Research Article

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Long term results of liver transplantation for Wilson's disease: Experience in France

Olivier Guillaud[1,*], Jérôme Dumortier[1], Rodolphe Sobesky[2,23,24,25], Dominique Debray[3], Philippe Wolf[4], Claire Vanlemmens[5], François Durand[6], Yvon Calmus[7], Christophe Duvoux[8], Sébastien Dharancy[9], Nassim Kamar[10], Karim Boudjema[11], Pierre Henri Bernard[12], Georges-Philippe Pageaux[13], Ephrem Salamé[14], Jean Gugenheim[15], Alain Lachaux[16], Dalila Habes[17,25], Sylvie Radenne[18], Jean Hardwigsen[19], Olivier Chazouillères[20], Jean-Marc Trocello[21], France Woimant[21], Philippe Ichai[2,23,24,25], Sophie Branchereau[17,25], Olivier Soubrane[22], Denis Castaing[2,23,24,25], Emmanuel Jacquemin[17,25], Didier Samuel[2,23,24,25], Jean-Charles Duclos-Vallée[2,23,24,25]

[1]*Centre National de Référence de la Maladie de Wilson/Fédération des Spécialités Digestives, Hôpital Édouard Herriot, Hospices Civils de Lyon, Lyon, France;* [2]*Centre National de Référence de la Maladie de Wilson/Centre Hépato-Biliaire, Hôpital Paul Brousse, AP-HP, Villejuif, France;* [3]*Service d'Hépatologie Pédiatrique, Hôpital Necker-Enfants Malades, AP-HP, Paris, France;* [4]*Service de Chirurgie générale et Transplantation, Hôpital Hautefeuille, CHU Strasbourg, France;* [5]*Service d'Hépatologie, Hôpital Jean Minjoz, CHU Besançon, France;* [6]*Service d'Hépatologie, Hôpital Beaujon, AP-HP, Clichy, France;* [7]*Service de Chirurgie, Hôpital Cochin, AP-HP, Paris, France* [8]*Service d'Hépatologie, Hôpital Henri Mondor, AP-HP, Créteil, France;* [9]*Service d'Hépato-Gastroentérologie, Hôpital Claude Huriez, CHRU Lille, Lille, France;* [10]*Service de Néphrologie-Hypertension artérielle-Dialyse-Transplantation, Hôpital Rangueil, CHU de Toulouse, France;* [11]*Service de Chirurgie Hépatobiliaire et Digestive, Hôpital de Pontchaillou, CHU de Rennes, France;* [12]*Service d'Hépatologie et de Gastroentérologie, Hôpital Pellegrin, Bordeaux, France;* [13]*Fédération Médico-Chirurgicale des Maladies de l'Appareil Digestif, Hôpital Saint-Eloi, Montpellier, France;* [14]*Service de Chirurgie Digestive, CHU Bretonneau, Tours, France;* [15]*Service de Chirurgie Digestive, Hôpital L'Archet 2, CHU Nice, Nice, France;* [16]*Centre National de Référence de la Maladie de Wilson/Service de Pédiatrie, Hôpital Femme Mère Enfant, Hospices Civils de Lyon, Bron, France;* [17]*Centre National de Référence de la Maladie de Wilson/Service d'Hépatologie et de Transplantation Hépatique Pédiatriques, Hôpital Bicêtre, AP-HP, Le Kremlin-Bicêtre, France;* [18]*Service d'Hépatologie, Hôpital de la Croix-Rousse, Hospices civils de Lyon, Lyon, France;* [19]*Service de Chirurgie Digestive, Hôpital la Conception, Marseille, France;* [20]*Service d'Hépatologie, Hôpital St Antoine, AP-HP, Paris, France;* [21]*Centre National de Référence de la Maladie de Wilson/Service de Neurologie, Hôpital Lariboisière, AP-HP, Paris, France;* [22]*Service de chirurgie hépatobiliaire et transplantation hépatique, Hôpital St Antoine, AP-HP, Paris, France;* [23]*UMR 785, INSERM, France;* [24]*UMR-S 785, Univ Paris-Sud, Villejuif, France;* [25]*DHU Hepatinov, Villejuif, France*

Background & Aims: Liver transplantation (LT) is the therapeutic option for severe complications of Wilson's disease (WD). We aimed to report on the long-term outcome of WD patients following LT.

Methods: The medical records of 121 French patients transplanted for WD between 1985 and 2009 were reviewed retrospectively. Seventy-five patients were adults (median age: 29 years, (18–66)) and 46 were children (median age: 14 years, (7–17)). The indication for LT was (1) fulminant/subfulminant hepatitis (n = 64, 53%), median age = 16 years (7–53), (2) decompensated cirrhosis (n = 50, 41%), median age = 31.5 years (12–66) or (3) severe neurological disease (n = 7, 6%), median age = 21.5 years (14.5–42). Median post-transplant follow-up was 72 months (0–23.5).

Results: Actuarial patient survival rates were 87% at 5, 10, and 15 years. Male gender, pre-transplant renal insufficiency, non elective procedure, and neurological indication were significantly associated with poorer survival rate. None of these factors remained statistically significant under multivariate analysis. In patients transplanted for hepatic indications, the prognosis was poorer in case of fulminant or subfulminant course, non elective procedure, pretransplant renal insufficiency and in patients transplanted before 2000. Multivariate analysis disclosed that only recent period of LT was associated with better prognosis. At last visit, the median calculated glomerular filtration rate was 93 ml/min (33–180); 11/93 patients (12%) had stage II renal insufficiency and none had stage III.

Received 19 July 2013; received in revised form 14 October 2013; accepted 23 October 2013; available online 6 November 2013

* Corresponding author. Address: pavillon H, Hôpital Edouard Herriot, 69437 Lyon Cedex 03, France. Tel.: +33 4 72 11 01 46; fax: +33 4 72 11 01 47.
E-mail address: olivier.guillaud@chu-lyon.fr (O. Guillaud).

Abbreviations: LT, liver transplantation; WD, Wilson's disease; FHF, fulminant hepatic failure; SFHF, subfulminant hepatic failure; CLD, chronic liver disease; CNI, calcineurin-inhibitor; MMF, mycophenolate mofetil; HCC, hepatocellular carcinoma; HAT, hepatic artery thrombosis; BP, blood pressure; BMI, body mass index; PNF, primary non function; ALF, acute liver failure; n.a., not available.

Conclusions: Liver failure associated with WD is a rare indication for LT (<1%), which achieves an excellent long-term outcome, including renal function.

Introduction

Wilson's disease (WD) is a rare autosomal recessive disorder affecting the metabolism of copper, which has a prevalence of 1 per 30,000 in the general population [1]. The gene defect was identified in 1993, involving mutations in the *ATP7B* gene located on the long arm of chromosome 13. The accumulation of copper in different organs is due to a reduced excretion of copper via the bile, leading to clinical manifestations that are particularly of the hepatic and neuropsychiatric type. Most symptoms first appear during the second and third decades of life. In both children and adults, the hepatic form of the disease usually presents through either the accidental discovery of abnormal liver function test results or as chronic liver disease, and rarely as acute liver failure. Copper chelating agents such as D-penicillamine and trientine hydrochloride, and copper absorption blockers such as zinc salts, are effective and have markedly modified the prognosis of WD [2]. Nevertheless, in patients with advanced disease and decompensated cirrhosis or fulminant liver failure, liver transplantation (LT) appears to be the only effective treatment [3–5]. In addition, the indications for LT in neurologically affected patients who do not improve under medication remain controversial [6,7].

Because few data are available in the field, the aim of the present study was to evaluate the long-term outcome of WD patients following LT, in a large French multicenter cohort and with particular focus on survival rates and late-onset complications.

Patients and methods

Study design

The medical records of 128 patients with a diagnosis of WD and who were transplanted in France between January 1985 and December 2009, were reviewed retrospectively; seven patients were excluded from the analysis because of missing data and/or an uncertain diagnosis. During the same period, 10,150 LT were performed in France (data available from the French Agence de la Biomédecine). The diagnosis of WD was based on the presence of liver disease and/or neurological symptoms and a combination of the following criteria: (1) positive family history, (2) low serum ceruloplasmin (<0.20 g/L), (3) elevated liver copper (>250 μg/g dry weight), (4) presence of the Kayser-Fleischer ring, (5) elevated baseline 24 h urinary copper excretion (>100 μg/24 h), (6) elevated 24 h urinary copper excretion following the administration of 2 × 500-mg doses of penicillamine (>1000 μg/24 h), and (7) Coombs' negative hemolytic anemia. The results on 24 h urinary copper excretion levels were not always available prior to transplant and the diagnosis could be made retrospectively according to the biological and pathological results, particularly in case of fulminant hepatic failure. Other causes of liver disease such as autoimmune liver disease, acute or chronic viral hepatitis, α1-anti-trypsin deficiency and other conditions were excluded by appropriate investigations [8,9].

In addition, a genetic mutational analysis for WD was available in 59 (46%) patients but was not usually used for the initial diagnosis, especially in cases of acute hepatic failure. Genomic DNA was extracted from whole venous blood samples. Whenever possible, SSCP and dHPLC analyses were performed, followed by sequencing of the 21 exons and their flanking introns.

Fulminant hepatic failure (FHF) was defined as the presentation in asymptomatic patients of evidence of acute liver injury and hepatic encephalopathy within 2 weeks of the onset of symptoms. A diagnosis of subfulminant hepatic failure (SFHF) was attributed to those asymptomatic patients who presented with evidence of acute liver hepatic injury and hepatic encephalopathy between 2 and 12 weeks after the onset of symptoms. FHF and SFHF patients without previously known underlying disease were analyzed in the **F-SF group**. Five patients with a diagnosis of WD who presented with FHF or SFHF after the discontinuation of their drug therapy were included in the same F-SF group because they shared the same presentation. Other patients suffered from either severe chronic liver disease (CLD) with or without neurological impairment (**CLD group**) or severe neurological symptoms unresponsive to drug therapy and were transplanted because of the neurological indication only, without any history of hepatic failure (**Neuro group**). Patients who were at home prior to the transplant were considered to have undergone an elective transplantation.

All patients received grafts from cadaveric or living donors. Their initial immunosuppressive regimen was based on a calcineurin-inhibitor (CNI): cyclosporine or tacrolimus. The patients also received 500 mg IV methylprednisolone after reperfusion. As from 1985, patients initially received cyclosporine (Sandimmun® or Neoral®, Novartis Pharma; Rueil-Malmaison, France) and were treated at a dose of 2.0–4.0 mg/kg/day orally in two divided intakes with target trough whole blood concentrations of 200–250 ng/ml for the first month post-transplant, followed by 100–200 ng/ml thereafter. Since 1996, patients may also have received tacrolimus (Prograf®, Astellas, Nanterre, France) initially, and were treated at a dose of 0.08–0.12 mg/kg/day orally in two divided intakes, with target trough whole blood concentrations of 10–15 ng/ml for the first month post-transplant, followed by 5–10 ng/ml thereafter. Starting on postoperative day 1, methylprednisolone was tapered from 200 to 20 mg within 5 days; thereafter, methylprednisolone was maintained at 20 mg/day and then tapered by 2.5 mg/month to reach a maintenance dose of 0–5 mg/day at 6 months post-transplantation. Azathioprin or mycophenolate mofetil (MMF) (since 1996) or sirolimus/everolimus (since 2002) was either administered as part of an initial triple immunosuppressive regimen, or introduced during follow-up as a maintenance immunosuppressive agent. Outpatient follow-up visits were usually ensured once a week during the first month after leaving hospital, twice a month during the second and third months, monthly during the first year, and every 3–6 months thereafter, regardless of the duration of the observation period after transplantation. Additional visits also were performed if necessitated by specific problems. Wide-ranging laboratory investigations, including hematology, liver parameters, coagulation, electrolytes, total protein, renal parameters, fast blood glucose, lipid profile, and blood CNI trough levels, were carried out at each visit.

Statistics

Statistical analysis was performed with SPSS 13.0. Survival rates were evaluated using the Kaplan-Meier method starting from the date of LT to that of death, the last clinical visit or the data cut-off point (February 1st, 2010); survival curves were compared using the log-rank test. Risk factors for death were analyzed by multivariate logistic regression. For multivariate analysis, categorical data were analyzed using the Chi-square or Fisher's exact test. Values in this paper are shown as median with ranges and mean ± SD. p values lower than or equal to 0.05 were considered to be statistically significant.

Results

Study population

This report concerns 75 adults (age >18 years) and 46 children who underwent LT for Wilson's disease between January 1985 and December 2009 in 18 different transplant centers throughout France. Each center performed a median of four transplants (range: 1–30). There were 64 patients in the F-SF group, 50 patients in the CLD group, and seven patients in the Neuro group. The clinical features and laboratory test findings for patients at the time of their listing for LT are summarized in Table 1. The median age of all patients was 22 years (range: 7–66), and 71 were female (59%). Thirty-eight percent of the patients were children. Sixty-nine percent of all patients, or 89% in the F-SF group (92% of those without any history of treatment discontinuation) and only 30% in the CLD group were transplanted during the first three decades of life (Fig. 1A and B). Patients with a fulminant or