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ORIGINAL ARTICLE

CEREBROVASCULAR COMPLICATIONS AFTER LIVING DONOR LIVER TRANSPLANTATION

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Aim: *Central nervous system complications are an important cause of morbidity and mortality in transplant recipients. However, cerebrovascular complications (CVC) after living donor liver transplantation (LDLT) have seldom been reported.*
Methods: *Between June 1990 and December 2007, 1297 patients underwent LDLT at Kyoto University Hospital. A retrospective review of all patients who developed CVC after LDLT was performed.*
Results: *Of 1297 patients who received living donor liver transplantation (LDLT) at Kyoto University Hospital between June 1990 and December 2007, 14 (1.1%) developed CVC, including 11 with intracerebral hemorrhage and 3 with cerebral infarction. The onset of intracerebral hemorrhage was within 60 days (range, 1 to 58 days; median, 7 days) after LDLT. Twelve of fourteen patients died from CVC, for a mortality rate of 85.7%. Two patients had aspergillosis. Four cases had undergone retransplantation, and three patients had fulminant hepatic failure. Craniotomy with hematoma evacuation was performed in one patient.*
Conclusion: *Though CVC is not a very common post-transplant complication, it carries a poor prognosis, as it occurs mostly in critically ill and complicated cases. Therefore, every effort should be made to prevent CVC.*

Keyword: *Neurological, hepatic, recipient.*

INTRODUCTION

Since its first success in 1989, living donor liver transplantation (LDLT) has become widely accepted as the treatment of choice for end-stage liver disease.[1] Central nervous system complications are an important cause of morbidity and mortality in transplant recipients.[2] The reported incidence of central nervous system involvement varies widely from 9.7% to 42% .[3-7] However, cerebrovascular complications (CVC) after living LDLT have seldom been reported. Herein, 11 patients with intracerebral hemorrhage (ICH) and 3 patients with cerebral infarction after LDLT are reported.

PATIENTS AND METHODS

Between June 1990 and December 2007, 1297 patients underwent LDLT at Kyoto University Hospital. The transplant procedures were performed as described elsewhere.[8] The immunosuppressant protocol consisted of tacrolimus or cyclosporine and low-dose steroid.[9]

A retrospective review of 14 patients who developed CVC after LDLT was performed.

CVC was diagnosed by computed tomography and/or magnetic resonance imaging when any neurological manifestations occurred.

The clinical and laboratory data, as well as the outcomes, of these patients were reviewed. The data are presented as median and range or as mean ± SD.

RESULTS

Fourteen patients (1.1%) developed CVC. Eleven patients were diagnosed as having ICH, and 3 patients were diagnosed as having cerebral infarction on brain

computed tomography and/or magnetic resonance imaging.

There were 6 men and 8 women; their ages ranged from 1 to 59 years (median 43 years). The underlying liver disease included biliary atresia in 4 patients, hepatitis B or C virus-related cirrhosis in 3, fulminant hepatic failure in 3, primary biliary cirrhosis in 2, hepatocellular carcinoma in 1, and alcoholic liver cirrhosis in 1 patient. With respect to their preoperative status, 6 patients were in the intensive care unit, 5 patients were hospitalized, and 3 patients were at home. With respect to their relationship to the recipient, the donors consisted of 4 mothers, 4 sisters, 2 husbands, 1 father, 1 son, 1 daughter, and 1 wife. With respect to ABO blood type combinations, there were 9 identical and 5 incompatible cases. The graft-to-recipient weight ratio ranged from 0.61% to 2.08% (median 1.06%). The graft types were right lobe in 8 cases, left lobe in 4 cases, and left lateral segment in 2 cases.

These patients' clinical details are listed in Table 1. Their laboratory data at the time of LDLT were: prothrombin time, 18.5 ± 5.8 sec; activated partial thromboplastin time, 35 ± 3.3 sec; and platelet count, 6.9 ± 3.05 x 109/L). The operative time was 700 ± 273 min, blood loss during surgery was 6798 ± 5719 mL, and blood transfusion requirements were 12.8 ± 12 units.

Table 1. Clinical data of patients with CVC after LDLT.

					Parameter			
Patient No.	**Age (Years)**	**Sex**	**Disease**	**CVC**	**CVC onset (days after LDLT)**	**Outcome**	**Survival after LDLT Days**	**Possible Cause**
1	14	M	BA	Infarct	11	Death	19	Tac Toxicity
2	8	M	BA	ICH	5	Death	54	Tac Toxicity
3	43	F	PBC	Infarct	6	Death	22	Tac Toxicity
4	48	F	PBC	Infarct	9	Survived		Tac Toxicity
5	47	F	HCV-LC	ICH	5	Death	40	Tac Toxicity
6	11	F	BA,RT	ICH	1	Death	20	Severe HC
7	8	F	BA,RT	ICH	1	Death	3	Severe HC
8	1	M	FHF,RT	ICH	26	Death	28	Severe HC
9	55	F	HBV,LC	ICH	48	Death	50	Severe HC
10	42	F	FHF	ICH	58	Death	79	Severe HC
11	45	F	HCC	ICH	11	Death	48	Aspergillosis
12	59	M	FHF	ICH	7	Death	12	Aspergillosis
13	59	M	ALC,RT	ICH	3	Death	4	Amoebaisis
14	55	M	HBV,LC	ICH	47	Death	323	Severe HTN

Abbreviations: M, male; F, female; BA, biliary atresia; RT, retransplantation; PBC, primary biliary cirrhosis; FHF, fulminant hepatic failure; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; ALC, alcoholic liver cirrhosis; HCV, hepatitis C virus; LC, liver cirrhosis; CVC, cerebrovascular complication; ICH, intracerebral hemorrhage; HC, hepatic coma; HTN, hypertension, Tac; Tacrolimus.

The onset of CVC was within 60 days (range, 1 to 58 days; median, 7 days) after LDLT. ICH occurred in the parietal or frontal lobes. One patient underwent craniotomy and hematoma evacuation, but the patient died.

Twelve patients with CVC died within 80 days (range, 1 to 58 days; median, 7 days) after LDLT and within 50 days (range, 2 to 49 days; median, 15 days) after the onset of CVC, while one patient died from other causes 323 days after LDLT.

The patients were divided into five categories based on the possible causes of the cerebrovascular complications. The first group (n=5) develop CVC after a relatively good postoperative course that was most probably due to Tacrolimus toxicity.

The second group (n=5) suffered from severe hepatic coma after transplantation without recovery of consciousness. The third group (n=2) developed CVC due to Aspergillus infection.

One patient (Fourth group) developed CVC due to angiopathy caused by severe hypertension and diabetes mellitus. The last patient had (Fifth group) an interesting

course; his original disease was fulminant hepatic failure caused by HBV, and shortly after transplantation, he developed intestinal amoebiasis followed by amoebic hepatitis, and then developed sudden loss of consciousness and cerebral bleeding.

DISCUSSION

Neurological complications are commonly encountered in patients undergoing LT, with a reported incidence of 9.7% to 42%.[3-7] These complications are a major cause of morbidity and mortality after LT,[10] and, of these complications, intracerebral hemorrhage is the most severe.[11]

The incidence of intracerebral bleeding was 1.5 % in a report by Bronster et al.,[2] which was similar to our incidence of 1.1 %, while Kim et al. reported an incidence of 4.1 %.[11]

Regarding possible causes of ICH

Wang et al.[12] hypothesized that massive blood loss during LT may cause hypotension, which results in cerebral infarction and cerebral hemorrhage in the presence of coagulopathy during the postoperative period. Moreover, Wjidicks et al.[13] reported that overwhelming infections, thrombocytopenia, or both may trigger cerebral hemorrhage, usually during the first two months after LDLT.

Tacrolimus is an immunosuppressive agent tacrolimus (FK506) which is associated with severe neurological complications, particularly in the early postoperative period after LT. Follow-up studies have revealed a more frequent occurrence of late neurotoxicity among patients treated with Tacrolimus. In addition, if late neurological complications develop, the mortality rate is significantly higher.[14]

Aspergillus is an airborne fungus present in all environments, both inside and outside the hospital. Only a few species cause human illness.Mortality associated with invasive aspergillosis is nearly 100% if the disease is not treated.[15]

It was difficult to identify the factors that were the prime contributors to CVC in the present cases. We believe that the risk factors predisposing to CVC are many. CVC occurred in patients who required intensive care management, and in the majority of cases, the occurrence of CVC was related to the patients' critical condition, such as fulminant hepatic failure, and it was unlikely to occur in uncomplicated cases.

Hemorrhage and infarcts may occur throughout the postoperative period. Infarcts tend to occur within 1 week, whereas hemorrhage occurs within 1 month.[16]

Singh et al. reported that hemorrhagic events and infarcts occurred a median of 27 and 5 days, respectively, after LT,[17] and other research on liver transplant recipients indicated that 75% to 87% of neurological complications developed during the first month after transplantation.[2] In the present study, CVC occurred within 60 days after LDLT, with a median of 7 days.

Hemorrhage in the central nervous system typically occurs in the frontal and parietal lobes, but less commonly in the subcortical regions,[16] which is in line with the present results. Although craniotomy and hematoma evacuation were performed in one case, they did not alter the outcome. Even in the presence of midline shift, it is questionable whether craniotomy would be of value.[11]

ICH has been strongly associated with mortality.[18] In several clinical series, 66% of patients with ICH after orthotopic LT died.[19] In the present study, the mortality was 85.7% which is close to that reported by Wang et al[12] (80%).

In conclusion, though CVC is not a very common post-transplant complication, it carries a poor prognosis, as it occurs mostly in critically ill and complicated cases. Therefore, every effort should be made to prevent CVC.

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