Influence of Liver Transplantation on Neuropsychiatric Manifestations of Wilson Disease

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ABSTRACT

Objectives. This study sought to evaluate the effect of liver transplantation on the neuropsychological manifestations of Wilson disease.

Materials and Methods. Nine of 42 Wilson disease patients had neuropsychological symptoms before liver transplantation. They were 7 male and 2 female subjects with a median age of 19 years (range 10 to 25). They were analyzed for their preoperative and postoperative hepatic, neurological, and psychological scores described by the Unified Wilson Disease Rating Scale after a mean 36.6 months of follow-up.

Results. Preoperative mean Model for End-Stage Liver Disease and Child-Pugh scores were 18.3 (range 15 to 26) and 8.9 (range 6 to 12), respectively. One patient had acute postoperative ischemic stroke unrelated to Wilson disease and was excluded from the statistical analysis. Preoperative and postoperative hepatic, neurological, and psychological scores of the remaining 8 patients were 7.4 ± 2.3 vs 2.4 ± 1.3 ($P = .0005$), 17.7 ± 11.7 vs 12.7 ± 12.5 ($P = .055$), and 9.0 ± 1.7 vs 7.0 ± 2.1 ($P = .033$).

Conclusions. Liver transplantation for Wilson disease can provide some improvement of the neuropsychological symptoms in addition to the hepatic recovery.

WILSON DISEASE (WD) is an autosomal-recessive disorder caused by a mutation in the ATP7B gene, with resultant impairment of biliary excretion of copper. It has a prevalence of 1 per 30,000 in the general population [1]. The accumulation of copper in different organs is due to a reduced excretion of copper via the bile, leading to hepatic and neuropsychiatric manifestations [2].

Copper chelating agents such as D-penicillamine and trientine hydrochloride, as well as copper absorption blockers such as zinc salts, are effective and have markedly improved the prognosis of WD [1,2]. Nevertheless, WD is an indication for liver transplantation (LT) in cases of decompensate liver disease or fulminant liver failure when medical treatment options fail [3]. However, its use for treatment of progressive neurological deterioration is still controversial [4–6]. Because few data are available in the field, the aim of the present study was to evaluate the effect of LT on outcomes of hepatic and especially neuropsychiatric manifestations in patients with WD.

MATERIALS AND METHODS

Data were derived from a prospectively collected database at the Turgut Ozal Medical Center of Inonu University from March 2002 to August 2014. We performed 1042 living donor liver transplantations (LDLTs) and 282 deceased donor liver transplantations in patients with end-stage liver disease at our center. We investigated the pretransplantation characteristics of patients who were diagnosed with WD with neuropsychiatric manifestations (9 of 42 WD patients who underwent LT), including Model for End-Stage Liver Disease (MELD) and Child-Pugh score and the donors' relationships to their respective patients. Other examined features consisted of operation time, graft type, graft weight, actual graft-to-recipient weight ratio (GRWR, %), postoperative complications, and survival outcomes. Table 1 shows the patient characteristics. Nine patients, including 5 adults and 4 children (7 male, 2 female), underwent LT. The diagnosis of WD was based on the presence of liver disease associated with at least 2 of the following criteria:

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Table 1. Patient Characteristics

Patient	Age (y)	Sex	Body Mass Index	MELD	Child-Pugh	Donor's Relationship
1	24	Male	21.3	25	C-12	Mother
2	14	Male	13	15	B-7	Deceased
3	10	Female	18.3	26	C-12	Deceased
4	12	Male	15.6	15	A-6	Father
5	19	Male	18.6	15	A-6	Father
6	23	Male	17	15	B-7	Sister
7	23	Female	27.9	17	B-9	Father
8	25	Male	25.4	17	B-9	Cousin
9	16	Male	21.2	20	C-12	Sister

Abbreviation: MELD, Model for End-Stage Liver Disease.

positive family history, low serum ceruloplasmin (<20 mg/dL), presence of Kayser-Fleischer rings, elevated 24-hour urinary copper excretion (>50 μg/d), Coombs-negative hemolytic anemia, or presence of elevated liver copper (>250 μg/g) [7]. The median age was 19 years old; patient ages ranged from 10 to 25 years. The patients were monitored until August 2014, and their medical records were retrospectively reviewed. The patients with or without parents were asked to complete a questionnaire about their preoperative and postoperative hepatic, neurological, and neuropsychiatric symptoms at follow-up examinations. The questionnaire was completed by all patients, and a score was developed to describe the evolution of hepatic, neurological, and neuropsychological symptoms. The parameters included in the scoring system are shown in Table 2. The score range for hepatic symptoms was 0 to 17 points (0 = no symptoms), for neurological symptoms was 12 to 60 points (12 = no symptoms), and for neuropsychological symptoms was 0 to 19 points (0 = no symptoms). The items of the scores correspond in part to items selected by the EuroWilson registry and in part to items used by neurological evaluation scales for WD (Unified Wilson Disease Rating Scale) [6–9].

Donor relationship was familial for 7 donors (3 fathers, 1 mothers, 2 sister, 1 cousin) who underwent LDLT, and unrelated for 2 donors (2 deceased) who underwent deceased donor liver transplantations. Blood types were compatible in all cases. Donations were voluntary and altruistic in all cases, written informed consent had been obtained from both donor and recipient before surgery, and all LTs were approved by the Ethics Committee of Turgut Ozal Medical Center.

Preoperative radiographic assessment was done by ultrasound (US) and computed tomography (CT). Magnetic resonance imaging (MRI) was not used at preoperative evaluation routinely. Piggyback technique was used in all patients. The details of our surgical technique have been described previously [10]. Standard immunosuppressive therapy was used with low-dose corticosteroids, mycophenolate mofetil, and tacrolimus. Cyclosporine A was preferred to tacrolimus in children and patients with diabetes mellitus. Induction therapy with basiliximab was administered in patients with a creatinine value over normal. Doppler US was used at the early postoperative period, and CT scan was used on postoperative day 10 to confirm patency of the hepatic vasculature.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows, version 13.0 (SPSS Inc., Chicago, Illinois, United States). Categorical data are defined as percentage and numbers, and measurable data are defined by median or mean ± standard deviation. Paired Student t test was used for statistical analysis. Survival analysis was performed by the life table method. A value of $P \leq .05$ was considered significant.

RESULTS

Preoperative mean MELD and Child-Pugh scores were 18.3 (range 15 to 26) and 8.9 (range 6 to 12), respectively. The

Table 2. Items on the Patient Questionnaire

	Hepatic Score	Psychiatric Score	Neurological Score
Points per item	Symptom present, 1 point Symptom absent, 0 point	Symptom present, 1 point Symptom absent, 0 point	Range from 1 point (symptom absent) to 5 points (most severe affection)
Range	0–17	0–19	12–60
Items	Feeling of general ill health	Change in mood	Tremor at rest
	Weight loss	Anxiety	Intentional tremor
	Jaundice	Hallucination	Involuntary movements
	Dark urine	Change in mood noticed by patient	Change in speech
	Pale stools	Deteriorating cognitive performance	Salivation or drooling
	Pruritus	Needing more time to complete work	Dysphagia
	Bleeding/melena	Forgetfulness	Gait abnormalities
	Esophageal varices	Tiredness	Change in handwriting
	Hepatomegaly	Loss of interpersonal skills	Concentration
	Splenomegaly	Seclusiveness	Mobility
	Abdominal pain	Moodiness	Oromandibular or cervical
	Lower limb edema	Loss of interest in previous leisure pursuits	Dystonia
	Abdominal swelling	Sadness	Dysarthria
	Spider naevi	Inner tension	
	Other cutaneous signs of liver disease	Eating disorder	
	Ascites	Deteriorating standard of personal hygiene	
	Hepatic encephalopathy	Change in sexual behavior or preferences	
		Abuse of alcohol or other recreational drugs	
		Suicidal thoughts	

Table 3. Surgical Details and Outcomes

Patients	Operating Time (min)	Liver Graft	GRWR (%)	LOS (d)	Outcome	Follow-Up (mos)	Complications and Management
1	365	RL	1.5	16	Alive	63	(–)
2	370	Whole	4.3	15	Alive	55	(–)
3	410	RL (split)	5.2	72	Alive	29	Biliary stricture (biliary stent)
4	300	LL	1	35	Alive	40	Biliary leakage (repeat laparotomy)
5	400	RL	1.3	16	Alive	24	(–)
6	320	RL	1.3	20	Alive	17	Hepatic artery thrombosis (cadaveric re-transplantation)
7	265	RL	1.1	114	Alive	15	Cerebrovascular accident (resolved over time) Hepatic venous outflow obstruction (vascular stent) Graft failure (cadaveric re-transplantation)
8	340	RL	1.2	27	Alive	6	(–)
9	380	RL	1	15	Alive	81	(–)

Abbreviations: RL, right lobe; LL, left lobe.

median body mass index was 18.6 (range 15.1 to 30.8). Right lobe grafts in 7 patients (split graft in 1 patient), left lobe graft in 1 patient, and whole liver graft in 1 patient were transplanted. Average GRWR was 1.98% (range 1% to 5.2%). Multiple bile duct orifices had to be reconstructed in one of the grafts (11.1%). Biliary reconstructions in all patients were duct-to-duct anastomosis. Hepatic veins of all grafts with LDLT were enveloped like a circumferential fence by autologous saphenous vein. Hepatic artery anastomosis was made with a surgical telescope (4.5 or 8 magnification). The mean operative time was 350 minutes (range 265 to 410). The cold ischemia duration was less than 60 minutes in all patients. The median hospital stay was 20 days (range 15 to 114 days).

The surgical complications and outcomes of the individual patients are summarized in Table 3. One patient developed major biliary leakage, which was treated with repeat laparotomy. There was only 1 case with biliary stricture in the long term. A biliary stent was inserted percutaneously after balloon dilatation in this case. Hepatic artery thrombosis was seen in 1 patient at postoperative day 2 and was treated with cadaveric retransplantation. One patient developed hepatic outflow obstruction at 22 days after LDLT. Graft failure developed at postoperative day 80 after failed balloon dilatation and interventional thrombectomy, and cadaveric retransplantation was performed. Acute ischemic stroke occurred after retransplantation and was resolved with medical treatment. This patient was excluded from the statistical analysis because of confused neurological symptoms due to WD and stroke.

The hepatic symptom score obtained from the patients' questionnaires showed a decrease after LT. The individual hepatic symptom scores of 8 patients are shown in Fig 1. All patients underwent transplantation for chronic liver disease. The mean hepatic scores for the preoperative and postoperative period were 7.4 ± 2.3 vs 2.4 ± 1.3 ($P = .0005$).

The mean neurological symptom scores for the preoperative and postoperative period were 17.7 ± 11.7 vs 12.7 ± 12.5 ($P = .055$). Only 1 patient's neurological symptoms progressed during posttransplantation follow-up. The mean psychiatric symptom scores for the preoperative and postoperative period were 9.0 ± 1.7 vs 7.0 ± 2.1 ($P = .033$). One patient's psychiatric symptoms progressed during transplantation follow-up and in 2 patients stayed the same, whereas the remaining patients had some improvement. As a result, although hepatic symptoms improved in all patients (100%), neurological and psychiatric symptoms improved in 7 patients (87.5%) and in 5 patients (62.5%), respectively.

In-hospital mortality, which was defined as any death within the same hospital admission for LT, regardless of the number of days after LT, did not occur. All patients are still alive at a mean follow-up of 36.6 months (range 6 to 81 months). All patients followed up as outpatients had good liver function.

DISCUSSION

Since the first success with transplant surgery in 1969, many reports in the literature have considered WD an excellent indication for transplantation in cases that were unresponsive to drug therapy or that were too severe. This treatment can reverse biochemical and clinical signs and offer long-term survival [3,11–13]. The neurological aspects of WD and its indication for LT is a topic that evokes much discussion among specialists. This study retrospectively analyzed WD patients who underwent transplantation, describing their clinical features before and after LT. Our results clearly confirm that WD is a rare indication for LT, but this surgery can achieve a very good long-term outcome even in cases of liver failure with neurological manifestations. Also, LT for WD can provide some improvements on neuropsychological symptoms, in addition to the hepatic recovery.

We performed more than 1300 liver transplantations, and there were only 42 WD patients (3.2%). Therefore, WD is an uncommon indication for liver transplantation, and neurological manifestations are rare. This can be explained by successful medical treatment, which contains copper chelating agents to promote copper excretion from the body, or zinc to reduce copper absorption, or both.

The effect of LT on neurological manifestations is still controversial. There are only a few studies in the literature [14,15]. Wang et al. [16] showed neurological improvements

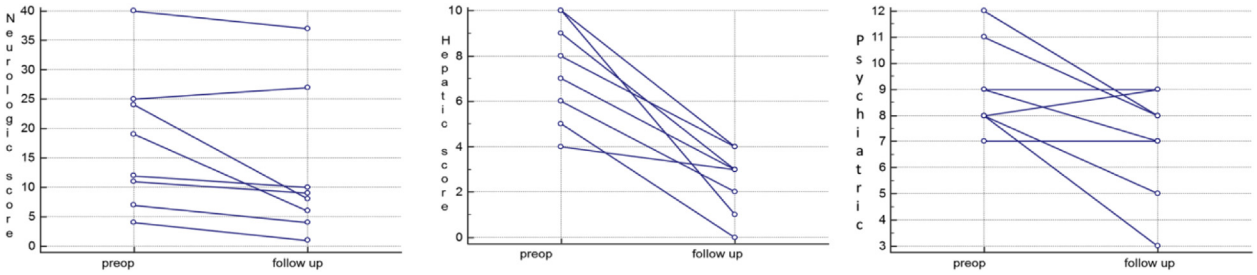

Fig 1. Changing of hepatic, neurological, and psychiatric scores with liver transplantation.

in 8 of 9 patients (88.9%) who underwent LDLT for neurological complications. In a review of 41 neurologically affected patients with WD, LT reversed neurological deterioration in 78% of patients, whereas the remaining patients did not present any change in their neurological status [14]. According to Eghtesad et al. [17], neurological improvement (58%) can be obtained in patients with liver failure and neurological manifestations. Similarly in our series, neurological improvement was seen in 7 of 8 patients (87.5%) who received LT for hepatic failure with neurological complications.

Neurological deterioration was detected after the LT in 2 patients. Although 1 of them had acute ischemic stroke and confused neurological symptoms due to WD and stroke, neurological improvement cannot be obtained in all patients and therefore careful patient selection and timing of LT are important for those affected by neurological symptoms as well as liver disease. Geissler et al. [18] reported that 2 of 6 WD patients with mixed hepatic and neurological symptoms fully recovered after LT. They suggested that in such cases an early decision for LT is justified because neurological deficits may become irreversible. Likewise, Eghtesad et al. [17] indicated the benefit and importance of performing transplantation before neurological impairment becomes irreversible.

Another debate is whether progressive neurological disease due to WD without liver failure is an indication for liver transplantation. Bax et al. [19] reported the case of a 15-year-old patient with neurological manifestations due to WD without liver failure who returned almost to normal after LT. In a multicenter French study with 121 WD patients [3], 94% of patients underwent transplantation for predominant liver disease, whereas 6% received LT because of a purely neurological indication. Unlike in the study by Bax et al., they advocated that patients with purely neurological symptoms also seemed to have a significantly worse prognosis after LT when compared with hepatic patients. Also, the same study reported that all 3 patients with severe axial Parkinson syndrome died (of infection) with a functional graft but without any neurological improvement. Likewise, in a recent report summarizing the experience of a consortium of Italian centers, individuals with both neuropsychiatric and hepatic dysfunction had a lower mean survival rate than patients with hepatic dysfunction alone [20]. Unlike the previously reported studies, in our series we did not observe hospital mortality in any patients, and also all patients are still alive with an acceptable morbidity rate at a mean follow-up of 36.6 months. Moreover, hepatic improvement in all patients (100%), neurological improvement in 7 of 8 patients (87.5%), and psychiatric improvement in 5 of 8 (67.5%) patients were achieved with an excellent survival rate. This can be explained by our approach in WD patients with mixed hepatic and neurological involvement, which includes a complete hepatic and neurological evaluation and an early decision for LT. Therefore, in this series, the patient's mean MELD score was significantly lower compared with results from our first 304 LDLTs [10]. However, the number of patients is not high enough to shed light on this area.

Although it is clearly difficult to evaluate psychiatric outcomes due to the complexity of the presenting signs and the variety of factors potentially influencing clinical outcomes, such as immunosuppressive therapy, WD itself, and major surgery, moderate psychiatric improvement was observed in our series. Generally, the presence of psychiatric symptoms has been accepted as a partial contraindication for LT [20]. However, our data showed that even WD-related psychiatric symptoms can be treated with LT. Therefore, close collaboration with psychiatrists and neurologists is essential for an accurate decision.

In conclusion, LT is an effective and safe therapy for WD patients with end-stage liver disease, even in the presence of neuropsychiatric involvement. WD patients with mixed hepatic and neurological manifestations must be considered carefully, and a decision should be made without delay based on the stage of the neurological damage and its irreversibility to achieve significant hepatic and neurological improvement.

REFERENCES

[1] Ala A, Walker AP, Ashkan K, et al. Wilson's disease. Lancet 2007;369:397–408.

[2] Stremmel W, Meyerrose KW, Niederau C, et al. Wilson disease: clinical presentation, treatment, and survival. Ann Intern Med 1991;115:720–6.

[3] Guillaud O, Dumortier J, Sobesky R, et al. Long term results of liver transplantation for Wilson's disease: experience in France. J Hepatol 2014;60:579–89.

[4] Mason AL, Marsh W, Alpers DH. Intractable neurological Wilson's disease treated with orthotopic liver transplantation. Dig Dis Sci 1993;38:1746–50.

[5] Kassam N, Witt N, Kneteman N, et al. Liver transplantation for neuropsychiatric Wilson disease. Can J Gastroenterol 1998;12: 65–8.

[6] Weiss KH, Schäfer M, Gotthardt DN, et al. Outcome and development of symptoms after orthotopic liver transplantation for Wilson disease. Clin Transplant 2013;27:914–22.

[7] Yoshitoshi EY, Takada Y, Oike F, et al. Long-term outcomes for 32 cases of Wilson's disease after living-donor liver transplantation. Transplantation 2009;87:261–7.

[8] Leinweber B, Möller JC, Scherag A, et al. Evaluation of the Unified Wilson's Disease Rating Scale (UWDRS) in German patients with treated Wilson's disease. Mov Disord 2008;23:54–62.

[9] Członkowska A, Tarnacka B, Möller JC, et al. Unified Wilson's Disease Rating Scale—a proposal for the neurological scoring of Wilson's disease patients. Neurol Neurochir Pol 2007;41:1–12.

[10] Yilmaz S, Kayaalp C, Ara C, et al. Single-center analysis of the first 304 living-donor liver transplantations in 3 years. Hepatogastroenterology 2013;60:1105–9.

[11] DuBois RS, Rodgerson DO, Martineau, et al. Orthotopic liver transplantation for Wilson's disease. Lancet 1971;1: 505–8.

[12] Schilsky ML, Scheinberg IH, Sternlieb I. Liver transplantation for Wilson's disease: indications and outcome. Hepatology 1994;19:583–7.

[13] Dhawan A, Taylor RM, Cheeseman P, et al. Wilson's disease in children: 37-year experience and revised King's score for liver transplantation. Liver Transpl 2005;11:441–8.

[14] Stracciari A, Tempestini A, Borghi A, et al. Effect of liver transplantation on neurological manifestations in Wilson disease. Arch Neurol 2000;57:384–6.

[15] Schumacher G, Platz KP, Mueller AR, et al. Liver transplantation in neurological Wilson's disease. Transplant Proc 2001;33:1518–9.

[16] Wang XH, Cheng F, Zhang F, et al. Living-related liver transplantation for Wilson's disease. Transpl Int 2005;18:651–6.

[17] Eghtesad B, Nezakatgoo N, Geraci LC, et al. Liver transplantation for Wilson's disease: a single-center experience. Liver Transpl Surg 1999;5:467–74.

[18] Geissler I, Heinemann K, Rohm S, et al. Liver transplantation for hepatic and neurological Wilson's disease. Transplant Proc 2003;35:1445–6.

[19] Bax RT, Hässler A, Luck W, et al. Cerebral manifestation of Wilson's disease successfully treated with liver transplantation. Neurology 1998;51:863–5.

[20] Medici V, Mirante VG, Fassati LR, et al. Liver transplantation for Wilson's disease: the burden of neurological and psychiatric disorders. Liver Transpl 2005;11:1056–63.