

## **Clinical analysis of neurological complications following liver transplantation.**

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### **Abstract**

**Background:** To investigate the etiological factors and clinical features of neurological complications following liver transplantation.

**Methods:** The clinical data of 474 patients who had undergone orthotopic liver transplantation between April, 2002 and September, 2013 in our hospital were retrospectively analysed.

**Results:** There were 58 patients with neurological and nervous system complications among the 474 cases, of which 16 patients recovered from encephalopathy following both symptomatic and supportive treatment, 3 patients with seizure (1 death) and 6 patients with intracranial haemorrhage after the operation. Among 7 cases with infection in the central nervous system, 2 patients died of fungus infection. There were 11 cases with extrapyramidal damage and 15 cases with peripheral neuropathy. Neurological complications following orthotopic liver transplantation were associated with hepatic encephalopathy before transplantation, infection after transplantation and the administration of immuno-suppressants.

**Conclusion:** Neurological complications following liver transplantation are commonly seen and have a variety of etiological factors and/or clinical symptoms. Prompt and specific treatment for different etiologies can control the complications, thereby providing the patients the best chance for long term survival.

**Keywords:** Liver transplantation, Neurological complications, Nervous system diseases.

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### **Introduction**

The incidence of neurological complications is reportedly high following liver transplantation, ranging from 8.3%-42.0% [1,2]. Encephalopathy and seizures were the most common complications [3,4]. Several commonly associated clinical characteristics are as follows: it occurs at an early stage typically within 1-3 weeks of the surgery, no focal neurological sign is observed, and no specific signs appear on brain Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) and the cerebrospinal fluid is normal. Therefore, they are difficult to diagnose, and early attention is provided. Encephalopathy is the most frequently neurological complication after orthotopic liver transplantation [5]. Up to 80% of the patients exhibit a certain degree of encephalopathy during their postoperative period [6]. These symptoms occur typically, but not exclusively, within 1 month of surgery. The risk of encephalopathy after orthotopic liver transplantation is proposed to be involved in the presence of preoperative hepatic encephalopathy. However, this hypothesis has not been confirmed. In addition, function of the new liver, such as altered water and electrolyte balance and acid-base osmotic pressure, may also induce hepatic encephalopathy, metabolic

encephalopathy or cerebral oedema. Demyelination of the Central Nervous System (CNS), known as Central Pontine Myelinolysis (CPM), comprises 8%-10% of the CNS complications that occurs following orthotopic liver transplantation with an unfavourable prognosis, which is the main cause of early death in patients [7]. Currently, the etiology is not clear and there is a report that this condition is associated with electrolyte disturbances and immune inhibitors [8]. The objective of the present study is to identify the causes and consequences of neurological complications in liver transplantation recipients. We performed a retrospective analysis on the pathogenesis, clinical features and principles of management of 58 patients following liver transplantations to improve diagnosis and seek better treatment for CNS lesions.

### **Material and Methods**

#### ***Clinical data***

**Patients:** Retrospective analysis was performed on 474 orthotopic liver transplantation patients treated at our clinical center between April 2002 and September 2013. This study included 394 male and 80 female patients aged between 19

years and 79 years, with an average age of 48.2 years. 203 cases were primary carcinoma of the liver, 98 cases with either acute or chronic hepatitis, 158 cases with post-hepatic cirrhosis and 15 cases with alcoholic cirrhosis.

**Liver transplants:** Liver transplants were from cadavers without any evidence of liver disease such as fatty liver, malignant tumors etc. and the related lab tests were normal. The time of cold ischemia was 3.0 to 11.6 hours, with an average of 6.07 hours. The time of warm ischemia was 3 to 7 minutes, with an average of 4 minutes.

### ***Surgical method and post-operative treatment***

The data included 427 cases of classic orthotopic liver transplantations and 47 cases of "piggyback" orthotopic liver transplantations. The immunosuppression protocol following the procedure was Tacrolimus (FK506) or Cyclosporin (CsA) combined with cortical hormone (Prednisone, Pred) and Mycophenolate Mofetil (MMF).

Furthermore, the dose of FK506 or CsA was adjusted according to the plasma concentration and the trough concentration of FK506 was maintained between 8 to 12 ng/ml at the early stages of treatment. The trough concentration of FK506 was maintained in the range of 5 to 8 ng/ml. The trough concentration of CsA was maintained in the range of 200 to 300 µmol/l at the early stages following surgery. The CsA trough concentration was maintained in the range of 50 to 150 µmol/l.

### **Results**

Among the 474 liver transplantation recipients, neurological complications of varying degrees were observed in 58 subjects within 1-3 weeks after the surgery. As shown in Table 1, among the 58 subjects with neurological complications, encephalopathy was found in 16 subjects (27.59%). Demyelination of the Central Nervous System (CNS) was found in 2 subjects. After the intracranial pressure was reduced by dehydration and nerve nutrition supplementation, these subjects were rehabilitated. Seizure was reported in 3 subjects (5.17%), one of whom failed to respond to medical treatment with diazepam and phenytoin sodium. 6 subjects were found to have intracranial haemorrhage and underwent surgery. These patients exhibited different degrees of cerebral sequelae with a comparatively low quality of life. 7 subjects (12.07%) were found to have CNS infection. Two died of fungal infection, and the others were rehabilitated after reducing the intracranial pressure and providing antibiotic treatment. Extrapyrimal damage was found in 11 cases (18.97%) and peripheral neuropathy was observed in 15 subjects (25.86%). Mild cases were given neurotrophic drugs and severe cases were given L-dopa. All of these cases recovered after treatment.

**Table 1.** Classification of 58 patients with neurological complications out of 474 liver transplantation recipients.

Neurological complications	Cases (n)	Cases (%)
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Encephalopathy	16	27.59
Seizure	3	5.17
Intracranial haemorrhage	6	10.34
CNS infection	7	12.07
Extrapyrimal damage	11	18.97
peripheral neuropathy	15	25.86

### **Discussion**

The incidence of neurological complications is reportedly high following liver transplantation, ranging from 8.3%-42.0% [1,2]. Encephalopathy and seizures were the most common complications [3,4]. It has been confirmed that the occurrence of neurological complications in adult living-donor liver transplantation did not influence the clinical outcome and that living-donor liver transplantation is associated with a lower incidence of neurological complications than cadaveric liver transplantation (20.4% vs. 26.7%, respectively). There is a significantly lower incidence of neurological complications in patients who received a living donor liver transplantation compared with patients who had received a cadaveric graft [9,10].

We reported in the present study that the occurrence rate of neurological complication after liver transplantation in adults was 12.2% (58/474), including encephalopathy, seizure, intracranial haemorrhage, CNS infection, extrapyramidal damage and peripheral neuropathy. The results were similar with the report by Lee et al. showing that the occurrence rate of neurological complication after liver transplantation in adults was 13.9% (71/512), including encephalopathy, tremors, seizure and peripheral neuropathy [11]. However, both our results and reports by Lee et al. were different from investigation on children by Lee et al. demonstrating that neurological complication occurred in 41 of 190 (21.6%) children patients after liver transplantation, including seizures and encephalopathy [12].

Extrapyrimal damage and peripheral neuropathy are mainly related with immunosuppression neurotoxicity. However, the specific mechanism is not clear. The possibilities for the high frequency (18.97% for extrapyramidal damage and 25.86% for peripheral neuropathy) in the present study might be the high dose of immunosuppressant. The symptoms include numbness, pain, and limb tremor in the distal end of the limb, which is lighter and reversible. The prognosis is better and no special treatment is needed.

There are two other types of CNS infection that require monitoring, viral encephalitis and intracranial fungal infection. The symptoms of viral encephalitis are often mild and atypical so the condition may go undiagnosed. For intracranial fungal infection, most extracranial fungal infections have a high incidence and mortality rate. Thus, compared with general infections, the identification, diagnosis and treatment become much difficult. The initial anti-fungal drugs are limited to Fluconazole, Amphotericin B liposome [13,14]. Thus, proper

postoperative management is critical to reduce the CNS infection in patients with liver transplantations.

FK506 and CsA are the calmodulin inhibitors to induce neural systemic side effects following liver transplantation without a clear mechanism of action [3,15]. The neurotoxic effect of FK506 is stronger than that of CsA, and the incidence of tremor and insomnia are also higher than that of CsA. If the side effects of drug occur, the drug dose should be adjusted in a timely manner, or the drug should be replaced with alternative treatment. Complications of this kind of symptom are always mild and reversible with a good prognosis.

Overall, for nervous system complications associated with liver transplantation, special attention should be paid to the factors such as clinical drug concentrations, body index or clinical manifestations. With the use of CT, MRI or cerebrospinal fluid monitoring, successful diagnosis and treatment should be possible. If treated appropriately and timely, most nervous system complications will not negatively affect the long-term survival of the patients [16-22].

In conclusion, the neurological complications following liver transplantation are commonly seen and have a variety of etiological features or/and clinical symptoms. Prompt and specific treatment for specific etiological factors can limit the complications, so patients have a better chance of long term survival [23-25].

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## **Competing Interest**

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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