Central Pontine Myelinolysis After Orthotopic Liver Transplant—A Rare Complication

Ahmad J. Al-Sarraf, Mazhar Haque, Morris Pudek, Eric M. Yoshida

Abstract

Central pontine myelinolysis is a rare but devastating cause of morbidity and mortality after orthotopic liver transplant. The exact cause of central pontine myelinolysis is uncertain. However, rapid correction of hyponatremia has been described as a major factor. We describe a patient with central pontine myelinolysis after orthotopic liver transplant in the absence of significant hyponatremia. Although rapid correction of hypernatremia has been reported in association with central pontine myelinolysis, to our knowledge, in this case, where the serum sodium went from normal to hypernatremic, later diagnosis of central pontine myelinolysis in a postliver transplant setting is unique. We also discuss factors that may contribute to the development of central pontine myelinolysis after orthotopic liver transplant and its pathophysiology.

Key words: Hypernatremia, Hyponatremia, Neurologic complication

Orthotopic liver transplant is the treatment of choice for many acute and chronic end-stage liver diseases as well as selected cases of primary liver malignancy. With the increased number of orthotopic liver transplant, some neurologic complications have become apparent. Central pontine myelinolysis is a rare and severe neurologic complication characterized by acute central pontine neuronal demyelination along with severe occasionally irreversible manifestations (1). Central pontine myelinolysis was first described in 1959 (2) and reported after orthotopic liver transplant in 1978 (3). We report a patient diagnosed with central pontine myelinolysis after orthotopic liver transplant in the absence of significant hyponatremia. We suggest that several factors may contribute to the development of central pontine myelinolysis after orthotopic liver transplant.

Case report

A 46-year-old Asian woman underwent orthotopic liver transplant owing to end-stage decompensated cryptogenic cirrhosis with hepatic encephalopathy. Her Child-Turcotte-Pugh score was 10, and her MELD score was 29. She required multiple blood transfusions during surgery. The posttransplant period was complicated with renal impairment, steroid resistant rejection requiring anti-T-cell-depleting immunosuppressant. Unfortunately, she developed hepatic artery thrombosis and lost her graft. However, clinically she was neurologically unremarkable. She underwent a second transplant a month after the initial one. This was an ABO mismatch donor (recipient B Rh +ve, donor O Rh +ve). Her pretransplant laboratory values show total bilirubin 30 (normal, 0-18 μmol/L), direct bilirubin, 19 (normal, 0-5 μmol/L), aspartate aminotransferase, 102 IU/L, alanine aminotransferase, 89 (normal, 20-65 U/L), glutamate-pyruvate transaminase, 487 (normal, 10-55 IU/L), and serum creatinine, 123 (normal, 40-95 μmol/L). Her blood electrolytes are shown in Table 1.

There were no neurologic events noted after her first transplant. She was conscious and had stable vital body signs on postoperative day 1 after her second transplant. On the second postoperative day...
after her second transplant, the patient presented with unusual lethargy, indistinct pronunciation, and dysphasia. On her third postoperative day, the patient’s level of consciousness deteriorated with poor light reflex. She developed quadriplegia and anarthria. She followed movement with horizontal eye movement, but did not follow commands, and the Babinski sign was positive bilaterally.

The patient remained in the intensive care unit, comatose, with ventilatory support. Her renal and liver functions became essentially normal. Noncontrast computed tomography scan of the head was performed with no definite answers. Initial electroencephalogram showed diffuse metabolic encephalopathy. She was started on antiepileptic medication without any progress and no subsequent improvement in electroencephalogram. She had a magnetic resonance scan of the head, which showed increased signal in the brain stem with relatively central sparing the cortical spinal tracts as well as the periphery of the pons (Figure). These findings are suggestive of central pontine myelinolysis. The patient was diagnosed with central pontine myelinolysis. On day 9 after surgery, the patient received a tracheotomy. Until the writing of this case report, she showed some neurologic improvement around 6 weeks after the first event. She could turn her head voluntarily, but still had no response to verbal command.

Central pontine myelinolysis is a clinical syndrome characterized by quadriplegia and pseudobulbar paralysis and loss of consciousness (4). Two to 7 days after the onset of treatment of the underlying disease, correction of hydrostatic imbalance, the following symptoms may develop: progressive lethargy, dysarthria, ophthalmoplegia, dysphasia, quadriparesis, ataxia, and changes in reflexes (5). As a consequence, a locked-in syndrome (quadriplegia, anarthria, a capacity to follow the examiner with the eyes but not to follow command, and bilateral Babinski signs) develop. Central pontine myelinolysis can be reversible; however, the patient usually dies after several days or weeks. Magnetic resonance imaging plays an essential role in determining the number and extension of the lesion (6). The incidence of central pontine myelinolysis after liver transplant is approximately 5% to 10% (7-9). Many studies have examined the cause of central pontine myelinolysis after liver transplant (10-14). The largest of these studies was by Lee and associates (13), which showed that central pontine myelinolysis is likely to develop in patients with more severe preoperative dysfunction and greater changes in electrolyte imbalance.

The exact cause of central pontine myelinolysis is uncertain, although rapid correction of hyponatremia might be an important factor; other factors may include alcohol abuse and liver transplant (15). Other risk factors such as adrenal insufficiency, malnutrition, chronic renal failure, and the duration of operation and high cyclosporine levels have been identified (13-18).

Central pontine myelinolysis is associated with a rapid correction of hyponatremia exceeding 18 mmol/L in the first 48 hours. A multicenter study (19) demonstrated that not all patients with hyponatremia developed central pontine myelinolysis, but the incremental change in serum sodium 48 hour after orthotopic liver transplant in patients with central pontine myelinolysis was 19.5 ± 6.54 mmol/L, which was higher than that in patients without central pontine myelinolysis. Postoperatively, plasma osmolality also was increased. The study suggested that rapid correction of hyponatremia and abrupt change of plasma osmolality might contribute to the development of central pontine myelinolysis. In patients with liver

**Table.** Blood electrolytes as shown pretransplant, after first transplant, and after second transplant.

<table>
<thead>
<tr>
<th></th>
<th>Pretransplant</th>
<th>Postfirst transplant (day 2)</th>
<th>Preoperative second transplant</th>
<th>Postoperative second transplant (day 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mmol/L)</td>
<td>133</td>
<td>148</td>
<td>144</td>
<td>158</td>
</tr>
<tr>
<td>Magnesium (mmol/L)</td>
<td>0.92</td>
<td>1.72</td>
<td>1.1</td>
<td>1.27</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.4</td>
<td>3.6</td>
<td>3.9</td>
<td>4.5</td>
</tr>
</tbody>
</table>

**Figure.** Magnetic resonance imaging showed high-signal intensity on T2-weighted images of the central pons.
failure, glial cells do not have adequate glucose or glycogen supply, and hence, small derangements lead to energy depletion and cell death (20).

In liver disease, an osmolyte called myo-inositol is deficient (21). Osmolytes normally protect the brain from sudden changes in serum osmolality, so when they are deficient, the patient becomes at risk of developing central pontine myelinolysis. Another factor that predisposes to central pontine myelinolysis in patients with liver failure is the depletion of glycogen supplies in the brain. Glial cells in the brain use glucose to activate the Na+-K+ATPase pump in response to hyponatremia, but in the absence of glucose stores, small electrolyte derangements lead to energy depletion and cell death (15). Our patient differs from the classic cases of central pontine myelinolysis as hyponatremia was not present.

Before the second transplant, the serum sodium was near the upper limit of normal and immediately posttransplant, was greater than normal (ie, hypernatremic). Although rapid correction of hypernatremia has been reported in association with central pontine myelinolysis (22), to our knowledge, our situation, where the serum sodium went from normal to hypernatremic, appears to be unique, especially in the setting of orthotopic liver transplant. In terms of orthotopic liver transplant, neurologic events, usually as a consequence of calcineurin inhibitor agents (ie, cyclosporine/tacrolimus) are well recognized.

Dunn and associates (18) verified beyond a doubt the neurotoxicity of cyclosporine in transplanted patients. Cyclosporine-associated akinetic mutism after liver transplant also has been reported by Bird and associates (23) in 3 cases. The cyclosporine level in all patients was within the normal range and monitored regularly. The cyclosporine level in patients with central nervous system complications was higher than that in patients without central nervous system complications. A previous study suggested (24) that cyclosporine neurotoxicity could lead to white matter lesions. Interestingly, Bird and associates reported that (23) hypomagnesemia was noted preoperatively in patients after orthotopic liver transplant. Similarly, Yu and associates (14) documented low magnesium level in all their patients preoperatively. Hypomagnesemia might account for cyclosporine neurotoxicity and was associated with development of central pontine myelinolysis after orthotopic liver transplant, although the mechanism of central pontine myelinolysis was not clear.

Yu and associates (14) also suggested that surgical operation time in patients with central pontine myelinolysis was significantly longer than that in patients without central nervous system complications. They concluded that that central nervous system lesion in liver transplant recipients might be related to intraoperative bleeding, which resulted in prolonged low blood perfusion. It may be that calcineurin inhibitor agents, in combination with postoperative hypernatremia or the serum sodium changes in the process of developing hypernatremia, predisposed this patient to central pontine myelinolysis.

In conclusion, central pontine myelinolysis has multifactor causes, related to deficiencies on glial energy supply and culminating in the process of cellular death (15). Slow correction of chronic hypernatremia or, in the case of our patient, avoidance of postoperative hypernatremia in the setting of orthotopic liver transplant, is crucial for the prevention of central pontine myelinolysis.

References


