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ORIGINAL ARTICLE

Living-related liver transplantation for Wilson's disease

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Summary

Orthotopic liver transplantation has been applied to the treatment of Wilson's disease (WD), living-related liver transplantation (LRLT) has also been indicated for WD with increasing frequency. Between January 2001 and November 2003, 22 LRLTs were performed on patients (19 pediatric, three adults) with WD in liver transplantation center. Two patients were transplanted because of a presentation coexistent with fulminant hepatic failure. Twenty presented with chronic advanced liver disease with ($n = 9$) or without ($n = 11$) associated neurologic manifestations. All the recipients had low serum ceruloplasmin levels with a mean value of 12.8 ± 3.2 mg/dl before transplantation and increased to an average of 26.0 ± 3.6 mg/dl after LRLT at the latest evaluation. The survival patients with neurologic manifestations such as tremor, dysarthia, dysphagia, dystonia and sialorrhea had improved after LRLT. This suggests that LRLT not only resolves the hepatic but also ameliorates the neurologic consequences of WD.

Introduction

Wilson's disease (WD) is a genetic disorder transmitted through a recessive gene located on chromosome 13. The basic defect remains unknown, but it is clear that the progressive accumulation of copper in the liver and other organs causes the clinicopathologic features of WD. It is characterized by accumulation of intracellular copper in the liver and central nervous system (CNS) [1], and patients present with a spectrum of clinical syndromes according to the most severely affected organ (acute liver failure, cirrhosis, neurologic or psychiatric syndromes) [2,3]. Liver transplantation with WD has a twofold aim: to save the patient's life when the disorder is expected to progress to hepatic (or other organ) failure and to cure the underlying metabolic defect. Unlike patients with biliary atresia who develop symptoms related to chronic liver disease, many patients with WD are transplanted to prevent potential complications. Although orthotopic liver transplantation (OLT) is currently only indicated in patients with severe liver disease [4,5], its role in the management of patients with significant neurologic or psychiatric symptoms is unknown. Although superior to that in patients with liver disease, mean survival of patients with isolated neurologic symptoms is <5 years [6], with conventional chelating agents failing to improve symptoms in a significant proportion [7]. Anecdotal reports of patients demonstrating improvement or resolution of neurologic symptoms after OLT in the presence of stable or normal liver function has fueled interest in this modality in patients with severe progressive neurologic manifestations [8–10]. However, before OLT can be applied to this subgroup, information regarding both outcome and quality of life after liver transplantation in patients with WD should be available. Recently, LRLT has also been used for WD [11–16]. Asonuma *et al.* [13] reported that LRLT from heterozygous carriers of the WD gene could also resolve clinical signs and symptoms of WD and correct the parameters of copper metabolism. In this paper, we reported our experience with LRLT for WD, especially with severe progressive neurologic manifestations.

Patients and methods

Between January 2001 and November 2003, 22 patients (16 female and six male patients, median age, 15.5 years; range, 8–21 years) consisted of 19 children (≤16 years)

and three adults received LRLT with WD at our center. Clinical and laboratory data were obtained from a review of the files of patients at Liver Transplantation Center of Jiangsu Province. All treatments had an informed consent of the children's parents and the approval of the Ethics Committee of Nanjing Medical University. Indications for transplantation were acute liver failure in two patients, and chronic liver disease with cirrhosis in 20 patients. All the recipients had low serum ceruloplasmin levels with a mean value of 12.8 ± 3.2 mg/dl before transplantation. In each case the diagnosis of WD was based upon combination of the presence of Kayser–Fleischer (K–F) rings, a low serum ceruloplasmin level, elevated 24 h urine copper excretion and quantitative hepatic copper measurement (see Table 1).

Six patients were treated with chelating agents (penicillamin) for 2–10 years before LRLT. Neither patient had received any chelating agent after undergoing LRLT. All patients complicated with portal hypertension and one with variceal bleeding. The interval between diagnosed WD and LRLT was 6.4 ± 2.6 years. The donors were 20 mothers and two fathers. The mean donor age was 35.0 ± 4.0 years (range, 30–45 years). All recipients received blood group compatible grafts. The grafts were two right lobes and 20 extend left lobes.

The neurological status of the patients was regularly examined by neurologists. The neurological status of each patient was carefully determined prior to LRLT and recorded in the patient's records. Their current disability and performance status were obtained utilizing a formal telephone questionnaire, with both the patients and the same neurologists being interviewed. As a result of these interviews and the data available from the most recent examination of each patient, the neurologic sequelae were compared with the patient's current disability and performance status.

Performance status assignment

Each patient was assigned a performance status immediately before LRLT based upon the following criteria according to Bellary *et al.* [17] report and our experience:

1 Status I: Home and working
2 Status II: Home without care but not working
3 Status III: Home with care, dependent
4 Status IVA: In hospital without liver failure
5 Status IVB: In hospital with liver failure.

Results

Pathology

The mean weight of the explanted livers was 1037 g (range 584–1438). All livers had established cirrhosis; in addition, two livers had confluent necrosis. Severe cholestasis, macrovesicular steatosis and extensive proliferation of bile ductules along with fibrous septa were observed consistently in all case.

Results of donors

All the donors were discharged from the hospital after a mean hospital stay of 8–16 days, and then resumed their normal life without any significant adverse sequelae. Two complications of bile leaks occurred, and required reoperation.

Graft and patient survival

End-to-end anastomosis of hepatic reconstruction was carried out. To achieve sufficient hepatic venous flow, a wide ostium and hepatic veins are required for anastomosis. Hepatic venoplasty of the graft, using the left and middle hepatic veins, is performed routinely at our institutions. Hepatic artery anastomosis used microsurgical techniques. Biliary and portal vein reconstruction performed as a direct end-to-end anastomosis. Two patients had hepatic artery thrombosis at POD 2 and 4 and underwent retransplantation of cadaveric OLT (including one case of reduce-sized liver transplantation). All survival recipients (21/22) enjoyed normal health with a good quality of life, and none had signs of recurrent WD after a mean follow-up period of 18.5 months (range 4–38 months). One patient died of severe rejection confirmed by biopsy after operation 3 months. Of 21 patients who are still alive, two had chronic rejection, defined as a

Table 1. Diagnostic criteria employed in the cases reported at presentation.

Parameters	Fulminant ($n = 2$)	Chronic advanced ($n = 20$)
Serum copper (normal range: 60–200 μg/dl)	186 ± 32.4 ($n = 4$)	118 ± 21.8 ($n = 20$)
Ceruloplasmin (normal range: 20–40 mg/dl)	12.6 ± 3.6 ($n = 4$)	12.8 ± 2.4 ($n = 20$)
24-h urinary copper (normal range: <50 μg)	2146.6 ± 426.8 ($n = 4$)	1846 ± 325.6 ($n = 20$)
Quantitative hepatic copper (normal range: 20–45 μg/g dry weight)	782.4 ± 116.8 ($n = 4$)	1028.4 ± 240.6 ($n = 20$)
Kayser–Fleischer rings (present/absent)	1/1	18/2

paucity of bile ducts, 22–28 months after their LRLT and were successfully rescued by switching their primary immunosuppression from cyclosporin A to tacrolimus. They are doing well, 4–6 months after the switch in immunosuppression. One patient had anastomotic stenosis 8 months after the original transplantation which was treated with Roux-en-Y hepaticojejunostomy.

Copper metabolism after transplantation

Copper metabolism of the WD recipients and the presence of K–F rings were compared before and after transplantation. After LRLT, all the recipients had normal serum ceruloplasmin concentrations in the first month. Marked reduction of urinary copper excretion occurred in the first 3 months, which became normal 6–9 months after operation. K–F rings were resolved completely after LRLT in 16 patients and partially in five (see Table 2).

Neurologic manifestation pre-LRLT and post-LRLT

Of the nine patients who had associated neurologic dysfunction, one died within 3 months of LRLT. All these patients had bradykinesia, dysarthria, dystonia, tremors, sialorrhea and rigidity. Three patients were totally dependent because of their crippling disability before the LRLT. The other six were mobile, but still dependent and were not able to lead normal lives because of bradykinesia, dysarthria and rigidity. Of the eight patients with neurologic dysfunction who have survived, the neurologic disability has improved in all patients (Table 3).

Improvement in neurologic status suggested that LRLT not only resolves the hepatic but also ameliorates the neurologic consequences of WD. As a result of their clinical improvement, six (patients 4, 5, 6, 7, 8, 9) have been able to go to school. The other two have been unable to find job or go to school because their long-standing disability. They are currently 29 months and 32 months post-LRLT with the major degree of recovery from pre-existing neurologic dysfunction.

Discussion

Wilson's disease is an autosomal recessive disorder characterized by the accumulation of copper in the liver, CNS, kidneys, eyes and other organs. Its incidence is roughly one in 30 000. The gene for WD, ATP7B, is located on chromosome 13. There are multiple mutations of the gene which give rise to WD, and most patients have two different mutations of the gene on each allele encoding the WD gene (compound heterozygotes).The diagnosis is made by the identification of low serum ceruloplasmin levels, increased urinary copper excretion, and K–F rings on ophthalmologic examination. If diagnosed early, before the onset of tissue damage, WD can be managed medically with an agent such as D-penicillamine. However, if this therapy is ineffective, or if patients have fulminant or subfulminant liver failure, liver transplantation is indicated. OLT has been shown to correct the WD phenotype and provide excellent long-term survival. Results of a series of 21 patients with OLT for WD were reported. Survival at 1 year was 87.5%, and those who survived had excellent long-term survival [18]. Anecdotal reports of neurologic recovery after liver transplantation have prompted investigators to consider this modality in patients with isolated neurologic disease and stable liver function [19–23].

Wilson's disease may be detected in the asymptomatic stage in siblings or offspring of patients with WD, or when the disease is considered for evaluation of abnormal biochemical parameters prior to the onset of signs or symptoms. Symptomatic presentations of WD include liver disease, which may manifest itself as hepatic insufficiency, chronic active hepatitis, or as a fulminant hepatitis associated with hemolysis. WD may also present with extra hepatic manifestations in the form of neurologic or psychiatric disease. The diagnosis of WD may be established by a combination of clinical, biochemical, and histochemical evaluations [24]. About 50% of patients with liver disease lack K–F rings [25]; however, these are almost invariably present when neurologic or psychiatric

Table 2. Follow-up results of tests used to assess Wilson's disease in LRLT survivors.

		Post-LRLT values			
Parameters	Pre-LRLT values	1 m	3 m	6 m	The last time
Serum copper	165.4 ± 25.6	106.2 ± 12.4	85.8 ± 10.6	72.5 ± 8.4	60.9 ± 7.4
Serum ceruloplasmin	12.8 ± 3.2	21.6 ± 2.1	24.8 ± 3.3	28.5 ± 4.4	26.0 ± 3.6
24-h urinary copper	2035.6 ± 378.5	380.8 ± 37.6	150.6 ± 24.5	75.5 ± 9.6	48.2 ± 5.8
Quantitative hepatic copper (μg/g dry weight)	904.6 ± 186.4	112.5 ± 12.1	94.2 ± 8.4	45.2 ± 5.2	42.6 ± 4.8
Kayser–Fleischer rings (present/absent)	19/3	14/8	10/12	6/15	5/16

Normal range: see Table 1.

Table 3. Patients with neurologic manifestation pre-LRLT and post-LRLT.

Patients	First symptoms before LRLT (years)	Age at LRLT (years)	First signs of improvement (weeks)	Time of follow-up (months)	Symptoms prior to LRLT	Residual symptoms after follow-up
1	10	21	6	3	Tremors ataxia Performance status – IVA	Died. Severe rejection plus multiple organ failure 3 months after LRLT
2	4	9	8	29	Tremors, dysarthria, sialorrhea, difficulty in walking – dependent Performance status – III	Minimal dysarthria, 80% improvement from baseline disability. Performance status – II
3	12	19	4	32	Tremors, bradykinesia, dysarthria, dystonia, sialorrhea and rigidity, difficulty in walking – dependent Performance status – III	Slight dysarthria, dystonia, and bradykinesia, 90%improvement Performance status – II
4	8	12	4	4	Tremors, dysarthria, rigidity Performance status – II	95% improvement. Minor tremors, normal speech and gait. Independent, cares for self, attends school Performance status – I
5	9	14	6	6	Tremors, dysarthria, rigidity, sialorrhea Performance status – II	95% improvement. No dysarthria/rigidity Performance status – I
6	7	14	5	16	Tremors, dysarthria, ataxia, sialorrhea Performance status – II	95% improvement. Minimal tremors Performance status – I
7	3	10	7	14	Tremors, bradykinesia, dysarthria, dystonia, sialorrhea and rigidity, difficulty in walking – dependent Performance status – III	90% improvement. Minimal dysarthria, no rigidity. Independent, cares for self, attends school Performance status – I
8	5	15	6	8	Tremors, bradykinesia, dysarthria, dystonia, and rigidity Performance status – II	No dysarthria, no tremors, 90% improvement Performance status – I
9	4	8	6	12	Tremors, ataxia Performance status – II	None Performance status – I

manifestations of WD are observed. The presence of K–F rings and a low level of ceruloplasmin is sufficient to diagnose WD. In this study, copper metabolism in the WD recipients and the presence of K–F rings are compared, before and after transplantation. After LRLT, all recipients showed a normalization of serum ceruloplasmin concentration and a marked reduction in urinary copper excretion. All donor ceruloplasmin levels were to be within the normal range for their laboratory, as were the post-transplant levels in the recipients. In addition to normalization of laboratory measures of copper abnormalities, 16 of 22 patients with K–F rings had complete resolution and the remaining five showed improvement following transplantation. Interestingly, Asonuma *et al.* [13] reported a donor with the mild abnormality in urinary copper excretion was not transmitted to the recipient. Despite these results, it is important to remember that 10% of WD heterozygotes will have low ceruloplasmin levels and that these individuals may be unsuitable as donors [26].

Although genotype/phenotype correlations in WD patients were reported, there were no information available comparing the copper metabolism in heterozygotes carrying each of the various single mutations. Nonsense, missense, frameshift and splice site mutations have all been identified in WD patients [27,28]. The implications for a heterozygote carrying a single mutation producing an abnormal protein are potentially quite different from those arising from a mutation that silences the allele leaving the normal protein product from the second allele. A rare functionally important mutation may be responsible for the abnormal ceruloplasmin in some heterozygotes and may have implications for function of allografts donated by those individuals. In our country it would be prudent to measure the ceruloplasmin of potential donors in WD families and to exclude or at least carefully

evaluate copper metabolism in those with low ceruloplasmin levels before proceeding to donation. Up to now, 186 OLTs had performed in our center and five patients were WD. Two WD patients underwent OLT because of the related donors (fathers and mothers) with abnormal copper metabolism (ceruloplasmin <20 mg/dl, 24 h urine copper >150 μg). Based on these findings, LRLT can be used safely in WD. Despite the excellent results, however, there are some questions that remain with respect to screening of potential WD heterozygote donors. Furthermore, our experience may not reveal whether decoppering after LRLT from heterozygote donors is slower than decoppering after cadaveric transplantation from nonrelated donors.

The fact that none of our transplanted recipients had persistent neurological abnormalities after LRLT, and K–F rings disappeared in most of the recipients, indicating that LRLT is indeed an effective and safe form of therapy for patients presenting with Wilsonian fulminant hepatic failure and end-stage hepatic insufficiency. After the liver transplantation, the serum ceruoplasmin level increases to the normal range and urinary copper excretion decreases. Among nine patients complicated with neurologic manifestations, all patients showed extrapyramidal sign and six patients with language handicap alleviated postoperation follow-up between 4 and 38 months. Recently, Suzuki *et al.* [11] reported a 17-year-old woman with severe neurologic manifestations, 12 months after LRLT, the patient's neurologic symptoms dramatically improved. Our study suggested that LRLT corrects the underlying metabolic defect of patients with WD and converts the copper kinetics from that characteristic of an individual affected with a homozygous. LRLT not only resolves the hepatic but also ameliorates the neurologic consequences of WD. Grafts chosen from heterozygote carriers do not appear to confer any risk of recurrence in recipients at least in the short term. Long-term follow-up should be continued to evaluate this specific therapy.

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