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REVIEW

# Liver transplantation for Wilson disease

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## Abstract

The aim of this paper is to review the current status of liver transplantation (LT) for Wilson disease (WD), focusing on indications and controversies, especially in patients with neuropsychiatric disease, and on identification of acute liver failure (ALF) cases related to WD. LT remains the treatment of choice for patients with ALF, as initial presentation of WD or when anti-copper agents are stopped, and for patients with chronic liver disease progressed to cirrhosis, unresponsive to chelating medications or not timely treated with copper chelating agents. The indication for LT in WD remains highly debated in patients with progressive neurological deterioration and failure to improve with appropriate medical treatment. In case of Wilsonian ALF, early identification is key as mortality is 100% without emergency LT. As many of the copper metabolism parameters are believed to be less reliable in ALF, simple biochemical tests have been proposed for diagnosis of acute WD with good sensitivity and specificity. LT corrects copper metabolism and complications resulting from WD with excellent 1 and 5 year survival. Living related liver transplantation represents an alternative to deceased donor LT with excellent long-term survival, without disease recurrence. Future options may include hepatocyte transplantation and gene therapy. Although both of these have shown promising results in animal models of WD, prospective human studies are much needed to demonstrate their long-term beneficial effects and their potential to replace the need for medical therapy and LT in patients with WD.



**Key words:** Wilson disease; Liver transplantation; Copper; Indications; Contraindications

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## INTRODUCTION

Over recent years, a burgeoning literature has attempted to describe indications and outcome of liver transplantation (LT) for Wilson disease (WD), a rare autosomal recessive disorder of copper metabolism with a prevalence of 1 in 30 000 in the general population. WD is an indication for LT in cases of acute liver failure or end stage liver disease when medical treatment options fail. LT will correct the underlying hepatic metabolic defect of WD, represented by impaired biliary copper excretion.

More than 300 mutations in the *ATP7B* gene, a gene that encodes a metal-transporting P-type adenosine triphosphatase, have been described in literature. These mutations can impair the protein function, leading to decreased hepatocellular excretion of copper into bile with its consequent accumulation in the liver and through the systemic circulation in the brain, cornea, heart, bones and kidney. The clinical manifestations are therefore heterogeneous, the most common being hepatic or neuro-

psychiatric signs and symptoms, for which the utility of LT is both poorly characterized and controversial. This review addresses the indications for and the controversies associated with LT for WD with a particular focus on the short and long term outcomes in terms of survival and clinical presentation. The authors also provide a future perspective on hepatocyte transplantation.

## EPIDEMIOLOGY

Since the first successful LT in 1971[1], more than 500 transplants have been performed in the United States to date for WD, which is the primary indication for LT in 0.5% and 1.5 % of adults and children respectively[2].

These percentages are significantly lower than those initially reported by Gitlin[3] in 2003, who estimated that WD accounts for 5%-8% of all indications for LT. WD is a rare disease that can be medically managed, some cases are misdiagnosed as acute liver failure (ALF) or chronic liver disease (CLD) of unknown etiology and some of the WD patients die before being listed or while waiting for LT. All these factors could explain the relatively small number of LTs performed recently for WD. Due to lack of consensus regarding the indication for LT in patients with severe neurological deficits, a selection is usually done in most transplant centers according to the severity of the neurological manifestations[2]. The number of LTs for WD with neurological disease remains unknown, as there is no information in the United Network of Organ Sharing (UNOS) database regarding the neurological status of the recipients, other than encephalopathy. There are currently more than 16 000 patients waiting for LT in United States according to UNOS and 1.4% of the current listed adult patients are listed for "metabolic disease". The percentage of patients with WD waiting for LT remains unpublished. In children, metabolic liver diseases are the second indication for LT after biliary atresia. Fifteen percent of children enrolled in the studies in the pediatric liver transplantation (SPLIT) registry underwent LT for metabolic diseases[4] and 7.6% for WD. However, it should be noted that the enrollment in SPLIT was voluntary and therefore potentially biased.

Most patients with WD become symptomatic between the first and the fourth decade of life[5], although the age at presentation can vary from two[6] to seventy years old[7]. The average age at transplant is 15 years old (range 4-18 years) in children with WD and 30 years old (range 19-68 years) in adults[2,8].

The early onset (before 10 years old) is associated with more hepatic (83%) than neuro-psychiatric disorders (17%), compared with late age of onset when neuro-psychiatric symptoms are present in about 74% of cases compared with 24% cases with only liver manifestations[9,10]. The type of mutation may explain these findings, with missense mutation being associated with predominantly neurological and later presentation, while a deletion of the gene is associated with predominantly hepatic and earlier presentation[9,10]. A female predominance in the WD induced ALF has been described in the literature[2,11] with 78% and 64% of cases being females in children and adults, respectively[2]. The explanation for this remarkable finding remains unknown; however, data from an animal model of WD suggest that hormonal factors influence the development of early liver failure. The ovariectomy of female LEC rats delays the onset of liver failure[12].

## INDICATIONS FOR LIVER TRANSPLANT

There are two main indications for LT in WD. The first is ALF that may be the initial presentation of WD or can occur when anti-copper agents are stopped. The second is CLD progressed to cirrhosis and portal hypertension and unresponsive to chelating medications, or is not timely treated with copper chelating agents. The indication for LT in WD is widely debated in patients with progressive neurological deterioration and failure to improve with correct medical treatment.

## DIAGNOSIS OF WD IN CASES OF ACUTE LIVER FAILURE

Five percent of all WD patients present with ALF and they account for 4%-6% of all LTs performed in United States for ALF[13]. In these cases, early identification is key as mortality is 100% without emergency LT. The diagnosis of WD is based on a broad combination of laboratory tests and clinical features including: 24 h urine copper, hepatic copper concentration, ceruloplasmin, presence of *ATP7B* gene mutation, Kayser- Fleisher ring, neurological symptoms or brain magnetic resnane iamge findings and presence of hemolytic anemia. The diagnosis of WD in ALF is more difficult as many of the copper metabolism parameters, including serum and urinary copper and reduced serum ceruloplasmin, are believed to be less reliable and specific[14,15], whereas Kayser-Fleisher rings are only detectable in 50% of the cases[16] and many tests for copper metabolism parameters are not always available. Ceruloplasmin levels were reported to not be helpful with five cases of idiopathic liver failure[14]. Due to the difficulty in reaching the diagnosis of WD in the setting of ALF, there has been considerable interest in identifying simple biochemical tests for diagnosis. In 1991, Berman was the first to describe, in six patients, that the ratio of alkaline phosphatase to total serum bilirubin lower than 2 and aspartate aminotransferase (AST) to alanine aminotransferase (ALT) greater than 4 provided high sensitivity and specificity for fulminant WD[17]. A recent study done by Korman *et al*[18] in a cohort of 16 patients with ALF due to WD showed that a combined ratio of alkaline phosphatase to total serum bilirubin lower than 2 and AST to ALT greater than 2.2 had a sensitivity and specificity of 100% for fulminant WD. It is important to note that all the pa-

tients in this cohort had a very high model for end-stage liver disease (MELD) score and it is still unclear whether these screening tests apply in the early stages of clinical course of ALF secondary to WD. A prior study done by Eisenbach *et al*[19] found the ratio of alkaline phosphatase to serum bilirubin or AST to ALT to be unhelpful in a series of seven adults with a mean MELD score of 28. Furthermore, this ratio is not always helpful in children, likely because of the effect of bone-derived alkaline phosphatase. Small studies failed to confirm these correlations in the pediatric population[20-23]. Koppikar *et al*[24] showed that the Wilson Index, a score composed of bilirubin, international normalized ratio, AST, white blood cell and albumin, is helpful in identifying children with Wilsonian ALF in whom LT is indicated. All children with a score higher than 11 died without transplantation, whereas all those with a score less than 11 survived, the method having a 93% sensitivity and 98% specificity.

## BRIDGE TO LIVER TRANSPLANT

Supportive measures for ALF due to WD which may help bridge patients to transplantation have been proposed over the years: exchange transfusion, plasmapheresis, the molecular adsorbent recycling system (MARS), fractionated plasma separation and absorption (FPSA), albumin dialysis and early institution of renal replacement therapy[25,26]. All these treatments are thought to lower circulating copper levels, to reduce hemolysis and secondary organ damage due to copper complexes accumulation. As reported by Jhang *et al*[27] and Asfaha *et al*[28], plasmapheresis is an effective method to reduce circulating copper and improve hemolysis and renal injury. MARS has been associated with improved renal and liver function, improved encephalopathy and short term survival[29,30] and used successfully in patients with ALF, allowing the removal of copper in the urine through chelation with penicillamine[31]. Sen *et al*[25] reported two patients successfully treated and bridged to transplant with MARS.

Although it has been shown that bio-artificial liver devices may improve encephalopathy and have considerable effects on acute or chronic liver failure, such as reduction of bilirubin, albumin-bound toxins or cardiovascular stabilization[32,33], a large randomized multicenter trial failed to show increased survival in these patients[34]. Unfortunately, the lack of information in UNOS database regarding the use of these modalities before LT prevents larger clinical trials. It is still believed that the use of aggressive plasmapheresis, FPSA or MARS to support patients with ALF related to WD waiting for transplant may improve future outcomes.

## INDICATION FOR LIVER TRANSPLANT IN NEUROLOGICAL WD

Most of the data on LT for neurological WD come from case reports or case series describing patients who received LT because of liver function deterioration. The decision to perform LT was based on deteriorating neurological status, despite stable liver function only in a few cases[35,36]. Whether transplantation is indicated for progressive neurological disease due to WD without liver failure is highly debatable. LT reverses neurological deterioration in many WD patients; approximately 78% of patients improve or stabilize[37], as observed by Stracciari in a study that included 41 neurologically affected patients, while the remaining did not present any change in their neurological status[38]. Eghtesad *et al*[22] described total or partial neurological improvement in 10 of 17 patients (58.8%), advocating the benefit and importance of performing transplantation before neurological impairment becomes irreversible. Wang *et al*[39] showed neurological improvements in 8 of 9 patients (88.9%) who received living-related liver transplant (LRLT) for neurological complications. Marin *et al*[40] reported four patients with compensated cirrhosis and progressive neurological deterioration who underwent LT for WD. One of four died due to post LT infections while the other three experienced neurological improvement. To further the debate, Bax *et al*[36] reported the case of a 15 year old without significant liver disease, bedridden with severe incapacitating dysarthria despite maximal medical therapy, who returned almost to normal after LT. Geissler *et al*[41] reported that two of the six WD patients with mixed hepatic and neurological symptoms fully recovered after LT. He suggested that in such cases, an early decision for LT is justified because neurological deficits may become irreversible. However, the hypothesis that better results could be obtained in patients undergoing LT early after the onset of neurological symptoms has not been confirmed[37]. According to Cheng, the outcome was favorable in two patients in whom LRLT was performed because of severely disabling neurological symptoms. This finding substantiated the opinion of Mason *et al*[35] who suggested that, even though their patient died, LT should be considered for patients with severe, progressive neurological impairments. However, few data are available on the outcome of cognitive performance, long-term survival or predictors of outcome. These findings are in contrast with experience reported by Medici *et al*[20]. According to their retrospective multicenter Italian study in 2005 in 37 patients with WD who underwent LT, the combination of neuropsychiatric and hepatic symptoms was the only factor influencing survival after LT[20], with neuropsychiatric patients showing a significantly lower survival rate than the other WD patients. Patients with liver disease alone and those with both hepatic and neuropsychiatric conditions had a mean survival of 135 mo (range 118-152 mo) and 79 mo (range 46-113 mo), respectively ($P = 0.04$). The presence of neuropsychiatric symptoms was a negative prognostic factor, even with improvement or complete resolution of the neurological symptoms. According to Wang *et al*[42] who analyzed post transplant data (LRLT) in 15 patients

with mixed hepatic and mild or moderate neurological involvement, the survival of these patients was slightly lower than that of those without neurological involvement, but this decrease was not statistically significant. Among patients with severe neurological involvement, the survival decreased markedly compared with that of patients without neurological symptoms. These results are consistent with the prior reports from Medici *et al*[20], Ala *et al*[11] and Roberts *et al*[43], which advocated that patients with long standing neurological impairment from WD are unlikely to recover after LT transplantation, contraindicating transplant in such cases. Combined hepatic and neurological disease must be carefully assessed to determine the severity of neuropsychiatric disease. Some experts consider isolated neuropsychiatric symptoms a contraindication for LT because these patients may improve with medical therapy whereas many may worsen from post transplant care and they argue that the patients should not be exposed to the risk of LT when this may not improve symptoms.

## POST LIVER TRANSPLANT SURVIVAL

Several reports show excellent post LT survival both at one year and long-term in most WD patients, with some differences depending on clinical presentation, ALF or CLD, age at transplant, the "era" at transplant and the center's experience.

Medical urgency reflected by the UNOS status (pre transplant intensive care unit-bound) and the severity of the underlying liver disease reflected by a MELD score above 20 are predictors of pre- transplantation mortality[44] and also independent factors predictive of patient post-transplantation survival[45]. In 2002, Schilsky reported 85% 1 year survival of all WD patients undergoing LT[46]. In a larger study, Arnon *et al*[2] reported higher 1 and 5 year survival rates for children and adults with WD for both graft and patient, regardless of the clinical presentation. There was a slightly higher survival for patient and graft in CLD compared with ALF presentation but the difference was not statistically significant. The overall 1 and 5 year patient and graft survival rates after transplantation for CLD in children were 100%, higher compared with transplantation for ALF which showed a 90% 1 year patient survival and 87.5% 5 year patient survival, compared with 87% 1 year graft survival and 82.5% 5 year graft survival. Similarly, the overall 1 and 5 year patient survival rates after transplantation for CLD in adults were 94.7% and 90.1%. One year graft survival was 89.5% compared with 85.5% at 5 years. The overall 1 and 5 year patient survival rates after transplantation for ALF were 90.3% compared with 89.7%. The graft survival rates were 87.1% at 1 year and 86.2% at 5 years[2]. The good outcome of these patients can be attributed to the relatively young age at transplant, low rate of comorbidities, lack of disease recurrence and low rate of hepatocellular carcinoma.

Data from the SPLIT registry between December 1995 and June 2008 shows the same results with excellent 1 and 5 year patient survival of 96% and 91.4%, respectively and 96% and 91.4% for graft survival. Children who underwent LT for metabolic disease had similarly excellent patient survival as, and better graft survival than, those who received a liver allograft for other indications[4].

However none of these studies looked at the subgroup of patients with mixed hepatic and neuropsychiatric disease. In the study published by Medici *at al*[20] in 2005, the overall patient survival rates at 3, 6 and 12 mo and at 3, 5 and 10 years after transplantation were similar to other publications.

## LRLT AND AUXILIARY PARTIAL ORTHOTOPIC LIVER TRANSPLANT

As the scarcity of organs is a worldwide problem, LRLT represents an alternative to deceased donor LT. This is important especially in pediatric patients and in some countries where cadaveric transplantation is not allowed. Heterozygosity for the WD gene mutation is associated with abnormal serum copper and ceruloplasmin levels in 28%-35% of subjects[47]. Despite some unresolved problems with respect to screening for heterozygotes status and the risk of abnormal copper metabolism after transplantation, the use of a living related donor heterozygote for WD has been proven safe and there are multiple reports in literature showing improvement in copper metabolism without evidence of recurrence of WD after long-term follow-up[39,48]. Cheng showed an excellent patient survival at 1 and 5 years after LRLT: 91.7% and 75%, as well as graft survival 86.1% and 75%, respectively[45]. Similarly Yoshitoshi showed 1, 5, 10 year cumulative patient survival rates of 90.6%, 83.7%, 80%[49]. These results are compatible with the outcomes reported for deceased donor LT.

Auxiliary partial liver transplant has been performed with success, showing normalization of serum ceruloplasmin and liver tests, as well as improvement in neurological status[50]. However, according to Kasahara experience with auxiliary partial orthotopic liver transplant, patients had worse survival than those with classical LDLT, mainly due to post-transplant surgical complications, the most common being biliary strictures and graft failure due to stealing syndrome[51]. Another drawback of this technique as an indication for LT for CLD is the potential risk of carcinogenesis of the remnant native liver[50].

## POST LIVER TRANSPLANT COPPER METABOLISM

Copper metabolism normalizes quickly after transplant. Copper overload slowly resolves in extrahepatic organs but it is still unclear whether de-coppering after LRLT from heterozygote donors is slower than de-coppering after cadaveric transplantation from non-related donors. Normalization of serum ceruloplasmin is usually seen in the first month post LT. Most patients have marked reduction in urinary copper excretion with normalization

between 6 to 9 mo after transplant and complete resolution of K-F rings is seen in more than 60% of cases with partial resolution in all of the post transplant patients[45,52].

## FUTURE: LIVER CELL TRANSPLANTATION AND GENE THERAPY

Both approaches are potential exciting future treatments for WD and could offer cures for this disorder since current medical therapy is a lifelong commitment and patients often suffer from noncompliance-related complications. At present, only data from preclinical studies on animal models of WD are available. In the light of donor organ shortage, cell transplantation is emerging as an exciting alternative for whole liver transplantation with many advantages: it is less invasive, requires fewer organs and can be repeated several times if needed. But this leads to the question of the type and source of cells to be used. If human primary hepatocytes are not a realistic option due to the shortage of organ donors and inability to survive, expand and proliferate *in vitro* for prolonged periods of time, xenogenic hepatocytes cannot completely replace the synthesis of human plasma proteins and they are problematic from an immunological point of view. Hepatoma cell lines provide an endless support but often lack important metabolic and synthetic properties due to genetic alterations. Fetal hepatocytes and stem cells remain interesting candidates to establish hepatocyte-related cell lines[53,54]. Gene therapy for WD would be based on transfection of hepatocyte cells with normal *ATP7B* gene. Researchers in this field are currently seeking vectors that can transduce non-replicating cells, with long-term expression and proper cellular localization of *ATP7B*. The difficulties they are currently facing are transient expression of the transgene and low transfection efficiency, with need of repeat transfection due to inadequate cell numbers[55]. In most animal studies, cell proliferation was enhanced by preconditioning the host liver and nearly total repopulation with transplanted cells was achieved[56], but the methods used for preconditioning can hardly be translated to humans. Since the first use of LCT in human patients in 1992[52], less than 100 patients have been transplanted, mainly for inborn error or metabolism such as urea cycle disorder, Crigler-Najjar Syndrome or glycogen storage disease. LCT effect was transient in all studies with the longest duration of beneficial effects of 36 mo, reported in a 47 year old woman with glycogen storage disease[57], while the mean duration of positive effects in other cases was less than 10 mo. In most of the reported cases, LCT was used as a bridging method to LT. The small number of human studies with LCT is due to the technical difficulties that need to be overcome, including identifying the ideal cell line that can survive, expand and proliferate *in vitro*, develop safe techniques for expansion of cells *in vitro* and finding the ideal route of administration as portal vein administration is not realistic in patients with cirrhosis due to reversal of flow. Furthermore, LCT may require cells from multiple donors, lifelong immunosuppression and may need to be repeated if adequate cell survival or repopulation is not achieved. Prospective human studies are much needed to demonstrate the benefit of both these techniques, with the goal of achieving metabolic correction and replacing the need for medical therapy and LT in patients with WD.

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