Living Donor Liver Transplantation for Pediatric Acute Liver Failure and Prolonged Hepatic Encephalopathy: A Case Report

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Abstract:

Background

Liver transplantation (LT) is the definitive treatment for selected patients with acute liver failure (ALF). Diffuse cerebral edema is a relative contraindication and is associated with poor outcomes after LT. There is very limited literature on outcomes of pediatric ALF in the setting of prolonged grade 4 hepatic encephalopathy and diffuse cerebral edema.

Case presentation

Here, we report a 2-year follow-up in a 7-year-old girl with hepatitis A-induced ALF. At the time of transplant, there was hepatic coma and diffuse brain edema necessitating mechanical ventilation, multiple episodes of seizures, and subdural hematomas on imaging. Due to donor issues, the liver transplant was performed after 72 hours of initial presentation. There was delayed extubation, and the post-operative course was complicated by neurocognitive impairment. At the time of discharge, there was impaired swallowing, speech, and mobility. Extensive home-based rehabilitation with percutaneous endoscopic gastrostomy feeding was required. The child made a gradual recovery, and three years after transplant, meets the majority of the developmental criteria for age.

Conclusion

Although Liver transplant was once considered an absolute contraindication to diffuse brain edema in ALF but with meticulous perioperative care, acceptable results can be achieved.

Keywords

Acute liver failure; Diffuse brain edema; Liver Transplant; Subdural hemorrhage; grade 4 encephalopathy

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Introduction

Acute liver failure (ALF) is defined as the presence of coagulopathy (international normalized ratio > 1.5) and HE along with severe acute liver injury without preexisting liver disease [1]. In the past, ALF was associated with high short-term mortality, with only 20-30% patients making spontaneous recovery. With improvement in critical care and better understanding of pathophysiology, survival has improved substantially. The decision to proceed with LT in patients with grade 4 encephalopathy and ALF remain controversial [2]. With limited existing evidence, it appears that prolonged HE (> 48 hours) is associated with poor post-transplant outcomes [3]. This is a bigger challenge in the pediatric age group, where there are no specific prognostic scores, to categorize patients into high and low risk for treatment failure. At best, experience with LT in ALF in the pediatric age group remains limited to a few

institutional reports and lacks granularity with regards to neurological status [4,5]. In exclusively living donor liver transplant (LDLT) settings, selection of a suitable donor can be a time-consuming process. The impact of prolonged hepatic coma (> 48 hours) on neurological outcomes after LT remains to be determined. Herein, we report the outcome after pediatric LDLT with prolonged grade 4 encephalopathy.

Case presentation

A 7-year-old girl presented to the emergency department with a three-day history of fever, vomiting, and bleeding from the tooth extraction site. On examination, she was jaundiced with an altered state of consciousness and dropped Glasgow coma scale (GCS) to 6/15. She was intubated in the emergency department due to deteriorating GCS and was admitted to the pediatric ICU. Her laboratory workup showed a normal complete blood count and electrolytes. The total bilirubin was 7.33mg/dl, Aspartate transaminase (AST) 2987U/L, Alanine transaminase (ALT) 4621U/L, activated partial thromboplastin time was 42 seconds, and international normalized ratio (INR) was not recordable. Her initial ammonia was 384 ug/dl at presentation. Arterial blood gas showed a pH of 7.44 with arterial lactate of 5.3(0.5-2.2). Her Hepatitis A IgM was positive, and she was diagnosed with ALF. Over the next few hours, her clinical condition worsened, and she fulfilled the King's College criteria (KCC) for LT. After discussion in the transplant evaluation committee, LT was considered the best treatment option, and the family was counseled to search for a suitable donor. During this time, she received the standard medical treatment for ALF, which included elevation of the head end of the bed to 30 degrees, hyperventilation, correction of fluid imbalance, use of hypertonic saline and mannitol, and a mean arterial pressure goal between 65-70 mm Hg. Due to high ammonia levels, continuous renal replacement therapy was started. In addition, periodic evaluation of brain stem reflexes was performed. As a routine, we perform brain CT in all patients with grade 4 encephalopathy. Her initial Computerized tomography (CT) brain was done within six hours of admission and showed no brain edema (Figure 1).

Figure 1, CT brain performed 6 hours post-admission showed no cerebral edema and normal lateral ventricles (black arrow).

The child had multiple episodes of partial seizures for which Levetiracetam was given. A repeat CT scan was performed, which showed diffuse cerebral edema with compression of lateral ventricles and blurring of the gray-white matter interface. The family was counseled about her deteriorating neurological status due to cerebral edema and partial seizures. However, since the brainstem reflexes were intact, she was not removed from the transplant list. Eventually,

the family was able to find a suitable related living donor. At this time, CT brain was performed 54 hours after the onset of grade 4 encephalopathy. There was persistent cerebral edema with a new finding of subdural hemorrhage (Figure 2A and 2B).

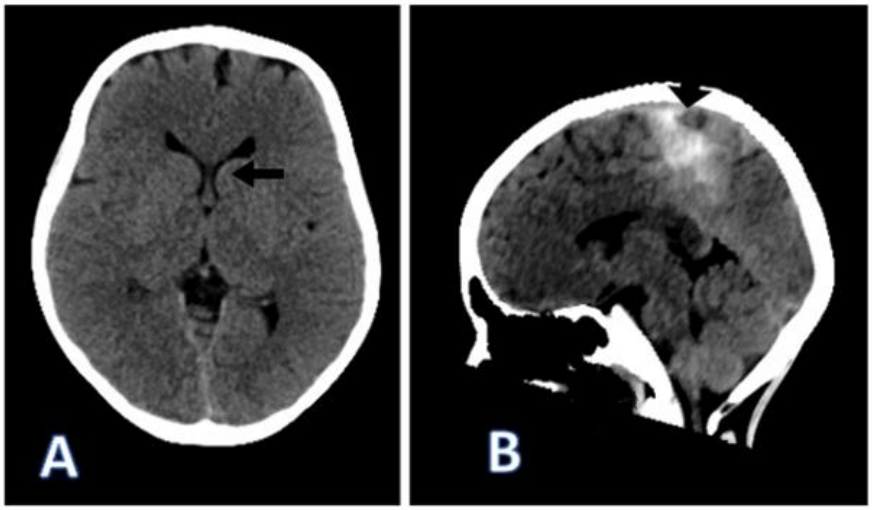

Figure 2 (A). CT brain at 54 hours after developing grade 4 encephalopathy showed diffuse cerebral edema with compression on lateral ventricle (black arrow), (B) Subdural hemorrhage (black arrow).

The brain stem reflexes were intact, and the family was keen on transplant despite the risk of poor outcome and the chance of irreversible brain injury.

The patient underwent an uneventful LDLT and received a right lobe graft, weighing 934 grams, with a graft-to-recipient weight ratio of 2.07. The intraoperative findings included an acutely inflamed non-cirrhotic liver. Postoperatively, her GCS began to improve within 48 hours of transplantation. Her CT on the 3rd postoperative day showed substantial improvement in cerebral edema (Figure 3).

Figure 3: Transplant day 3 shows resolution of cerebral edema.

The patient's neurological status improved slowly, and she met extubation criteria on the 8th postoperative day. An MRI brain was performed on the 12th postoperative day, which showed intact gray-white matter differentiation with trace subdural hemorrhage. She remained in the ICU for 20 days. At the time of shifting from the ICU, her GCS was 10/15, there was limited limb mobility, and no neck holding. Endoscopic nasojejunal feeding was initiated due to a poor swallowing reflex. With extensive physical rehabilitation, she was discharged on the 35th postoperative day with a GCS of 10/15 and a muscle power of 2/5. An extensive home-based rehabilitation plan was formulated. For anticipated prolonged feeding, NJ tube was replaced with percutaneous endoscopic feeding. Her immunosuppression consisted of tacrolimus and low-dose steroids and she had stable liver functions at 1 month, 6 month, 1 year, 2 year and 3 year post transplant (Table 1).

Table 1 Showing Liver function tests and Tacrolimus trough level before and after Liver transplant.

Parameters	Pre-transplant	1-month	6-month	1-year	2-year	3-year
AST (U/L)	2987	91	97	17	32	20
ALT (U/L)	4621	73	262	21	20	18
Total Bilirubin(mg/dl)	7.33	5.43	0.32	0.27	0.38	0.42
Direct Bilirubin (mg/dl)	5.04	3.80	0.23	0.14	0.1	0.15
GGT (U/L)	61	990	921	73	46	25
Alkaline phosphatase (U/L)	418	993	491	330	250	247
Tacrolimus level ng/ml	-	3.29	3.02	6.27	6.76	6.39
Tacrolimus Dose mg/day in two divided doses	-	3 (1.5+1.5)	3.5 (2+1.5)	4 (2+2)	4.5 (2+2.5)	4.5 (2+2.5)

The patient made a gradual recovery in the following months. Approximately one year after transplant, the PEG tube was removed due to restoration of swallowing reflex, return of speech, and ability to walk. She is able to play with siblings and friends and communicate in simple language. At present, there is a developmental delay, and she is still not fit to join school again but is making gradual recovery.

Discussion

In the setting of ALF, cerebral edema represents an ominous sign. The impact of spontaneous subdural hemorrhage on the outcome of LT in ALF remains unknown. The current report and the previously published limited experience indicate that with careful selection, LT might provide survival benefit and acceptable quality of life in these high acuity patients. In contrast to adult ALF, pediatric ALF is not a well-understood entity. The well-established criteria like the KCC, Model for end stage liver disease (MELD) score, and ALF index have not been validated in pediatric ALF. It is important that pediatric ALF is prognosticated early. This way, transplant can be offered at a suitable time, and catastrophic neurological complications can be prevented [6].

Risk factors for poor post-transplant outcomes include sepsis, pulmonary complications, and cerebral edema [3-5]. In a recent single-center study on pediatric ALF, 6/31(19.3%) post-transplant survivors and 8/10(80%) non-survivors had pre-transplant cerebral edema on CT (P =0.001). In multivariate analysis, cerebral edema was one of the strongest predictors of post-transplant death [4]. Yang and colleagues reported outcomes in 11 patients who underwent LT for ALF. All patients were intubated due to grade 4 HE, and 4 patients had mild cerebral edema [3]. Patients were grouped based on the time between the onset of HE and transplantation. All patients transplanted within 48 hours made full neurological recovery and were extubated within 48 hours. Patients transplanted after 48 hours of the onset of HE had neurological complications and delayed extubation. The 3-year survival was 85.7% and 33% in the early and late transplant groups. In our patient, although the

duration between onset of HE and LT was more than 48 hours, there were certain reassuring features that supported our decision to proceed with LT. Despite prolonged HE, subdural hematoma, and seizures before transplant, the patient was cleared by the neurology and hepatology teams for transplant. This was due to intact brainstem reflexes, persistent but non-progressive cerebral edema, and absence of hemodynamic instability. We also believe that continuous renal replacement therapy (CRRT) was a useful adjunct in preventing the progression of cerebral edema. In fact, it has been shown that various bio-artificial systems and renal replacement therapy might prolong transplant free survival in patients with ALF [6]. More specifically, CRRT reduces ammonia levels and might be a useful bridge to transplant. We were able to control ammonia levels and perhaps prevent progression of cerebral edema despite prolonged HE in our patient [7].

Occasionally, despite HE, acceptable post-transplant outcomes have been reported, specifically with monitoring of intracranial pressure. Kamat and colleagues reviewed 14 intubated children with ALF and grade 3-4 HE [8]. There was documented cerebral edema on imaging in 5(35.7%) patients. There were two (14%) deaths on the waiting list, four (28%) patients had spontaneous recovery, and 8/8(100%) transplanted patients had complete recovery. Although it remains unclear if any of the post-transplant survivors had cerebral edema on pre-transplant CT, the results are encouraging. Good functional outcomes have been reported even in the setting of cerebral herniation with non-ALF etiology and in patients undergoing LT after successful management of intracranial bleed [9,10]. However, due to varying patient populations and indications for transplantation, due deliberation is required before denying LT to a child with ALF.

Despite the use of CRRT, effective management of hyperammonemia, and no hemodynamic instability, there was delayed extubation and neurological complications in our patient. The child was completely dependent for the initial few months after transplant and made gradual recovery towards normal life. Our patient required extensive home-based physiotherapy and percutaneous endoscopic gastrostomy feeding. A rigorous follow-up was required with fluctuating levels of immunosuppression, infections, mood disturbances, and PEG-related complications. In the end, the outcome was acceptable, but such extensive support might not be available for all patients and should be considered in decision making leading to transplant.

Conclusion:

To the best of our knowledge, the current report represents the first near-normal post-transplant neurological recovery in pediatric ALF with prolonged HE, cerebral edema, and subdural hemorrhage. This acceptable outcome may be attributed to meticulous ICU management, effective seizure control, sepsis prevention, and renal replacement therapy for hyperammonemia. The risks involved with LT and the need for a robust postoperative support system should be carefully considered when offering LT in such challenging scenarios.

Ethical approval:

This study was approved by the ethical committee of Shifa International Hospital Islamabad.

Consent for publication:

Family gave consent to publish the case report without revealing the patient's identity.

Data availability

The data is available from the corresponding author upon reasonable request

Competing interest

The authors have no conflicts of interest.

Funding information

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