



Comprehensive analysis of the efficacy of liver transplantation in pediatric patients with Wilson's disease

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Abstract

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Aim: The aim of the present study is to evaluate the results of liver transplantation (LT) in pediatric Wilson disease (WD) with a specific sub-analysis in patients with neuropsychiatric symptoms.

Materials and Methods: Demographic, operative, laboratory and neurologic findings of 23 pediatric patients with WD that underwent LT were analyzed by examining the patient charts.

Results: Median age of the patients was 13 (7 to 17) years. Median Wilson's Index scores of the patients were 7 (5-13). Median Child-Pugh Score, MELD-Na and PELD scores of the patients were 10 (5-12), 19 (8-34) and 25.4 (8.4-30.7); respectively. Eight patients (34.8%) had Kayser-Fleischer rings on examination. Five patients (21.7%) presented with acute decompensated Wilson's disease. Fifteen patients (65.2%) received living donor liver transplantation. Totally, 10 patients (43.4%) had nervous system involvement in the preoperative period. Two patients fully recovered; 2 patients showed partial recovery. On the other hand, 4 patients showed no improvement and 2 patients had progression of their disease in the postoperative period.

Conclusion: The results of the present study show that LT is an effective and safe alternative in end-stage liver failure in WD. However, in these patients, nervous system involvement may not improve despite successful LT.



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Introduction

Wilson's disease (WD) is an autosomal recessive metabolic disorder that results from defective hepatocyte-bile copper elimination and accumulation of copper in the body of the individual [1]. Its prevalence in general population is 1/30.000 [2]. Altered excretion of copper results in accumulation in different tissues such as liver, brain, cornea, heart, musculoskeletal, urinary and endocrine system which results in hepatic and neuropsychiatric symptoms [2, 3]. ATP7B encodes p type adenosine triphosphatase that has a role in copper transportation. It is defective in WD and is first defined in 1993 [4]. Chelators such as D-penicillamine and trientine hydrochloride reduce the absorption of copper and zinc which results in better prognosis in patients with WD [5]. However, in patients with ineffective medical therapy and/or decompensated fulminant liver failure liver transplantation is in-

dicated [6].

The damage to the central and peripheral nervous system has been shown in Wilson's disease. These lesions are due to disturbances in the copper metabolism leading to development of reactive oxygen species that damage the nerve tissue [7,8]. Common lesions in peripheral and central nervous system are focal demyelinated areas [7]. Furthermore, the peripheral nerve damage observed in WD is a separate entity from the damage to the basal ganglia that is observed during the natural history of the disease. This suggests that peripheral nervous system is involved separately and can be observed in any time point during the course of the disease [9]. It is still unknown whether this is a continuum of a disease process ascending from the periphery and affecting the central nervous system.

An indication of liver transplantation for WD is straight forward. However, despite stable liver disease, worsening of the neurologic sequel of WD is a controversial point for liver transplantation. Globally and including our institution, it is a common practice to perform liver transplan-

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tation for WD with progressive neurologic symptoms despite adequate medical therapy [10]. Following liver transplantation, successful resolution of the neurological symptoms to a certain degree have been reported by various researchers [11–13].

We believe discussion of our results can guide the other institutions during the decision-making process for liver transplantation in WD. The aim of the present study is to discuss the results of liver transplantation for WD related liver failure in terms of pretransplant condition, post-transplant prognosis, complications and the neurologic status of the patients. Special attention is given to the neurologic status of the patients before liver transplantation and the outcomes of liver transplantation in patients with neuro-Wilson are especially analyzed.

Materials and Methods

Study population

Between March 2002 and July 2018 2224 liver transplantations for end stage liver disease have been performed in Inonu University Institute of Liver Transplantation. The living donor and cadaveric donor liver transplantations were performed in 1806 (81.2%) and 418 patients (18.8%); respectively. Twenty-three pediatric patients received liver transplantation for WD during the study period. In patients who were transplanted for indeterminate liver cirrhosis with explant pathology of WD were excluded from the study. Ethical approval was obtained for study from the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (Date: 24.11.2020, Decision Number: 2020/1283).

Evaluation of the patients with Wilson's disease

Patients Wilson's disease can present with chronic liver failure or fulminant hepatic failure. In the process evaluation of the patients with chronic liver disease, we assess the severity of the disease with different scoring systems according to the age of the patients. In patients 12 years old or younger, the severity of liver disease are evaluated using the Pediatric End Stage Liver Disease (PELD) scoring system. In patients older than 12 years, the severity of liver disease is evaluated using Model For End Stage Liver Disease (MELD) scoring system. Patients with MELD/PELD score greater than 14 were evaluated for liver transplantation. Patients with neurologic manifestations of the Wilson's disease with extensive neurologic involvement were discussed in a multidisciplinary transplant committee involving transplant surgeons, pediatric gastroenterologists and neurologists. Only after a consensus of all the departments, evaluation and preparation for liver transplantation was initiated. All the patients with chronic liver disease received dietary copper restriction (≤ 1 gr/day), zinc (50-75 μ g/day) plus either trientine or D-penicillamine (20mg/kg/day). In patients with high risk of progression of neurologic symptoms, trientine was used as the first line therapeutic agent. Only after proper medical therapy, patients who needed liver transplantation proceeded with the procedure.

All the patients with fulminant hepatic failure due to Wilson's disease underwent liver transplantation under emer-

gency conditions and the regular treatment modalities and dietary modifications could not be applied.

Study parameters

The prospective database was retrospectively evaluated for demographic, clinical and operative characteristics of the patients. Laboratory parameters of the patients and the 24-hour urinary copper excretion were also evaluated for the study. Pediatric end stage liver disease (PELD) score (for patients aged between 0-12 years), model for end stage liver disease-sodium (MELD-Na) score (for patients between 12-18 years), Child-Pugh Score (CPS), New Wilson's Index (NWI) were calculated and evaluated in the study.

Statistical analyses

Descriptive statistical methods were used regarding the data presented in the study. The continuous data such as the scores, age etc. were expressed as numbers for each patient and also were given as median and range for the whole study population. Furthermore, the discrete data are expressed as percentage of the study population. The 1-3- years of survival were expressed as percentage using the Kaplan-Meier Estimates. All statistical analyses were performed using the Statistical Package for Social Sciences software version 20 (SPSSv20, IBM, USA).

Results

General demographic characteristics of the patients

There were 23 pediatric patients with Wilson's disease that had liver transplantation. Eleven patients (47.8%) were female and 12 patients (52.2%) were male. Median age of the patients was 13 ranging from 7 to 17 years. Median Wilson's Index scores of the patients were 7 (5-13). Median Child-Pugh Score, MELD-Na and PELD scores of the patients were 10 (5-12), 19 (8-34) and 25.4 (8.4-30.7), respectively. In the present study, 18 patients (78.2%) had a MELD/PELD score greater than 14. Only in 4 patients (17.4%) had a MELD/PELD score less than 14 and these patients had WD with extensive neurologic involvement. Eight patients (34.8%) had Kayser-Fleischer rings on examination. In 6 patients (26.1%) Kayser-Fleischer status is unknown because the patients did not go to the appointment at the ophthalmology department. Fifteen patients (65.2%) received living donor liver transplantation. The demographic, clinical, operative and biochemical parameters of the patients are summarized in Table 1.

Fifteen of the 23 patients (65.2%) in the present study received dietary modification together with zinc plus trientine or D-penicillamine in the preoperative period. Eight patients (34.8%) that did not receive a preoperative proper therapy and these patients underwent emergency liver transplantation for fulminant hepatic failure.

Six patients died (26.1%) and 17 (73.9%) are still alive. The median follow-up period of the deceased patients was 273.5 (1-1890) days. There were three patients (13%) who died in the post-transplant first week and only one of these patients (33.3%) was operated under emergency conditions due to acute decompensated Wilson's disease. Other two patients underwent elective liver transplantation. All three

Table 1. The demographic, clinical and transplantation related characteristics of the patients.

Patient Characteristics	Values
Gender	
Female	11 (47.8%)
Male	12 (52.2%)
Age (years)	13 (7-17)
Kayser-Fleischer Rings	
No (n,%)	9 (39.1%)
Yes	8 (34.8%)
Not investigated	6 (26.1%)
Acute liver failure on presentation	
No	20 (87%)
Yes	3 (13%)
NS symptoms	
Absent	13 (56.6%)
Present	10 (43.4%)
Child-Pugh Scores	
A	2 (8.7%)
B	9 (39.1%)
C	12 (52.2%)
MELD-Na Score	19 (8-34)
PELD Score	25.4 (8.4-30.7)
Graft Type	
Deceased Donor	8 (34.8%)
Living Donor	15 (65.2%)
Final status of the patients	
Alive	17 (73.9%)
Dead	6 (26.1%)
NS Symptoms	
Apathy	1 (10%)
Spasticity and tremor	1 (10%)
Seizures	2 (20%)
Disorders of speech and gait	6 (60%)
Albumin (g/dL)	2.7 (0.9-3.8)
Total Bilirubin (mg/dL)	3.9 (0.3-34.7)
Creatinine (mg/dL)	0.5 (0.4-0.7)
Aspartate Aminotransferase (IU/mL)	740 (92-3710)
Leukocyte (cells/mm ³)	5000 (1800-13.300)
International normalized Ratio	1.9 (0.3-34.7)
24-hour urinary copper excretion (µg/24hour)	188 (0-4999)

*The continuous variables are expressed as median (Range) and categorical variables are expressed as number of individuals and percentage of the study population. NS: Nervous system. MELD-Na: Model for end stage liver disease-sodium. PELD: Pediatric end stage liver disease. NS: Nervous system.

patients received living donor liver transplantation. The 17 patients who are still alive have a median follow up period of 1041(603-3109) days. The 1-3-years of survival of the patients are 87%, 81%, respectively (Figure 1).

Table 2. Summary of the demographic, clinical and graft related characteristics of the patients with and without mortality.

Patient Characteristics	ALIVE	DEAD	p-value
Gender			0.14
Female	10 (58.8%)	1 (16.7%)	
Male	7 (41.2%)	5 (83.3%)	
Age (years)	13 (10-17)	11 (7-15)	0.12
Kayser-Fleischer Rings			0.86
No (n,%)	6 (35.3%)	3 (50.0%)	
Yes	7 (41.2%)	1 (16.7%)	
Not investigated	4 (23.5%)	2 (33.3%)	
Acute liver failure on presentation			0.87
No	13 (76.4%)	2 (33.3%)	
Yes	4 (23.6%)	4 (66.7%)	
NS symptoms			0.97
Absent	9 (52.9%)	4 (66.6%)	
Present	8 (47.1%)	2 (33.4%)	
Child-Pugh Scores			0.43
A	2 (11.8%)	-	
B	7 (41.2%)	2 (33.3%)	
C	8 (47.1%)	4 (66.7%)	
MELD-Na Score	19 (8-31)	29 (10-34)	0.16
PELD Score	10.1 (8.4-30.7)	26.2 (25.4-27.1)	0.8
Graft Type			0.47
Deceased Donor	5 (29.4%)	3 (50.0%)	
Living Donor	12 (70.6%)	3 (50.0%)	
Albumin (g/dL)	2.6 (3-3.8)	2.8 (1.8-3.2)	0.9
Total Bilirubin (mg/dL)	3.7 (0.3-34.7)	7.15 (0.6-33.5)	0.56
Creatinine (mg/dL)	0.5 (0.4-0.7)	0.5 (0.5-0.6)	0.97
Aspartate Aminotransferase (IU/mL)	730 (92-3710)	925 (410-1700)	0.53
Leukocyte (cells/mm ³)	4900 (1900-10,700)	8950 (1800-13,700)	0.18
International normalized Ratio	1.8 (1.1-3.1)	3.5 (1.4-4)	0.052
24-hour urinary copper excretion (µg/24hour)	160 (0-4070)	791 (0-4999)	0.28

All the dependent variables are compared with Mann-Whitney U test.

*The continuous variables are expressed as median (Range) and categorical variables are expressed as number of individuals and percentage of the study population. NS: Nervous system. MELD-Na: Model for end stage liver disease-sodium. PELD: Pediatric end stage liver disease.

Spectrum of nervous system involvement in patients with Wilson's disease

Totally, 10 patients (43.4%) had nervous system involvement in the preoperative period. Spectrum of the symp-

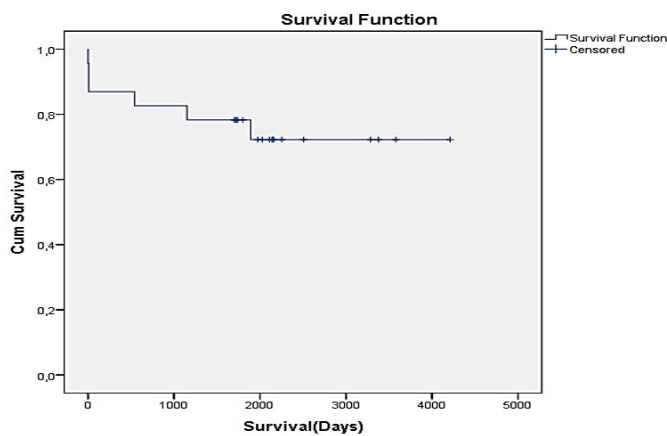


Figure 1. Summary of the survival of the patients with Wilson's disease. The 1, 3, and 5-year survival of the patients are 87, 81 and 54% respectively.

toms is summarized in Table 1. The most frequent nervous system complaint was disorders of speech and gait, which was present in 6 patients (60%) from patients with all neurological symptoms. Additionally, seizures were present in 2 patients (20%), apathy was present 1 patient (10%) and tremor and spasticity were present in 1 patient (10%). Thirteen patients (56.6%) in our study had no nervous system involvement what so ever.

The effects of liver transplantation on nervous system disorders related to Wilson's disease

Six patients with disorders of speech and gait had variable response following liver transplantation. Two patients showed full and another 2 patients with disorders of speech and gait showed partial recovery following liver transplantation. The remaining two patients showed no improvement and the symptoms remained following liver transplantation. Similarly, 2 patients with seizures did not show any improvement following liver transplantation. In addition, patients with apathy (n=1) and spasticity (n=1) experienced postoperative seizures which was considered as progression of symptoms.

Evaluation of the patients with mortality

There was no statistically significant difference in terms of demographic, clinical and operative characteristics between patients with and without mortality and it is summarized in Table 2. However, there were some differences in certain parameters that are worth emphasizing: i) The median MELD scores of the patients with and without mortality were 29 (10-34) and 19 (8-31); respectively, ii) Median PELD scores were also higher in patients with mortality [26.2 (25.4-27.1) versus 10.1 (8.4-30.7)], iii) The frequency of deceased donor liver transplantation was higher in patients with mortality (50% versus 29.4%) when compared to living donor liver transplantation.

In the postoperative course, 2 patients were re-transplanted (ABO mismatch), one of which was re-transplanted for chronic rejection 16 months after the index operation and the other was re-transplanted for primary

non-function 5 days after the index operations. Six patients (26%, including the chronic rejection patient) died in the postoperative period. The re-transplanted patient with chronic rejection died due to duodenum perforation that resulted in intraabdominal sepsis. Two patients died due to pneumonia, one patient died due to cerebrovascular occlusion (CVO), the remaining two patients had index transplant operation due to acute liver failure and one patient did not receive following the operation and the other experienced portal vein thrombosis on postoperative first day. Although the patients were re-operated and the portal venous flow recovered, patient died of graft failure and sepsis while waiting for emergency re-transplantation. The 1, 3-year survival of the patients are 87, 81; respectively (Figure 1).

The early postoperative course of the patients

There were two (8.9%) reoperations in the early postoperative period which was due to portal vein thrombosis in one patient who was re-operated and portal vein thrombectomy and re-anastomosis was performed. One patient had a bleeding from the hepatic arterial anastomosis site who was re-operated and hemostasis was performed.

Five (21.7%) patients suffered from anastomotic biliary leak. One patient was operated for biliary peritonitis and one patient was conservatively managed. Remaining 3 (60%) patient received a successful ERCP treatment. Seven (30%) patients suffered anastomotic biliary strictures. Four of the seven patients underwent endoscopic retrograde cholangio-pancreatico-ductography (ERCP) and were successfully treated. Three (57.2%) patients had an unsuccessful ERCP attempt, 2 received percutaneous transhepatic cholangiography (PTC) assisted drainage catheter, 1 underwent hepaticojejunostomy (HJ).

Discussion

Together with the advancements in surgical technique and the knowledge of the liver anatomy, great achievements have been obtained in partial liver graft transplantations in pediatric patients [14]. Wilson's disease is an autosomal recessive disorder that is predominantly seen as hepatic phenotype during childhood [15]. Currently, liver transplantation offers the only chance to cure the underlying metabolic disease and provide a more normal life to the patients. The neuropsychiatric symptoms of WD can be subtle during childhood and can be missed by the physicians in the field [15]. Traditionally, liver transplantation is performed for progressive deterioration of the liver function and the neuropsychiatric symptoms are usually neglected [16].

The pathophysiology of neurologic impairment in Wilson's disease is not thoroughly understood. It is hypothesized that it is due to accumulation of copper in brain causing focal demyelinated areas in the brain and porto-systemic shunts contribute to the disease process in directly [17, 18]. Dubbioso et al. [18] have shown that early treated patients do not show overt or subtle neurologic findings. Weiss et al. [10] have analyzed the results of liver transplantation in WD and have concluded that it is a safe and effective alternative in the treatment of patients with

neuropsychiatric complaints. On the other hand, there are studies that report continuation of symptoms despite chelation therapy or transplantation [10, 19]. We have also observed that central nervous system involvement in WD did not resolve in the postoperative period; however, some neurologic deficits showed partial improvement. From the diagnosis until the transplantation, they have already lost time and had a certain level of nervous system damage. For this reason, the central nervous system improvement was not pronounced in these patients following liver transplantation. LT is a rescue therapeutic option that should be carefully discussed in selected patients with continuous neurologic worsening over months despite adequate decoppering therapies. The management of transplanted patients with severe neurologic WD is complex and should be handled by experienced multidisciplinary teams to improve long-term survival. LT may not be the solution for every patient but has a place as a rescue therapy while waiting for future therapies [20].

In the present study, the patient survival in 1 to 3-years was 87% and 81%; respectively. Mortality rate is not affected by the urgency status of the transplant procedure [21,22]. Since the overall success rate of liver transplantation for WD is very well, the indications for transplantation for this disease should be revised and early liver transplantation for patients without or subtle neuro-psychiatric symptoms should be considered because if liver transplantation is performed in a timely manner the existing neurologic symptoms have a high probability to resolve and outcome of the procedure is very good. The increase in MELD and PELD scores causes deterioration in the patient's condition.

LDLT seems to be a good option for patients with WD. Our results suggest that % 50 of the cases with mortality received deceased donor graft. This contradicts with the study of Agalar et al. [23]; in their study involving 18 patients with WD who received either full-size DDLT or LDT, showed no difference in terms of survival periods. Guillard et al. [6] stated that LDLT from the close relatives of the patients for this hereditary disease was controversial but they have performed 4 LDLT in their series and stated that results were acceptable for grafts obtained from heterozygous donors. Prolonged warm and cold ischemia times and the quality of the grafts provided may affect the outcome of deceased donor liver transplantation [24-26]. This is also valid for transplantation performed for WD. LDLT is readily available and the transplantation can be performed electively with a readily available liver graft which may increase the success rates of the procedure [24-26].

The degree of involvement of the nervous system must be evaluated accurately. In the present study, some patients with nervous system involvement had a marginal response after liver transplantation. Overall, we could achieve in 4 of the 10 patients with neurologic involvement stable disease and 2 patients had worsening of the neurologic symptoms which may be attributable to the indirect effects of the ischemia reperfusion injury during liver transplantation. However, our results suggest that transplantation should be performed before the development of neurologic symptoms.

Five patients received emergency liver transplantation for acute liver failure. All five patients had Grade III encephalopathy according to West-Haven criteria and they showed a progressive clinical prognosis. In a single institution study by Cheng et al. [21] have shown that 6.25% of their patients with WD showed acute liver failure. Our rate of acute liver failure was 21.7% which is rather higher than the reported rates. This observation may be due to the fact our institution is a tertiary referral center in Turkey and majority pediatric and adult cases who required emergency liver transplantations are referred to our institution.

Biliary leak (17.3%) and stenosis (30%) were the two most common complications seen in our study population. Biliary leaks were observed within the first month following the operation and stenosis were observed starting from the postoperative 3rd month following the operation. Guillard et al. [6] have reported that biliary stenosis rate among the patients with WD was 12%. In the present study we present our results in pediatric patients may be higher due to the fact that we deal with smaller ducts in the pediatric patients and the anastomosis in pediatric group is technically more demanding.

There are many limitations to our study. The main limitation is the small number of patients that have been included. The retrospective nature of the study limits the available data for evaluation. However, a pattern emerges and we can see that liver transplantation is useful in subset of patients with WD who have neuropsychiatric symptoms and also LDLT provides better outcome for patients with WD when compared to DDLT.

Conclusion

Patients with WD that have end-stage liver disease and neurologic involvement are a special sub -group that requires thorough evaluation. Neurologic involvement is a bad prognostic factor that adversely affects the patient's survival. In specialized centers, liver transplantation is an effective therapeutic modality for the treatment of acute and chronic forms of Wilson 's disease. It eliminates the disease process and adverse systemic effects of copper accumulation. In WD, the outcome of the patients will be better provided that liver transplantation is performed before the development of symptoms involving the nervous system. Survival rates following liver transplantation for WD related liver disease is better than results of transplantation for other end stage liver disease etiologies.

Highlights

- Mortality rate in patients with Wilson 's disease is not affected from the emergency status of the transplant procedure performed.
- The outcome of liver transplantation in pediatric patients with Wilson 's disease is very good provided that it is performed before the development of nervous system symptoms.
- Survival benefit of living donor liver transplantation is better than deceased donor liver transplantation.

Ethics approval

Ethical approval for this study was obtained from Inonu University, Health Sciences Non-Interventional Clinical Research Ethics Committee (Date: 24.11.2020, Decision Number: 2020/1283).

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