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Case Report

Living Related Liver Transplantation for Acute Fulminant Hepatitis B: Experience from Two Possible Hyper-Acute Cases

JUN INOUE, YOSHIYUKI UENO, NORIATSU KANNO, HIDEAKI ANZAI, YASUTERU KONDO, YUKI MORITOKI, EMIKO MIKAMI, MASANORI CHIBA, TAKAYUKI KOGURE, FUTOSHI NAGASAKI, KOJI FUKUSHIMA, TAKAO IWASAKI, SUSUMU SATOMI[1] and TOORU SHIMOSEGAWA

Division of Gastroenterology, [1]Division of Transplant Surgery, Tohoku University Graduate School of Medicine, Sendai, Japan

INOUE, J., UENO, Y., KANNO, N., ANZAI, H., KONDO, Y., MORITOKI, Y., MIKAMI, E., CHIBA, M., KOGURE, T., NAGASAKI, F., FUKUSHIMA, K., IWASAKI, T., SATOMI, S. and SHIMOSEGAWA, T. *Living Related Liver Transplantation for Acute Fulminant Hepatitis B: Experience from Two Possible Hyper-Acute Cases*. Tohoku J. Exp. Med., 2005, **205** (2), 197-204 —— Fulminant hepatic failure, which is represented by fulminant hepatitis, is fatal in most cases unless prompt liver transplantation is performed. Even if liver transplantation is performed, irreversible neurological damage is often complicated. In this case report, we describe two cases of fulminant hepatitis induced by acute hepatitis B virus infection, both of which were successfully rescued by living related liver transplantation without significant complications. The case 1 was a 45-year-old Japanese male. He complained general malaise and anorexia. His local physician diagnosed him as acute hepatitis B, and referred to our hospital. Due to severe coagulopathy, plasma exchange was performed 3 times. However, his hepatic coma progressed rapidly along with rapid decrease of both his direct/indirect bilirubin (D/T) ratio and serum blood urea nitrogen (BUN) levels. Living related liver transplantation was performed under the diagnosis of acute fulminant hepatitis B. The case 2 was a 34-year-old Japanese male. His complaints were fever and skin rush. He was referred to our hospital under the diagnosis of acute hepatitis B. On the second day after admission, he developed grade II hepatic coma, which deteriorated into grade III in spite of intensive therapy including plasma exchange. He also demonstrated rapid decrease of both D/T ratio and serum BUN level. Living related liver transplantation was performed on the next day. Both cases recovered without any evidence of neurological sequelae. In general, it is extremely difficult to rescue fulminant hepatitis by conservative treatments, particularly in cases with rapid progression. Although emergency liver transplantation may be an only option to rescue in such a case, living related liver transplantation has an advantage in view of urgent organ donation over cadeveric transplantation. ———— fulminant hepatitis; living related liver transplantation

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Address for reprints: Yoshiyuki Ueno, M.D., PhD. Division of Gastroenterology, Tohoku University Graduate School of Medicine, 1-1, Seiryo, Aobaku, Sendai 980-8574, Japan.

e-mail: yueno@mail.tains.tohoku.ac.jp

Recently, the number of living related liver transplantation (LRLT) is increasing in Japan (Mochida and Fujiwara 2001). Regarding fulminant hepatitis, the survival is reported to be better if patients undergo LRLT compared with conventional medical therapy (Zhu et al. 2002). However, in rapidly progressive cases, in which hepatic function completely starves within a few days, it is difficult to perform liver transplantation because of insufficient time for preparing liver donation (Lopez et al. 1988; Lorber 1988). Moreover, even if liver transplantation is performed, irreversible neurological damages due to brain edema may remain (Kadono et al. 2001). Also, acute infection with hepatitis B virus (HBV) causes so-called 'hyper-acute fulminant hepatitis', which has extremely high mortality (Ogrady et al. 1993). In this report, we describe two cases of acute fulminant hepatitis caused by HBV infection, which successfully recovered without major complications including any neurological sequelae.

Case Reports

Case 1

Present illness. A 45-year-old Japanese male without notable past medical or familial history, experienced general malaise, anorexia and dark urine on July 1st, 2003. A local physician diagnosed as acute viral hepatitis B with severe liver dysfunctions as well as the presence of ascites, and referred to the neighboring hospital. However, his liver tests worsened on July 6th, demonstrating aspartate aminotransferase (AST) 4096 IU/liter, alanine aminotransferase (ALT) 6063 IU/liter, total bilirubin (T-Bil) 11.8 mg/100 ml, prothrombin activity (PT) 9.3%, NH_3 387 μg/liter. Plasma exchange was performed on the same day and he was referred to Tohoku University hospital on the following July 7th. On admission, he was 165 cm in height, 63.0 kg in body weight, and his blood pressure was 133/64 mmHg, pulse 72/minutes, and body temperature 36.9°C. Grade I hepatic coma and jaundice were detected. Peripheral edema, vascular spider, palmar erythema, hepatomegaly and splenomegaly were not observed.

Laboratory findings (Table 1). On admission, both transaminase levels (AST 75 IU/liter, ALT 671 IU/liter) were decreased compared to those at the previous hospital. PT was improved to 20.0%, which would attribute to plasma exchange. However, D/T ratio (0.28, total bilirubin: 9.2 mg/100 ml per direct bilirubin: 2.7 mg/100 ml), serum BUN (1.0 mg/100 ml), and uremic acid (UA) (1.2 mg/100 ml) were also decreased, which suggested the deterioration of liver functions. PT (%) was improved to 20.0% due to plasma exchanges. Hepatitis B surface (HBs) antigen became negative, although his IgM type anti-hepatitis B core (HBc) antibody was strongly positive, suggesting that the patient had acute HBV infection.

Clinical course (Fig. 1). His hepatic encephalopathy worsened from grade I to grade III on July 7th, in spite of performing three times of plasma exchanges. His D/T ratio and BUN levels also worsened rapidly. Abdominal CT scan demonstrated apparent hepatic atrophy and presence of moderate ascites (Fig. 2a). Brain CT scan did not demonstrate the presence of cerebral edema (Fig. 2b). Using two Japanese models for prognosis of fulminant hepatitis (Muto et al. 1994; Takahashi et al. 1994), we evaluated the prognosis, revealing extremely poor prognosis, mortality of 100%. Since informed consent had been obtained when consciousness was alert, LRLT was performed on July 8th, with the right hepatic lobe of his wife as a graft (637 g). The recipient's liver was atrophic and weighed only 556 g. FK506, mycophenolate mofetil and methylprednisolone were used for postoperative immuno-suppression. Lamivudine was used to prevent post operative re-infection. He was discharged without any neurological disorder on September 3rd. The pathological findings of recipient's liver demonstrated massive collapse of hepatic parenchyma with necrosis and hemorrhage. Viable hepatocytes were sporadic, demonstrating ballooning and the bile plug (Fig. 3).

Case 2

Present illness. A 34-years-old Japanese male, without notable medical and familial history

TABLE 1. *Laboratory data on admission (July 8, 2003)*

WBC	13400/μl	LDH	437 IU/liter	HGF	2.78 ng/ml
RBC	371 × 10^4/ml	ChE	226 IU/liter	PT	20.0%
Hb	11.1 g/100 ml	AMY	262 IU/liter	APTT	45.9 sec
Ht	33.6%	TP	5.0 g/100 ml	FBG	158 mg/100 ml
PLT	117 × 10^3/ml	Alb	3.0 g/100 ml	AT III	38%
Seg	64%	Na	136 mEq/liter	D-dimer	5.8 mg/100 ml
Band	7%	K	5.2 mEq/liter	HBs Ag	0.3 (–)
Eosi	0%	Cl	103 mEq/liter	HBs Ab	71.0 (+)
Baso	0%	BUN	1 mg/100 ml	HBe Ag	0.8 (–)
Lymph	18%	Cr	0.6 mg/100 ml	HBe Ab	88 (+)
Mono	9%	UA	1.2 mg/100 ml	IgM HBc	8.0 (+)
AST	75 IU/liter	T-Cho	163 mg/100 ml	HBV DNA (TMA)	< 3.7 LGE/ml
ALT	671 IU/liter	Glu	322 mg/100 ml	HCV Ab	(–)
T-Bil	9.8 mg/100 ml	NH3	112 mg/100 ml	HAV IgM	(–)
D-Bil	2.7 mg/100 ml			EBV IgM	(–)
D/T ratio	0.28			HSV IgM	(–)
ALP	279 IU/liter			CMV IgM	(–)
γ-GTP	41 IU/liter				

γ-GTP, gamma glutamil transpeptidase; ChE, chorine esterase; TP, total protein; Alb, albumin; T-Cho, total cholesterol; Glu, glucose; HGF, hepatocyte growth factor; APTT, activated partial thromboplastin time; FBG, fibrinogen; AT-III, antithrombin III; Ag, antigen; Ab, antibody; HCV, hepatitis C virus; HAV, hepatitis A virus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; CMV, cytomegalovirus.

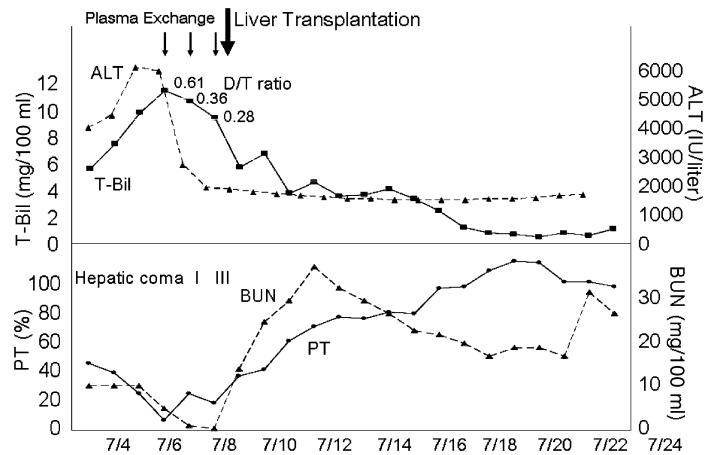

Fig. 1. Clinical Course of Case 1.

except for receiving blood transfusion when he was a pupil. On August 2nd, 2003, the patient experienced headache and nausea. On August 3rd, he was feverish and developed skin rash on his lower legs, which extended to the whole body. On August 6th, he was admitted to a nearby hospital, where he was diagnosed as acute hepatitis B with severe liver dysfunction (AST 6590 IU/liter, ALT 6810 IU/liter, T-Bil 3.7 mg/100 ml, and PT 33%). So, he was referred to Tohoku University

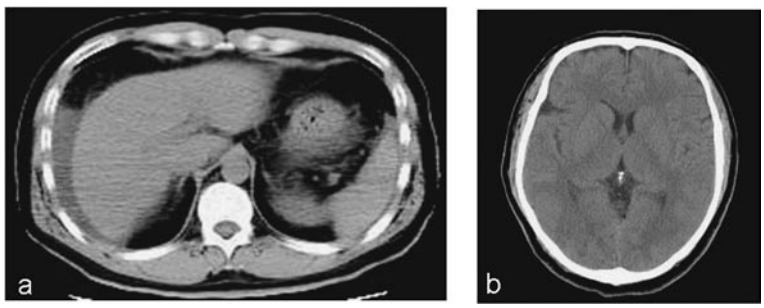

Fig. 2. CT scan of case 1.
a: Abdominal CT scan demonstrated marked hepatic atrophy and presence of moderate ascites (July 7th).
b: Brain CT scan did not demonstrate apparent cerebral edema (July 8th).

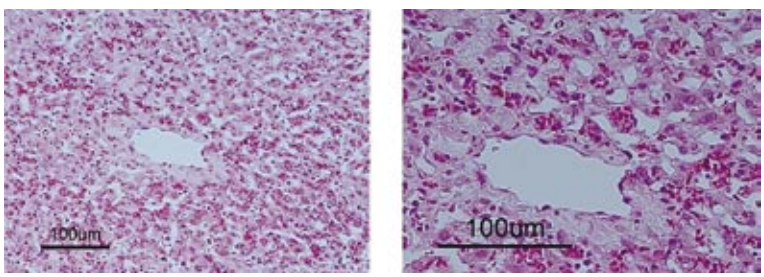

Fig. 3. Histological Findings of the explanted liver (case 1).
Explanted liver demonstrated massive collapse of hepatic parenchyma (left, original magnification × 20). Massive necrosis and hemorrhage were apparent (right, original magnification × 40). The remaining hepatocytes developed ballooning and bile plug.

Hospital on the same day. His physical findings on admission showed 189 cm in height, 70.0 kg in body weight, 131/60 mmHg of blood pressure, 61/minutes of pulse, and 36.6°C of body temperature. His skin was icteric and systemic rash was observed, though peripheral edema, vascular spider, palmar erythema, hepatomegaly, splenomegaly, and disturbance of consciousness were absent.

Laboratory Findings (Table 2). On admission, remarkable elevations of transaminases and total bilirubin (AST 4819 IU/liter, ALT 6320 IU/liter, T-Bil 6.5 mg/100 ml, D-Bil 3.5 mg/100 ml) and decreases of D/T ratio (0.54), BUN (6 mg/100 ml), and PT (19%) were detected. HBs antigen were weakly positive and HBs antibody were positive. HBV-DNA concentration was 5.1 log genome equivalent (LGE/ml).

Clinical course (Fig. 4). Different from case 1, the abdominal CT scan on admission demonstrated neither the hepatic atrophy nor the presence of ascites. However, he developed grade II hepatic coma on the following day, which deteriorated to grade III on August 8th, thus he was diagnosed as an acute form of fulminant hepatitis. D/T ratio, serum BUN levels and PT test fell to 0.23, 2 mg/100 ml and 9%, respectively. In spite of repeating plasma exchanges, his consciousness level declined. Prognostic models for fulminant hepatitis revealed that his mortality was calculated to be 100% (Takahashi's 0.99, Muto's 0.18) (Muto et al. 1994; Takahashi et al. 1994). Although the brain CT did not demonstrate neither cerebral edema nor atrophy, the electroencephalogram (EEG) revealed the presence of tri-phase wave without lower voltage, findings of severe hepatic encephalopathy. Thus, emergency LRLT was performed on August 8th using right hepatic lobe (900 g) of his brother as a graft. The explanted liver weighed 596 g, demonstrating marked atrophy. FK506 and methylprednisolone were used as im-

TABLE 2. *Laboratory data on admission (Case 2, August 6th)*

WBC	7600/ml	ChE	253 IU/liter	AFP	3.0 ng/ml
RBC	444 × 10^4/ml	AMY	53 IU/liter	HGF	1.20 ng/ml
Hb	13.0 g/100 ml	TP	6.2 g/100 ml	PT	19.0%
Ht	37.9%	Alb	4.2 g/100 ml	APTT	51.0 sec
PLT	113 × 10^3/ml	Na	138 mEq/liter	FBG	311 mg/100 ml
Seg	44%	K	4.0 mEq/liter	AT III	52%
Band	52%	Cl	99 mEq/liter	D-dimer	8.0 mg/100 ml
Eosi	0%	Ca	9.5 mEq/liter	HBs Ag	35.1 (+)
Baso	0%	BUN	6 mg/100 ml	HBs Ab	510.6 (+)
Lymph	3%	Cr	0.6 mg/100 ml	HBe Ag	3.6 (±)
Mono	1%	UA	3.2 mg/100 ml	HBe Ab	57.1 (+)
AST	4810 IU/liter	T-Cho	126 mg/100 ml	HBc Ab	4.51 (+)
ALT	6320 IU/liter	Glu	204 mg/100 ml	HBV DNA (TMA)	5.1 LGE/ml
T-Bil	6.5 mg/100 ml	NH3	111 mg/100 ml	HCV Ab	0.1 (–)
D-Bil	4.0 mg/100 ml			HAV IgM	0.1 (–)
D/T ratio	0.62			EBV IgM	< 10 (–)
ALP	435 IU/liter			HSV IgM	0.48 (–)
g-GTP	134 IU/liter			CMV IgM	0.22 (–)
LDH	4390 IU/liter				

γ-GTP, gamma glutamil transpeptidase; ChE, chorine esterase; TP, total protein; Alb, albumin; T-Cho, total cholesterol; Glu, glucose; HGF, hepatocyte growth factor; APTT, activated partial thromboplastin time; FBG, fibrinogen; AT-III, antithrombin III; Ag, antigen; Ab, antibody; HCV, hepatitis C virus; HAV, hepatitis A virus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; CMV, cytomegalovirus.

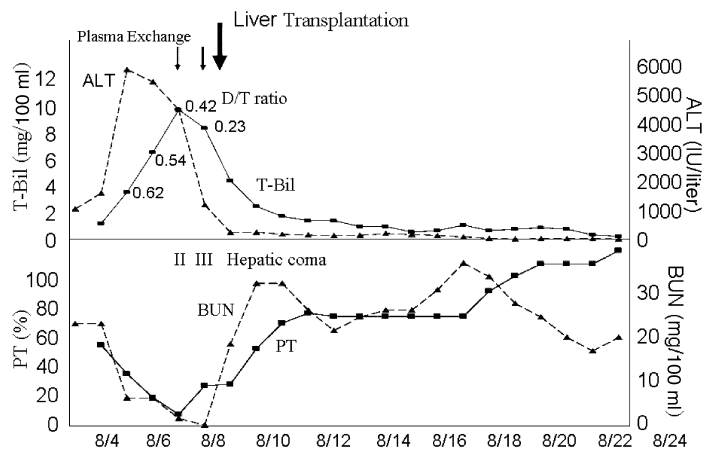

Fig. 4. Clinical Course of Case 2.

muno-suppressive agents. Although he experienced acute rejection on August 31st, he was rescued by pulsed administration of methylprednisolone. Lamivudine was also administrated to prevent post-operative re-infection of HBV. He was discharged on October 4th, without developing any complications including neurological abnormality.

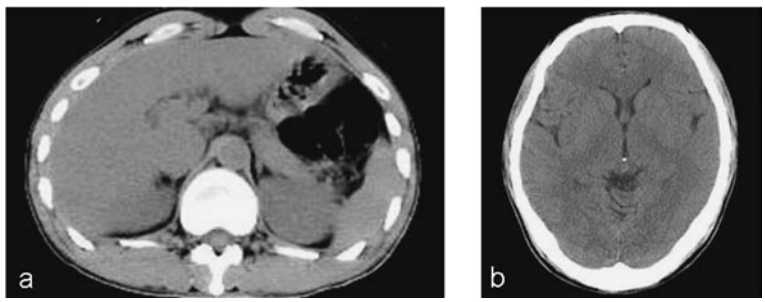

Fig. 5. CT scan of case 2.
a: Abdominal CT scan demonstrated neither hepatic atrophy nor presence of ascites (August 6th).
b: Brain CT scan did not demonstrate apparent cerebral edema (August 8th).

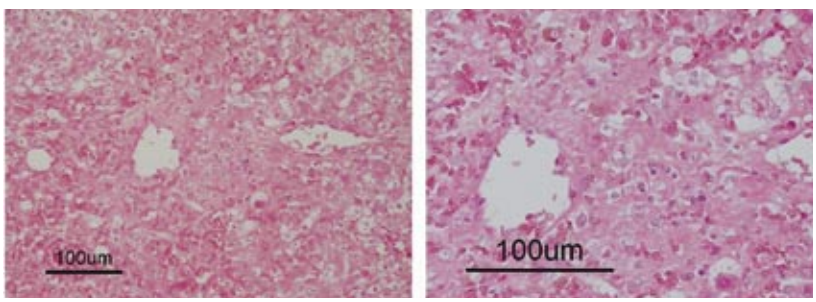

Fig. 6. Histological Findings of the explanted liver (case 2).
Explanted liver demonstrated massive hepatic collapse consisting of necrosis and hemorrhage (left, original magnification × 20). The formation of bridging fibrosis was not apparent. Lymphocytic infiltrations were predominant although eosinophils and plasma cells were sporadic (right, original magnification × 40) (H&E).

His explanted liver demonstrated massive collapse of hepatic parenchyma, massive necrosis and hemorrhage without any evidence of fibrosis (Fig. 6).

Discussion

Compared with subacute form of fulminant hepatitis, acute form of fulminant hepatitis is reported to generate better clinical outcomes in general. However, there is a distinct subgroup of acute form of fulminant hepatitis with poor prognosis, so-called "hyper-acute" type of fulminant hepatitis. To our knowledge, 9 cases have been reported and only 2 cases were successfully rescued by liver transplantation. The characteristic features of "hyper-acute" fulminant hepatitis include: i) rapid decrease of serum D/T ratio due to the termination of bilirubin conjunction in hepatocytes, ii) dramatic decrease of PT % as well as serum BUN levels, which reflects the termination of the urea cycle. Our two cases have almost fulfilled these criteria and developed apparent hepatic atrophy by the time of LRLT. Of note, the case 2 developed hepatic atrophy (596 g) in spite of the preserved hepatic volume evaluated by CT scan 2 days before operation. This could reflect that the shrinkage of liver could occur in very short time period, although the critical clinical setting as like fulminant hepatitis is very difficult to validate this hypothesis by using CT scans or similar modalities.

The term "hyper-acute" hepatic failure was first advocated by Ogrady et al. (1993) and they classified acute hepatic failure into 3 categories; hyperacute, acute, and subacute according to the periods from the onset of jaundice to the development of hepatic encephalopathy. With their criteria, "hyper-acute" means development of encephalopathy within 7 days after onset of jaundice. However, this term has not been generally used in

Japan (Takahashi 1981).

"Hyper-acute" fulminant hepatitis develops cerebral edema rapidly, which may not recover even after liver transplantation. Therefore, the prompt decision for liver transplantation is required not to impair prognosis in acute form of fulminant hepatitis, especially in "hyper-acute" form.

The indication of liver transplantation for fulminant hepatic failure has been described previously (Lopez et al. 1988; Lorber 1988; Takahashi et al. 1994; Zhu et al. 2002). The group of King's college hospital advocated a classification based on the paracetanol toxicity (Ogrady et al. 1989). In Japan, Muto (1991) proposed other type of criteria in 1990. Their criteria, however, reflect a paucity of organ donation in Japan, so they excluded an acute form of fulminant hepatitis and acute exacerbation of chronic hepatitis B from the indication of liver transplantation. In Japan, the most commonly used criteria are the national guideline by Japanese acute hepatic failure study group proposed in 1996 (Table 3) (Sugihara et al. 1996). This guideline is originally designed for cadeveric transplantation, although many transplant centers have used this guideline for LRLT. With this guideline, however, potentially curative patients could be excluded from candidates for liver transplantation without giving any chance because these criteria demand re-evaluation after 5 days of intensive medical therapy: it may be possible to perform re-evaluation in a subacute form of fulminant hepatitis, though it may be often difficult to perform re-evaluation not only in an acute type but also in a hyper-acute type. Although some more simple and practical indication criteria have been proposed by other groups, they are not necessarily feasible for the evaluation of an acute type (Kitamura et al. 1999; Yamanaka et al. 2001). Thus, a further study is needed to establish more practical indication criteria for it.

In view of serological studies, HBs antigen as well as serum HBV-DNA was negative in the case 1, while HBs antigen was weakly positive and HBs antibody turned to be positive on admission to our hospital in the case 2. Both these findings suggest rapid elimination of HBV from hosts, which may have resulted from massive hepatic necrosis. Because residual liver functions rapidly collapse and also consciousness levels deteriorate within a couple of days, fulminant hepatic failure, especially acute and hyper-acute types, poses a challenge, allowing only a limited period of time for evaluation and decision to carry out liver transplantation. In this regard, precise as well as prompt decision making is required. Assessment of physical findings and virological markers is in-

TABLE 3. *Guideline for liver transplantation for fulminant hepatitis in Japan (Japanese acute liver failure study group 1996) (translated from Sugihara et al. 1996)*

I) Registration of the patients with hepatic coma if the patients satisfy at least following 2 items

1. age > 45 years old
2. subacute form
3. PT test < 10%
4. serum Total bilirubin ≧ 18 mg/100 ml
5. Direct/Indirect bilirubin ratio ≦ 0.67

II) Re-evaluation of the same patients after 5 days for confirm the indication for liver transplantation

If the patients satisfy the below;

More than 2 items: predict as 'survive' and decline the registration for liver transplantation,

or

None or 1 item: predict as death and continue registration for liver transplantation

1. the improvement of hepatic coma by more than II grades, or within grade I coma
2. the improvement of PT test more value more than 50%

dispensable. Moreover, new guidelines for liver transplantation, which is applicable to acute and hyper-acute hepatic failure, are urgently needed to establish.

Conclusion

Some subgroups of acute fulminant hepatitis form a distinct group which demonstrates extremely higher mortality through the rapid termination of hepatic functions. However, LRLT performed through appropriate clinical judgments can rescue such patients with poor prognosis without any neurological complications.

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