Outcome of Living Donor Liver Transplantation for Wilson's Disease in Adults: A Single Center Experience

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Introduction: Although liver transplantation is a definitive cure for Wilson's disease (WD), there is limited data about results of living donor liver transplantation (LDLT) in adults. **Material and methods:** 18 adults underwent LDLT for WD. The presentations before LDLT were decompensated cirrhosis ($n = 16$), acute on chronic liver failure ($n = 1$) and acute liver failure ($n = 1$). The donors were parents ($n = 2$), siblings ($n = 3$), cousin ($n = 1$), daughter ($n = 1$), nephew ($n = 1$), spouse or relatives of spouse ($n = 9$) and from swap transplantation ($n = 1$). All genetically related donors were negative for screening of WD. **Results:** The study cohort comprised of 15 males and 3 females, aged 32 ± 10 years. Severity of liver disease (excluding acute liver failure patient) was as follows; Child's score 10 ± 2 , model for end-stage liver disease (MELD) score 18 ± 6 . The graft to recipient weight ratio was 1 ± 0.2 . The ICU and hospital stay were 5.5 ± 0.9 and 15 ± 5 days. Two patients died in first month after liver transplantation, rest of patients are doing well at median 15 (8–38 months). Two patients had acute cellular rejection that responded to steroids, one had hepatic artery thrombosis and 2 had biliary strictures. Three patients had neurological symptoms; 2 of these patients had partial recovery while one had complete recovery. There was no significant difference between LDLT from genetically related or unrelated donors. **Conclusion:** LDLT for WD in adults is associated with good outcomes. (J CLIN EXP HEPATOL 2018;8:132–135)

Wilson's disease (WD) is caused by mutations of chromosome ATP7B on chromosome 13 that affects copper metabolism. It occurs as autosomal recessive/sporadic pattern. The defect of ATP7B results in impaired copper excretion into bile, thus causing copper overload and toxicity. WD may present as liver disease (ranging from acute liver failure to cirrhosis) or as neurological/psychiatric symptoms.^{1–5} WD although uncommon, constitutes an important indication of liver transplantation in pediatric and adult population. While primary management is medical, liver transplantation is needed in selected group of patients like decompensated liver disease, severe neurologic symptoms and acute liver failure.^{3,4} Liver transplantation cures the basic defect and is treatment option for liver failure or neurological symptoms of WD.^{6–8} While cadaveric liver transplantation is

more common form in west, living donor liver transplantation (LDLT) is more common in India and Asia due to shortage of cadaveric organs. There are some studies that have shown good results of LDLT for WD, however, mixed pediatric (mainly) and adult population is represented.^{9–11} In the current study, we present our experience of LDLT for adults with WD.

MATERIALS AND METHODS

The study was conducted at a tertiary care center in North India and was approved by Institutional ethical committee. We maintain prospective database of all transplant recipients; the current study included retrospective analysis of all liver transplantation recipients (age >18 years at the time of transplantation) who underwent LDLT for WD. The donors were family members or spouse/relatives of spouse. All genetically related donors were negative for screening of WD using serum ceruloplasmin, copper studies and examination for KF rings. Genetic testing of donors was not done. The diagnosis of WD was made as per recommendations of AASLD (presence of low ceruloplasmin, KF ring and high 24 h urinary copper) or EASL (Leipzig score).^{3,4} The age and BMI limits for donors at our center are 18–55 years and 17–34 kg/m² respectively. The donors were medically and psychologically fit. We aim for a graft to recipient weight ratio >0.8 and adequate

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Abbreviations: LDLT: living donor liver transplantation; MELD: model for end-stage liver disease; WD: Wilson's disease

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remnant in donors. A liver biopsy was done for donors with liver attenuation index (difference of liver and splenic attenuation on non-contrast CT abdomen) <5 , dyslipidemia, BMI >28 kg/m². We do not accept donors with $>20\%$ steatosis on liver biopsy. A total of 2 donors had liver biopsy during evaluation; one of these had normal biopsy while the second biopsy was suggestive of 10% steatosis (donor of recipient number 13 in Table 1). Hospital authorization committee cleared all donors and recipients. Copper content was not measured in explants and genetic testing was not done as all patients with cirrhosis had diagnosis of WD by AASLD or EASL definition and were referred to us for transplantation. The immunosuppression protocol at our center consisted of calcineurin inhibitors (tacrolimus), mycophenolate and steroids (tapered over 3 months). Data is shown as number, percentage, mean (SD) or median (25–75 IQR).

RESULTS

The study cohort comprised of 15 males and 3 females, age 32 ± 10 years. The clinical presentation of these patients included decompensated cirrhosis ($n = 16$), acute

on chronic liver failure due to anti-tubercular therapy ($n = 1$) and acute liver failure ($n = 1$). The individual patient data is shown in Table 1. The diagnosis of WD was made at median of 3 years (2–6 years) before liver transplantation; all the patients were being treated with zinc and D-penicillamine at the time of liver transplantation, except the one patient who presented with acute liver failure. All the patients with decompensated cirrhosis were referred from gastroenterologists/other centers, as they could not improve with medical therapy and had refractory ascites and/or recurrent hepatic encephalopathy. The mean ceruloplasmin at the time of liver transplantation was 14 ± 4 mg/dl and 24-h urinary copper values were 256 ± 173 µg/day; 7 of the patients had KF rings. The laboratory parameters before liver transplantation were as follows; serum bilirubin 3 (2.1–7.3) mg/dl, serum albumin 2.7 (2.2–3.1) g/dl, INR 1.56 (1.36–2.07). The female patient with acute liver failure had prothrombin time >200 s, serum ceruloplasmin 8 mg/dl, 24 h urinary copper 188 mcg, low serum copper (34 mcg/dl, normal range 80–155 for females), serum bilirubin 7.5 (indirect 2.2) mg/dl, AST 308 IU/L, ALT 666 IU/L, ALP 149 IU/L, serum lactate dehydrogenase 1079 U/L (normal range 313–618).

Table 1 Individual Patient Characteristics ($n = 18$).

S. no.	Age/sex	Presentation	Donor	Comments/follow up
1	20 M	Decompensated cirrhosis (jaundice and ascites)	Brother in law	Uneventful course
2	49 M	Decompensated cirrhosis (jaundice and ascites)	Brother in law	Acute cellular rejection
3	18 M	Decompensated cirrhosis (jaundice, HE)	Mother	Uneventful course
4	22 M	Decompensated cirrhosis (jaundice, HE)	Brother	Tremors pre LT, improved
5	42 M	Decompensated cirrhosis (jaundice, ascites, HE)	Wife	Severe dysarthria, partial improvement
6	31 F	Acute on chronic liver failure, had jaundice, ascites, HE	Husband	Uneventful course
7	28 M	Decompensated cirrhosis (ascites)	Wife	Dysarthria before transplantation, partial improvement
8	33 M	Decompensated cirrhosis (jaundice, ascites, HE)	Wife	Died due to sepsis in first month
9	52 M	Decompensated cirrhosis (jaundice, ascites, hepatic hydrothorax, HE)	Daughter	Uneventful course
10	19 M	Decompensated cirrhosis (jaundice, ascites)	Swap	Uneventful course
11	20 F	Acute liver failure	Mother	Fulfilled King's college hospital criteria
12	38 M	Decompensated cirrhosis (ascites, hepatorenal syndrome, HE)	Wife	Uneventful course
13	51 M	Decompensated cirrhosis (jaundice, HE)	Sister	Uneventful course
14	31 M	Decompensated cirrhosis (ascites, HE, hepatic hydrothorax)	Cousin brother	Acute cellular rejection
15	31 M	Decompensated cirrhosis (jaundice, ascites, hepatorenal syndrome)	Sister	Uneventful course
16	35 M	Decompensated cirrhosis (jaundice, ascites)	Wife	Anastomotic biliary stricture, managed with ERCP and stenting
17	28 F	Decompensated cirrhosis (jaundice, ascites)	Nephew	Died due to sepsis in first month
18	36 M	Decompensated cirrhosis (jaundice, ascites, spontaneous bacterial peritonitis)	Brother in law	Needed re-exploration for hepatic artery thrombosis, anastomotic biliary stricture

HE: hepatic encephalopathy.

The microscopy of explant showed extensive micro and macrovesicular steatosis, centrilobular necrosis, Ishak's fibrosis score 1/4 and Orcein stain was positive. Her etiological work up was negative for all other etiologies including viral and autoimmune. In view of above-mentioned investigations, a diagnosis of WD related acute liver failure was made.

All the donors were related (family) donors. The mean (SD) donor age was 36 ± 10 years. The donors were parents ($n = 2$), siblings ($n = 3$), cousin ($n = 1$), daughter ($n = 1$), spouse or relatives of spouse ($n = 9$) and from swap transplantation ($n = 1$). All genetically related donors were negative for screening of WD using serum ceruloplasmin, copper studies and examination for KF rings. Liver biopsy was done in 2 donors; it showed 10% steatosis in one (number 13 in Table 1) while other was normal. Severity of liver disease in recipients was as follows: Child's score 10 ± 2 , model for end-stage liver disease (MELD) score 18 ± 6 . Two patients had history of hepatorenal syndrome as shown in Table 1 and renal functions were normal at the time of LDLT. The graft to recipient weight ratio (GRWR) was 1 ± 0.2 . The ICU and hospital stay was 5.5 ± 0.9 and 15 ± 5 days. There was no new neurological complication encountered during hospital stay or follow up. Four patients had culture positive infections and two of these died at first month after LDLT due to sepsis, rest of patients are doing well at a median follow up of 15 months (8–38 months). The patients with mortality as outcome had Child's score of 11, 12 and MELD score of 20 and 23 before LDLT. Two patients had biopsy proven acute cellular rejection that responded to steroid pulses. Two patients had anastomotic biliary stricture. One patient had hepatic artery thrombosis and needed re-exploration. He is doing fine at 6 months of follow up. Three patients had neurological symptoms prior to LDLT as shown in Table 1; 2 of these patients had partial recovery while one had complete recovery. The biochemical tests of WD were not done in post transplant follow up as patients did well and none had worsening of neurological symptoms. There was no significant difference regarding outcomes between LDLT from genetically related or unrelated donors.

EXPLANT FINDINGS

All patients with clinical diagnosis of decompensated cirrhosis ($n = 16$) had cirrhosis on explant. The explant of patient with ACLF showed loss of native liver architecture with areas of hepatocytes collapse (necrosis), bile duct proliferation and regeneration nodules. The explant of patient with acute liver failure (ALF) showed extensive micro-macrovesicular steatosis, centrilobular necrosis, ballooning degeneration, ductular reaction and mixed inflammatory cell infiltrate in portal tracts with Kupffer cell hyperplasia.

DISCUSSION

The presentations of WD range from asymptomatic hepatomegaly/raised liver enzymes to cirrhosis and acute liver failure.⁴ WD may also present as neurological or psychiatric symptoms.^{1–4} Liver transplantation for WD is mainly described in the setting of pediatric population and deceased donor liver transplantation.⁶ Arnon et al. analyzed UNOS database and reported 170 pediatric and 400 adult liver transplantations for WD. The 5 year survival rates were 89% for children and 86% for adults.⁶ We also found an good survival rate for these patients. The better outcomes can be attributed to younger age of recipients (thus no co-morbidities) and absence of malignancies. LDLT with heterozygous living donor has been shown to be safe and studies have shown improvement in copper metabolism parameters without recurrence of disease in long term follow up.^{4,9–11,8,12–14} Wang et al. described their experience of 22 (19 pediatric) LDLT for WD, only one patient died at follow up of mean 18.5 (range 4–38) months; neurological disability ($n = 8$) improved to a major degree in 6/8 patients.⁹ Cheng et al. showed 91% and 75% survival at 1 and 5 years after LDLT in a series of 36 LDLT for WD.¹⁰ Yoshitoshi et al. showed 80% survival at 10 years in a series of 32 LDLT (mean age 16 years) for WD. In their series 90% donors were parents (carriers for WD). The author also noted improvement in copper metabolism parameters after LDLT.¹¹ In a series from Iran of 107 liver transplantations for WD, the authors noted 80% survival at 5 years.⁷ Neurological disabilities also show an improvement after liver transplantation in multiple studies.^{7–9,12} Wang et al. showed that neurological disability improved to a major degree in 6/8 patients.⁹ In the study by Lankarani et al., 56% of 107 patients had some degree of neurological impairment which improved in two third of patients.⁷ Yagci et al. looked at neurological and psychiatric scores in WD patients ($n = 8$) before and after liver transplantation and found significant improvement in both.¹² A multicentre French study (abstract form) described role of liver transplantation in WD with severe neurological symptoms not improving with medical therapy. All the patients had compensated liver disease. A total of 17 patients underwent liver transplantation; moderate to major improvement of neurological symptoms was seen in 11/13 survivors.¹³ We also noted improvement of neurological symptoms in all 3 patients, including complete recovery in one.

One of the patients in current series had acute liver failure due to WD. WD presenting as ALF is uncommon with a high mortality of almost 100%, thus timely diagnosis is very important.¹⁴ It is difficult to diagnose WD in acute liver failure.^{15,16} Although the patient with acute liver failure in the current series could not fulfill these^{15,16} criteria, a diagnosis of WD was kept in view of low ceruloplasmin, high urinary copper, low serum copper,

hemolysis and explant findings were all suggestive of WD in absence of other etiologies. As discussed earlier, the data about liver transplantation for WD is available mainly in setting of pediatric age group and deceased donor liver transplantation. The strength of current study is inclusion of adult patients and LDLT setting. To conclude, we report 18 cases of WD in adults who underwent LDLT and found good outcome in this cohort.

CONFLICTS OF INTEREST

The authors have none to declare.

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