Rapid progression of encephalopathy in a patient with hepatitis B infection

Nobuyuki Takemura, Yasuhiko Sugawara*, Sumihito Tamura, Junichi Kakeno, Yuichi Matsui, Masatoshi Makuuchi

Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, the University of Tokyo, Tokyo, Japan.

SUMMARY **The mortality rate of fulminant hepatic failure was high until liver transplantation was presented as a potential therapy. We encountered a patient with hyperacute fulminant hepatic failure due to hepatitis B virus infection. Living donor liver transplantation was planned but abandoned because her brain edema progressed too rapidly to complete the donor evaluation. The present case reveals the limitation of living donor liver transplantation as a treatment for hyperacute fulminant hepatic failure.**

Key Words: Fulminant hepatic failure, brain edema, hepatic encephalopathy, hyperacute, fulminant hepatitis B

Introduction

Fulminant hepatic failure (FHF) is characterized by the acute onset of progressive jaundice, increased liver transaminase, prolonged prothrombin time, decreased liver size, and hepatic encephalopathy. The 1-year survival rate ranges from 65% to 92% in deceased donor liver transplantation (*1-4*) and 59% to 90% in living donor liver transplantation (LDLT, *5-7*). We encountered a patient with a rapid course of FHF and here discuss the indications of LDLT for FHF.

Case Report

A 22-year-old previously healthy woman felt general malaise on April 16th, 2004. Her body temperature became elevated 3 days after onset, and she was admitted to a hospital on April 21st. The patient was conscious and lucid; physical examination revealed no abnormalities except for mild conjunctival jaundice. Biochemical data were as follows: total bilirubin, 5.7 mg/dl (normal, 0.3-1.3 mg/dl); direct bilirubin, 3.5 mg/dl (0.0-0.2 mg/dl); serum aspartate aminotransferase, 6,090 IU/l (9-38 IU/l); serum alanine aminotransferase, 6,410 IU/l (4-36 IU/l); prothrombin time, 51.8 sec (10-13.5 sec); and ammonia, 111 μg/dl (< 90 μg/dl). Serologic analysis was positive for hepatitis B surface antigen, negative for hepatitis B surface antibody, positive for hepatitis B envelope antigen, negative for hepatitis B envelope antibody, and positive for IgM-hepatitis B core antibody.

Plasma exchange and hemodiafiltration were started. Methylprednisolone (1 g), interferon beta (3×10^6 U), and lamivudine (100 mg) were administrated. In spite of intensive medical care, the patient's consciousness was disturbed. She developed stage 2 encephalopathy (*3,8*, Table 1) 12 h after admission. She was diagnosed with hyperacute FHF due to hepatitis B infection (*9*).

She was transferred to our hospital on April 22nd for liver transplantation. On admission, her electroencephalogram showed diffuse slow waves. Computed tomography of the brain performed immediately after admission revealed mild brain edema. She was responsive only to noxious stimuli and her neurologic status had advanced to stage 4/grade 2. Corneal light reflex was preserved. Abdominal computed tomography revealed a total liver volume of 772 mL, corresponding to 80% of her standard liver volume (*10*).

Plasma exchange and hemodiafiltration were continued after admission to our hospital. Urgent transplantation was prepared although transplantation

**Correspondence to :* Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, the University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan;
e-mail: yasusuga-tky@umin.ac.jp

Received June 6, 2007
Accepted June 25, 2007

Table 1. Hepatic encephalopathy and coma classifications (*3,8*)

	Encephalopathy classification
Stage 1	Slowness of mentation and affect, euphoria
Stage 2	Drowsiness, inappropriate behavior, presence of asterixis
Stage 3	Incoherent words, marked confusion, reaction to vocal stimuli
Stage 4	Deep coma without vocal stimuli
	Coma sub-classification for encephalopathy stages 3 and 4
Grade 1	Uncoordinated reactivity to vocal stimuli
Grade 2	Absence of reactivity to vocal stimuli, coordinated response to nociceptive stimuli
Grade 3	Uncoordinated response to nociceptive stimuli
Grade 4	Brain death

was not indicated for the patient according to the criteria of the King's College group (*11*), Takahashi *et al.* (*12*), or Yoshiba *et al.* (*13*). The patient's 42-year-old mother was willing to donate part of her liver and we began the necessary physical, psychological, and biochemical examinations. During evaluation of the patient's mother as a potential donor, however, the patient's neurologic status progressed to stage 4 encephalopathy and grade 3 coma on April 23rd. An electroencephalogram showed electrocortical silence. Brain computed tomography showed that the sylvian fissures and cerebral sulcus had completely disappeared. LDLT was abandoned and the patient died 12 h after her arrival at our hospital (36 h after the onset of encephalopathy).

Discussion

In the present case, encephalopathy progressed rapidly. The time period between the appearance of jaundice and the development of encephalopathy was 36 h and the patient was classified as hyperacute (*9*). Evaluation and preparation of the potential living donor was not completed in time. Hattori *et al.* encountered two patients who suffered brain death within 3 days while awaiting LDLT (*14*). Donor safety must remain the first priority in high acuity situations, however, and the donor work-up is more difficult due to the time constraints (*15*). Careful screening for any conditions that represent an increased risk to the donor is essential. The same exclusion criteria that apply in elective situations must also apply in emergent cases, and no exceptions should be made to accommodate the needs of the recipient.

The incidence of neurologic death is 4% to 11% after deceased donor liver transplantation for FHF (*3,16*), suggesting that preoperative evaluation of the neurologic status or prediction of the neurologic results after transplantation is difficult. Whether LDLT should be performed for FHF with severe encephalopathy and brain edema is controversial. The Kyoto group treated a patient that developed widespread brain necrosis after LDLT with preoperatively diffuse brain edema (*14*), though the patient ultimately died of sepsis without neurologic recovery. Sterneck *et al.* reported three FHF patients that died of cerebral herniation after LDLT (*17*). Intracranial pressure is now monitored to evaluate brain edema (*18,19*) in patients with grade 3 or 4 coma. It is not used in our department, however, to avoid complications including hemorrhage and infection. The intracranial hemorrhage rate is 8% to 10%, which includes 2.7 % to 3.4% in fetal cases (*20,21*).

During donor evaluation, LDLT was contraindicated due to the advancement of the patient's encephalopathy. In high acuity situations, donor selection should be completed as soon as possible in the event of sudden progression of encephalopathy. The present case reveals the limitations of LDLT as a treatment for hyperacute FHF.

Acknowledgements

This work was supported by a Grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan and Grants-in-aid for Research on HIV/AIDS and Research on Measures for Intractable Diseases from the Ministry of Health, Labor and Welfare of Japan.

References

1. Munoz SJ, Moritz MJ, Martin P, Jarrell BE, Maddrey WC. Liver transplantation for fulminant hepatocellular failure. Transplant Proc 1993;25:1773-1775.
2. Ascher NL, Lake JR, Emond JC, Roberts JP. Liver transplantation for fulminant hepatic failure. Arch Surg 1993;128:677-682.
3. Bismuth H, Samuel D, Castaing D, Adam R, Saliba F, Johann M, Azoulay D, Ducot B, Chiche L. Orthotopic liver transplantation in fulminant and subfulminant hepatitis. The Paul Brousse experience. Ann Surg 1995;222:109-119.
4. Farmer DG, Anselmo DM, Ghobrial RM, *et al*. Liver transplantation for fulminant hepatic failure. Ann Surg 2003;5:666-675.
5. Miwa S, Hashikura Y, Mita A, Kubota T, Chisuwa H, Nakazawa Y, Ikegami T, Terada M, Miyagawa S, Kawasaki S. Living-related liver transplantation for patients with fulminant and subfulminant hepatic failure. Hepatology 1999;30:1521-1526.
6. Uemoto S, Inomata Y, Sakurai T, Egawa H, Fujita S, Kiuchi T, Hayashi M, Yasutomi M, Yamabe H, Tanaka K.

Living donor liver transplantation for fulminant hepatic failure. Transplantation 2000;70:152-157.
7. Nishizaki T, Hiroshige S, Ikegami T, Uchiyama H, Hashimoto K, Soejima Y, Shimada M. Living-donor liver transplantation for fulminant hepatic failure in adult patients with a left-lobe graft. Surgery 2002;131 (1 Suppl): S182-189.
8. Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis 1970;3:282-298.
9. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet 1993;342:273-275.
10. Urata K, Kawasaki S, Matsunami H, Hashikura Y, Ikegami T, Ishizone S, Momose Y, Komiyama A, Makuuchi M. Calculation of child and adult standard liver volume for liver transplantation. Hepatology 1995;21:1317-1321.
11. O'Grady JG, Alexander GJ, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. Gastroenterology 1989;97:439-445.
12. Takahashi Y, Kumada H, Shimizu M, Tanikawa K, Kumashiro R, Omata M, Ehata T, Tsuji T, Ukida M, Yasunaga M. A multicenter study on the prognosis of fulminant viral hepatitis: early prediction for liver transplantation. Hepatology 1994;19:1065-1071.
13. Yoshiba M, Sekiyama K, Inoue K, Yamada M, Kako M, Nagai K, Takatori M, Iwabuchi S, Sumino Y, Tanaka K, Hakozaki Y, Hasegawa K, Shibuya A. Accurate prediction of fulminant hepatic failure in severe acute viral hepatitis: multicenter study. J Gastroenterol 2002;37:916-921.
14. Hattori H, Higuchi Y, Tsuji M, Inomata Y, Uemoto S, Asonuma K, Egawa H, Kiuchi T, Furusho K, Yamaoka Y, Tanaka K. Living-related liver transplantation and neurological outcome in children with fulminant hepatic failure. Transplantation 1998;65:686-692.
15. Marcos A, Ham JM, Fisher RA, Olzinski AT, Shiffman ML, Sanyal AJ, Luketic VA, Sterling RK, Posner MP. Emergency adult to adult living donor liver transplantation for fulminant hepatic failure. Transplantation 2000;69:2202-2205.
16. Devlin J, Wendon J, Heaton N, Tan KC, Williams R. Pretransplantation clinical status and outcome of emergency transplantation for acute liver failure. Hepatology 1995;21:1018-1024.
17. Sterneck M, Fischer L, Buggisch P, Malago M, Rogiers X, Burdelski M, Greten H, Broelsch CE. Transplantation of complete and split liver grafts for patients with fulminant hepatic failure. Z Gastroenterol 1996;34:795-800.
18. Munoz SJ, Robinson M, Northrup B, Bell R, Moritz M, Jarrell B, Martin P, Maddrey WC. Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. Hepatology 1991;13:209-212.
19. Detry O, Arkadopoulos N, Ting P, Kahaku E, Margulies J, Arnaout W, Colquhoun SD, Rozga J, Demetriou AA. Intracranial pressure during liver transplantation for fulminant hepatic failure. Transplantation 1999;67:767-770.
20. Blei AT, Olafsson S, Webster S, Levy R. Complications of intracranial pressure monitoring in fulminant hepatic failure. Lancet 1993;341:157-158.
21. Vaquero J, Fontana RJ, Larson AM, Bass NM, Davern TJ, Shakil AO, Han S, Harrison ME, Stravitz TR, Munoz S, Brown R, Lee WM, Blei AT. Complications and use of intracranial pressure monitoring in patients with acute liver failure and severe encephalopathy. Liver Transpl 2005;11:1581-1589.