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Liver transplantation for fulminant hepatitis at Stanford University

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Background. To review the clinical characteristics and outcomes of 26 patients evaluated for liver transplantation for fulminant hepatic failure at Stanford University and Lucile Packard Children's Hospital in an attempt to identify risk factors and prognostic predictors of survival. ***Methods.*** A retrospective review of the records of 26 consecutive patients who were evaluated for possible liver transplantation for acute liver failure from May 1, 1995, to January 1, 2000. Pretransplant patient demographics and clinical characteristics were collected, and the data were analyzed by univariate and multivariate analysis. ***Results.*** Clinical assessment of encephalopathy did not predict outcome. Patients with abnormal computed tomography (CT) of the brain had a twofold increase in mortality compared with those patients with normal studies ($p = 0.03$). Patients requiring mechanical ventilation and continuous venovenous hemofiltration (CVVH) also had a poor prognosis. ***Conclusion.*** Predictors of poor outcome after fulminant hepatic failure include abnormal CT scan, mechanical ventilation, and requirement for hemofiltration.

Key words: fulminant hepatic failure, liver transplant, encephalopathy

Introduction

Fulminant hepatic failure has been defined as massive hepatic necrosis with encephalopathy within 8 weeks from the onset of illness in a person without antecedent liver disease.[1,2] Although a relatively uncommon event, its presentation is often fatal. The overall mortality exceeds 70%.[3–7] The likelihood of spontaneous recovery is critical in the decision-making process. With clinical progression of disease, medical support alone has proven unsuccessful, and liver transplantation is currently the only viable option for these patients.[8–10] Presently, in the United States, 6% of all liver transplants in adults and 11% of those in children are performed for fulminant hepatic failure.[11] With the use of liver transplantation as a modality of treatment, the post-transplant survival rates have been reported to be similar to or better than survival rates for those who undergo orthotopic liver transplantation for chronic liver disease.[9,10,12–14] Early determination of prognosis and prompt decision-making regarding the need for transplantation are important in these patients. The timing of transplantation is crucial in determining the success of therapy. To perform an orthotopic liver transplant too early, when a patient may recover liver function, would subject the patient to lifelong immunosuppression, yet to wait too long may result in permanent neurologic impairment or mortality. In acute liver failure, the criteria for liver transplantation have not been standardized in the United States. The King's College Hospital (KCH) criteria have been the most widely quoted prognostic criteria (Table 1).[3] Studies have attempted to examine the KCH criteria's applicability in the United States.[15,16] Overall, most have found that meeting the KCH criteria is a strong positive indicator for need of transplantation. However, failure to fulfill the KCH does not predict survival.[16] The Pittsburgh review of their experience as well as others shows that the KCH criteria's ability to predict which patients will survive without transplantation is lower, especially in those cases not caused by acetaminophen.[15] Alternatively, a large number of patients with acidosis survived without transplantation in the Pittsburgh review. This would indicate other factors that may be important in predicting survival. Anand et al.[17] suggested that increased white-cell count and hyperkalemia are indicative of poor prognosis. The identification of factors that are of

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Table 1. King's College Hospital prognostic criteria for non-survival among patients with acute liver failure

Acetaminophen patients
pH < 7.30 (irrespective of grade of encephalopathy)
or
Prothrombin time >100 s (INR >6.5) and serum creatinine >300 μmol/l (>3.4 mg/dl) in patients with grade III or IV encephalopathy
Non-acetaminophen patients
Prothrombin time >100 s (INR >6.5; irrespective of grade of encephalopathy)
or
Any three of the following variables (irrespective of the grade of encephalopathy):
Age <10 or >40 years
Cause: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reaction
Duration of jaundice before onset of encephalopathy >7 days
Prothrombin time >50 s (INR >3.5)
Serum bilirubin >300 μmol/l (>17.5 mg/dl)

INR, International normalized ratio

Table 2. Clinical stages of encephalopathy

Stage I	Variable impairment of higher centers, hyperreflexia, reversal of sleep rhythm, asterixis uncommon
Stage II	Inappropriate behavior, confusion, drowsiness, asterixis present
Stage III	Increasing obtundation, hyperreflexia, marked confusion, asterixis
Stage IVa	Comatose but may respond to painful stimuli, unable to elicit asterixis, brainstem reflexes intact
Stage IVb	Comatose, extensor or flexor posturing, intact or partially absent brainstem reflexes

practical significance is paramount in the delineation of selection criteria for transplantation.

We reviewed our most recent 5-year experience with fulminant hepatic failure in an effort to understand and characterize factors that may predict overall outcome and risk factors associated with survival. We analyzed both clinical and radiographic pretransplant variables as well as post-transplant graft and patient survival.

Methods

Twenty-six patients were referred for evaluation of fulminant hepatic failure at Stanford University and Lucile Packard Children's Hospital over a 5-year period, from May 1995 to January 2000. All patients had developed jaundice and encephalopathy without prior history of chronic liver disease. Encephalopathy was graded I to IV: stage I, depression of responsiveness; stage II, drowsiness, confusion, hyperreflexia, and asterixis; stage III, stuporous, but still arousable; and stage IV, comatose, may not respond to noxious stimuli (Table 2). Clinical characteristics were collected from the patients' records and included age, sex, diagnosis, duration of disease, ventilatory dependency, use of vasopressor agents, need for dialysis, intracranial pressure (ICP) monitoring, coma stage, length of stay in the intensive care unit (ICU) and ward prior to transplantation, and outcome. Computed tomographic (CT) scans were utilized to evaluate those patients who had equivocal or worsening neurologic examination results. CT scans were defined as abnormal if there was evidence of cerebral edema causing compression or narrowing of the ambient cisterns, hypodensity in the thalamus with effacement of the ventricles, or any type of impending herniation. Of the 26 patients, 20 underwent transplantation. Patients were excluded from transplantation if they developed sepsis. Two patients underwent open frozen-section biopsy at the time an organ became available, because there seemed to be a possibility of recovery. On the basis of the histologic findings, the transplantations were terminated. Patients who underwent transplantation had standard dual immunosuppressive therapy with methylprednisolone and tacrolimus. Cytomegalovirus (CMV) prophylaxis was given in the form of ganciclovir if the CMV IgG was negative in the recipient and positive in the donor. Otherwise, the patient was given acyclovir.

Statistical analyses were performed comparing the preoperative risk variables and postoperative outcomes by Fisher's exact test, and actuarial survival curves were calculated by the Kaplan-Meier product-limit estimate and the log-rank test. Significance was defined at $p \leq 0.05$.

Results

Of the 26 patients referred, 20 patients underwent transplantation. Of the six patients who did not undergo transplantation, three died (one child and two adults), and all developed disseminated sepsis and multiorgan failure. Three patients recovered. One patient was an 18-year-old man who developed fulminant liver failure after amantadine poisoning. He presented with a history of fever and chills. There was no history of drug abuse. His liver function, tests, including synthetic function, improved after 4 days of medical therapy. The other two patients who recovered were 4 and 6 years old. Both patients developed fulminant failure from unknown etiologies. The first case was that of a 4-year-old girl who presented with low-grade fever and increasing obtundation. The patient was transferred to our

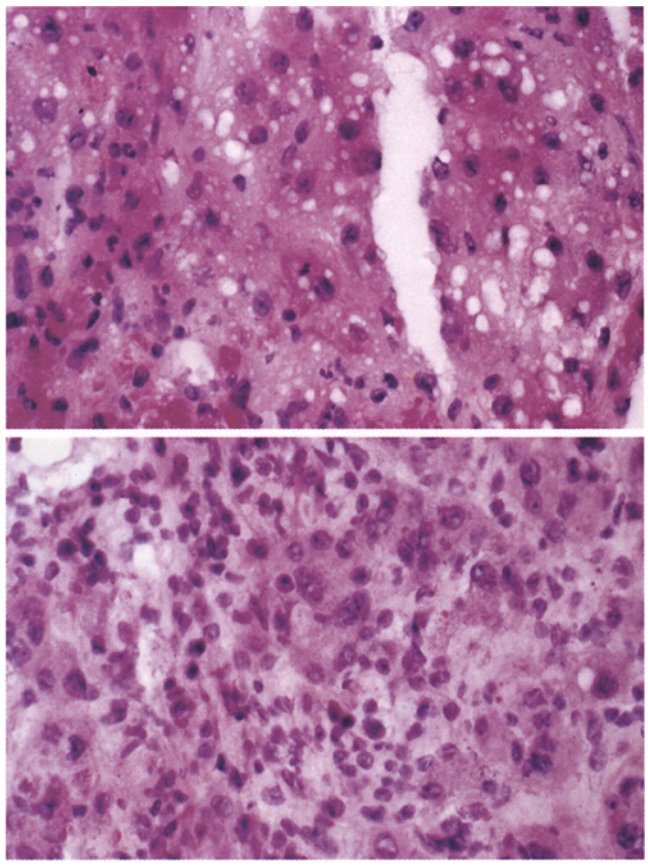

Fig. 1a,b. Liver biopsy at the time of transplantation showing derangement of the liver architecture and areas of necrosis and cell dropout (**a**). Viable hepatocytes and mitotic figures were present (**b**). Hematoxylin and eosin, ×100

center with an ammonia level of 130 mg/dl. The liver transaminases varied between 3000 and 8500 U/l, with a bilirubin level of 3.5 mg/dl. The patient's international normalized ratio (INR) was 2.14. She continued to progress into stage III coma and needed intubation for airway protection. Continuous venovenous hemofiltration (CVVH) was also initiated. The patient was listed for transplantation, and a cadaveric donor became available on the second hospital day. The patient was brought to the operating room, and at the time of transplantation an open liver biopsy was performed (Fig. 1). The frozen section showed extensive necrosis (approximately 60%) with islands of viable hepatocytes. Scattered mitoses were also present. On the basis of the biopsy, the liver transplantation was aborted, and the patient recovered fully with medical management. The second case was that of a 6-year-old girl who presented in a similar manner. She was only in stage II encephalopathy and was not intubated. An open biopsy performed at the time a liver allograft became available showed evidence of viable hepatocytes, and the transplantation was aborted. The patient recovered and was

Table 3. Etiology of fulminant hepatic failure

Adult		Pediatric	
Etiology	No.	Etiology	No.
Unknown	2	Unknown	10
Viral (HBV)	1	Viral	2
Drug-induced	1	Drug-induced	1
Autoimmune	2	Other (s/p BMT)	1

HBV, Hepatitis B virus; s/p BMT, bone marrow transplantation

discharged home 13 days postoperatively. In both of these instances, the etiology of the liver failure was never identified.

Twenty patients underwent orthotopic liver transplantation. Their ages ranged from 6 months to 61 years. Six were adults and 14 were children; 6 were male and 14 were female. The etiologies of the liver failure were varied (Table 3). The patients were stratified on the basis of their requirement for ventilatory support, use of vasopressor agents (e.g. dopamine, epinephrine), need for dialysis, and preoperative coma stage. The patient profiles are listed in Table 4. There were seven deaths in the group undergoing transplantation. Two were fadults; one died of overwhelming aspergillus infection and the second never recovered neurologic function. The remaining five deaths were in the pediatric population. Two deaths were secondary to primary graft nonfunction. One $2^1/_2$-year-old child died 32 days post-transplant from pancreatitis. One child developed intractable rejection, and one child developed fibrosis with rejection approximately $3^1/_2$ months after transplantation. Only three patients were taking some form of vasopressor agent. There was no difference in survival between the patients who needed vasopressor agents and those who did not. Thirteen of the 20 patients required ventilatory support. The patients requiring ventilatory support prior to transplantation had a 58% survival, as compared with 87.5% survival among those patients not requiring the ventilator (p = 0.17). As part of therapy, seven patients were placed on CVVH. The survival in the group that did not require CVVH was 84.6%, as compared with 42% in the CVVH-dependent group (p = 0.02). A difference was also noted in the patients who had abnormal CT scans. The clinical preoperative coma stage ranged from II to IVb. Nine patients were in stage III coma, and four had progressed to stage IV at the time of transplantation. The remaining seven patients were in stage II coma. CT of the brain was obtained in 10 patients because of worsening neurologic examination result or inability to assess neurologic status. All four patients in stage IV coma underwent a CT scan. Of those four, the patient in stage IVa had normal ventricles and normal sulci, and those in stage IVb all had abnormal scans. Six other CT

Table 4. Demographics of patients undergoing transplantation

Patient no	Sex	Age (yr)	Ventilator	Pressor	CVVH	Coma stage	Abnormal preoperative CT	Outcome
1	M	3	N	N	N	II	N	Alive
2	F	0.58	Y	Y	N	II	N	Alive
3	F	31	N	N	N	III	N	Alive
4	F	42	Y	Y	N	III	N	Alive
5	M	5	Y	Y	Y	IVa	N	Alive
6	F	61	N	N	N	II	N	Alive
7	F	2.5	Y	Y	Y	III	Y	Dead
8	F	0.5	N	N	Y	II	N	Alive
9	M	2	Y	Y	N	II	N	Dead
10	F	4.5	Y	Y	N	III	N	Alive
11	F	34	Y	N	N	III	N	Alive
12	F	5	N	N	N	III	N	Alive
13	F	56	Y	N	Y	III	Y	Dead
14	F	2	Y	Y	Y	III	N	Dead
15	M	0.5	N	N	N	II	N	Alive
16	F	0.66	N	N	N	II	Y	Dead
17	M	6	N	N	N	III	N	Alive
18	M	6	Y	Y	N	IVb	Y	Alive
19	F	56	Y	Y	Y	IVb	Y	Dead
20	F	0.57	Y	N	Y	IVb	Y	Dead

CVVH, Continuous venovenous hemofiltration; CT, Computed tomography; M, male; F, female; N, no; Y, yes

scans were performed: two in adults in stage III coma and one in a child in stage III coma. The remaining three scans were performed on pediatric patients in stage II coma. The patients with abnormal CT scans had a twofold increase in mortality versus those patients with normal scans ($p = 0.03$). Only one child who survived had an abnormal CT scan (Fig. 2). His CT scan showed effacement of the cisterns, loss of the fourth ventricle, and loss of the gray and white matter distinction. Initially, he had neurologic deficits affecting his occipital lobe, resulting in both double vision and peripheral blindness. Over the 8-month period post-transplant, his double vision disappeared and his peripheral blindness improved. The survival of patients who were both ventilator dependent and required CVVH was 16.7%, as compared with 85.7% of those patients who did not have both preoperative factors ($p = 0.0002$). The clinical stage of encephalopathy before transplantation did not predict survival ($p = 0.4$). Other factors, such as age of the recipient, age of the donor, type of transplant (full size vs. segmental transplantation), length of preoperative stay, and underlying liver disease, also did not influence survival.

Discussion

At our center, fulminant hepatic failure was seen more frequently in children, and the cause of the failure was unknown in the majority of pediatric patients. It is interesting that the clinical stage of encephalopathy was not particularly helpful for predicting outcome. However, using an objective radiographic measure was predictive. All patients with an abnormal CT scan died, except for one who survived with prolonged neurologic deficits. In our study population, the need for mechanical ventilation in combination with CVVH was also associated with poor prognosis. No patient survived who was dependent on a ventilator, required CVVH, and had an abnormal CT scan preoperatively.

The identification of absolute contraindications to orthotopic liver transplant is imperative, because the rate-limiting factor in cadaveric liver transplantation for fulminant hepatic failure (as well as chronic liver diseases) is the shortage of organs. The timing of transplantation is essential to the eventual outcome.[18,19] Alper et al. reviewed a series of children with fulminant hepatic failure who developed encephalopathy and evidence of cerebral edema on CT scan.[19] They found that the presence of cerebral edema in children was an objective measure that correlated with poor outcome, and that the clinical staging of encephalopathy was correlated with poor outcome to a lesser degree. With radiographic evidence of cerebral edema, one could argue that termination of care would be an option.

The decision whether to proceed with transplantation becomes crucial. In London, the King's College Hospital outlined selection criteria that have become the most widely applied and studied. The selection criteria are based on the etiology of the liver failure. Although the criteria have strong positive predictive value, it has been shown that a failure to fulfill the criteria does not ensure survival, especially in the non-acetaminophen group. Berneau et al. in Clichy used serum factor V levels as

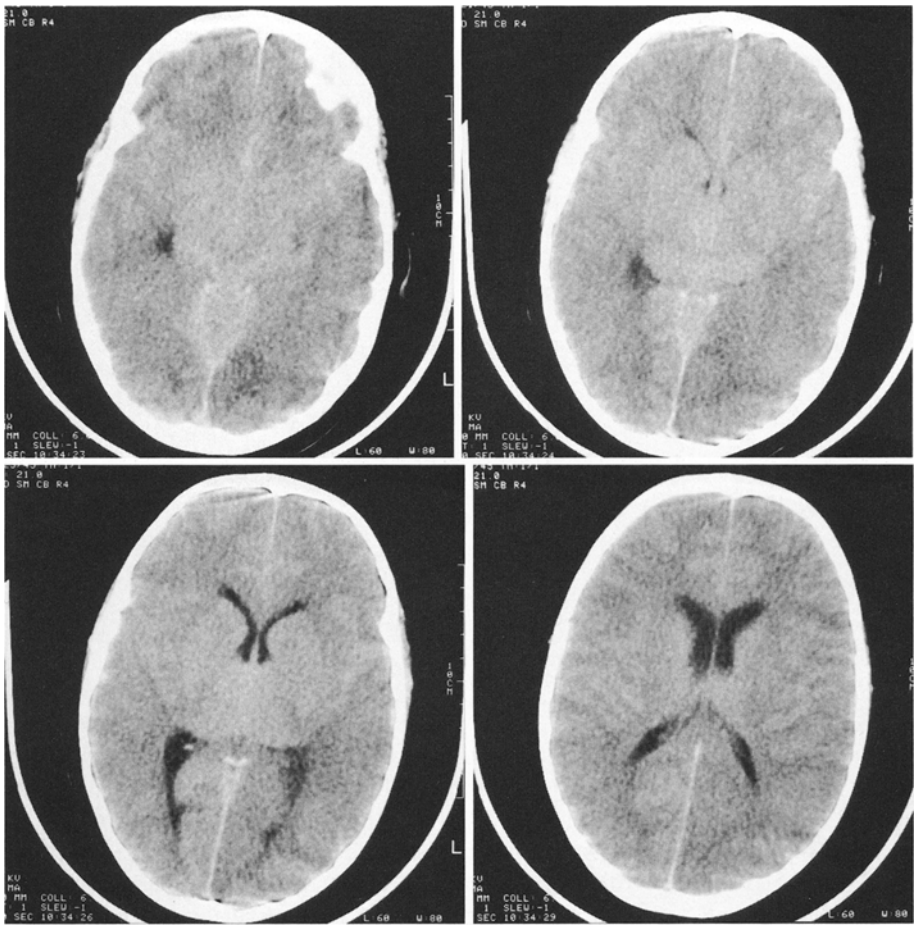

Fig. 2. Computerized tomography images of the brain showing edema, effacement of the cisterns, loss of the fourth ventricle, and loss of distinction of gray and white matter

the basis of selection.[20] A level <20% in patients younger than 30 years or <30% in patients aged 30 years or older, associated with the presence of encephalopathy, is an indication to list for transplantation. However, Pauwels et al., in a series of 81 encephalopathic patients, subsequently found the Clichy criteria to have less ability to correctly identify patients who will survive without orthotopic liver transplantation.[21] By contrast, the positive predictive values of both the Clichy series and the King's College Hospital criteria were similarly high.[21,22] Two other groups in North America have suggested the addition of transjugular biopsy and radiologic assessment of hepatic volume in the decision algorithm.[23–26] The Acute Physiology and Chronic Health Evaluation II score, group-specific component protein concentrations, factor VIII/V ratios, and serial prothrombin times have also been suggested as possible prognostic indicators.[27–30] All these indices have differing levels of reported accuracy.

In conclusion, our review confirms the need to use objective measures such as CT scan and biopsy to aid in the decision algorithm. Fulminant hepatic failure continues to be associated with high morbidity and mortality. After unsuccessful attempts at medical modalities, liver transplantation has continued to be the mainstay treatment. In certain situations in which the King's College Hospital criteria are not met, it may be beneficial to utilize other factors, such as biopsy, to better define those patients who will benefit from transplantation. Failure to fulfill current prognostic criteria does not predict recovery, especially in the non-acetaminophen cases; therefore, liver transplantation still needs to be considered for this group. Also, given the proportion of children who undergo liver transplantation for fulminant hepatic failure, it is important not only to refine the prognostic criteria, but also to develop criteria that would address the pediatric population.

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