Can the liver with Gilbert's syndrome be used as graft of living-related liver transplantation?

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Abstract: Gilbert's syndrome is the common cause of non hemolytic unconjugated hyperbilirubinemia with a prevalance of 3〜7%. Gilbert's syndrome may introduce a selection of potential liver donors from brain death patients. We present a case of living-related liver transplantation (LRLT) from a donor with Gilbert's syndrome. A 22-year-old woman had been diagnosed as having liver cirrhosis at the age of 5. She underwent liver transplantation with the donor's left lobe as the graft. The donor, who was the father of the patient, had been diagnosed with Gilbert's syndrome. Although the recipient was well until 11 months after surgery, she died of subacute fulminant hepatitis 16 months after surgery. However, it was clear that the liver with Gilbert's syndrome could be used as a graft of living-related liver transplantation for adult recipients. J. Med. Invest. 44 : 219-221, 1998

Key Words : Gilbert's syndrome, hyperbilirubinemia, unconjugated bilirubin, living-ralated liver transplantation

INTRODUCTION

Gilbert's syndrome is a common cause of benign hyperbilirubinemia in the general population. It was first described by Augustin Nicolas Gilbert and co-workers in 1900 (1). Clinically manifest Gilbert's syndrome with a stable elevated serum unconjugated hyperbilirubinemia, or with unconjugated hyperbilirubinemia after a 24-h fast, occurs with a frequency varying between 2% and 12% (2-6). Although there are various possible causes of hyperbilirubinemia after liver transplantation, for example, during episodes of rejection, cholestasis, cholangitis or hemolysis, Gilbert's syndrome should be considered an additional potential cause. However, in case of liver transplantation from a cadaveric body, it is impossible to diagnose the donor as Gilbert's syndrome. We have not been able to identify any report in which donor was diagnosed as Gilbert's syndrome before liver trnasplantation. We only found reports in which the donor was suspected as Gilbert's syndrome after diagnosis as Gilbert's syndrome for a recipient after cadaveric liver transplantation (7-10). There is no information on whether a liver with Gilbert's syndrome can be used as a graft of living-related liver transplantation. We describe the clinical course of an adult patient who underwent living-related liver transplantation (LRLT) from a donor who was diagnosed as Gilbert's syndrome before operation.

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CASE REPORT

Donor : The patient's 57-year-old father was the candidate for LRLT. Although histological findings in the preoperative liver biopsy specimens showed slight fatty infiltration, his efforts to reduce caloric intake resulted in successful improvement fatty infiltration of the liver within 6 months. Preoperative his hepatic function was normal except for hyperbilirubinemia. Laboratory data showed alanine aminotransferase(ALT) 10 international units(IU)/L (normal, 3-30IU/L), aspartate aminotransferase(AST) 12IU/L (normal, 10-30 IU/L), alkaline phosphatase(ALP) 147 IU/L (normal, 81-231 IU/L), lactic dehydrogenase(LDH) 270 IU/L (normal, 237-454 IU/L), γ-glutamyl transpeptidase(γ-GTP) 37 IU/L (normal, 7-22 IU/L), cholinesterase 349 IU/L (normal, 200-460 IU/L), total bilirubin 2.3 mg/dl (normal, 0.1-1.0 mg/dl), conjugated bilirubin 0.3 mg/dl (normal, 0-0.4 mg/dl), total protein 6.7g/dl (normal, 6.3-8.2g/dl) and serum albumin 4.0 g/dl (normal, 3.5-5.1 g/dl). He was diagnosed as Gilbert's syndrome because of an increase of unconjugated serum bilirubin during low caloric intake (Fig.1) and nicotinic acid test (Fig.2). The standard liver volume for the patient was calculated to be 900 ml on the basis of body weight. Volumetric analysis with computed tomography revealed that the left lobe volume of the donor's liver was 512 ml, corresponding to 56% of the recipient standard liver volume.

Recipient : A 22-year-old woman had been diagnosed as having liver cirrhosis at the age of 5. She had undergone devascularization and transection of the esophagus, and splenectomy for esophageal varices at the age of 8. Complications such as spontaneous bacterial peritonitis

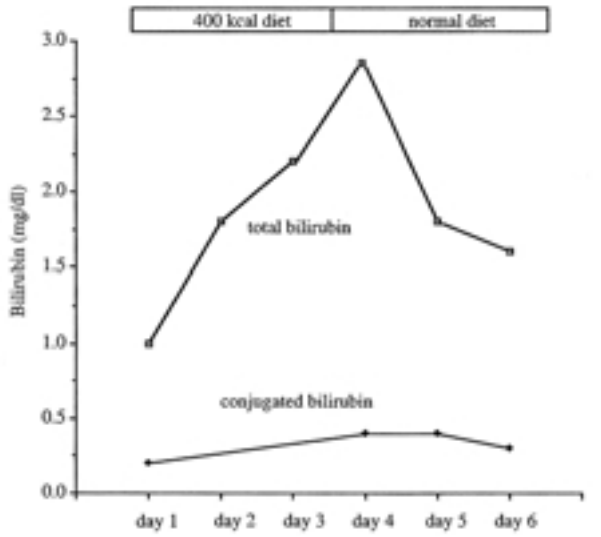

Fig.1. Low caloric intake test : Bilirubin levels after 3 days under 400 kcal diet. Total bilirubin levels increased within 72 hours up to 2.8 mg/dl due to increase of unconjugated bilirubin.

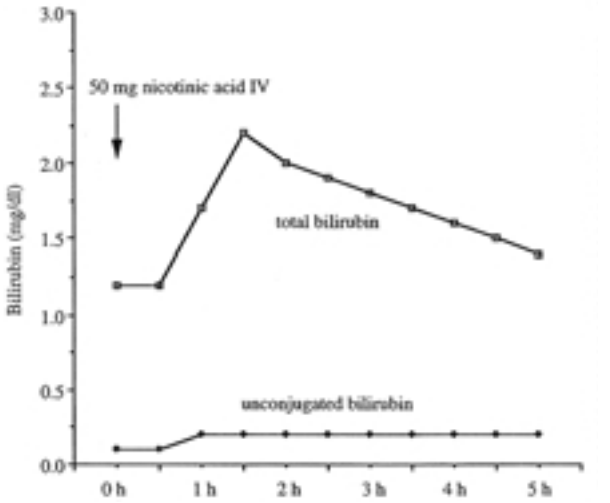

Fig. 2 . Nicotinic acid test : IV administration of 50mg nicotinic acid. Unconjugated bilirubin levels increased within 2 hours up to 2.2 mg/dl due to increase of unconjugated bilirubin.

and nonspecific colitis sometimes appeared from 17 years old, and icterus and ascites had appeared on all such occasions. These complications frequently occured from 22 years old. Laboratory data before liver transplantation showed ALT 129 IU/L (normal, 3-30 IU/L), AST 141 IU/L (normal, 10-30 IU/L), ALP 1316 IU/L (normal, 81-231 IU/L), LDH 457 IU/L (normal, 237-454 IU/L), γ-GTP 446 IU/L (normal, 7-22 IU/L), cholinesterase 137 IU/L (normal, 200-460IU/L), total bilirubin 6.5mg/dl (normal, 0.1-1.0mg/dl), conjugated bilirubin 4.2 mg/dl (normal, 0-0.4 mg/dl), total protein 8.0 g/dl (normal, 6.3-8.2 g/dl) and serum albumin 2.8 g/dl (normal, 3.5-5.1 g/dl).

The patient and her family members were informed that LRLT might be possible, and they indicated that the patient's 57-year-old father was willing to act as the donor. This proporsal was submitted to the ethical committee of The University of Tokushima, School of Medicine and was accepted.

On March 28 th, 1995, the patient underwent LRLT with the donor's left lobe as the graft. The graft weight was 440g and the graft corresponded to 49% of the recipient's standard liver volume. Volumetric analysis showed rapid enlargement of graft to 683ml as early as one week after the operation. Although the recipient had acute rejection and stenosis of hepaticojejunostomy within 6months, unconjugated bilirubin-dominant hyperbilirubineia never appeared. The recipient was well until 11 months after surgery. Changes of ALP, ALT, AST and bilirubin in the recipient within 4 weeks after operation are shown in Figures 3 and 4. Although she suffered from acute hepatitis due to Hepatitis B virus and died of subacute fulminant hepatitis 16 months after liver transplantation, the recipient had kept good liver function up to 1 year. Postoperative course of the donor was uneventful and he returned to work after dischraging from the hospital.

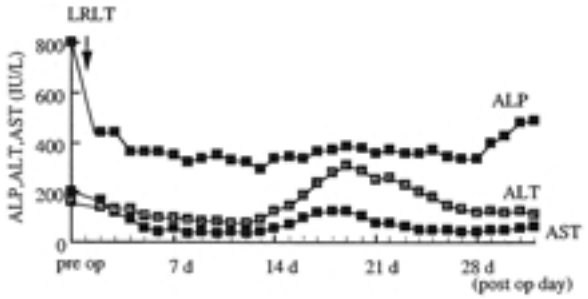

Fig.3. Changes of ALP, ALT and AST : Alkaline phosphatase (ALP), alanine aminotransferas(ALT) and aspartate aminotransferase(AST) levels in serum gradually decreased, but not within normal range in 1 month after LRLT.

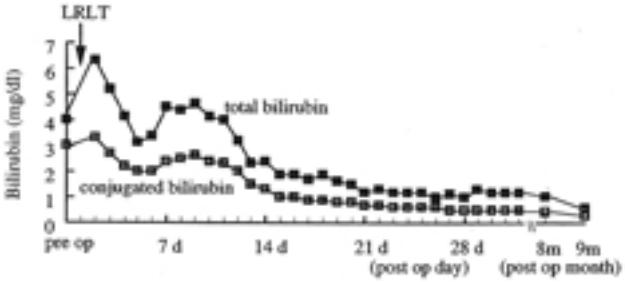

Fig.4. Changes of bilirubin : Bilirubin levels in serum decreased after LRLT and unconjugated hyperbilirubinemia never appeared.

DISCUSSION

Estimates of the prevalence of Gilbert's syndrome range from 3% to 7% in the general population, and up to 12% in the male population (11, 12). Gilbert's syndrome can be transferred from the donor to a recipient. The reason why it seems that the prevalence of Gilbert's syndrome in the post liver-transplant population is significantly lower than in the general population is that in case of cadaveric liver transplantation, an unexplained hyperbilirubinemia in a potential donor may cause the transplant team to reject a potential donor (10). Furthermore, because brain death donors at the time of organ donation usually are on ventilators and have many complications in intensive care

units, it is very difficult for the transplant team to diagnose donors as Gilbert's syndrome.

In case of cadaveric liver transplantation, the diagnosis that the donor was Gilbert's syndrome is only speculation from the fact that the recipient was diagnosed as Gilbert's syndrome after liver transplantation. However, in case of LRLT, the donor can be diagnosed as Gilbert's syndrome before the operation from an increase in unconjugated bilirubin levels during low caloric intake and nicotinic acid test. But now, it is not clear whether the liver with Gilbert's syndrome can be used as a graft or not. Gates reported that those recipients who did seem to have Gilbert's syndrome had excellent long term survival and completely normal graft function by analysis of 3 patients with Gilbert's syndrome out of their 229 post-transplant patients (10). However, a report in which one case whose total and conjugated bilirubin levels were 1.5 and 0.6 mg/dl, respectively, was diagnosed as having Gilbert's syndrome, which eliminated him as a candidate (13). They also mentioned that in accordance with their policy to make every effort to avoid any possible postoperative increase in serum bilirubin level, even though the other liver function tests for the donor candidate were completely normal, they were compelled to pass over the primary candidate for the secondary one (13). However, they are changing their opinion to relaxing their guidelines for donor selection, because slight elevation of serum bilirubin poses little direct hazard to the living-related liver transplantation from their experiences. In our case, if possible, we selected the patient's mother instead of the father as a donor. But the mother could not be a donor because she sufferred from primary biliary cirrhosis. We think that intermittent hyperbilirubinemia caused by Gilbert's syndrome in the recipient does not lead to poor outcome of LRLT because patients with Gilbert's syndrome have no damage in the liver, as in our patient's donor. Furthermore, hyperbilirubinemia due to Gilbert's syndrome does not always appear in the recipient, as in our case.

In a recent study, it was shown that patients with Gilbert's syndrome had an $A(TA)_7$ TAA instead of an $A(TA)_6$ TAA sequence in the bilirubin UDP-glucuronosyltransferase-gene promotor region on both alleles. It is possible that a liver from a donor with the $A(TA)_7TAA/A(TA)_7TAA$ genotype causes clinically manifest Gilbert's syndrome in the recipient (14). Jansen also mentioned that a liver with Gilbert's syndrome genotype usually has few consequences for the recipient and an isolated unconjugated bilirubin serum level in the donor is no reason not to use that liver for organ donation (14). Although, in our case, the donor was diagnosed as Gilbert's syndrome by both 3-day low caloric test and nicotinic acid test, our recipient did not clinically manifest Gilbert's syndrome, probably because the expression of Gilbert's syndrome is influenced by food intake, cigarette smoking, alcohol consumption, medication and the fat content of the diet in addition to the promotor region abnormality.

We conclude that the liver with Gilbert's syndrome can be used as a graft of living-related liver transplantation. However, it is very important for the transplant surgeons to be aware that Gilbert's syndrome can be transferred from the donor to a recipient because unexplained post-transplant hyperbilirubinemia causes confusion and gives a complicated evaluation to the recipient.

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