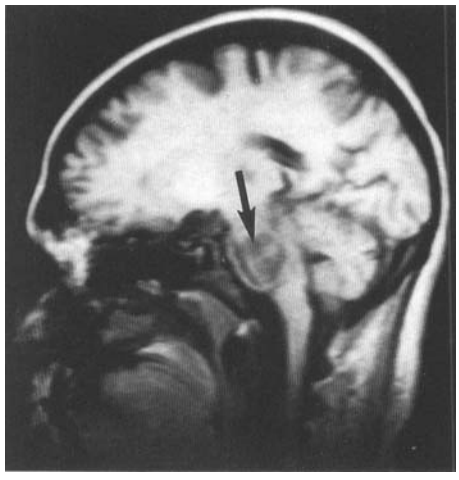

Fig. 2. Magnetic resonance imaging in patient 1 (T1): sagittal section demonstrates a hypointense abnormality, in the pons *(arrow)*

In view of the failing renal function in this patient, cyclosporin was only started on day 6 postoperatively at a dose of 2 mg/h, then 3 mg/h (whole blood cyclosporin level 111 ng/ml on day 7). Administration was maintained thereafter.

Case 2

Mr. D, 32 years old, presented with a familial hemochromatosis with a progressive deterioration in liver function that in October 1989 was heralded by the onset of ascites accompanied by oliguria, grade 3 hepatic encephalopathy with severe metabolic and coagulation disturbances (serum sodium 120 mmol/l, serum creatinine 230 µmol/l, normal values 60–125 µmol/l, thrombocytopenia and factor V activity 15%). In the presence of renal failure, venovenous hemofiltration, combined with infusion of 10% hypertonic saline (10 mmol/h), was begun 10 h before surgery to correct the hyponatremia. Emergency OLT was carried out on 15 November 1989. The operation lasted 13 h and the patient was transfused with an overall volume of 38.2 l, including 15.5 l of fresh frozen plasma, 9.6 l of red blood cells, 11.6 l of autotransfusion, and 1.5 l of 4% human albumin. Despite continuous hemofiltration using a substitution fluid with a sodium concentration of 140 mmol/l, serum sodium had reached 150 mmol/l by the end of surgery (Fig. 1). Consciousness was fully regained 8 h later in the intensive care unit. On the 2nd postoperative day, diffuse myoclonia was observed. On the 6th day after surgery, the patient was conscious but no verbal response could be obtained from him. He developed diffuse myoclonic jerks, followed by an asymmetric flaccid tetraparesis, rapidly progressing to facial diplegia and pseudobulbar palsy. A tracheal tube was inserted after the onset of increasing pharyngolaryngeal obstruction accompanied by bronchopulmonary infectious episodes. By the 3rd postoperative week, full flaccid tetraplegia had developed with loss of all voluntary oculocephalogyric motoricity.

On day 104 postoperatively, MRI showed a hypointense signal in T1 and a hyperintense signal in T2 in a butterfly distribution involving the posterior part of the pons, which appeared enlarged, indicating an edematous reaction. Sleep EEG displayed a loss of circadian rhythmicity with sleep cycles appearing throughout the day and night. There was marked alteration in somesthetic and auditory evoked potentials.

In this patient cyclosporin had been started on day 2 postoperatively at a dose of 36 mg/day and had been increased to 60 mg/day on day 5 and to 96 mg/day on day 10 (maximum whole blood cyclosporin level 255 ng/ml on day 11 postoperatively). As cyclosporin toxicity was suspected, dosage was decreased to 72 mg/day on day 22 (cyclosporin whole blood level 154 ng/ml), and administration was kept up thereafter.

In the 20th month after OLT, the neurological state is now stable. The patient is still mute and paraplegic but with a normal level of consciousness. The deficit in his arms has regressed, especially on the right side, and the patient can write and move around in a wheelchair. He is now living at home.

Discussion

There is a relatively high incidence of CPM after OLT. Indeed, a recent review of the literature has revealed 11 studies including 37 cases of CPM after OLT [1, 2, 4, 6, 7, 9, 13, 14, 16, 17, 19]. The incidence may well be underestimated as in the past the diagnosis of CPM tended to be based on postmortem findings [5, 7, 17]. The high incidence of CPM after OLT is thought to stem from predisposing conditions in patients with end-stage liver disease that are exacerbated by surgery and certain postoperative treatments.

Malnutrition, poor clinical condition, and encephalopathy are common features of transplanted patients who develop CPM. Patients with end-stage hepatic insufficiency present all of these characteristics, and probably the best way of preventing CPM is to perform transplantation at an earlier stage of the hepatic disease. Abrupt changes in sodium and plasma osmolality are frequently seen in the perioperative period of liver transplantation, especially during the surgical procedure, and may account for the appearance of CPM. Severe preoperative hyponatremia is not a prerequisite; indeed, two of the patients reported by Wszolek et al. [19] had preoperative serum sodium concentrations of 132 and 134 mmol/l. It appears to be the extent of the rise in serum sodium (hypernatremia after moderate or normal natremia, or normonatremia after severe hyponatremia) that triggers CPM in predisposed individuals. The appropriate rate of rise of sodium concentration above which CPM can develop has been arbitrarily limited to 12 mmol/l per day over the first 24 h [12, 18], with a slower correction over the ensuing 24 h. In the cases reported here, patient 1 benefitted from a natremia correction that was slightly below these figures, which probably do not represent an adequate safety margin. In all four well-documented cases reported by Wszolek et al. [19], as well as in our two patients, there was an abrupt rise in serum sodium concentration on the day of surgery. Intraoperative changes in plasma osmolality have recently been demonstrated by Holt et al. [10] and they can be accounted for by the inevitable imbalance between input and output of sodium during surgery. Input is considerably increased as a consequence of bleeding: the sodium content for fresh frozen plasma is around 165 mmol/l, 150 mmol/l for 4% albumin solution, and 140 mmol/l for red blood cells (Bordeaux University Hospital values), i.e., well above the serum sodium of a patient with hyponatremia. Correction of blood loss will thus inevitably lead to a rapid rise in serum sodium concentration. Apart from sodium, plasma glucose is not readily regulated during or immediately after surgery, giving rise to alterations in osmolality that may play a role in the development of CPM. During the same intraoperative period, sodium excretion is often altered. Advanced cirrhosis is commonly

associated with some degree of renal insufficiency. This may be exacerbated by any intraoperative hemodynamic instability and by clamping of the inferior vena cava, especially in the absence of a venovenous bypass. In such cases, when severe renal insufficiency develops during surgery, sodium output may drop sharply. Thus, in many candidates for emergency OLT, the extra sodium input and the reduced sodium excretion yield a rapid increase in serum sodium concentration. Therefore, the variations in serum sodium concentration must be carefully monitored and controlled before and during surgery. Given enough time before surgery, hyponatremia should be corrected along the lines suggested by Oh et al. [15], using hypertonic saline solution, if necessary, or by continuous hemofiltration in oliguric or anuric patients, as suggested by Larner et al. [11]. On the other hand, if the patient goes to surgery with hyponatremia, the main objective is to increase the sodium output in order to counterbalance the unavoidable extra intraoperative sodium input (fresh frozen plasma, albumin, and antibiotic solutions). Under these circumstances, the best way of controlling sodium output is by renal assistance, preferably via pump-assisted venovenous hemofiltration, which is not affected by hemodynamic disturbances. In one of the patients of Larner et al. [11] who did not develop CPM, as well as in our second patient, fluid replacement with isotonic saline solution did not prevent a marked increase in sodium serum concentration during surgery. Therefore, sodium-free replacement fluids (glucose solutions enriched in potassium, phosphorus, calcium, and magnesium) should be used and sodium should be administered independently using hypertonic solution (sodium chloride and sodium bicarbonate), whose rate of infusion is computed from the sodium input and output, the acid-base status, and the results of serum sodium determinations. In addition, strict monitoring of glucose levels and matched administration of insulin should help prevent hyperglycemic hyperosmolarity.

Cyclosporin probably favors the development of CPM. De Groen et al. [8] and Boon et al. [3] have reported that cyclosporin, especially in a hypocholesterolemic patient, can lead to diffuse abnormalities of white matter, essentially in a posterior distribution, giving rise to the following neurological disorders: tremors, seizures and paresthesias, and, in a few cases, severe manifestations such as confusion, cortical blindness, tetraplegia, and coma. Recently, Bird et al. [2] reported three cases of cyclosporin-associated akinetic mutism, two of them with CPM lesions on MRI. The clinical signs disappeared on withdrawal of cyclosporin. Recently, one case of CPM following liver transplantation was reported in a patient treated with FK506 [16]. Both cyclosporin and FK506 probably exert their neurotoxicity through the same mechanism [16]. Although there is no direct evidence that these drugs favor CPM, these reports suggest that they should be discontinued or the doses reduced in patients exhibiting neurological signs of acute lesions of white matter, including CPM.

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