Neurological Complications after Liver Transplantation

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This was a single-centre, prospective study to assess the frequency of neurological complications and their impact on prolonged hospitalization in 137 liver transplant patients presenting between September 1997 and June 2010. Neurological complications were seen in 22 (16%) patients during their postoperative stay in the intensive care unit. Complications included new-onset, recurrent headache (five patients), generalized seizures (four patients), dysarthria (two patients), delirium with agitation (three patients), persistent flapping tremor (two patients), alteration in level of consciousness (three patients), central pontine myelinolysis (one patient), myopathy (one patient) and visual hallucinations (one patient). Seizures were associated with immunosuppressive drug toxicity (tacrolimus). Myopathy presenting as quadriplegia was diagnosed by muscle biopsy. The patient with central pontine myelinolysis lived in a persistent vegetative state for 2 years and died of pneumonia. In conclusion, neurological complications are frequently encountered after liver transplantation, and are an important cause of severe morbidity and prolonged intensive care unit and hospital stay.

KEY WORDS: LIVER TRANSPLANTATION; NEUROLOGICAL DISORDER; IMMUNOSUPPRESSIVE DRUGS; INTENSIVE CARE UNIT

Introduction

The increasing number of patients waiting for organ donation has led to a greater need for organ transplantation. Liver transplantation is a complex medical-surgical procedure, accepted as the best treatment option for patients with terminal hepatic insufficiency of various aetiologies. Surgical techniques and immunosuppressive drug regimens have improved greatly since the first liver transplant was performed in 1963, although many postoperative complications are still encountered. The incidence of central nervous system (CNS) complications during the postoperative period varies widely from 10 to 42%. The most common CNS complications are confusion, seizures, posterior leukoencephalopathy syndrome and the neurotoxic side-effects of immunosuppressive drugs, any of which may require prolonged intensive care or hospital stays. In addition, neurological complications are a significant cause of morbidity and mortality in patients who undergo liver transplantation.
This paper reports the findings of a prospective, single-centre study that evaluated postoperative neurological complications following liver transplantation during the period of stay in the intensive care unit (ICU).

Patients and methods

PATIENTS
Consecutive patients who underwent liver transplantation at the Akdeniz University Hospital, Antalya, Turkey, between September 1997 and June 2010 were included in this observational study. Those who survived the intraoperative or very early (first 24-h) postoperative period were followed up for neurological complications during their ICU stay. Patients who did not give authorization and written informed consent to take part in this research, on admission to the study, were excluded.

The study was approved by the Institutional Review Board of Akdeniz University.

POSTOPERATIVE NEUROLOGICAL ASSESSMENTS
Clinical neurological changes were evaluated by intensive care physicians and neurologists. Laboratory studies (including serum immunosuppressant drug levels), electromyography (EMG), electroencephalography (EEG), computed tomography (CT) and magnetic resonance imaging (MRI) were performed when indicated, according to standard hospital protocols, if the patient showed signs of neurological impairment.

IMMUNOSUPPRESSION
From the day of operation, tacrolimus was administered orally twice a day (total daily dose of 0.1 – 0.15 mg/kg body weight) for 1 year and then reduced. The dosage of tacrolimus was titrated based on daily serum measurements, to achieve therapeutic levels of 10 – 14 ng/ml. Patients who showed toxicity to tacrolimus received cyclosporine A (6 – 8 mg/kg orally twice a day). Simultaneously, from the day of operation, methylprednisolone (1 mg/kg per day) was given intravenously and tapered following surgery, according to standard hospital practice.

STATISTICAL ANALYSES
All data are presented as mean ± SD. Statistical analyses were carried out using the JMP software package, version 7 (SAS Institute, Cary, NC, USA). Continuous variables were compared using the Kruskal–Wallis or Student’s t-test, and categorical variables were compared using the $\chi^2$-test or Fisher’s exact test. A $P$-value < 0.05 was considered to be statistically significant.

Results
The study initially recruited 172 consecutive patients who underwent liver transplantation. Indications for liver transplantation of those included in the study are shown in Table 1. The patient population comprised 107 (62%) males and 65 (38%) females with a mean age of 38.0 years (range 1 – 68 years). The intraoperative and early postoperative mortality rate was 20% (35 patients), leaving 137 patients in the study. Only those patients who survived their stay in the ICU were included in the analysis. Of the surviving patients, 85 (62%) were male and 52 (38%) were female, with a mean age of 37.0 years (range 4 – 65 years).

In all patients, the mean ± SD cold ischaemia time was 5.09 ± 0.96 h (range 4 – 7 h), the warm ischaemia time was < 2 min and the mean ± SD operating time was 5.61 ± 1.34 h (range 3.3 – 11.50 h). The mean ± SD length of mechanical ventilation for patients

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Neurological complications after liver transplantation with and without neurological complications was 11.9 ± 9.9 (range 5 – 40 days) and 2.5 ± 1.3 days (range 1 – 5 days) (P < 0.001), respectively. The mean ± SD ICU stay of patients with and without neurological complications was 16.9 ± 14.8 (range 6 – 62 days) and 4.0 ± 1.9 days (range 1 – 7 days) (P < 0.001), respectively. Percutaneous tracheostomy was performed in four patients with neurological complications due to prolonged mechanical ventilation.

Neurological complications were seen in 22 of 137 patients (16%), none of whom had a history of neurological symptoms before transplantation. Complications included: recurrent headache (five patients); generalized seizures (four patients); dysarthria (two patients); delirium with agitation (three patients); persistent flapping tremor (two patients); alteration in level of consciousness (three patients); central pontine myelinolysis (one patient); myopathy (one patient); and visual hallucinations (one patient). No patient had more than one neurological complication.

The five patients with recurrent headaches had normal CT and MRI findings and no underlying cause for their headaches could be found. Symptoms resolved with simple analgesic drug treatment such as paracetamol. No patient required long-term analgesic.

Serum tacrolimus levels were elevated in three of the four patients who had seizures (25.8, 28.4 and 29.0 ng/ml), but were normal in one patient (11.6 ng/ml). Patients who experienced seizures were initially treated with anticonvulsants including phenytoin, phenobarbital and benzodiazepines, at standard therapeutic doses. Symptoms resolved after cessation of tacrolimus treatment and MRI findings indicated tacrolimus toxicity. In such patients, cyclosporine A was administered as an alternative to tacrolimus. No patient required long-term anticonvulsant therapy.

After the onset of seizures, EEG was performed. Generalized seizures were recorded and the diagnosis was confirmed by appropriate seizure patterns on the EEG. Initial CT examination showed parieto-occipital subcortical white-matter hypodensities with cortical involvement in the posterior parietal lobes (Fig. 1). MRI studies showed extensive involvement of the cortex and white matter in the frontal, parietal, temporal and occipital lobes, which resolved after the cessation of seizures (Fig. 2). Prolonged mechanical ventilation of these patients (20, 25, 26 and 40 days) necessitated percutaneous tracheostomy. The durations of ICU stay were 25, 30, 32 and 46 days, respectively. All four of these patients were treated successfully; however, long-term mechanical ventilation led to critical illness neuropathy in these patients.

Speech disorders in the form of dysarthria occurred in two patients, but CT and MRI findings were normal and the patients fully and spontaneously recovered within 2 weeks.

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**TABLE 1:**

Indications for liver transplantation in the patients (n = 137) included in the present study investigating neurological complications post-transplantation

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B without delta coinfection</td>
<td>71</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>28</td>
</tr>
<tr>
<td>Hepatitis C + alcohol abuse</td>
<td>7</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>10</td>
</tr>
<tr>
<td>Drug-related (paracetamol)</td>
<td>1</td>
</tr>
<tr>
<td>Hepatitis B + hepatocellular carcinoma</td>
<td>5</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7</td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>2</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>1</td>
</tr>
<tr>
<td>Fulminant hepatitis</td>
<td>3</td>
</tr>
</tbody>
</table>

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Delirium with agitation was seen in three patients in the early postoperative period (days 3 – 5) and was treated with chlorpromazine. Patients recovered completely within a few days.

Quadriplegia was seen in one patient in the very early postoperative period (day 2), in whom a diagnosis of myopathy was confirmed by EMG and muscle biopsy. EMG revealed significant diffuse myogenic findings in the proximal muscles in the legs and in the arms. No neuromuscular junction-blocking agent was used postoperatively and methylprednisolone was gradually tapered, ending at day 5 postoperatively. Muscle biopsy showed degeneration, regeneration and changes in diameter of myosin filaments. Percutaneous tracheostomy was performed on day 7 after surgery and the patient was admitted to the ICU because of the need for prolonged mechanical ventilation. The patient required mechanical ventilation for 28 days and was discharged from the ICU on day 32 and from the hospital on day 58 after ICU admission.

The single patient with central pontine myelinolysis remained unconscious at 3 days postoperatively. Brain CT showed normal findings. After 7 days, during which the patient’s clinical status had not improved, percutaneous tracheostomy was performed. A T2-weighted MRI revealed hyperintense areas within the centre of the pons, bilateral basal ganglia and internal capsule on day
10 postoperatively. The patient remained in a persistent vegetative state and died of pneumonia after 2 years. In this patient, the central pontine myelinolysis was thought to be associated with a rapid intraoperative increase in sodium levels (from 124 to 146 mEq/l): levels had been low preoperatively due to underlying disease.

The onset of visual hallucinations in one patient occurred one week postoperatively. Hallucinations disappeared spontaneously within 10 days without any medication. The serum level of the immunosuppressive agent cyclosporine A was 195 ng/ml (normal range 100 – 400 ng/ml) in this patient, during this period.

Discussion
The rate of early neurological complications following liver transplantation in the present study (16%) was similar to those found in previous reports, in which complication rates ranged from 10 to 42%.2 – 5,7 – 9 The reported incidence of seizure following liver transplantation varies widely, with frequencies ranging from 0 to 42%.9,11 – 14 The incidence of seizure in the present study was 3% (four patients). The aetiology of post-transplant seizures has frequently been ascribed to immunosuppressant drugs.15 Radiological examination of seizure patients in the present study revealed parieto-occipital subcortical white-matter
hypodensities, with cortical involvement in the posterior parietal lobes, and extensive involvement of the cortex and white matter in the frontal, parietal, temporal and occipital lobes. These findings suggested that these lesions could have developed due to cerebral infarctions. After the resolution of neurological symptoms and improvement in MRI results it was confirmed that the neurological pathology was related to tacrolimus toxicity. Because of this, a different immunosuppressive drug (cyclosporine A) was used in these patients.

Mild neurological symptoms including headache, paraesthesia, tremor, sleep disturbance, photophobia and dysaesthesia have been reported in 40–60% of patients treated with tacrolimus; major neurological complications such as confusion, seizures, cortical blindness, encephalopathy and coma can occur in 5–8% of patients receiving tacrolimus. Adams et al. found that seizures were the most common neurological complication reported after liver transplantation, occurring in 25% of 52 patients, while Vogt et al. reported seizures in 8 of 19 (42%) patients following liver transplantation.

Acute myopathy is a condition observed in critically ill patients with status asthmaticus. The use of neuromuscular junction blocking agents and high-dose corticosteroids is common in these patients. The symptoms of acute myopathy are non-specific, have sudden onset and prolonged duration. Acute myopathy has been reported in 7% of liver transplantation cases and the only common pathological finding is the selective loss of thick myosin filaments at muscle biopsy. The patient with acute myopathy in the present study was treated intraoperatively with intravenous vecuronium and 1 g of methylprednisolone.

Central pontine myelinolysis is a demyelinating disease of the pons, occasionally occurring in other areas of the central nervous system, and is associated with the rapid correction of hyponatraemia. Previous studies have found an association between central pontine myelinolysis and hyponatraemia ranging from 30% to 61%, although the rapid change in sodium levels may play a more important role than hyponatraemia. A prospective, multicentre study conducted over a period of 4 years found the incidence of central pontine myelinolysis among liver transplant patients to be approximately 0.29%. Central pontine myelinolysis usually occurs within the first 30 days following organ transplantation. The patient with central pontine myelinosis in the present study developed hyponatraemia preoperatively, and sodium levels increased intraoperatively due to aggressive therapy with sodium bicarbonate, which was required for the correction of metabolic acidosis.

Headaches in the early postoperative period may be associated with hypertension, fever, infection, immunosuppressive agents, or, uncommonly, intracerebral haemorrhage. Viral or fungal CNS infections are rare causes of headache in immunorestricted patients, and usually occur in the first year after transplantation. Chronic headaches are frequently associated with immunosuppressive therapy. Five patients in the present study had acute severe headache after transplantation, but all investigations were normal.

In conclusion, the present study demonstrated that neurological complications are frequently encountered after liver transplantation, being observed in 16% of patients. The mean ICU stay and length of mechanical ventilation were significantly higher in patients with, rather than those without, neurological complications. The toxic effect of...
immunosuppressive drugs should be considered as a major factor in the aetiology of neurological complications.

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Conflicts of interest
The authors had no conflicts of interest to declare in relation to this article.

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