Central pontine myelinolysis following orthotopic liver transplant: association with cyclosporine toxicity

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Summary
Central pontine myelinolysis can occur after orthotopic liver transplantation leading to high mortality and serious morbidity. In our case, central pontine myelinolysis was associated with wide fluctuations in cyclosporine levels during an episode of hypocholesterolaemia, which may have precipitated central pontine myelinolysis.

Keywords: central pontine myelinolysis, liver transplantation, cyclosporine

Introduction
Central pontine myelinolysis is a distinctive lesion seen after a variety of conditions (box 1). With the widespread application of orthotopic liver transplantation, neurological complications such as central pontine myelinolysis has again come into focus.

Since the introduction of cyclosporine and the new immunosuppressent FK506, neurological toxicity has been increasingly recognised as a complication of both therapies (box 2). Also reported are instances of akinetic mutism, severe dyskinesia and pseudo-bulbar palsies. It has been shown that cyclosporine neurotoxicity is specifically aggravated by low magnesium and low cholesterol levels.

We report a case of central pontine myelinolysis after orthotopic liver transplantation in which high cyclosporine levels may have led to seizure activity, and central routine myelinolysis subsequently developed due to re-initiation of cyclosporine during an episode of hypocholesterolaemia.

Case report
A 50-year-old white man with end-stage liver disease secondary to cryptogenic cirrhosis was transplanted uneventfully with an ABO-compatible liver. During surgery there was no evidence of haemodynamic disturbances such as excessive blood loss or re-perfusion syndrome. Neurologic examination before transplantation was normal. His immunosuppressive protocol consisted of Imuran (iv 2 mg/kg), methylprednisolone (iv 1 mg/kg) and iv cyclosporine (2 mg/kg by continuous infusion) and switched to po medication when tolerated. He was extubated on the second day and was awake and neurologically stable, as were his other systems.

Central pontine myelinolysis: causes
- rapid correction of sodium and osmolality in patients who have underlying liver disease
- malnutrition
- alcoholism
- pneumonia
- advanced malignancies
- lymphoma
- severe burns
- haemorrhagic pancreatitis

Neurological complications of cyclosporine toxicity
- headache
- tremors
- convulsions
- coma
- ataxia
- quadriaparesis
- cerebral blindness

Box 1

Box 2

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On the fourth day, he developed tremors followed by typical grand mal seizures. The seizures were controlled by a combination of dilantin and phenobarbitone and by stopping cyclosporine. There was no evidence of a focal central nervous system (CNS) lesion, all cranial nerves were intact and reflexes were normal. During the time he was off cyclosporine, he continued to receive steroids and Imuran. On day 14 when intravenous cyclosporine was re-initiated, he developed global aphasia, bilateral facial nerve paralysis, quadriplegia, and loss of anal sphincter tone. It was noted at this point that cholesterol levels were low. Figure 1 shows cyclosporine (trough levels, the horizontal band on the X axis shows therapeutic levels) and serum cholesterol levels.

Computed tomography (CT) scan of the head on day 4 and repeated on day 14, showed generalised atrophy with prominent ventricles but no evidence of central pontine myelinolysis. As we suspected central pontine myelinolysis, magnetic resonance imaging (MRI) of the head was obtained which showed abnormal signals on the sagittal T2-weighted image in the thalamic and pontine areas (figure 2) and also on axial T1-weighted image (figure 3). These MRI findings were typical of central pontine myelinolysis. Lumbar puncture showed no evidence of infection.

He has made a slow recovery, being able to follow commands that are not physically taxing. MRI of the head at 1 and 6 months later (not shown) again showed evidence of central pontine myelinolysis. The cortical spinal tracts remained spared. There were gyriiform and pial enhancements which were not present earlier, the significance of which is not clear.

Discussion

Central pontine myelinolysis is a serious complication after orthotopic liver transplantation, which results in high mortality, but some recover to a variable extent, both clinically, as shown in our case, and radiographically. In our case serum sodium and magnesium were within normal limits. Serum cholesterol was the only variable which went to subnormal levels at two weeks posttransplant. The first seizure (marked by arrow in figure 1) occurred when the cyclosporine level precipitously dropped from 300 to 20 (monoclonal method measuring the parent compound), followed by unusually rapid fluctuations of cyclosporine levels when this drug was reintroduced. More significant was the fact that cyclosporine was restarted on day 14 (marked by arrow in figure 1) during a period of hypocholesterolaemia. This combination of IV cyclosporine and low cholesterol may have aggravated neurological toxicity. Other authors have found similar association between serious neurological toxicity after liver transplantation and hypocholesterolaemia. The patient was not on any drugs known to increase cyclosporine levels.

Central pontine myelinolysis is probably the most devastating neurological complication which can follow orthotopic liver transplantation. Other neurological manifestations which
Learning points

- Central pontine myelinolysis may occur following liver transplantation.
- Cyclosporine neurotoxicity is aggravated by low magnesium and cholesterol levels.

may be part of the central pontine myelinolysis syndrome include confusional state, psychosis, cortical blindness, focal paralysis, aphasia, ataxia, visual hallucinations, and seizures. The nature of the brain lesions seen on CT and MRI in central pontine myelinolysis is not clear. High cyclosporine levels in one series correlated with seizure activity, which may be a harbinger of central pontine myelinolysis, although this association has not been consistently demonstrated. In one autopsy series, CNS lesions that purportedly accounted for seizures and central pontine myelinolysis were found in 19 of 21 cases, however, these authors did not consider cyclosporine to be a significant factor.

In our case neurological symptoms may have been precipitated by rapid fluctuations in cyclosporine levels in combination with low cholesterol. Another explanation for central pontine myelinolysis could be an idiosyncratic reaction of cyclosporine as this drug readily crosses the blood–brain barrier and could be an idiosyncratic response. Care should also be taken to correct cholesterol abnormalities. CT scan may fail to detect the lesions associated with central pontine myelinolysis. MRI has been found to be more sensitive and specific, particularly in the early period, as shown by our case.

In summary, central pontine myelinolysis occurred in our patient despite careful fluid–electrolyte management and uneventful surgery and was probably related to intravenous cyclosporine. Low serum cholesterol may also have contributed to central pontine myelinolysis.

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