

Neurological Complications associated with Pediatric Liver Transplant in Namazi Hospital: One-Year Follow-Up

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ABSTRACT

Background: 13%–43% of liver transplant (LT) recipients experience severe neurologic events with increased morbidity and mortality.

Objective: To evaluate the incidence of neurological complications after LT in pediatric patients in Namazi Hospital.

Methods: The medical records of 101 children aged between 1 and 18 years who underwent LT between May 2016 and May 2017 at Namazi Hospital were reviewed. Demographic data, the occurrence of neurological complications, and preoperative variables that may predict the complications and outcomes were evaluated. The mean±SD follow-up duration was 10.1±1.9 months.

Results: The mean±SD age of patients at the time of LT was 8.2±5.3 years; 51.5% were male. The most common cause of LT was biliary atresia (16.8%), progressive familial intrahepatic cholestasis (16.8%), and Wilson's disease (13.9%). The mean±SD PELD score was 18.2±1.1. After 1-year follow-up 74 73.3% patients were alive. 16 (15.8%) patients developed convulsion (2 had encephalopathy). 3 (3.0%) patients had signs of peripheral neuropathy, 3 (3.0%) complained from headache, and 1 developed dystonia.

Conclusion: Compared to other centers, neurological complications were less common in our center. The major neurological manifestation after LT was convulsion. There was no correlation between age, sex and the underlying disease and development of neurological complications.

KEYWORDS: Neurological complication; Pediatric; Liver transplant

INTRODUCTION

When liver transplantation (LT) was first performed in 1963, it was considered a high risk treatment with a 1-year survival of only 20% [1]. By introducing immunosuppressive drugs such as cyclosporine A in 1983 [2] and tacrolimus that prevent allograft rejection [3], the survival rate has increased from 20% to nearly 80%, during the last 20 years [4]. For the increased safety and improved logistic facilities, the number of transplanted patients is continuously increasing [5]. However, the toxic side-effects of the drugs, including toxicity to

the central nervous system (CNS), have been noted with their widespread clinical use [6, 7].

The rate of neurological complications (NC) following LT is reported from 10% to 47% [8, 9]. These complications include changes in mental status ranging from mild encephalopathy to coma, severe headache, depression, psychotic disorders, seizures, and stroke [10, 11]. About 13% to 43% of LT recipients experienced severe neurologic events (SNE) with increased morbidity and mortality [8, 10].

Owing to longer stays in hospital, the health care costs increase. The health-related quality of life of these patients decreases [10]. Causes of altered mental status after LT include factors related to recipient pre-LT status,

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intra-operative factors and post-LT factors. The drug-specific toxicity of the immunosuppressive agents was considered the main effect [12, 13]. However, in a proportion of post-LT patients a clear cause for their altered sensorium cannot be identified [12].

The risk of neurologic events (NE) occurring after LT is relatively high [8, 12, 14]. The reason for this increase remains unexplained; possible causes include surgical procedure complexity, structural CNS problems, changes resulting from hepatic encephalopathy (HE), metabolic disturbances and drugs used following LT [9, 12]. Neurotoxicity secondary to use of calcineurin inhibitors (CNI) has been studied in the past [6, 15, 16]. However, controversy persists over which patients are at greater risk for developing NEs following LT. Increased mortality and morbidity, in the form of greater incidence of acute cellular rejection (ACR), prolonged hospital stay, higher rates of in-hospital infections and poorer quality of life have all been associated with NEs [12, 17]. Ultimately, LT costs are probably higher in these patients, making early identification of those potentially at risk for developing NE important, in order to implement measures attempting to reduce NEs incidence [12, 17].

LT is the only successful treatment modality for pediatric patients with end-stage liver disease [18]. NCs after pediatric LT have been reported in 8%–46% of patients [14, 19], with high morbidity and mortality rates. Several studies report that NC rates are higher, and complications are more severe in pediatric than in adult patients [14, 20]. Although the causes of NCs are not clear, studies suggest that use of immunosuppressants, graft dysfunction, pre-operative hepatic encephalopathy, and electrolyte and metabolic derangements are involved [12, 17]. As the indications for LT in children differ from those in adults, different types of NCs and different risk factors for NCs are expected [14, 19, 20].

Based on literature review and the importance of NCs associated with LT in pediatrics, we conducted this study to evaluate the incidence of NCs after LT in pediatric patients in

Namazi Hospital.

METHOD AND MATERIALS

The medical records of all children aged between 1 and 18 years who had underwent LT and consulted with pediatric neurologist between 2016 and 2017 in Namazi Hospital, a tertiary medical center in Shiraz, southern Iran, were retrospectively reviewed. Demographic data, occurrence of NCs, and pre-operative variables that might predict NCs and their outcomes, including graft and patient survival, were evaluated. Pre-operative variables included age, sex, Pediatric End-Stage Liver Disease (PELD) score, primary liver disease, and laboratory variables (pre-operative serum sodium, potassium, total bilirubin, and creatinine levels, as well as white blood cell and platelet counts, and hemoglobin were also assessed.

Patients who developed NC, underwent EEG or neuroimaging. Patients with pre-operative hepatic encephalopathy persisting after LT were excluded from the analysis to make the onset of the NCs clear.

NCs are defined as newly developed neurological problems after LT. Pre-existing neurological problems before LT were considered pre-transplant neurological problems. In our study, we defined encephalopathy as a persistent mental change without any focal neurological signs, even after extubation and discontinuation of sedatives. All NCs were confirmed by a consultant pediatric neurologist or psychiatrist at the time of the event. All patients underwent standardized neurological examinations before LT. Newly developed symptoms after LT were evaluated by a pediatric neurologist. When possible, EEG and brain CT or MRI were performed to exclude structural brain lesions, brain abscess or stroke.

The immunosuppressant regimen was changed for these patients, from a tacrolimus-based regimen, including azathioprine and steroid, to an FK506-based regimen that included steroids.

Table 1: The underlying disease of patients who underwent liver transplantation

Underlying disease	n (%)
Biliary atresia	17 (16.8)
PFIC	17 (16.8)
Wilson disease	14 (13.9)
Tyrosinemia	10 (9.9)
Auto immune hepatitis	8 (7.9)
Crigler Najjar	6 (5.9)
Cryptogenic	6 (5.9)
Hyperoxaluria	3 (3.0)
Paucity of bile duct	2 (2.0)
Hyper cholesterolemia	2 (2.0)
HCC	2 (2.0)
Acute liver Failure	2 (2.0)
Neonatal Hepatitis	2 (2.0)
GSD	2 (2.0)
MSUD	1 (1.0)
Alagille syndrome	1 (1.0)
Urea cycle disease	1 (1.0)
Methyl Malonic acidemia	1 (1.0)
PSC	1 (1.0)
Hepatoblastoma	1 (1.0)
Neonatal sclerosing cholangitis	1 (1.0)

All patients received co-medication, including prophylactic CMV medication (gancyclovir or acyclovir), trimethoprim/sulfamethoxazole, ulcer prophylaxis (H_2 -blocker or antacid) and an antifungal agent. The first line antiepileptic drug used in post-LT patients who developed convulsion was levetiracetam (42–60 mg/kg/day based on age category); the second one was topiramate (75–200 mg bid based on weight category). All patients were followed for one year or until death.

Statistical Analysis

Categorical variables in patients with and without NCs were compared using χ^2 test. Continuous variables were compared with Student's t test. Kaplan-Meier method and log-rank test were used for survival analysis. Cox proportional hazard model was used to identify the risk factors for NCs in these patients. All tests used were two-sided; a p value <0.05 was considered statistically significant. Analyses were

performed with SPSS® for Windows® ver 18.0 (SPSS, Inc, Chicago, IL, USA).

RESULTS

One-hundred and one patients were studied. The mean±SD age of patients at the time of LT was 8.2±5.3 years; 51.5% were male and 47.5% were female. The most common cause of LT was biliary atresia (16.8%), progressive familial intrahepatic cholestasis (PFIC) (16.8%) and Wilson's disease (13.9%) (Table 1).

Perioperative laboratory data of patients are presented in Table 2. Liver function test was normal in nine (8.9%) patients; 92 (91.1%) had increased liver enzymes. The mean±SD PELD score was 18.2±1.1 (range: 4–40). The immunosuppressant regimen declared that 92 (91.1%) patients received steroids and 19 (20.7%) received cyclosporine A. After one-year follow-up, 74 (73.3%) patients were alive. Liver biopsy results revealed that nine (8.9%) patients had mild to severe signs of rejection during one year after LT. At the time of hospital admission after LT, 16 (15.8%) patients developed convulsion; two developed encephalopathy. EEG and brain CT without contrast were done for these patients; there were not abnormal findings. Two patients with encephalopathy died during the hospital stay. Anticonvulsant drugs were started for patients with convulsion; no one had any episode of recurrent convulsion within the follow-up period. At the first year, three patients developed signs of peripheral neuropathy, three complained of headache and only one patient developed dystonia. There was not significant correlation between age ($p=0.658$), sex ($p=1.0$), the underlying disease ($p=0.978$), steroid use ($p=1.0$), outcome ($p=0.67$), and neurologic complications.

DISCUSSION

There are few studies that evaluated NCs developed after LT in pediatric patients. Their results revealed that the incidence of NCs after LT in pediatric patients vary from 8% to

Table 2: Laboratory results of the study population recorded at the last follow-up visit

Parameter	Mean±SD (range)
Sodium	140.2±6.4 (129–163)
Potassium	4.5±0.9 (1.9–6.9)
BUN	19.6±15.1 (1.0–75.0)
Creatinine	0.6±1.1 (0.1–9.4)
Hemoglobin	9.1±1.4 (6.2–12.9)
WBC ×10 ³	15.8±26.2 (0.2–200)
Platelet count ×10 ³	192.2±123.7 (9.0–550.0)
Total bilirubin	3.0±4.5 (0.2–20.2)
Direct bilirubin	1.5±2.3 (0.1–10.0)
Alkaline phosphatase	460.6±301.8 (117.0–1740.0)

46%. The incidence of NCs after LT in this study during a one-year follow-up (24.7%) was comparable to the incidence reported in the literature. Previous studies found that the most common NCs are convulsion and encephalopathy, which usually occur in the first three months after LT. For example, in Lee, *et al*, study [21], 46 NCs occurred in 41 patients after LT, the most common being seizure and encephalopathy. Of the 46 NCs, 24 (52%) occurred within three months after LT. Likewise, we found that 15.8% of patients developed convulsion and 1.9% had encephalopathy. In previous studies, several factors such as cerebral structural lesions, infection, hypoxic ischemic injury, metabolic derangements, and treatment with immunosuppressive agents, were found as causes of seizure [22]. In Erol, *et al*, study [17], the most common NCs were seizure (seven episodes in six patients), and immunosuppressive agents (tacrolimus and cyclosporine) were the primary causes of NCs. Uremia with hypertension, hypoxia, and hypomagnesemia were other causes of NCs. Similar to our results, 15% of patients studied by Erol, *et al*, developed convulsion [17]. In their study, NCs were reversed by discontinuation or reduction in dosage of immunosuppressive agents, correction of hypomagnesemia, uremia, and hypertension. There was no electrolyte imbalance or metabolic disturbance in patient who had convulsion in our study. The convulsion was not changed with change in the immunosuppressive medication or reduction of the doses administered; it was con-

trolled by diazepam and phenytoin.

Major complaints in patients treated with immunosuppressive agents such as tacrolimus and cyclosporine, are tremor and headache, which are considered mild neurotoxic adverse effects [23]. We found three patients with signs of peripheral neuropathy, three complained of headache and one developed dystonia. In Erol, *et al*, study [17], tremor occurred as a minor complaint and was documented in only one patient (2.5%). On the contrary, Fu, *et al* [24], reported a higher rate of NCs with encephalopathy being the most frequent (56.8%) NC followed by tremor (26.5%), hallucinations (11.2%), and seizure (8.2%). Also, Dehghani, *et al* [25], reported that the most common NCs were tremor (16.7%), convulsion (12.5%), and headache (10.4%). The high incidence of movement disorders (such as dystonia and tremor) in other studies may be attributed to the higher dosage of tacrolimus used in their patients [25].

Like previous studies in pediatric patients, headache was also a minor complication in our study (3% of patients). The reasons for headache after LT are use of high-dose steroid, and treatment with other immunosuppressive agents such as tacrolimus and cyclosporine. Encephalopathy and hypertension can also cause headache after LT [12, 25]. In our study, reported episodes of headaches were mostly mild and intermittent; more severe forms including migraine were not reported.

Ghosh, *et al* [20], found that early and late NCs occurred in 14% (9/65), and 16.9% (11/65) of patients; they noted that NCs are common in children after LT, seizures being the most common. In contrary to previous studies and also ours, they found that delayed complications occur more often than early complications. We could not explain the difference, so further studies with larger number of patients and longer follow up are needed.

Recently, Erol, *et al*, showed that patients with Wilson's disease have a higher incidence of NCs (60%) compared with those without the disease (26.7%). However, this difference was not significant [17]. In Dehghani, *et al* [25] study, children with autoimmune cirrhosis experienced a higher rate of NCs (80%) compared with children without autoimmune cirrhosis (37.2%). We, however, found that the incidence of NCs was not related to the underlying disease.

Finally, the mortality rate in our study was 26.7%, similar to the overall rate reported by Erol, *et al* [17] (22.5%). Menegaux, *et al* [26], found a higher mortality rate in pediatric patients (50%) than in adults (14%); they observed that pediatric and adult patients with NCs had a higher mortality rate than those without NCs. Other studies supported our findings that the mortality after LT is not linked with occurrence of NCs [27, 28].

In conclusion, as NCs after pediatric LTs are common and associated with short- and long-term morbidity, we recommend close monitoring and appropriate risk management in order to improve the long-term outcomes of pediatric patients who undergo LT. Also early detection and appropriate management of NCs are important.

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