Transpl Int (2003) 16: 879–884
DOI 10.1007/s00147-003-0613-3

CASE REPORT

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Glycogenosis storage type I diseases and evolutive adenomatosis: an indication for liver transplantation

Received: 21 August 2002
Revised: 20 December 2002
Accepted: 20 December 2002
Published online: 7 August 2003

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Abstract We report on two cases of type I glycogen storage disease (GSD) complicated by malignant tumors. A 23-year-old man had GSD Ia with adenomatosis. He underwent transplantation for rapidly growing and radiologically changing adenomata. At histological examination, one adenoma had become a hepatocellular carcinoma. A 22-year-old, HBV-infected woman had GSD type Ib with adenomatosis. At follow-up, several tumors showed changing morphological characteristics. Pre-transplant laparotomy confirmed the presence of a metastatic cholangiocarcinoma. Liver transplantation should be considered in GSD type I patients with adenomatosis, especially when tumor characteristics change. Regular detailed Doppler ultrasound and magnetic nuclear resonance screening during childhood and adolescence are, therefore, mandatory in order for the timing of transplantation to be optimized.

Keywords Glycogen storage disease type I · Liver adenoma · Adenomatosis · Hepatocellular cancer · Liver transplantation · Cholangiocellular cancer

Introduction

Glycogen storage diseases (GSDs) are inherited disorders characterized by excessive intracellular accumulation of glycogen. GSD type I, or von Gierke's disease, is one of the most common types of liver glycogenosis [1, 2, 3].

Despite major progress in medical treatment, GSD type I remains associated with the development of hepatocellular adenoma(ta) and carcinoma. The development of potentially malignant liver tumors makes these young patients eligible for liver transplantation (LT) [2]. We report here on the evolution of GSD types Ia and Ib, complicated by malignant tumor (trans)formation.

Materials and methods

Between February 1983 and March 2002, three children and one adult (4/1,055 patients—0.38%) successfully underwent transplantation at our institute for GSD type Ia (Table 1). Indications for LT were: unresponsiveness to medical therapy in a 7-year-old boy [4]; non-compliance with medical therapy in a 13-year-old girl presenting with adenomatosis; adenomatosis and growth retardation in a 14-year-old girl; degenerating adenomatosis in a 23-year-old man. A 22-two-year-old woman with GSD type Ib and adenomatosis could not undergo transplantation because of diffuse extrahepatic malignant tumor spread. The two latter patients are discussed in detail because of the relevance to the timing of LT.

Case 1

A 23-year-old man was referred for LT for GSD type I and adenomatosis. GSD had been diagnosed when he was only a few weeks old, presenting as recurrent hypoglycemia and hepatosplenomegaly. Family history revealed that a male sibling had died from infection at the age of 1.5 years. The patient had shown significant growth and pubertal retardation. At the age of 16, he showed a growth profile and osseous age corresponding to that of a 10-year-old child (135 cm <P3; 28.5 kg <P3). He developed chronic acidosis (lactic acid up to 12 mmol.), hyperlipidemia, and hyperuricemia. Ultrasound (US) examination revealed enlarged kidneys.

Due to his fear of undergoing a liver biopsy, which had been suggested in order for a definitive diagnosis to be made, he refused further medical follow-up. He re-presented at the age of 16.3 years as he was worried about his height and sexual retardation. By the age of 18, his height was only 129 cm, and he finally agreed to adequate nutritional therapy. Nightly raw starch supplementation was commenced, which normalized his glycemia and lactic and uric acid levels. He started working full-time at night in order to comply with his diet and, most importantly, to improve his quality of life. Six months later, he was admitted for the first time to the transplant unit. Clinical examination revealed marked hepatomegaly and collateral venous circulation. His weight was 30 kg (<P3) and his height was 135 cm (<P3). Doppler-US (DUS) confirmed the presence of adenomata; the right kidney was hyperechogenic, indicating probable glycogenic renal infiltration. Magnetic nuclear resonance imaging and a CT scan of the liver showed several encapsulated liver tumors that were taking up contrast medium (Fig. 1). Bone X-ray showed poor global density; osseous age was calculated to be that of an 11-year-old. Diagnosis of GSD type I was confirmed by liver biopsy.

Table 1 Université Catholique de Louvain liver-transplant experience in GSD type Ia (*OLT* orthotopic liver transplantation, *PB-LT* piggy-back implantation with inferior vena cava preservation)

Gender	Age (years)	Adequate medical treatment	Indication	Liver weight (g)	Graft type	Metabolic correction	Follow-up (months)	Outcome	Current immunosuppression
M	7	Yes	Unresponsiveness to medical therapy; growth retardation; cardiac insufficiency due to glycogenosis	2,880	Whole-liver classical OLT using ABO incompatible graft (OLT 39)	+	195	Hepatic artery thrombosis; re-OLT excellent; late anastomotic biliary stricture; hepaticojejunostomy	Cyclosporine–azathioprine
M	23	No	Impaired quality of life; adenomatosis; Malignancy confirmed at pathological examination; growth retardation	2,150	Whole-liver PB-LT; (OLT 876)	+	72	Late portal vein thrombosis; meso-portal shunt; excellent; chronic, non-specific hepatitis	Cyclosporine–azathioprine
F	14	Yes	Adenomatosis; growth retardation	2,335	Left split liver; PB-LT; (OLT 1073)	+	28	Excellent	Tacrolimus–steroids
F	13	No	Metabolic complications due to lack of compliance to medical therapy; three adenomata	2,400	Whole-liver PB-LT; (OLT 1096)	+	24	Excellent	Tacrolimus–steroids

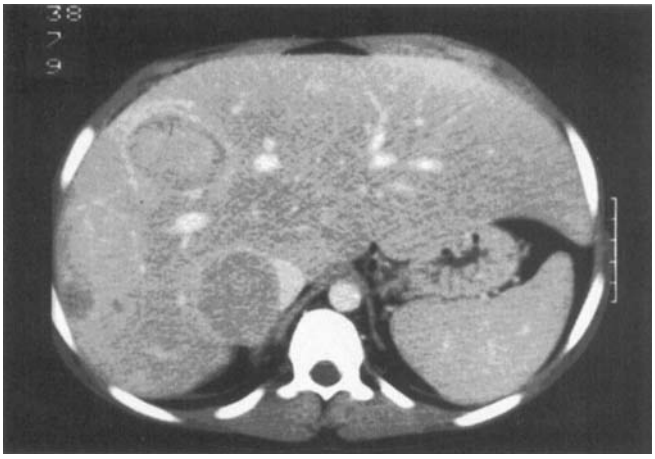

Fig. 1 CT scan showing several adenomata in GSD type Ia liver disease. One adenoma compresses the right hepatic vein and intrahepatic vena cava

Over 2.5 years of adequate nutritional therapy, he grew from 129 to 149.5 cm, and his weight rose from 33.8 to 41.5 kg. Pubertal development remained retarded (stage Tanner II). DUS of the liver showed a changed pattern in the parenchyma; the adenomatous lesions had grown but remained well encapsulated. The biggest lesion however, localized in segment IV, showed enhanced central arterial vascularisation. Due to this finding, US-guided biopsy and cytology of this lesion were performed, and the results were compatible with adenoma. Tumor markers (αFP, CEA, CA 19.9) remained negative throughout follow-up. In view of the possible degenerative signs of the main liver tumor and his poor quality of life, the patient himself requested a radical solution.

He underwent transplantation at the age of 23.6; at that time his height was 166 cm and his weight was 45 kg. LT was performed with preservation of the inferior vena cava. Histological examination of the hepatectomy specimen confirmed GSD type Ia and polyadenomatosis. The liver weighted 2,150 g. All tumors but one had the typical appearance of an adenoma. The largest adenoma corresponded to hepatocellular carcinoma (HCCA) with loss of the reticulin network (Fig. 2). Late post-LT follow-up was complicated by portal vein thrombosis that was corrected by mesenterico-portal shunting. Six years post-LT, he is alive and extremely well on cyclosporine monotherapy. Freedom from metabolic disturbances and nocturnal feeding has given him an optimal quality of life (WHO status I and Karnofsky score of 90%). Height and weight remained identical throughout the post-LT period.

Case 2

A 22-year-old woman had been diagnosed with GSD type Ib at the age of 11 months. She was hospitalized at 6 months of age with a rubella infection; at that time, hepatomegaly with venous collateral circulation was noted. US showed hepatomegaly and nephromegaly. At the age of 2.2 years, she presented with severe hypoglycemia, severe developmental retardation, hematuria, and frequent urinary infections. At that time she underwent surgical removal of a bladder stone. Hepatomegaly and nephromegaly progressed steadily. At the age of 6 years she had frequent seizures that required valproate treatment. Biochemistry showed neutropenia, moderate acidosis, hyperuricemia, and elevation of liver enzymes.

Once the diagnosis of GSD type Ib was confirmed by liver biopsy, she commenced supplemental nutritional therapy. At 8.6 years, she was re-hospitalized with alimentary intolerance and severe infectious mononucleosis syndrome. At that time she was found to be HBsAg and HbcAb positive and HBeAg negative. Transaminase levels were three times the normal levels. Her weight was 8 kg (< P3) and her height 106 cm (< P3). There were no signs of liver adenomata.

Despite the nutritional changes, her lactic acid levels remained very high (59 mmol/l), but supplementation resulted in increases in weight [(43.9 kg—P10) and height (148.5 cm—P3) by the age of 21]. Pubertal development remained retarded. Menstruation started when she was 17, but she rapidly became amenorrheic. At the age of 21, she underwent DUS, CT scan and magnetic nuclear resonance (MNR) imaging, which showed several adenomata in the

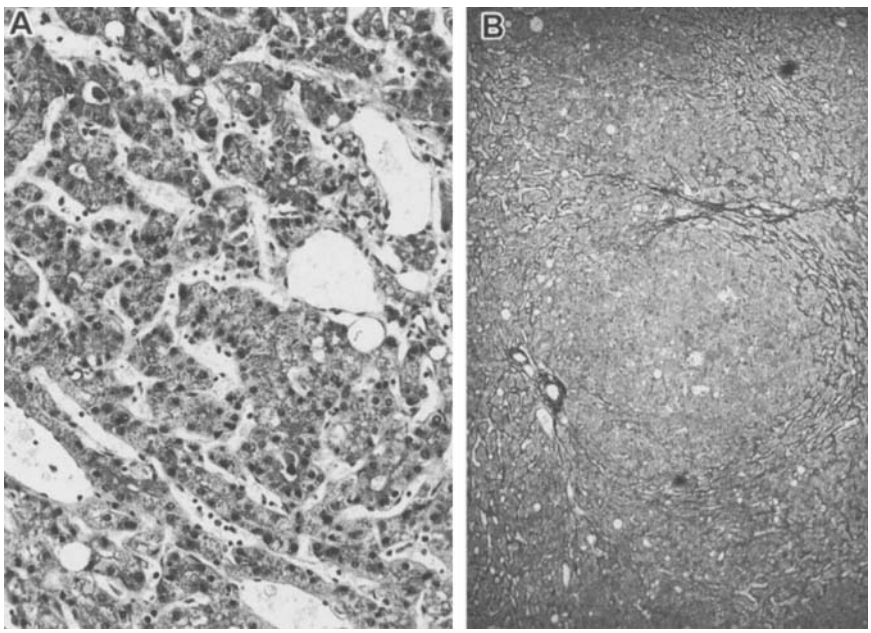

Fig. 2 **A** Hepatocellular carcinoma that had developed in one of the adenomata of the GSD type Ia patient (× 282). **B** Low-power magnification (× 63) of the degenerated lesion clearly shows the absence of reticulin network

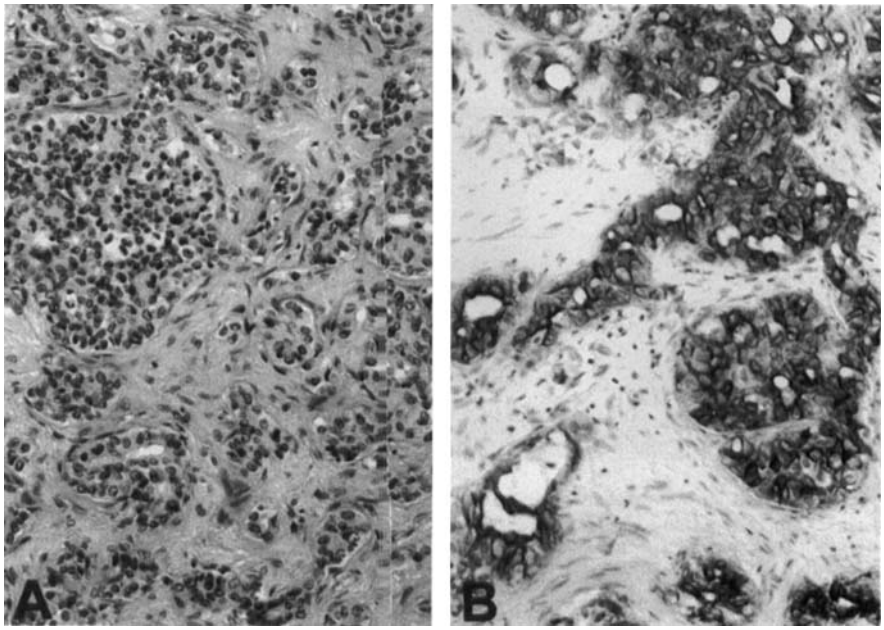

Fig. 3A, B Typical tubular architecture of the cholangiocarcinoma that had developed in the GSD Ib patient. **A** With a strong and diffuse cytokeratin 7 expression in neoplastic cells, indicating that these do not correspond to hepatocellular cells (**B**). Magnification × 217

presence of portal hypertension. The largest tumor had a diameter of 7 cm. At that time, she was still leukopenic (3,250 mm^3), liver tests continued to give elevated results and triglycerides levels remained high (223 mg/dl). Liver biopsy confirmed intra-cytoplasmatic and intra-nuclear glycogen overload. At clinical examination there was hepatosplenomegaly but no ascites; paresis of left upper eyelid was also noted. Liver resection was proposed but refused by the patient.

Two years later, at the age of 22 years, she presented with severe right upper quadrant pain and diarrhea. At clinical examination, the left liver lobe was large and painful. Biochemistry revealed severe inflammatory syndrome and elevated transaminases (three-times normal) and GGT (ten-times normal); alpha-feto-protein level was 2.8 ng/ml. HBs-antigenemia remained positive; HCV-antibodies were negative. DUS, CT-scan and MNR imaging showed several heterogeneous, hypervascular bi-lobar liver tumors, many of which had grown significantly. There was no intra-tumoral bleeding. Two large heterogeneous lesions in the right lobe of the liver had highly vascularized intra-tumoral septa and tumor periphery. Some lesions contained calcifications. Thoraco-abdominal and bone examinations did not reveal any extrahepatic tumor spread.

Peritoneal carcinomatosis was found on a pre-transplant exploratory laparotomy. Surgical biopsies of one of the liver tumors were taken for histological examination; surprisingly these showed cholangiocarcinoma with a strong diffuse cytokeratin 7 expression (Fig. 3). There were no signs of liver fibrosis or cirrhosis. Immunohistochemistry of tumoral tissue and of the surrounding normal liver tissue was positive for HBc antigen. She died 4 months later.

Discussion

GSDs are inherited autosomal recessive metabolic diseases in which the concentration and structure of glycogen in body tissues are abnormal. GSD type I is one of the most common types of liver glycogenosis [5, 6]. Type Ia is caused by a deficiency of the enzyme glucose-6 phosphatase, and type Ib is caused by a deficiency of G-6-P microsomial translocase. Both diseases have almost identical biochemical and clinical manifestations: hypoglycemia, lactic acidosis, hyperlipidemia, hyperuricemia, hemorrhagic diathesis, hepatomegaly, growth retardation, and sexual immaturity [1, 3]. GSD type Ib has further specificities, such as neutropenia, impaired neutrophil migration, and frequent infectious syndromes [7].

Adequate medical treatment gives good short-term results in GSD type I diseases [8]. Treatment has changed from portosystemic diversion (ameliorating all the disease manifestations except hypoglycemia) [9] to round-the-clock alimentation using combinations of continuous or intermittent nasogastric feeding and raw starch supplementation [8]. If adequate nutritional therapy is started early, preferably within 2 years, the incidence of liver adenoma formation and proteinuria will be lower [3, 8, 10]. Adequate diet may also result in adenoma regression. Despite individualized and well-controlled medical therapy, the long-term outlook of patients remains compromised by the risks of hepatocellular cancer transformation, atherosclerosis, and progressive renal disease [11, 12]. Hypoglycemia and severe lactic acidosis are the initial life-threatening complications. During adolescence or adulthood, uric acid nephropathy and glomerulosclerosis lead to renal insufficiency, and adenomatosis becomes more prevalent [3, 13, 14]. Liver adenomata develop in most (50 to 80%) GSD type I patients by the time they reach their second or third decade of life [2, 3, 13].

Adenoma formation in GSD type I is probably related to constant hormonal stimulation of the liver by persistent peripheral hypoglycemia; some authors think the impaired ratio between insulinic and glucagonic

immunoreactivity is responsible for tumor formation [14, 15]. These hypotheses, which have been confirmed both with experimental rat models and clinical experience, stress the beneficial role of early nocturnal enteral nutrition [16]. The transformation of adenomata into hepatocellular cancer has been documented in approximately 10% of GSD type I patients [15]. The risk is high during the third decade of life, particularly if appropriate nutritional therapy is not given, as demonstrated in our two cases. The first report of liver cell carcinoma in GSD type I was made by Zangeneh et al. in 1969 [17]; more cases were published subsequently [15]. The mean age of liver adenoma detection is 21.5 years (range 3 to 40), and the mean age at diagnosis of HCCA is 25.5 years (range 14 to 31). Two-thirds of the patients are male. Tumor markers are frequently normal. Adenomata are diagnosed 2–5 years (mean 4 years) before the development of HCCA. HCCA has not been observed in the absence of a pre-existing adenoma [14]. So far, only one case of liver adenoma has been described in a patient with type Ib glycogenosis [17]. Case 2 is, to our knowledge, the first description of the development of a malignant tumor, in this case a cholangiocarcinoma, in GSD Ib. It should be emphasized that this young woman had HBV infection and sub-optimal dietary therapy.

To date, several GSD type I patients have undergone transplantation, and 12 cases have been reported in detail [1, 3, 4, 7, 13, 18, 19, 20]. Indications for transplantation were based on the progression of adenomatous lesions (10×), suspicion of malignant transformation of an adenoma (1×) and unresponsiveness to medical therapy, insufficient control of hypoglycemia, and growth and sexual retardation (1×) [4].

LT is a specific and radical option that allows the metabolic disease and most of its consequences to be corrected [1]. The benefit of LT for children lies in the improvement of quality of life by preventing hypoglycemic episodes, by rendering them independent of continuous feeding, by improving sexual maturation and growth (which has been observed late into the third decade of life) [21], and by preventing or stabilizing renal disease. There is evidence that renal disease depends on the early timing of medical therapy and transplantation [3, 4]. In the case of GSD Ib, LT corrects only the metabolic disease; neutropenia may persist, and continuous administration of granulocyte colony stimulating factor may be needed [7].

In adolescents and adults the benefit of LT lies in controlling the adenomatous liver cell disease with its inherent risks of degeneration and severe bleeding. Better knowledge of the natural history of the disease, the low risk of an elective transplant procedure in a non-cirrhotic patient, and the side effects of nephrotoxic immunosuppression in a patient with potential glomerulopathy implicate a different approach towards transplantation for GSD. The indication for LT in children is clear in cases of uncontrollable manifestations of the metabolic disease (despite adequate nutritional therapy), or in cases of lack of compliance with medical therapy. In adolescents, regular follow-up of GSD is mandatory once adenoma formation has been documented. The potential degeneration and further development of adenomas, despite adequate dietary measures, and the difficulty of making an early diagnosis of HCCA, justify this. Follow-up should include DUS three to four times yearly, and yearly MNR imaging. Development of adenoma(ta) accompanied by changing tumor characteristics, such as intra-tumoral vascularisation and modified echogenicity, make it mandatory for the patient to be listed for LT.

References

1. Malatack JJ, Finegold DN, Iwatsuki S, Shaw BW Jr, Gartner JC, Zitelli BJ, Roc T, Starzl TE (1983) Liver transplantation for type I glycogen storage disease. Lancet 1:1073–1075
2. Labrune P, Trioche P, Duvaltier I, Chevalier P, Odievre M (1997) Hepatocellular adenomas in glycogen storage disease type I and III. J Pediatr Gastroenterol Nutr 24:276–279
3. Matern D, Starzl TE, Arnaout W, Barnard J, Bynon JS, Dhawan A, Emond J, Haagsma EB, Hug C, Lachaux A, Smit GP, Chen YT (1999) Liver transplantation for glycogen storage disease types I, III and IV. Eur J Pediatr 15:S43–S48
4. Sokal EM, Lopez-Silvarre Y, Buts JP, Otte JB (1993) Orthotopic liver transplantation of type I glycogenosis unresponsive to medical therapy. J Pediatr Gastroenterol Nutr 16:465–467
5. Cohen A, O'Grady J, Mowat AP, Williams R (1989) Liver transplantation for metabolic disorders. J Clin Gastroenterol 3:767–786
6. Kuzuya T, Matsuda A, Yoshida S, Narisawa K, Tada K, Saito T, Matsushita M (1983) An adult case of type Ib glycogen storage disease. Enzymatic and histochemical studies. N Engl J Med 308:566–569
7. Lachaux A, Boillot O, Stamm D, Canterino I, Dumontet C, Regnier F, Floret D, Hermier M (1993) Treatment with lenograstim (glycosylated recombinant human granulocyte colony-stimulating factor) and orthotopic liver transplantation for glycogen storage disease type Ib. J Pediatr 6:1005–1008
8. Greene HL, Slonim AE, O'Neill JA, Burr IM (1976) Continuous nocturnal intragastric feeding for management of type I glycogen storage disease. N Engl J Med 794:423–425
9. Starzl TE, Porter KA, Francavilla A (1983) The Eck fistula in animals and humans. Curr Probl Surg 20:687–752

10. Parker I, Burn I, Slonim A, Ghisham FK, Greene H (1981) Regression of hepatic adenomas in type Ia glycogen storage disease with dietary therapy. Gastroenterology 81:534–536
11. Limmer J, Fleig WE, Leupold D, Bittner R, Distschuneit H, Beger HG (1988) Hepatocellular carcinoma in type I glycogen storage disease. Hepatology 8:531–537
12. Wolfsdorf JI, Crigler H (1999) Effect of continuous glucose therapy begun in infancy on the long-term clinical course of patients with type I glycogen storage disease. J Pediatr Gastroenterol Nutr 29:136–143
13. Faivre L, Houssin D, Valayer J, Brouard J, Hdchouel M, Bernard O (1999) Long-term outcome of liver transplantation in patients with glycogen storage disease type Ia. J Inherit Metab Dis 22:723–732
14. Kharsa G, Degott C, Filoche B, Hedde JP, Potet F, Benhamou JP (1990) Hepatic adenoma and hepatocellular carcinoma in 3 brothers with type I glycogenosis. Gastroenterol Clin Biol 14:84–89
15. Coire CI, Qizilbash AH, Castelli MF (1987) Hepatic adenomata in type Ia glycogen storage disease. Arch Pathol Lab Med 111:166–169
16. Bannasch P (1968) The cytoplasm of hepatocytes during carcinogenesis. Electron and light microscopical investigations of the nitrosomorpholine-intoxicated rat liver; recent results. Cancer Res 19:1–100
17. Zangeneh F, Limbeck GA, Brown BI, Emch YR, Arcasoy MM, Goldenberg VE, Keley VC (1969) Hepatorenal glycogenosis (type I glycogenosis) and carcinoma of the liver. J Pediatr 74:773–783
18. Leese T, Farges O, Bismuth H (1988) Liver cell adenomas. A 12-year surgical experience from a specialist hepatobiliary unit. Ann Surg 208:558–564
19. Chen CQ, Chen YS, Liu PP, Chiang YF, Huang TL, Eng HL (1997) Living related donor liver transplantation. J Gastroenterol Hepatol 12:S342–S345
20. Pratschke J, Steinmuller T, Bechstein WO, Neuhaus R, Tullius SG, Jonas S, Schumacher G, Luck W, Becker M, Neuhaus P (1998) Orthotopic liver transplantation for hepatic associated metabolic disorders. Clin Transpl 12:228–232
21. Kirschner BS, Baker AL, Thorp FK (1991) Growth in adulthood after liver transplantation for glycogen storage disease type I. Gastroenterology 101:238–241