Annals of Medical Research
DOI: 10.5455/annalsmedres.2019.04.189 2019;26(7):1217-21

Original Article

Liver transplantation in Wilson's disease: Long-term experience of single center

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Abstract

Aim: Liver transplantation (LT) is the most effective treatment method for preventing progressive and lethal complications of Wilson's disease (WD). Despite the deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT) are performed in many centers for WD, a limited number of reports were published, about long-term results. The aim of this study is to share the long-term outcomes of single center.

Material and Methods: Patients who underwent LT for the WD, between 1997 and 2017 were included. Patient's survival data, death causes, neurological symptoms and follow-up data were analyzed retrospectively.

Results: Eighteen patients (8DDLT, 10LDLT) with the median age of 17.11±9.88 (6-43) were included. Donor relationship was familial in all LDLT patients. Median follow-up time was 80.57±67.59 (0.23-240.9) months and the median survival time was 173.74±25.13 months. Two patients (11.1%) died in the perioperative period (0-90 days) and totally 3 patients (16.6%) died in the postoperative 0-12 month's period. The survival rates of the patient's at 1-, 5- and 10 years were 83.3%, 75% and 67.3%, respectively. After LT, neurological symptoms disappeared in 6 of 7 patients and no improvement was observed in one patient. During follow-up period, chronic rejection was seen in 5 patients, 3 patients were treated with medical procedure and 2 patients died due to chronic rejection.

Conclusions: Our findings are consistent with the literature, long-term survival is achieved in patients with no mortality, in the postoperative 0-12 month period and after LT, neurological symptoms are disappeared in most of the patients; according to this data, LT is an effective treatment method for the WD and complications.

Keywords: Wilson disease; liver transplantation; long term results; living donor.

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive genetic abnormality, that leads to impairment of cellular copper transport, impaired biliary copper excretion leads to copper accumulation often in liver, brain, central nervous system and cornea, progressive hepatic, neurological, psychiatric manifestations may be observed as a result of this accumulation (1).

LT is indicated, in cases of acute liver failure and end stage liver disease (2,3). LT is the most effective treatment method for preventing progressive and lethal complications of WD. Despite DDLT and LDLT are performed in many centers for WD, a limited number of reports were published, about long-term results. The aim of this study is to share the long-term outcomes of patients who underwent DDLT or LDLT at our center for the WD.

MATERIAL and METHODS

Patients who underwent LT for the WD, between 1997 and 2017 at the Dokuz Eylul University Hospital were included to the study. Patient's demographics, family history, presenting symptoms, pre – postoperative neurological status, presence of Kayser-Fleischer (K-F) ring, urinary copper excretion levels, blood ceruloplasmin levels, operation data, and perioperative morbidity – mortality and post-transplant follow-up data were analyzed retrospectively from the prospectively collected database. Mortality in the postoperative hospital stay or 0-90 days of LT was recorded as perioperative mortality.

Received: 08.04.2019 **Accepted:** 15.05.2019 **Available online:** 24.06.2019
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Child-Turcotte-Pugh (CTP) and Model for End-stage Liver Disease (MELD) classification were used for preoperative evaluation. The study was accepted by the university ethical committee, and all patients gave their informed consent.

Liver Transplantation procedures including DDLT and LDLT were performed by the same surgical team. Calci-neurin inhibitors and mycophenolate mofetil plus prednisolone-based immunosuppression regimens were used for all patients during the early post-transplant period. All patients underwent regular follow-up examinations in outpatient clinics. Neurologic and ophthalmologic examinations were performed by experienced doctors. Chronic rejection was diagnosed with liver biopsy and/or clinical observation.

All statistical analyses were performed with using SPSS 22.0 statistical package (SPSS, Chicago, Ill); Overall Survival (OS) was calculated as elapsed time from the operation date to time of death. Kaplan – Meier (K-M) estimator was used to calculate the OS rates and groups were compared with log-rank test.

RESULTS

Between 1997 and 2017, 18 patients (12 children - 6 adults and 10 females - 8 males) underwent LT (8 DDLT – 10 LDLT) for WD at our center. Donor relationship was familial in all LDLT patients (3 fathers, 3 mothers, 1 brother, 1 cousin, 1 uncle and 1 mother). All patients underwent LT for chronic WD. Patients' demographics are summarized in table 1.

Table 1. Patients' demographics and follow-up data

Case	Age	Gender	Tx year	Tx type	Graft	Neurological ymptoms (preop)	Neurological symptoms (postop)	K-F ring	K-F ring	Follow-up time (months)	death cause
1	7	M	1997	DDLT	Full size	–	–	No	No	63.57	Chronic Rejection
2	17	F	1998	LDLT	Right liver	Dystonia + Tremor	–	No	No	240.90	Alive
3	7	F	1999	LDLT	S 2-3	–	–	Yes	?	0.23	Cerebrovascular Disease
4	15	M	2002	DDLT	Full size	Dystonia+ Tremor +	–	Yes	No	195.23	Alive
5	7	M	2007	LDLT	Right liver	–	–	No	No	133.97	Alive
6	12	F	2007	LDLT	Left liver	–	–	No	No	131.17	Alive
7	6	M	2008	DDLT	Full size	–	–	No	?	0.83	Arterial Thrombosis
8	24	F	2008	LDLT	Right liver	Involuntary Movements+ Dysautonomia+ Tremor	–	Yes	No	118.73	Alive
9	26	M	2009	DDLT	Full size	Dystonia + Tremor + Headache	–	Yes	No	112.07	Alive
10	10	F	2009	LDLT	Left liver	–	–	No	No	106.83	Alive
11	13	F	2011	DDLT	Full size	–	–	Yes	No	89.77	Alive
12	14	M	2011	LDLT	Right liver	–	–	Yes	No	72.97	Chronic Rejection
13	33	M	2013	DDLT	Full size	Dysarthria + Dystonia +Dysautonomia+ Tremor	Dysarthria + Dystonia +Dysautonomia + Tremor	Yes	No	65.80	Alive
14	43	M	2014	DDLT	Full size	–	–	Yes	?	9.07	Tuberculosis Pneumonia
15	26	F	2015	LDLT	Right liver	Involuntary Movements	–	Yes	No	41.33	Alive
16	14	F	2016	LDLT	Right liver	–	–	No	No	27.10	Alive
17	15	F	2016	LDLT	S 2-3	–	–	No	No	26.17	Alive
18	18	F	2017	DDLT	Full size	Dystonia + Tremor	–	No	No	14.63	Alive

Abbreviations: M: Male; F: Female; Tx: Transplantation; DDLT: Deceased Donor Liver Transplantation; LDLT: Living Donor Liver Transplantation; Preop: Preoperatively; Postop: Postoperatively

The median age at the transplantation was 17.11±9.88 (range=6–43). Four (22%) patients had family history of WD. All patients had low serum ceruloplasmin levels and high urinary copper excretion levels prior to transplantation. The median preoperative blood ceruloplasmin level was 16.25±15.64 (range=2.8–27.8) mg/dL and median preoperative urinary copper excretion amount was as 394.9±128.4 (range=214–657) µg/24 hours. During preoperative period, 7 (38%) patients had neurological symptoms and K-F ring was identified in 9 (50%) patients. The median CTP and MELD score were 10.5±1.75 and 22.77±7.47 respectively prior to LT.

All patients underwent LT due to chronic WD related cirrhosis and cirrhosis was confirmed at pathological examination of explants. Hepatocellular carcinoma (HCC) was not diagnosed in any explant. Eight patients underwent DDLT and all deceased grafts were full size liver. In 2 patients left lateral lobe (segment 2-3), in 2 patients left lobe (segment 2-3-4) and in 6 patients right lobe graft was used for LDLT. Types of grafts summarized at table 1.

Two patients (11.1%) died in the perioperative period (0-90 days), the causes of perioperative mortality were cerebrovascular disease in first patient (case 3) and hepatic arterial thrombosis in second patient (case 7). Totally 3 patients (16.6%) died in the postoperative 0-12 month's period. Case 14 died in postoperative ninth month due to tuberculosis pneumonia (table 1). On the postoperative third months survivor patient's median blood ceruloplasmin level was 39 ± 7.96 (range=21.6 – 50) mg/dL and median preoperative urinary copper excretion amount was as 14 ± 8.73 (range=6 – 34) µg/24 hours.

Median follow-up time was 80.57±67.59 (0.23 - 240.9) months and the median survival time was 173.74±25.13 months (K-M). The survival rates of the patient's at 1-, 5-, and 10 years were 83.3%, 75% and 67.3%, respectively. The median survival time in DDLT and LDLT groups were 127.91±67.73 and 191.64±30.52 months (K-M) respectively, there was no statistically difference between estimated survival times in DDLT and LDLT groups (p=0.435; log-rank). During follow-up period, chronic rejection was seen in 5 (28%) patients, 3 (17%) patients were treated with medical procedure and 2 (11%) patients died due to chronic rejection. Re-transplantation was not performed to any cases. During follow –up period K-F ring dissolved in 7 of 9 (78%) patients, unfortunately 2 patients (Case 3 and 14) were died in early period so we did not have any information about their K-F rings. Neurological symptoms were fully recovered in 6 of 7 (85%) patients. Patients' follow-up data was summarized in table 1.

DISCUSSION

WD is a rare disease with various clinical findings. Patients may be asymptomatic or may consult with hepatic, neurologic, or psychiatric abnormalities. WD is usually diagnosed between the age of 5 and 35 years (4). Some clinic and laboratory tests like presence of K-F rings; low serum ceruloplasmin value and high urinary copper excretion may help the diagnosis of WD (5). Almost 50% of patients with WD has K-F rings (6) and completely or partially dissolution occur after LT (2); in our series 50% patients with WD had K-F rings prior to LT and in 78% of patients K-F ring was completely dissolved.

Neurologic manifestations in WD can include dysarthria, dystonia, tremor, involuntary movements, dysautonomia, migraine, headaches, insomnia, parkinsonism or combination of them (7). Neurological findings are more common in adults (8) .Some authors reported that hepatic and neurological WD association indicated worse outcomes (9). Wide range of results have been reported for post-transplant neurological improvement (10–12). However, the general estimation is that patients will benefit from LT except patients with severe neurological status (2). In our series 39% had neurological WD addition to chronic hepatic WD, after LT, completely improvement was observed 85% of them, and only in one patient (Case 13) no neurological improvement was observed. Case 13 had multi neurologic manifestations prior to LT including dysarthria, dystonia, and dysautonomia; after LT, symptoms were worsened. The Unified Wilson's Disease Rating Scale is defined for the standardization of neurological symptoms at preoperative and postoperative period (13). Unfortunately no scales were used for assessment of neurological status in our series. It should be kept in mind that; neurological complications may occur in pediatric or adult patients group after LT (14,15).

LT is the most effective treatment method in WD. First successful LT with completely recuperation of copper metabolism was reported in 1971 (16). Patients with WD undergoing LT for fulminant or chronic liver failure , however there is no generally accepted discrimination between fulminant versus chronic liver disease in WD (8), all patients underwent LT for chronic hepatic WD in our series.

A few patients with WD, may have severe neurologic symptoms without chronic liver disease, auxiliary partial orthotopic liver transplantation can be reasonable treatment option for this group (17).

Liver Transplantation corrects the intrahepatic metabolic disorder and restore the copper elimination, also LT cures the renal defects (18), besides recurrence risk is nearly zero percent, unless liver donor has undiagnosed WD (19). LDLT is performed usually from heterozygous donors, although genetic origin of WD is theoretically risk factor for recurrence, series from different countries reported that LDLT from heterozygous donors is safe for in terms of recurrence (8,20–22). All partial grafts were received from heterozygous donors in our series, and in parallel with literature recurrence was not observed.

Although the association with HCC is rare in Wilson's disease, HCC has been diagnosed in both pediatric and adult patients (23,24) . All explants must be examined carefully, by experienced pathologist.

Favorable outcomes were obtained after LT in various reports; a publication based on the United Network for Organ Sharing data, with 68.5 months median follow-up time, reports the one- and five-year survival rates were similar for children and adults, which were 90 and 89 percent, respectively, for children and were 88 and 86 percent, respectively, for adults. Another study with 133 months follow up duration from Iran, declared 86 and 82 percent survival at one and five years respectively(25). Another publication from France reported 89 and 87 percent survival at one and five years respectively with 72 months follow-up time (26) and very recently European Liver Transplant Registry (ELTR) has published multi-center cohort study with 65 months follow-up duration and reported 87 and 84 percent survival at one and five years respectively (8). Our series has sufficient follow-up time with 80.57 months, and survival rate at first year (83%) is nearly similar with the literature. Zero to 12 months is the most crucial period after LT, ELTR data shows that age below than ten years old is a risk factor for poor survival (8), in our series two patients died perioperative period who were at the age of 6 and 7, and one patient died at the ninth month due to tuberculosis pneumonia. Patients who survived after one year had good outcomes. The reason of good outcomes are young age, low comorbidity rate, low recurrence rate and low prevalence of malignancies. On the other hand fifth year survival rate (75%) of our series is nearly unsatisfactory compared the literature. Two patients died after one to ten year period for the reason of chronic rejection. We observed chronic rejection in 28% of the patients, the reason for all rejections was the same, irregular using of immunosuppressant agents. Patients who undergo LT for the WD are usually teenager and compliance with the immunosuppression regimens is partially low in this age group. We aimed to share long term results of single center, potential limitations of this study are retrospective design, small number of patients, heterogeneity of adult-child patients and LDLT-DDLT and lack of formal neurological assessment.

CONCLUSION

In conclusion LT is the safe and efficient treatment option in WD and related complications. Patients who survived after first year have good long-term outcomes.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports
Ethical approval: This work has been approved by the Institutional Review Board.

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