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Can an Extended Right Lobe be Harvested from a Donor with Gilbert's Syndrome for Living-Donor Liver Transplantation? Case Report

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ABSTRACT

Gilbert's syndrome (GS) is a common cause of inherited benign unconjugated hyperbilirubinemia that occurs in the absence of overt hemolysis, other liver function test abnormalities, and structural liver disease. GS may not affect a patient's selection for living-donor liver transplantation (LDLT). Between February 2005 and April 2011, 446 LDLT procedures were performed at our institution. Two of the 446 living liver donors were diagnosed with GS. Both donors underwent extended right hepatectomies, and donors and recipients experienced no problem in the postoperative period. Their serum bilirubin levels returned to the normal range within 1–2 weeks postoperatively. In our opinion, extended right hepatectomy can be performed safely in living liver donors with GS if appropriate conditions are met and remnant volume is >30%. Livers with GS can be used successfully as grafts in LDLT recipients.

LIVER transplantation (LT) is considered to be the main therapeutic option for adult and pediatric patients with various liver diseases.[1] Although most transplantation operations undertaken in North America and Europe have been supplied by cadaveric donor pools, living donors constitute a large part of the donor pool in Turkey and several Asian countries.[2] Living donors are the sole suppliers of liver transplants in countries with insufficient cadaveric donor pools. Significant levels of morbidity and mortality associated with hepatectomy procedures undertaken in living donors may cause serious ethical and legal problems for surgeons and operation centers, given that donation is a voluntary and charitable act. With a few trivial exceptions, the criteria for living donor candidacy are similar in most countries where living-donor liver transplantation (LDLT) is undertaken. Numerous biochemical, hematologic, and serological tests, including the measurement of serum bilirubin level, have been cited as the first step of potential donor evaluation.[3,4] Hence, serum bilirubin level appears to be an important factor in the identification of living donor candidates.[4]

Under normal circumstances, serum bilirubin level is within the normal range in healthy subjects. The evaluation of living donor candidates in whom isolated hyperbilirubinemia has been detected can be challenging for surgeons. Conditions such as Gilbert's syndrome (GS), which causes subclinical unconjugated hyperbilirubinemia in a certain proportion of the general population, should be included in the differential diagnosis of this condition.

GS is a benign unconjugated hyperbilirubinemia that occurs in the absence of structural liver disease and overt hemolysis characterized by intermittent mild jaundice. In patients with GS, unconjugated hyperbilirubinemia occurs intermittently upon exposure to various types of stress, such as surgical intervention, fatigue, and/or poor diet.[4] Other liver function tests are normal, and no hemolysis or structural liver disease is present.[4–6] GS is genetically characterized by an extra TA element in the TATAA box of the promotor region upstream of the bilirubin uridine diphosphate-glucuronosyltransferase (UGT-1A1) coding region.[7] In this article, we aimed to determine whether extended right hepatectomy could be performed in LDLT donors with GS if appropriate conditions are met.

PATIENTS AND METHODS

Between February 2005 and April 2011, 446 LDLT procedures were performed at our institution. Two of the 446 donors (0.4%)

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had been previously diagnosed with GS at other medical centers. Meticulous biochemical analyses, performed both at our center and at others, revealed no pathology other than unconjugated hyperbilirubinemia in these 2 donor candidates. Ultrasonography (US) and computed tomography (CT) angiography were used in both cases to preoperatively evaluate parenchymal and vascular architectures, respectively. In both preoperative US-guided liver biopsies, no pathology other than <1% hepatosteatosis was detected. Following the depiction of the intrahepatic bile duct anatomy by intraoperative cholangiography, extended right donor hepatectomy procedures were performed by the same surgeon. A Cavitron Ultra-Sonic Aspirator (CUSA Excel; Integra, New Jersey, United States) was used during parenchymal transection, and the Pringle maneuver was applied at 20-minute intervals to minimize blood loss. Table 1 summarizes the preoperative and postoperative bilirubin levels of the donors and recipients.

RESULTS

Donor 1

A 21-year-old woman donor candidate (weight, 59 kg; height, 156 cm; body mass index [BMI], 24.2 kg/m^2) had been previously diagnosed with GS at another center. Viral markers for hepatitis A, B, and C were negative, and the serum total bilirubin level was 2.2 mg/dL, consisting mainly of the unconjugated form. Other liver function test results were normal. Liver volume was calculated using volumetric multi-slice CT; total volume was 1296 cm^3, right-lobe volume was 847 cm^3, and left-lobe volume was 449 cm^3. Remnant liver volume was 34.6% of total volume, and hepatosteatosis was <1%. A CT angiographic image of the vein in segment 4b is shown in Figure 1. After intraoperative cholangiography, a right-liver donor hepatectomy including the middle hepatic vein (MHV) was performed. The bloodless graft weight was 800 g, and the graft/recipient weight ratio (GRWR) was 1%. The donor's postoperative course was uneventful, and she returned to work after being discharged from the hospital.

The recipient was a 47-year-old man (weight, 77 kg; height, 173 cm; BMI, 24.2 kg/m^2) with end-stage liver failure due to hepatitis B virus (HBV) infection. His Child-Pugh score was 13 (class C), and his Model for End-Stage Liver Disease (MELD) score was 25. The recipient underwent LDLT with the donor's right lobe (800 g) as the graft. The recipient has been well to date, with no complication and a normal bilirubin level.

Table 1. Bilirubin Levels of Both Donors and Recipients

		Donor		Recipient	
Cases	Day	Total bil (mg/dL)	Indirect bil (mg/dL)	Total bil (mg/dL)	Indirect bil (mg/dL)
1	Preop	2.2	1.8	—	—
	Postop 1	2	1.3	13.9	7.2
	Postop 2	4.1	3.7	19.3	10.2
	Postop 7	0.6	0.3	17.9	6.1
	Postop 26	—	—	3.1	2.7
2	Preop	3.4	2.9	—	—
	Postop 1	4.6	4.1	3.1	2.7
	Postop 2	6.2	5.8	4.8	4.2
	Postop 8	1.6	0.7	1.6	0.8
	Postop 33	—	—	0.9	0.4

Abbreviations: bil, bilirubin; Preop, preoperative; Postop, postoperative.

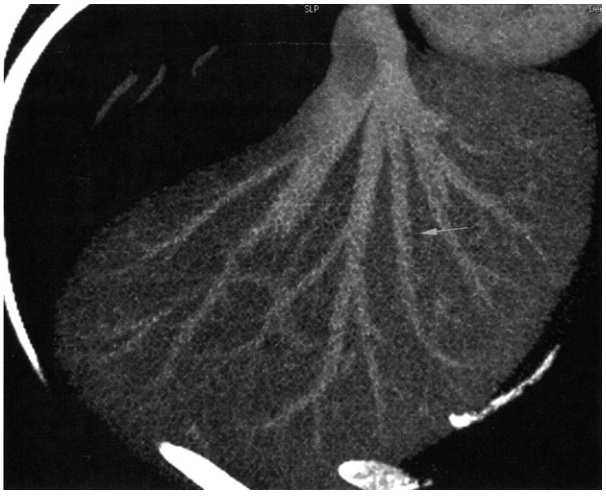

Fig 1. CT angiographic image of segment 4b vein.

Donor 2

A 20-year-old man donor candidate (weight, 53 kg; height, 174 cm; BMI, 17.3 kg/m^2) had been previously diagnosed with GS at another center. Viral markers for hepatitis A, B, and C were negative, and the serum total bilirubin level was 3.4 mg/dL, consisting mainly of the unconjugated form. Other liver function test results were normal. Liver volume was calculated using volumetric multi-slice CT; total volume was 988 cm^3, right-lobe volume was 641 cm^3, and left-lobe volume was 347 cm^3. Remnant liver volume was 35% of total volume, and hepatosteatosis was <1%. After intraoperative cholangiography, a right-liver donor hepatectomy including the MHV was performed (Fig 2). The bloodless graft weight was 655 g, and the GRWR was 1.1%.

Fig 2. Intraoperative view of MHV.

The donor's postoperative course was uneventful, and he returned to work after being discharged from the hospital.

The recipient was a 56-year-old man (weight, 60 kg; height, 168 cm; BMI, 21.3 kg/m^2) with hepatocellular carcinoma (HCC) resulting from liver cirrhosis due to HBV infection. His Child-Pugh score was 8 (class B), and his MELD score was 12. The preoperative alpha-fetoprotein (AFP) level was 612 IU/mL. HCC was diagnosed using multi-slice CT and the Milan criteria. The recipient underwent LDLT with the donor's right lobe (655 g) as the graft. The recipient has been well to date, with no complication or HCC recurrence and a normal bilirubin level.

DISCUSSION

The use of LDLT is rapidly increasing, and it has become a mainstream therapeutic alternative to cadaveric-donor LT for patients with end-stage liver disease and/or acute liver failure.[8,9] LDLTs constitute more than half of all LTs in most Asian countries, with Turkey ranking first. In our clinic, LDLTS constitute 76.3% of all orthotopic LTs performed to date. Donor safety is given primary emphasis at centers performing LDLTs, and the selection of living donor candidates is supposed to be systematic and based on a certain algorithm. Serum bilirubin level is an essential factor in the first step of evaluating living liver donor candidates.[3,10]

Isolated unconjugated hyperbilirubinemia can be defined as the repeated observation of total serum bilirubin concentrations that clearly exceed those found in normal individuals of the same age and gender, with direct-reacting bilirubin comprising <15%–20% of the total. Clinical forms of this condition vary widely from mild asymptomatic hyperbilirubinemia, as in GS, to severe forms frequently associated with kernicterus, as in Crigler-Najjar syndrome.[6]

GS is an autosomal-recessive condition with incomplete penetrance that was first described by Augustin Nicolas Gilbert in 1900.[5,8] It is a common cause of inherited benign unconjugated hyperbilirubinemia that occurs in the absence of hemolysis or underlying liver disease. GS is clinically apparent in 2%–13% of the general population and occurs more frequently in males than in females; ethnic differences in the incidence of GS have not been clarified[4,5,7,8]

As a rule, GS can be diagnosed by a thorough history and physical examination and can be confirmed using standard blood tests. Genetic testing can also confirm the diagnosis, although such testing is not widely available and is generally not required. The clinical diagnosis of GS is often based on the presence of mild unconjugated hyperbilirubinemia and/or intermittent jaundice occurring in the absence of hemolysis and other liver function test abnormalities. The generally accepted serum bilirubin level ranges from 1.0–6.0 mg/dL, consisting mainly of the unconjugated form.[8,11,12] The diagnosis may be confirmed by a 2-fold or greater increase in the serum bilirubin level in comparison with the baseline level after a 24-hour period of restricted diet or the intravenous administration of nicotinic acid.[8] This form of hyperbilirubinemia has been mainly attributed to a decrease in UGT-1A1 activity to 25%–30% of normal levels, leading to a reduction in bilirubin glucuronidation.[8,13] Having excluded other possible causes through differential diagnoses, we intended to perform genetic analysis in the 2 donors presented here; however, we could not find a center to provide support for such analysis.

Chisuva et al[9] identified GS in 7/11 donors with total bilirubin levels >2 mg/dL. No complication was reported in donors or recipients after LDLTs using donors with GS. In a retrospective analysis of 71 LDLTs, Kaneko et al[4] confirmed the presence of a defective UGT1A1 gene in 6 donor candidates suspected to have GS. No complication was documented following LDLT in these 6 donors or recipients. The authors concluded that the presence of GS was not a justifiable contraindication for LDLT and that livers from donors with GS could be implanted safely in recipients. They further advised that genetic analyses be undertaken during preoperative examination to confirm the presence of suspected GC in potential liver donor candidates.

Hyperbilirubinemia in liver transplant recipients may be puzzling and often prompts several investigations to rule out consequences such as rejection, cholestasis, cholangitis, viral infection, or hemolysis. The transfer of GS in the donor liver is another possible cause of hyperbilirubinemia. Kaneko et al.[4] used genetic analyses to document the development of GS in 3/6 recipients of liver grafts from donors with GS. Similarly, Te et al[8] detected mutations in the liver tissues of 5 recipients who developed benign hyperbilirubinemia following LT. Taken together, these findings suggest that the UGT-1A1 gene defect that is responsible for the genesis of GS can be transmitted from donors to recipients, manifesting as unconjugated hyperbilirubinemia in the recipients.

Within the scope of the current study, we think it would be appropriate to briefly discuss the extent of hepatectomy procedures undertaken in donors with known GS. A remnant liver volume of 28%–30% is widely considered to be acceptable for transplant surgery in otherwise healthy subjects. After providing the donor with a safe remnant liver volume, the harvesting of the MHV with a right hepatectomy is the most appropriate approach to ensure optimal drainage and a GRWR of ~1%.[14,15] In our experience, the addition of the MHV to the right hepatectomy graft is not a risky procedure in donors with a remnant hepatic volume >30% and pathological hepatosteatosis <5%. This remnant liver volume requirement can also be used for donors with GS, although perhaps not as strictly. In compliance with these principles, we performed extended right hepatectomies in both cases presented here.

In conclusion, livers from donors with GS can be used as grafts in LDLT. However, to avoid confusion and complicated evaluations caused by posttransplantation hyperbilirubinemia, the transplantation surgeon must be aware that GS can be transferred from the donor to the recipient.

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