P.O.Box 2345, Beijing 100023,China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

World J Gastroenterol 2003;9(12):2836-2838
World Journal of Gastroenterology
 ISSN 1007-9327

• CLINICAL RESEARCH •

Copper metabolism after living related liver transplantation for Wilson's disease

Xue-Hao Wang, Feng Cheng, Feng Zhang, Xiang-Cheng Li, Jian-Ming Qian, Lian-Bao Kong, Hao Zhang, Guo-Qiang Li

Xue-Hao Wang, Feng Cheng, Feng Zhang, Xiang-Cheng Li, Jian-Ming Qian, Lian-Bao Kong, Hao Zhang, Guo-Qiang Li, Liver Transplantation Center, First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China
Supported by the Basic Research Program Foundation of Jiangsu Province, No.BJ98025
Correspondence to: Feng Cheng, Liver Transplantation Center, First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, Jiangsu Province, China. docchengfeng@sohu.com
Telephone: +86-25-3718836-6476
Received: 2003-06-28 **Accepted:** 2003-08-16

Abstract

AIM: Liver transplantation is indicated for Wilson's disease (WD) patients with the fulminant form and end-stage liver failure. The aim of this study was to review our experience with living-related liver transplantation (LRLT) for WD.

METHODS: A retrospective review was made for WD undergoing LRLT at our hospital from January 2001 to Febuary 2003.

RESULTS: LRLT was carried out in 15 patients with WD, one of them had fulminant hepatic failure and the others had end-stage hepatic insufficiency. The mean age of the patients was 14.5±2.5 years (range 6 to 20 years). All the recipients had low serum ceruloplasmin levels with a mean value of 126.8±34.8 mg/L before transplantation. The serum ceruloplasmin levels increased to an average of 238.6±34.4 mg/L after LRLT at the latest evaluation, between 2 and 27 months after transplantation. A marked reduction in urinary copper excretion was observed in all the recipients after transplantation. Among the eight recipients with preoperative Kayser-Fleischer (K-F) rings, this abnormality resolved completely after LRLT in five patients and partially in three. All the recipients are alive and remain well, and none has developed signs of recurrent WD after a mean follow-up period of 15.4±9.3 months (range 2-27 months) except one who died of severe rejection. The donors were 14 mothers and 1 father. The serum ceruloplasmin levels were within normal limits in all the donors (mean: 220±22.4 mg/L). The mean donor age was 35.0±4.0 years (range, 30 to 45 years). Two donors had biliary leakage and required reoperation. Grafts were harvested as follows: four right lobe grafts without hepatic middle vein and eleven left lobe grafts with hepatic middle vein. The grafts were blood group-compatible in all recipents. Two patients had hepatic artery thrombosis and underwent retransplantation.

CONCLUSION: LRLT is a curative procedure in Wilson's disease manifested as fulminant hepatic failure and/or end-stage hepatic insufficiency. After liver transplantation, the serum ceruoplasmin level can increase to its normal range while urinary copper excretion decreases. Grafts chosen from heterozygote carriers do not appear to confer any risk of recurrence in recipients.

Wang XH, Cheng F, Zhang F, Li XC, Qian JM, Kong LB, Zhang H, Li GQ. Copper metabolism after living related liver transplantation for Wilson's disease. *World J Gastroenterol* 2003; 9(12): 2836-2838
http://www.wjgnet.com/1007-9327/9/2836.asp

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disease. Its clinical and pathological manifestations are the consequence of an excessive accumulation of copper in tissues, particularly in the liver, brain, cornea, and kidneys. Liver transplantation is indicated for fulminant form and end-stage liver disease of WD[1,2].Cadaveric liver transplantation has been reported to normalize copper metabolism in recipients[3,4]. Recently, LRLT has also been used for WD[5-14]. Asonuma *et al*[8] reported that LRLT from heterozygous carriers of the WD gene could also resolve clinical signs and symptoms of WD and correct the parameters of copper metabolism. In this study, we reported our experience with LRLT for hepatic complications of WD from January 2001 to February 2003.

MATERIALS AND METHODS

Clinical and laboratory data were obtained from a review of the files of patients from 2001 to 2003 at Liver Transplantation Center of Jiangsu Province. All treatments had an informed consent of the children' s parents and the approval of the Ethics Committee of Nanjing Medical University. Donors were selected based on blood type, liver function, negative serological test results(hepatitis B virus, hepatitis C,HIV),physical examination, psychosocial evaluation including alcohol abuse and liver volumes assessed by Doppler ultrasound equipment and computed tomography. The donors were 14 mothers and 1 father. The serum ceruloplasmin levels were within the normal limits in all donors (mean: 220±22.4 mg/L). The mean donor age was 35.0±4.0 years (range, 30 to 45 years). Serum ceruloplasmin and copper level were also normal in all donors who gave an informed consent.

The diagnosis of WD was maded on the basis of a combination of the findings, including hepatic and/or neurological clinical abnormalities ,the presence of Kayser-Fleischer rings (KFR), elevated 24-hr urine copper (>100 μg/24 hr), low cerulopasmin level (reference range 200-500 mg/L). The above mentioned routine laboratory data were obtained by using standard methods. No patient received any chelating agent and presented clinical signs of WD after LRLT.

Among the 15 patients with WD, one had fulminant hepatic failure and the others had end-stage hepatic insufficiency. Their mean age was 14.5±2.5years (range 6 to 20 years). Before transplantation, all recipients had a low serum ceruloplasmin level with a mean value of 126.8±34.8 mg/L and a high urinary copper excretion with a mean value of 1 825.6±187.4 μg/24 h. Eight recipients had preoperative Kayser-Fleischer (K-F) rings. Grafts were harvested as follows: four right lobe grafts without hepatic middle vein and eleven left lobe grafts with hepatic middle vein. The grafts were blood group-compatible in all recipents.

RESULTS

Donors

All the donors were discharged from the hospital after a mean hospital stay of 9-14 days, and then resumed their normal life without any significant adverse sequelae. Two complications of bile leaks occurred, and required reoperation.

Recipents

Two patients had hepatic artery thrombosis and underwent retransplantation. All the recipients enjoyed normal health with a good quality of life, and none had signs of recurrent WD after a mean follow-up period of 15.4±9.3 months (range 2-27 months). One patient died of severe rejection. Copper metabolism of the WD recipients and the presence of K-F rings were compared before and after transplantation. After LRLT, all the recipients had normal serum ceruloplasmin concentrations in the first month. Marked reduction of urinary copper excretion occurred in the first three months, which became normal 6-9 months after operation. Kayser-Fleischer (K-F) rings were resolved completely after LRLT in five patients and partially in three.

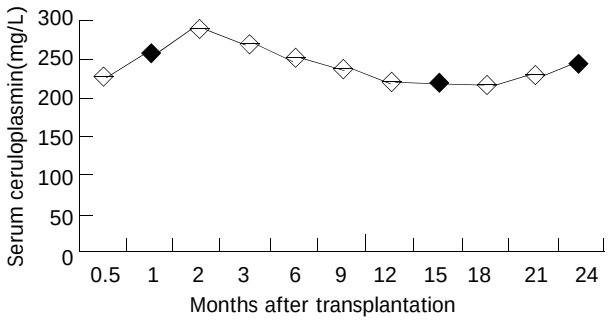

Figure 1 Changes in serum ceruloplasmin of postoperative recipients (Normal: 200-500 mg/L).

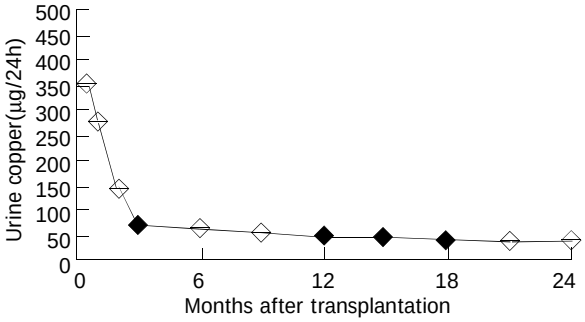

Figure 2 Changes in urine copper of postoperativ recipients (Normal: <50 μg/24 h).

DISCUSSION

Wilson's disease, first described by Kinnear Wilson in 1912, is an autosomal recessive condition with a prevalence in one of 30 000[15]. Its clinical and pathological manifestations are the consequence of an excessive accumulation of copper in tissues, particularly in the liver, brain, cornea, and kidneys. The WD gene is localized on the long arm of chromosome 13 and was recently cloned by several different research groups[16-19]. The gene product ATP7B is a copper transporting type ATPase. Establishing the diagnosis of Wilson's disease is usually straightforward if the major clinical and laboratory features are manifested as: typical hepatic and/or neurological symptoms and signs, Kayser-Fleischer rings, low serum caeruloplasmin concentrations, and increased urinary copper excretion.

It has been reported that the prognosis of fulminant WD is extremely poor and liver transplantation is currently the only available form of curative therapy when penicillamine therapy has failed or is no longer appropriate[20-22]. Cadaveric liver transplantation has been reported to normalize copper metabolism in recipients[3,4]. As scarcity of cadaveric donors is a serious problem in many countries, LRLT represents a critical form of rescue therapy in endstage liver disease. Recently, because of the shortage of donors for cadaveric liver transplantation, LRLT has also been indicated for WD[5-14]. Asonuma *et al*[8] reported that LRLT from heterozygous carriers of the WD gene could also resolve clinical signs and symptoms of WD and correct the parameters of copper metabolism.

The advantage of LRLT is that the donor liver can be obtained in an urgent situation when conservative therapy has failed. A successful transplantation of a liver from a living donor was performed in Australia in 1989 by Strong and colleagues[23], and the technique had been practised worldwide now, particularly in countries where cadaveric organs are not available. In general, the most important ethical dilemma with LRLT is that the process subjects a healthy person to a major operation. More than 1500 such surgeries in children have been performed throughout the world. Only two donors died. One died from pulmonary embolism, and the other died from an anesthetic accident. The patient with pulmonary embolisms was probably a poor surgical candidate. In neither case were there any technical complications related to the procedure. Both cases showed the importance of donor evaluation and selection in preventing living donor mortalities. In this study, 15 donors were discharged from the hospital and all resumed their normal life style without any significant adverse sequelae after a mean hospital stay of 15 days after the operation. Two complications of bile leakage occurred, and required a relaparotomy. The results, along with those from other centers, confirmed the general safety of the donor operation[24,25]. Hepatic arterial reconstruction is one of the most difficult procedures in living-donor liver transplantation (LDLT) because the artery used is generally small in diameter and has a short stalk. If hepatic artery thrombosis (HAT) occurred, the recipient clinical course would be unstable[26-30]. The introduction of microvascular hepatic arterial reconstruction has significantly decreased the incidence of HAT. In our group, HATs were recognized in 2 cases (13 %), retransplantations saved the patients. So surgeons who perform hepatic arterial reconstruction in LDLT should be well trained in microvascular techniques to decrease the incidence of HAT.

In this study, Copper metabolism in the WD recipients and the presence of K-F rings were compared before and after transplantation. After LRLT, all the recipients had a normal serum ceruloplasmin concentration and marked reduction in urinary copper excretion. All the donor ceruloplasmin levels were within the normal range, as were the post-transplant levels in the recipients. In addition to normal laboratory profiles of copper abnormalities, five out of eight patients with Kayser-Fleischer rings had a complete resolution and the remaining three showed improvement following transplantation. Despite these results, it is important to remember that about 10 % of WD heterozygotes would have low ceruloplasmin levels, so that they might be unsuitable as donors[31]. Based on the findings of this study, living related liver transplantation can be used safely in WD when appropriate cadaveric organs are unavailable. Despite the excellent results of the reported cases, there are some questions to be studied ,such as screening of potential WD heterozygote donors for uncommon abnormalities of copper metabolism, *etc*.

Furthermore, it is still unclear whether de-coppering after LRLT from heterozygote donors is slower than de-coppering after cadaveric transplantation from non-related donors. We

are reassured, however, by the fact that none of our transplanted recipients had persistent neurological abnormalities after LRLT, and K-F rings disappeared in most of the recipients, indicating that LRLT was indeed an effective and safe modality of therapy for patients with Wilsonian fulminant hepatic failure and end-stage hepatic insufficiency. After liver transplantation, serum ceruoplasmin level increased to normal range and urinary copper excretion decreased. Grafts chosen from heterozygote carriers did not appear to confer any risk of recurrence in the recipients, at least in the short term. Long-term follow-up should be continued to evaluate this specific therapy.

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Edited by Xu JY and Wang XL