Long-term results of liver transplantation for Wilson’s disease

Résultats à long terme de la transplantation hépatique pour maladie de Wilson

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Wilson’s disease is a hereditary defect in hepatic copper metabolism, causing hepatic, neurological and/or psychiatric manifestations. For patients with severe disease, liver transplantation is the treatment of choice. The aim of this study was to report the long-term outcome of patients who underwent liver transplantation for Wilson’s disease.

Patients and methods. — Thirteen patients with Wilson’s disease, transplanted in Lyon France between January 1987 and May 2006, were included in this study: eight women and five men, aged eight to 53 years (median 20 years, seven children and six adults). The diagnosis of Wilson’s disease was established before liver transplantation.

Results. — The indication for liver transplantation was chronic (69%) or fulminant liver failure (31%). The median follow-up after liver transplantation was 10 years with 100% patient survival. Copper metabolism returned to normal in all patients. None of the patients with exclusive liver disease required chelation treatment after liver transplantation and none developed neurological symptoms of Wilson’s disease.

Conclusion. — Liver transplantation totally reverses the abnormalities of copper metabolism and subsequent hepatic failure, but the course of neurological symptoms remains unpredictable. Long-term patient survival can be excellent without occurrence of neurological complications.
Introduction

Wilson’s disease is an autosomal recessive hereditary disease causing copper to accumulate within the cells of the liver and the central nervous system, leading to hepatic, neurological and/or psychiatric manifestations [1,2]. For patients with end-stage liver failure, liver transplantation is the treatment of choice [3,4]. This indication accounts for less than 5% of the liver transplantsations recorded in the European Liver Transplantation Registry (ELTR). Indications for liver transplantation were defined with precision for the first time in 1984 and included cases of severe liver disease causing acute liver failure or advanced cirrhosis, after failure of medical treatment or interruption of medical treatment [5]. Liver transplantation reverses the underlying hepatic metabolic abnormality. Data on the long-term results of liver transplantation for this indication are scarce due to the limited number of cases. We report the experience in Lyon France where 13 patients with Wilson’s disease underwent liver transplantation during the last 20 years.

Materials and methods

Thirteen patients (eight female, five male) with Wilson’s disease, who underwent liver transplantation in Lyon between January 1987 and May 2006, were included in this study. The patients were aged eight to 53 years at surgery (mean 20 years, seven children, six adults). Transplantations were performed at the Edouard-Herriot Hospital or the Croix-Rousse Hospital. All patients had symptomatic liver disease, associated with neurological manifestations in one.

The diagnosis of Wilson’s disease was established in all patients on the basis of recognized criteria (presence of Kayser Fleisher ring, low serum ceruoplasmin level, elevated urinary copper, elevated liver copper, compatible liver histology).

Results

Before liver transplantation

The clinical and biological data collected before liver transplantation are presented in Table 1. Mean serum ceruoplasmin level was 0.19 g/L (0.085 g/L in patients with fulminant disease and 0.24 g/L in patients with chronic disease (normal range 1.2—3.1 g/L)). Urinary copper was assayed in 11 patients: the mean value was 21.7 μmol/24 h (normal inferior than 1). Liver copper was assayed in seven patients: the mean value was 730 μg/g (range 160—1800) (normal inferior than 55 μg/g). Search for gene mutation was performed in nine patients and a mutation was identified in seven of them (Table 2). A Kayser Fleisher ring was identified in six patients.

Prior to transplantation treatments were D-penicillamine for seven patients and trientine for one patient. Five patients with fulminant hepatitis were not given medical treatment before liver transplantation.

At the time of liver transplantation

For the 13 patients, the indication for liver transplantation was chronic liver failure in nine (61.5%) and acute liver failure in four (38.5%). The time from diagnosis to liver transplantation was 38 months (range 0.5—216 months) for the patients with chronic liver failure and 14 days (range 5—30 days) for those with acute liver failure.

Two children received a living donor graft (father or mother). The eleven patients received a cadaver graft (partial liver and bipartition in two cases).

Elevated serum total bilirubin was noted in 12 of 13 patients, mean 253 μmol/L (588 μmol/L for fulminant hepatitis and 104 μmol/L for cirrhotic patients). Elevated alkaline phosphatase level was noted in four patients (mean three times normal), and elevated transaminase levels in nine, aspartate aminotransferase (ASAT, mean 596 IU/L) predominating over alanine aminotransferase (ALAT, mean 352 IU/L) in six patients. Five cases of hemolytic anemia were observed (negative Coombs test).

Four patients developed edematous ascitic decompensation, three had hepaticencephalopathy, two had upper gastrointestinal bleeding due to portal hypertension (esophageal variceal rupture) and one had kidney failure.
Table 1  Clinical and biological data before liver transplantation.  

<table>
<thead>
<tr>
<th>n</th>
<th>Cirrhosis</th>
<th>Fulminant hepatitis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td>9</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Ceruloplasmin (g/L)</td>
<td>0.24</td>
<td>0.085</td>
<td>0.19</td>
</tr>
<tr>
<td>Cupuria (µmol/24h)</td>
<td>19.45</td>
<td>28.06</td>
<td>21.77</td>
</tr>
<tr>
<td>Kayser Fleisher ring</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Hepatic copper (µg/g)</td>
<td>437</td>
<td>1121</td>
<td>730</td>
</tr>
<tr>
<td>ASAT &gt; ALAT</td>
<td>6</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Total bilirubin (µmol/L)</td>
<td>104</td>
<td>588</td>
<td>253</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>54</td>
<td>18</td>
<td>42</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>29.6</td>
<td>33.7</td>
<td>30.9</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Edemato-ascitic decompensation</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase.

Study of the operative specimens from the four patients who underwent transplantation for fulminant hepatitis showed severe steatosis, without constituted cirrhosis in three and with in one. Pathology confirmed cirrhosis in the nine other patients, associated with steatosis in one.

After liver transplantation

Mean patient follow-up after liver transplantation was 10 years (range 1–20 years) with 100% patient survival. After liver transplantation, liver tests improved progressively and signs of liver failure disappeared.

Immunosuppressive therapy included, for all patients, a calcineurin inhibitor and corticosteroids, sometimes combined with an antimetabolite (azathioprine or mofetil mycophenolate). Three of the 13 patients developed early transient kidney failure treated by hemodialysis for one (for three weeks after liver transplantation). Two episodes of acute rejection were observed in one patient. Another patient developed chronic rejection requiring retransplantation 13 years after the first transplantation.

None of the patients with exclusive liver disease (n = 12 patients) required chelation therapy after transplantation. One of the patients with marked neurological involvement before transplantation failed to exhibit any neurological improvement, with persistent progressive neurological deterioration under treatment with zinc acetate. All 12 of the patients who had exclusive liver disease remained free of neurological manifestations of Wilson’s disease. The Kayser Fleisher ring disappeared in all patients (six of six) and copper metabolism parameters (serum ceruloplasmin, elevated cupuria, elevated hepatic copper and compatible hepatic histology). If the diagnosis is established early, before the development of irreversible damage, Wilson’s disease can be controlled medically with a copper chelator such as D-penicillamine. If this treatment is unsuccessful, or if the disease is diagnosed in a context of fulminant hepatitis, liver transplantation is indicated [6]. No known biochemical or imaging marker can distinguish potential responders from non-responders [5]. A severity score based on bilirubin, INR, ASAT and white cell count has been proposed to determine the best time to proceed with liver transplantation [7]. A score at presentation greater than 11 is predictive of death with 93% sensitivity, 98% specificity and 88% positive predictive value.

Since the first liver transplantation for Wilson’s disease performed in 1969 [8], this treatment has been proposed for advanced symptomatic disease complicated by liver failure, and/or nonresponse to D-penicillamine [9]. Several studies have analyzed survival after transplantation and the reversibility of biochemical, radiological and neurological manifestations of the disease. From evidence available, it

Discussion

Wilson’s disease is related to mutation of the ATP/B gene leading to defective biliary secretion of copper. Diagnosis is established on the presence of a Kayser Fleisher ring, low serum ceruloplasmin, elevated cupuria, elevated hepatic copper and compatible hepatic histology. If the diagnosis is established early, before the development of irreversible damage, Wilson’s disease can be controlled medically with a copper chelator such as D-penicillamine. If this treatment is unsuccessful, or if the disease is diagnosed in a context of fulminant hepatitis, liver transplantation is indicated [6]. No known biochemical or imaging marker can distinguish potential responders from non-responders [5]. A severity score based on bilirubin, INR, ASAT and white cell count has been proposed to determine the best time to proceed with liver transplantation [7]. A score at presentation greater than 11 is predictive of death with 93% sensitivity, 98% specificity and 88% positive predictive value.

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Table 2  Genetic diagnosis of Wilson’s disease in the study group.  

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutation</th>
</tr>
</thead>
</table>
| 1 | 2 mutations: exon 3, p.I507fsX17, heterozygous  
Exon 15, p.P1134fsX14, heterozygous |
| 2 | 1 mutation: exon 2, c.576_577insG, heterozygous |
| 3 | 1 mutation: exon 10, p.K844KfsX29, heterozygous |
| 4 | 2 mutations: exon 14, p.H1069Q, heterozygous  
Exon 16, p.G1186S, heterozygous |
| 7 | 2 mutations: exon 2, p.Q289X, heterozygous  
Exon 14, p.A1063V, heterozygous |
| 11 | 1 mutation: exon 8 Trp 779 stop, homozygous |
| 13 | 1 mutation: exon 6, p.L6415, heterozygous |
can be concluded that Wilson’s disease is a hereditary defect of copper metabolism which can be treated by liver transplantation [10].

Female gender predominated in our series (61.5%) as in others reported by Sutcliffe et al. (18/24) [2], Schilsky et al. (16/21 patients) [5], Wang et al. (16/22) [6] and Emre et al. (8/11) [11]. This observation would suggest that a hormone factor participates in the expression of disease severity. In addition, the fact that eight of 13 patients were aged less than 20 years suggests that in children and adolescents, the fulminant form of Wilson’s disease predominates. Thus, Wilson’s disease should be entertained as a possible diagnosis in all children and adolescents presenting an episode of acute hepatitis, particularly if associated with hemolysis.

The referral center for Wilson’s disease in Lyon holds a registry of 47 families (53 Wilson’s disease patients) followed since the 1980s. Since inception of the registry, 24% of these patients have undergone liver transplantation. This corresponds to 41% of patients with histologically proven cirrhosis (31 patients). In our experience, the indication for liver transplantation has been rather frequent in this population.

In our patients, liver transplantation enabled cure in all patients with acute or chronic manifestations of Wilson’s disease. The fact that the Kayser Fleisher ring resolved reflects well the mobilization of copper in the organism after liver transplantation without the need to add a copper chelator. Thus, liver transplantation can be considered as an effective alternative in the event of unsuccessful medical treatment or if the initial presentation (fulminant hepatitis) precludes proper evaluation of medical treatment. Persistence of neurological symptoms would probably be the only indication for maintaining the chelator therapy. Nevertheless, as was observed in our patient, neither transplantation, nor maintenance of the chelator therapy can guarantee resolution of the neurological manifestations. The presence of neurological symptoms may reflect the existence of irreversible Wilson’s disease-related neurological damage, even if cases of improvement after liver transplantation have been reported [3,5,6,10].

Patient survival cannot be established with precision since available data come from small series, often accumulated over a long period of time because of the rare disease incidence. Results cannot be directly compared with those obtained in other patients with metabolic liver diseases where liver function is generally preserved. In addition, the larger proportion of these patients undergo transplantation in an emergency setting due to the fulminant hepatitis, a situation which may affect prognosis. In one recent study, the survival rates in 37 patients at one, three, five and 10 years were only 89.1, 82.9, 75.6 and 58.8%, respectively [12]. Our results are thus much more encouraging, but of course with a smaller cohort.

In conclusion, our experience demonstrates that liver transplantation corrects the copper metabolism disorder and liver complications resulting from Wilson’s disease, without associating chelator therapy after transplantation. These patients, like most patients with metabolic liver disease, can expect excellent long-term survival, without disease recurrence or development of neurological complications.

References