Liver transplantation for metabolic liver diseases in adults: indications and outcome

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Abstract
Orthotopic liver transplantation is the preferred treatment for many patients with complications of end-stage liver disease. For metabolic liver diseases liver transplantation does not only replace the diseased organ, but also can potentially correct the metabolic defect. Results of liver transplantation for metabolic diseases have been encouraging. In Wilson’s disease liver transplantation is considered an effective treatment for the fulminant form and for end-stage liver disease, associated with an excellent long-term outcome. However, it is still a matter of controversy whether liver transplantation should be considered in Wilson’s disease patients with severe neurological impairment. Liver transplantation for hereditary haemochromatosis is relatively uncommon and is associated with a decreased post-transplantation patient survival, most likely due to infections and cardiac complications. Reduction of iron overload prior to liver transplantation in patients with hereditary haemochromatosis might be associated with a better outcome.

Keywords: haemochromatosis; liver transplantation; metabolic diseases; Wilson’s disease

Wilson’s disease

Wilson’s disease (WD) is a rare autosomal-recessively inherited copper storage disease with an estimated prevalence of 1:30,000. It is caused by mutations of the WD gene ATP7B encoding a copper-transporting P-type ATPase that is expressed predominantly in the liver [1,2]. Mutations of the ATP7B gene can lead to an insufficient copper excretion into the bile. The subsequent copper accumulation primarily in the liver, brain, and cornea leads to the clinical manifestations of the disease. The onset of WD is highly variable. WD is common in younger subjects but might be diagnosed even as late as the eight decade of life [3,4]. Its clinical presentation shows a varied picture of hepatic, neurologic or psychiatric symptoms, which might occur predominately or present jointly [5]. Hepatic involvement of WD can present as acute or chronic liver disease and as fulminant liver failure [3].

Typically fulminant liver failure occurs in children or young adults and is more often observed in females. Early diagnosis of fulminant WD is essential because the mortality is high, and often OLT remains the only therapeutic option. However, the lack of sensitive and specific criteria for the diagnosis of fulminant WD has made this condition quite difficult to identify. Biochemical diagnosis of fulminant WD usually is suggested in presence of an acute hepatic insufficiency often accompanied by a Coombs-negative haemolytic anaemia, only moderately increased serum transaminases, a high serum bilirubin concentration, and a high urinary copper excretion [6]. As the diagnosis of fulminant WD is difficult to establish, multiple indices have been evaluated to indicate fulminant WD. Berman et al. [7] proposed an alkaline phosphatase—total bilirubin ratio of <2.0 as indicative for fulminant WD and Shaver et al. [8] proposed a low serum alkaline phosphatase as being suggestive of fulminant WD. However, there are reports that doubt the validity of these formerly proposed scores for diagnosis of fulminant WD [9–11].

As we published recently, low serum transaminase levels and a low serum cholinesterase activity are indicative for a fulminant WD [11]. A possible explanation for this observation is the fact that most patients presenting with fulminant WD already have evidence of cirrhosis and impaired organ function. Typically, the presence of WD is not recognized before rapid deterioration and onset of fulminant WD. Therefore, fulminant WD is considered one of the
special circumstances where acute liver failure can still be diagnosed in patients with pre-existing liver disease [3,12]. Although copper metabolism parameters remain the most accurate means for diagnosis of WD, they may be of limited value in fulminant WD. In the setting of fulminant WD serum copper can be in the normal range or even be elevated and ceruloplasmin, as an acute phase protein, might also be within the normal range [11]. A high urinary copper excretion is a strong indicator for fulminant WD [11], however, severe renal impairment and anuria are conditions occurring often in patients fulminant WD.

Treatment of WD is possible medically or by liver transplantation. The available medical treatments are copper-chelating agents (D-penicillamine and trientine) and zinc salts. Medical treatment with these drugs is mostly effective, except in patients with fulminant hepatic failure. In addition to the established drugs, tetrathiomolybdate is a new chelating agent that acts by forming a tripartite complex with copper and protein. Brewer et al. [13] have recently published a study suggesting that tetrathiomolybdate might be superior to trientine in WD patients presenting with neurologic disease. However tetrathiomolybdate is a new drug and the experience with it is very limited. Further studies are required to understand more about side-effects, toxicity and outcome under long-term treatment with that drug.

For WD patients with chronic liver disease liver transplantation should not be considered unless medical treatment has been administered for a suitable time-period. An effective medical treatment commonly results in a substantial hepatic improvement after about 4 to 12 months of therapy. The progression of liver disease under a sufficiently established, long-term (more than 2 years) therapy is a rare event. However, discontinuation and failure of medical treatment bare the risk of an acute or chronic deterioration of hepatic and neurological symptoms [14]. In patients showing progressive hepatic symptoms under medical therapy an insufficient dosage or non-compliance should be considered responsible for disease progression and, if possible, a readjustment of medical therapy should be performed before considering OLT.

For patients with end-stage liver disease unresponsive to medical therapy or with a fulminant liver failure OLT seems to be the only effective mode of treatment and in addition corrects the underlying hepatic genetic defect. However, the necessity for immunosuppression after OLT and the great shortage of donor organs implies that—if at all possible—WD should be treated medically. The first OLT for WD has been performed successfully in 1971 [15]. Since then, various studies have proven OLT as a therapeutic option for fulminant WD because of the poor prognosis without transplantation. This holds especially true for patients presenting with a higher-grade encephalopathy where OLT is the only therapeutic option [7,16]. In patients with acute liver failure without a higher-grade encephalopathy the criteria for transplantation are controversial. In these cases outcome without liver transplantation is not always fatal [11]. In 1986 Nazer et al. [17] have proposed a prognostic score for identification of patients with acute liver failure that will not survive without liver transplantation. In the last years this score has been used preferentially in children, but has shown only variable results [18]. Recently the scoring system introduced by Nazar et al. has been modified by Dhawan et al. [19]. This new score is based on the serum bilirubin, international normalised ratio, aspartate aminotransferase (AST), and white cell count at presentation and predicts the mortality without liver transplantation. Although this score has been evaluated prospectively in a small cohort of children with acute WD [19], it needs further validation, especially in older patients where it might be insufficient.

OLT for primary hepatic WD represents an excellent therapeutic option with a one-year patient survival of 80% to 90% [10,16,20,21]. Comparable good results have been published for living-related liver transplantation in patients with hepatic WD [22,23]. Less definitive indications for OLT exist for WD patients with respect to neurologic disease.

While former studies showed that liver transplantation resolves the hepatic consequences of WD, the outcome of the neurological manifestations is not unambiguous. From a pathophysiological point of view the neurological symptoms in WD are caused by copper toxicity. Reducing copper levels by OLT or medical treatment should stop further cerebral damage. However, neurological symptoms arising from the existing cerebral damage will usually not resolve before about half a year. Neurological symptoms that persist for more than two years under sufficient medical treatment have to be considered permanent and are unlikely to improve, neither by further anticopper therapy nor by OLT [24–26].

Some studies and several case reports showed an improvement of neurological symptoms after OLT. The percentage of patients showing improvement of neurological symptoms after OLT ranges from 56% [20] to 77% [27]. Even complete regression of neurological symptoms is possible [27–29]. However, also a severe worsening of neurological symptoms after OLT has been reported [27]. Although reports on improvement of neurological symptoms after OLT are encouraging, neuropsychiatric symptoms represent a negative prognostic factor for the outcome of OLT in WD patients. Medici et al. [27] could show that the survival of patients with mixed hepatic and neuropsychiatric symptoms is significantly lower than that of patients with sole liver disease. Therefore a combination of hepatic and neuropsychiatric conditions deserves careful neurological evaluation, which should contraindicate OLT in most patients with severe neurological impairment.
Hereditary haemochromatosis

The term hereditary haemochromatosis is generally reserved to describe an inherited disorder of iron metabolism characterized by increased intestinal iron absorption. The subsequently occurring progressive iron overload damages various organs, in particular the liver, but also the pancreas, heart, joints and endocrine glands [30]. Hereditary haemochromatosis has a prevalence of ~0.5% and is by that the most common single-gene inherited disorder in persons of northern European descent. Treatment of iron overload with phlebotomies is effective, simple, and safe. Therapeutic phlebotomies can at least stop progression of iron overload and in part even reverse the damage [31]. Hereditary haemochromatosis should be distinguished from secondary iron overload that can be caused by multiple blood transusions, anaemia with ineffective erythropoiesis, and chronic liver disease.

The most common form of hereditary haemochromatosis is caused by homozygosity for the C282Y mutation in the HFE gene. Although mutations of the HFE gene are very common particularly among persons with European ancestry the clinical penetrance is low [32–24]. The role of the liver in hereditary haemochromatosis has remained controversial for a long time. The recently identified iron-regulatory peptide-hormone hepcidin plays a central role in the pathogenesis of iron-overload disorders and evolved as the “missing link in haemochromatosis” between the liver and intestine. Nowadays, it is commonly accepted that the primary defect of HFE-associated haemochromatosis is located in the liver. This explains the observation that iron-reaccumulation is uncommon after OLT [35].

Although OLT cures the metabolic defect of hereditary haemochromatosis it is a rare indication for OLT. Only approximately 1% of patients who underwent OLT suffered from liver disease due to hereditary haemochromatosis [36,37]. This might in part be due to the fact that usually clinical symptoms do not manifest before the forth or fifth decade of life and progression to end-stage liver disease commonly occurs at an age when patients are too old to be considered for liver transplantation.

In nearly all studies, post-OLT survival of patients with hereditary haemochromatosis was reduced compared to reported post-OLT survival of other patients. Brandhagen [38] recently reported on the data obtained from the United Network for Organ Sharing (UNOS). In this report one and 5-year patient survival rates were 75 and 64% in patients with iron overload compared with 83 and 70% in the group without iron overload. Due to another study of Brandhagen et al. [39] it seems as if hepatic iron overload irrespective of the underlying reason results in a poorer post-OLT outcome. In this study, patients with and without HFE gene mutations had similarly reduced post-OLT survival compared to a matched group without iron overload. However, there are other reports that find no reduced 1-year post-OLT survival rate in patients with iron overload compared to controls [40]. Nevertheless, several studies noted an increase of infectious complications in patients with hereditary haemochromatosis in the first year after OLT [41,42], whereas in the later years cardiac complications are reported more frequently [43,44]. Sufficient iron depletion before OLT might improve the outcome after OLT as a few studies have noted an improved post-OLT survival in such patients [45,46].

These findings emphasize the need for an early diagnosis and adequate treatment of hereditary haemochromatosis. An adequate iron-depletion therapy can reduce progression of disease with no need for liver transplantation. If OLT is required in patients with hereditary haemochromatosis a preoperative adequate iron depletion is strongly recommended.

Conclusion

In summary, OLT is an excellent therapeutic option for fulminant WD, but can only be considered as a second line therapy for chronic hepatic disease when medical treatment fails. The overall survival after OLT for WD is satisfactory. Mild to moderate neurological symptoms represent a negative prognostic factor for OLT, while in general WD patients with severe neuropsychiatric symptoms should not be considered for OLT. Survival of patients who undergo OLT for hereditary haemochromatosis is reduced compared with most other indications. An adequate iron depletion therapy prior to transplantation might improve the post-OLT outcome.

Conflict of interest statement. None declared.

References


