



Clinical Study

Central nervous system complications after liver transplantation

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ABSTRACT

We investigated the diversity of central nervous system complications after liver transplantation in terms of clinical manifestations and temporal course. Liver transplantation is a lifesaving option for end stage liver disease patients but post-transplantation neurologic complications can hamper recovery. Between 1 January 2001 and 31 December 2010, patients who had undergone liver transplantation at a single tertiary university hospital were included. We reviewed their medical records and brain imaging data and classified central nervous system complications into four categories including vascular, metabolic, infectious and neoplastic. The onset of central nervous system complications was grouped into five post-transplantation intervals including acute (within 1 month), early subacute (1–3 months), late subacute (3–12 months), chronic (1–3 years), and long-term (after 3 years). During follow-up, 65 of 791 patients (8.2%) experienced central nervous system complications, with 30 occurring within 1 month after transplantation. Vascular etiology was the most common (27 patients; 41.5%), followed by metabolic (23; 35.4%), infectious (nine patients; 13.8%), and neoplastic (six patients). Metabolic encephalopathy with altered consciousness was the most common etiology during the acute period, followed by vascular disorders. An initial focal neurologic deficit was detected in vascular and neoplastic complications, whereas metabolic and infectious etiologies presented with non-focal symptoms. Our study shows that the etiology of central nervous system complications after liver transplantation changes over time, and initial symptoms can help to predict etiology.

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1. Introduction

Liver transplantation is one of the most dynamic fields in modern medicine and is a lifesaving option for patients with end stage liver disease. Since the first successful transplantation in 1967, liver transplantation has been performed in many centers worldwide saving thousands of liver failure patients. However, the post-transplantation clinical course may be associated with neurologic complications that hamper recovery or even lead to death. Several studies have focused on neurological complications after transplantation and revealed variable incidences and grave prognoses [1–3]. The incidence of central nervous system (CNS) complications after liver transplantation is variable among studies, ranging from 10% up to 75% due to different inclusion criteria, definition of CNS complications and observation period [4–6]. Most studies, if not all, have categorized neurological complications simply based on symptomatology such as headache or seizure, not by

pathophysiological etiologies, and few studies have focused on disease time course. For prompt and appropriate management, it is desirable to assess etiologic diagnosis based on the initial symptom onset of the CNS complication. One group has previously reported the temporal course of CNS complication after transplantation, revealing that most neurologic complications (80%) took place within 1 month after transplantation [7].

Considering the tremendous improvement in surgical technique and medical management, including intensive care, chemoprophylaxis against infection and immunosuppression, it is necessary to update the etiologic diversity and initial manifestation of CNS complications following liver transplantation.

2. Methods

Between 1 January 2001 and 31 December 2010, patients who had undergone liver transplantation and regularly visited the Outpatient Clinic at the Seoul National University Hospital were reviewed. Consecutive patients who had been referred to a neurologist for consultation because of neurologic complications were

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eligible to be included in the study, and we obtained their demographic and clinical information from medical records. Neurological complication was defined when a patient had symptoms or signs due to CNS dysfunction. After reviewing medical records and brain images, we grouped CNS complication etiologies into four categories, including metabolic, vascular, infectious and neoplastic. The onset of CNS complications was categorized into five post-transplantation intervals including acute (within 1 month), early subacute (1–3 months), late subacute (3–12 months), chronic (1–3 years), and long-term (after 3 years). Their initial manifestation, medication history, underlying liver disease, laboratory tests, as well as brain imaging data were recorded.

As vascular complications were the most common etiology of CNS complications, we further evaluated their subtypes and temporal pattern. Ischemic stroke was grouped into four subgroups including large artery disease (when a relevant artery harbors significant stenosis), small vessel occlusion (with typical location and size of lacunar infarction without large artery stenosis or embolic source), embolic infarction (when multiple infarctions are documented beyond a single vascular territory), and venous infarction (when infarction was attributable to cerebral venous thrombosis). Hemorrhagic complications were grouped according to main hematoma location, including intracerebral, subarachnoid and subdural hematoma (SDH). This study was approved by the Institutional Review Board of Seoul National University Hospital, Korea (H-1106-018-364), and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

3. Results

We studied 791 patients who had undergone liver transplantation and maintained follow-up after the procedure. Of these, 65 patients (8.2%) experienced CNS complications. The mean CNS complication onset age of the patients was 57.8 years (standard deviation: 10.2), and the median follow-up period after transplantation was 39 months (interquartile range: 13–72). The underlying liver disease profiles, CNS complication etiology distribution, and initial manifestations are summarized in Table 1. The majority of the patients had either liver cirrhosis with hepatocellular carcinoma following hepatitis B virus infection (33 patients) or liver cirrhosis following other viral hepatitis (24 patients). The most common CNS complication etiology was vascular (27 patients; 41.5%), followed by metabolic (23 patients; 35.4%), infectious (nine patients; 13.8%), and neoplastic (six patients). Representative brain imaging is shown in Figure 1.

3.1. Clinical manifestations

Altered consciousness was the most common initial manifestation, which could be due to any of the four etiologies (Table 2). Patients with metabolic encephalopathy presented with non-focal neurological deficits such as altered consciousness or seizure. Three patients who initially presented with altered consciousness were diagnosed with non-convulsive status epilepticus after electroencephalography (EEG) showed a generalized spike and wave complex. The focal neurologic deficits including hemiparesis, visual field defect, and unilateral involuntary movement were common in the vascular etiology. However, despite the absence of focal symptoms, a vascular complication could not be excluded because a considerable number of stroke patients presented with non-focal neurological deficit, especially those patients with multiple embolic infarction or venous infarction who presented with altered consciousness or seizure.

Table 1

Demographic variables, clinical manifestations and etiologic classifications of patients with central nervous system complications after liver transplantation

Variables	Patients, n
Age, years, mean \pm standard deviation	57.8 \pm 10.2
Sex (male: female)	47 : 18
Liver disease	
Hepatocellular carcinoma with liver cirrhosis	33
Liver cirrhosis due to other viral hepatitis	24
Idiopathic liver cirrhosis	5
Wilson disease	2
Acute fulminant hepatitis	1
Central neurological complication	
Cerebrovascular	27
Metabolic/toxic	23
Infectious	9
Neoplastic	6
Neurological manifestation	
Altered consciousness	25
Focal neurological deficit	15
Seizure	14
Headache	8
Irritability	2
Dizziness	1
Total patients	65

3.2. Temporal course of neurological complications

The etiology of CNS complications changed over time (Fig. 2). Regarding the onset, 30 patients (46.2%) had CNS complications that occurred within 1 month after transplantation. Metabolic complications were the most common in this acute period but this decreased as time elapsed and they were rarely observed after 1 year. Vascular complications frequently occurred within 1 month and remained as a major proportion of the complications throughout the follow-up period. The proportion of CNS neoplasms increased over time and an infectious etiology was only a minor contributor in all time periods.

3.3. Vascular complications

The vascular etiologies included both ischemic and hemorrhagic complications, with ischemic complications being more prevalent than hemorrhage (17 versus 10 patients; Table 3). Ischemic stroke within 1 month after surgery was not confined to a single vascular territory in many patients, suggesting embolic infarction and venous thrombosis were predominant during this period. The embolic source was identified in three out of seven patients, including two with atrial fibrillation and the other with infective endocarditis. Venous infarction was diagnosed in five patients, with two dying during hospitalization. The most common type of intracranial hemorrhage was SDH and this had a favorable outcome. The four patients who developed SDH within 1 month recovered completely without neurological deficit. Delayed hemorrhages included subarachnoid or intracerebral hemorrhages, which were associated with a poor functional outcome. Two intracerebral hemorrhage patients died and one of the two subarachnoid hemorrhage patients became bedridden.

3.4. Metabolic and other complications

Tacrolimus or cyclosporine induced metabolic encephalopathy was suspected in nine patients, and three of them had brain lesions involving the occipital and parietal lobes which were compatible with posterior reversible encephalopathy syndrome. All of the patients recovered spontaneously after medication adjustment. Altered consciousness due to hyponatremia was observed in six patients, and three of them were diagnosed with central pontine

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