Neuromuscular Complication After Liver Transplant in Children: A Single-Center Experience

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Abstract

***Objectives*: Neurologic complications are a significant cause of morbidity in children after liver transplant. In this study, we sought to evaluate the neurologic complications in children after liver transplant.**

***Materials and Methods*: All children aged younger than 18 years old who had undergone liver transplant between June 2004 and June 2007 were included in this prospective study. There were 30 boys (62.5%) and 18 girls (37.5%) (mean age, 9.6 ± 4.3 years; mean duration of follow-up, 21.6 ± 9.4 months). The most common indications for liver transplant were biliary atresia (n=12, 25%), Wilson disease (n=7, 14.6%), tyrosinemia (n=7, 14.6%), progressive familial intrahepatic cholestasis (n=6, 12.5%), and autoimmune cirrhosis (n=5, 10.4%).**

***Results:* Immunosuppressive medication consisted tacrolimus (n=44, 91.7%) or cyclosporine (n=4, 8.3%) combined with mycophenolate mofetil (n=33, 68.7%) and prednisolone (n=18, 37.5%). The most-common neurologic complications were tremor (n=8, 16.7%), convulsions (n=6, 12.5%), insomnia (n=6, 12.5%), headache (n=5, 10.4%), muscle cramps (n=5, 10.4%), paresthesia (n=3, 6.2%), and weakness (n=3, 6.2%).**

***Conclusions:* We conclude that the most-common neurologic complication after liver transplant in children in contrast to other studies is tremor, same as adult patients. This may be due to higher rate of use of tacrolimus in our patients.**

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Liver transplant is the treatment of choice in patients with end-stage liver disease (1). Patients with liver transplant develop multiple complications (2), and one of the most-significant complications is one that causes neurologic morbidity (3-6). Neurologic complications in patients with liver transplant can be due to underlying disease or immunosuppressive medications (7-8); they may be transient or permanent. Many studies have investigated neurologic complications in adults (9-13), but because the indications for liver transplant and the spectrum of complications differ in children (2-5), it is necessary to evaluate these problems in children. This study prospectively evaluates neurologic complications in children after liver transplant.

Patients and Methods

We prospectively assessed neuromuscular complications in 48 pediatric patients (aged younger than 18 years) after having undergone a liver transplant at the Organ Transplantation Center affiliated with Shiraz University of Medical Sciences between June 2004 and June 2007. The variables assessed were age, sex, cause of liver disease, duration of follow-up, graft type, the immuno-suppressive medication, and neurologic signs and symptoms (eg, tremor, headache, dizziness, insomnia, paresthesia, weakness, muscle cramps, convulsions, loss of concentration, and confusion).

All patients were evaluated for neurologic complications by the same pediatric neurologist, and work-ups (including electroencephalography, computed tomography, and magnetic resonance imaging of the brain) were performed when clinically indicated. Results are expressed as mean ± standard

deviation. Data were analyzed by a 2-tailed Fisher exact and chi-squared tests when appropriate. Statistical analyses were performed with SPSS software for Windows (Statistical Product and Service Solutions, version 12.0, SSPS Inc, Tokyo, Japan). Values for *P* less than .05 were considered statistically significant.

Results

The patients consisted of 30 boys (62.5%) and 18 girls (37.5%), (mean age, 9.6 ± 4.3 years; mean duration of follow-up, 21.6 ± 9.4 months). The most-common indications for liver transplant were biliary atresia (n=12, 25%), Wilson disease (n=7, 14.6%), tyrosinemia (n=7, 14.6%), progressive familial intrahepatic cholestasis (n=6, 12.4%), and autoimmune cirrhosis (n=5, 10.4%). The indications for liver transplant are shown in Table 1.

Immunosuppressive medication consisted of tacrolimus (n=44, 91.7%), mycophenolate mofetil (n=33, 68.7%), prednisolone (n=18, 37.5%), and cyclosporine (n=4, 8.3%). Of the 48 pediatric patients, 20 patients (41.7%, 11 boys and 9 girls) exhibited neurologic complications during first 6 months after undergoing liver transplant (mean age, 10.7 ± 4.8 years; range, 3-18 years). There was no statistically significant difference between age of patients with and without neurologic complications. These patients experienced 37 episodes of neurologic complications, because some of the patients had 2 or more separate episodes. The most-common neurologic complication was tremor (n=8, 16.7%). Other complications were included convulsions (n=6, 12.5%), insomnia (n=6, 12.5%), headache (n=5, 10.4%), muscle cramps (n=5, 10.4%), paresthesia (n=3, 6.2%), weakness (n=3, 6.2%), and dizziness (n=1, 2.1%). None of the patients with muscle cramps had hypocalcemia or hypomagnesemia. The demographic data for each patient with a neurologic complication are shown in Table 2.

Of the 6 patients with convulsions (12.5%), there was no electrolyte imbalance, and imaging studies were normal except in 1 patient who was taking tacrolimus where the magnetic resonance imaging of

Table 1. Indications for liver transplant and neurologic complications in 48 pediatric patients.

Underlying disease	Number of (%) patients	Neurologic complications (%)
Biliary atresia	12 (25)	4 (33.3)
Wilson disease	7 (14.6)	3 (42.8)
Tyrosinemia	7 (14.6)	2 (28.6)
Progressive familial intrahepatic cholestasis	6 (12.4)	4 (66.7)
Autoimmune cirrhosis	5 (10.4)	4 (80)
Cryptogenic cirrhosis	5 (10.4)	1 (20)
Crigler-Najjar syndrome	1 (2.1)	1 (100)
Congenital hepatic fibrosis	1 (2.1)	1 (100)
Fulminant hepatic failure	1 (2.1)	0 (0)
Primary sclerosing cholangitis	1 (2.1)	0 (0)
Idiopathic neonatal hepatitis	1 (2.1)	0 (0)
Hypercholesterolemia	1 (2.1)	0 (0)
Total	48 (100)	20

Table 2. Data for cases with neurologic complications.

Patient No.	Age (y) / sex	Indication for liver transplant	Graft type	Symptoms	Duration of follow-up (mo)	Immunosuppressive medication
1/1	17/ male	PFIC	Whole	Tremor	13	Tacrolimus, MM
2/2	13/ male	Wilson disease	Living	Tremor	12	Tacrolimus, MM
3/3	4/ female	PFIC	Living	Headache	14	Tacrolimus, MM
4/4	11/ male	Biliary atresia	Living	Insomnia	18	Tacrolimus
5/5	7/ female	Tyrosinemia	Split	Tremor	14	Tacrolimus, MM
6/6-8	3/ female	Crigler-Najjar syndrome	Living	Tremor, insomnia, weakness	15	Tacrolimus
7/9	12/ female	Autoimmune cirrhosis	Living	Muscle cramps	13	Tacrolimus, MM, prednisolone
8/10	13/ male	Biliary atresia	Living	Muscle cramps	22	Tacrolimus, MM
9/11,12	11/ male	Congenital hepatic fibrosis	Living	Headache, convulsion	18	Cyclosporine, MM
10/13-18	18/ female	PFIC	Whole	Headache, dizziness, insomnia, paresthesia, muscle cramps, weakness	18	Tacrolimus, MM
11/19	15/ male	Wilson disease	Whole	Tremor	16	Tacrolimus, MM
12/20-22	10/ male	PFIC	Whole	Tremor, insomnia, paresthesia	30	Cyclosporine, MM
13/23-25	15/ male	Wilson disease	Whole	Tremor, headache, muscle cramps	24	Tacrolimus, MM
14/26	3.5/ female	Biliary atresia	Living	Insomnia	18	Tacrolimus, MM
15/27-29	18/male	Autoimmune cirrhosis	Whole	Headache, weakness, muscle cramps	48	Cyclosporine, MM, prednisolone
16/30-33	14/ male	Cryptogenic cirrhosis	Whole	Tremor, insomnia, convulsion paresthesia	14	Tacrolimus, MM, prednisolone
17/34	10/ female	Autoimmune cirrhosis	Whole	Convulsion	13	Tacrolimus, MM, prednisolone
18/35	9.5/ female	Autoimmune cirrhosis	Living	Convulsion	17	Tacrolimus, MM, prednisolone
19/36	5/ male	Biliary atresia	Living	Convulsion	14	Tacrolimus, prednisolone
20/37	5/ female	Tyrosinemia	Living	Convulsion	15	Tacrolimus, MM

Abbreviations: MM, mycophenolate mofetil; PFIC, progressive familial intrahepatic cholestasis.

the brain showed leukoencephalopathy. This patient was 14-year-old boy who had undergone a liver transplant from deceased donor due to cryptogenic cirrhosis, about 4 months before developing generalized, tonic convulsions. His blood laboratory values were normal, and an electroencephalogram showed nonspecific changes, but magnetic resonance imaging of the brain in favor of leukoencephalopathy. His tacrolimus trough level at this time was 18 ng/mL. We decreased the dosage of tacrolimus, and maintained the trough level at approximately 8 ng/mL. His convulsions were controlled with gabapentin.

As mentioned above, the most-common neurologic complication was a tremor (n=8, 16.7%), that included 3 episodes in Wilson disease, 2 episodes in progressive familial intrahepatic cholestasis, and 1 episode in tyrosinemia, Crigler-Najjar syndrome, and cryptogenic cirrhosis.

Other more-common complications were convulsions (2 episodes in autoimmune cirrhosis, and 1 episode each in biliary atresia, tyrosinemia, congenital hepatic fibrosis, and cryptogenic cirrhosis), insomnia (2 episodes in biliary atresia, 2 episodes in progressive familial intrahepatic cholestasis, 1 episode in Crigler-Najjar syndrome, and 1 episode in cryptogenic cirrhosis), headache (2 episodes in Wilson disease, and 1 episode each in congenital hepatic fibrosis, progressive familial intrahepatic cholestasis, and autoimmune cirrhosis), and muscle cramps (2 episodes in autoimmune cirrhosis, and 1 episode each in progressive familial intrahepatic cholestasis, Wilson disease, and biliary atresia).

Of the 48 patients with liver transplants, 20 patients (41.7%) had neurologic complications, and when totaled, the incidence of these complications was 37 episodes (77.1%). The frequency of neurologic complications was compared in different types of chronic liver disease (Table 1). Patients with biliary atresia had a lower incidence of neurologic complications (33.3%) than did those without that disease (44.4%); however, this result was not statistically significant ($P > .05$). In patients with Wilson disease, the frequency of a neurologic complication (42.8%) was the same as in those without Wilson disease (41.5%). Also, in patients with tyrosinemia and cryptogenic cirrhosis, the frequency of a neurologic complication was lower than in those without these diseases (28.6% and 20% compared with 43.9% and 44.2%), which was not statistically significant ($P > .05$). On the other hand, the frequency of neurologic complications in autoimmune cirrhosis was higher than those patients without autoimmune cirrhosis (80% vs 37.2%); this result was statistically significant ($P = .029$). We found that the children with progressive familial intrahepatic cholestasis had a higher incidence of neurologic complications than did children without progressive familial intrahepatic cholestasis (66.7% vs 38.1%); however, this difference was not statistically significant ($P > .05$).

Discussion

To date, a few studies have evaluated neurologic complications in pediatric patients after liver transplant (2-5). These studies indicated the incidence of neurologic complications after liver transplant in pediatric patients range from 8% to 43% (2-5). In this study, of 48 pediatric patients with liver transplant, 20 patients (41.7%) developed 37 episodes of neurologic complications (77.1%), which is higher than the earlier studies, and may be due to the higher dosages of immunosuppressive medications in our patients.

In previous studies, seizures were the most-common neurologic complication in pediatric patients after having undergone a liver transplant (3-5). The cause of seizures after a liver transplant is multifactorial and includes metabolic derangements, treatment with immunosuppressive agents, hypoxic ischemic injury, cerebral structural lesions, and infection (14).

Erol and associates (3) documented 7 episodes of seizures in 6 of 40 pediatric patients after having undergone a liver transplant (15%). The majority of seizure episodes were caused by tacrolimus and cyclosporine (71.4%), and 1 episode was caused by hypomagnesemia (14.2%). In our study, convulsions were seen in 12.5% of patients, which is similar to the study by Erol and associates (3). In patients who developed convulsions, there were no metabolic derangements or electrolyte imbalances, and with a change in immunosuppressive medications, the convulsions subsided. (Those patients that received cyclosporine, were changed to tacrolimus, and those who received tacrolimus, the dosage was decreased). Diazepam and phenytoin were used to control the convulsive episodes. Patients received gabapentin for

maintenance anticonvulsant therapy. Only 1 patient needed an anticonvulsant medication for more than 1 month.

In 1 patient who received tacrolimus, magnetic resonance imaging of the brain showed leukoencephalopathy (2% of patients); that incidence is the same as in another report (15), but is lower than the incidence of 10% reported by Erol and associates (3). Our lower rate of leukoencephalopathy may be due to prospective nature of our study, in which each patient with abnormal neurologic signs and symptoms was seen by a pediatric neurologist and treated in a timely manner.

Also, in our study, we had only 1 case of fulminant hepatic failure, but in the Erol study, there were 9 cases of fulminant hepatic failure (3). We found only 1 study in the literature that compared the neurologic complications in pediatric patients who had fulminant hepatic failure, with patients who had other types of liver diseases, that concluded neurologic complications were higher in patients with fulminant hepatic failure (44%) when compared with patients with different types of liver disease (35%) (3).

Tremor and headache are major complaints in patients treated with immunosuppressive agents such as tacrolimus and cyclosporine, and are considered mild, neurotoxic, adverse effects (13). In other studies (3, 13), tremor occurred as a minor complaint. Erol and associates (3) documented that tremor developed in only 1 of 40 patients (2.5%) after undergoing a liver transplant. In our study, tremor occurred in 16.7% of pediatric patients, and was the most-common neurologic complication. This result contrasts with other studies (3, 13). A higher dosage of tacrolimus used in our patients may be contributory (the mean tacrolimus trough levels were 12.4 ± 6.3 ng/mL in our patients, and 8.5 ± 2.8 ng/mL in the Erol study).

Previous studies in pediatric patients (3-5) showed that headache occurred infrequently (2.5% of patients), but in our study, headache occurred at a higher incidence (10.4%). This also may be due to the dosage and type of immunosuppressive medication. The causes of headache after a liver transplant include use of high-dose steroid, and treatment with other immunosuppressive agents like tacrolimus and cyclosporine. Encephalopathy and hypertension are also causes of headache after a liver transplant.

One postulated mechanism behind the calcineurin-inhibitor–associated headache is vasoconstriction of the cerebral blood vessels (16). In a 1-year follow-up study of adult kidney transplant patients, headache was reported in 38% and 44% of patients receiving cyclosporine and tacrolimus, respectively (17). Headache is mostly mild and intermittent, but more severe forms, including migraine, have been reported (16). The headache may be dosage-related, and lowering the drug dosages often takes away the pain, as we observed in this study.

In 1 study, tremor, headache, and insomnia, were the most-frequently reported adverse events involving the neurologic system in liver transplant recipients. The authors concluded that headache was significantly correlated with the tacrolimus dosage. They also hypothesized that insomnia was not related to any dosing variable (18).

One recent study showed that children with Wilson disease experienced a higher incidence of neurologic complications (60%) than did the children without Wilson disease (26.7%) (3). But in this study, we noted that the rate of neurologic complications in patients with and without Wilson disease was the same.

In our study, children with autoimmune cirrhosis experienced a higher rate of neurologic complications (80%) compared with children without autoimmune cirrhosis (37.2%). But, we could not find any explanation for this, and further studies, with larger numbers of patients with autoimmune cirrhosis, are needed.

Children with progressive familial intrahepatic cholestasis experienced a higher rate of neurologic complications (66.7%) than did the children without progressive familial intrahepatic cholestasis (38.1%).

It seems that the spectrum of neurologic complications that develop in pediatric patients after a liver transplant is variable and is not related to underlying liver disease. It is usually reversible by decreasing the immunosuppressive dosage or changing to another drug. Collaboration with a pediatric neurologist for diagnosis and follow-up of neurologic complication in patients after liver transplant is essential.

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