Liver and liver cell transplantation for glycogen storage disease type IA

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Abstract

Glycogen storage disease type Ia (GSDIa) is an inherited disorder of glucose metabolism, due to the selective deficiency of the hepatic enzyme glucose-6-phosphatase. Clinical manifestations include severe hypoglycaemia three to four hours post-prandially, increased production of lactic acid, triglycerides and uric acid, hepatic glycogen storage disease with development of multiple adenomas and kidney disease with proteinuria. Liver transplantation is frequently performed in order to achieve metabolic control and when malignant transformation of adenomas is suspected. Long term outcome following transplantation is good, but immunosuppressive therapy can worsen the progression of associated kidney disease. Hepatocyte transplantation could be considered as a less invasive procedure in such patients. Our experience with hepatocyte transplantation in a 47 year-old woman affected by glycogen storage disease type Ia and suffering of severe fasting hypoglycaemia indicates that the procedure can partially correct some metabolic abnormalities and improve the quality of life in this disease. However, the metabolic improvement was reduced and finally abolished during long term follow-up, probably due to rejection or to senescence of transplanted cells. Moreover, the portal and pulmonary hypertension associated with the disease need to be evaluated for their possible influence on haemodynamic changes associated with cell infusion. Finally, hepatic adenomas need careful monitoring because of the possible risk of malignant transformation.

Glycogen storage disease type Ia (GSD-Ia) is caused by a deficiency of glucose-6-phosphatase. Patients are at risk of recurrent episodes of hypoglycaemia, secondary metabolic and hormonal abnormalities and long-term complications. One of the mainstays of treatment is uncooked cornstarch (UCCS) which was introduced as an alternative to continuous nocturnal nasogastric glucose and frequent daytime feeds (1). UCCS is given intermittently to provide stable blood glucose concentrations, reducing swings of insulin secretion. Depending on dosage and frequency of UCCS, normoglycaemia can be maintained for 6-9 hours. On the other hand, there have been concerns about its long term efficacy, e.g. secondary to impaired glucose adsorption as indicated by earlier in vivo and in vitro studies in GSD I (2). The lost of UCCS efficacy and the complications strictly related to the disease, glomerular dysfunction and the formation of hepatic adenoma, must be taken into account in the long term management of the disease.

Hepatic adenomas

Hepatic adenomas are now recognized as a common complication occurring in the majority of patients by the time they reach adulthood (3). Hepatic adenomas develop in 22%-75% of affected adults, according to the population studied, with approximately 10% risk of undergoing malignant transformation (4). Although the adenomas are usually first observed in the second and third decades of life, they may appear before puberty. Their aetiology is unclear, but they occur generally in postpubertal patients, and can be either single or multiple (5).The improvement of metabolic control and normalization of the endocrine milieu have been reported to be associated with shrinkage of the lesions or even their disappearance in a small number of cases (6). Ultrasonography is the preferred method of screening for hepatic adenomas, which appear as focal lesions. MR imaging or CT provides greater definition when malignancy is suspected because of a change in appearance from a small, well-circumscribed lesion to one that is larger and poorly marginated. In a recent report Lee (7) suggests that the increase in liver size and the onset of abdominal pain might be indications of malignant transformation.

Liver transplantation in GSD type IA

Liver transplantation is frequently considered for patients with GSD type IA and severely impaired metabolic control (8). Standard orthotopic liver transplantation is preferentially performed. Auxiliary transplantation, an attractive concept in inborn errors of metabolism, is technically complex and does not solve the problem of potential adenoma transformation. The number of liver transplantations performed for this disease is unknown, since a central registry is not available. From a review of literature and personal communications we are aware of 25 transplants in patients with GSD type I A (n = 21) and B (n = 4) (9). In most cases, liver transplantation was proposed because of multiple hepatic adenomas (10,11). Other indications have also been reported such as poor metabolic control (10), growth retardation (12), liver tumour (13), and suspicion of hepatocellular carcinoma [10,11]. The survival is 100% with a variable reported follow up period (range from 2 - 9 years). The age at transplantation ranged from 5 to 37

years. The metabolic effect of transplantation has been consistent. All reports emphasize the rapid normalisation of glucose metabolism, correction of hyperlipaemia, normal growth and a normal diet without needing frequent meals (14,15).

Only few reports deal with the long-term outcome after liver transplantation (16). Complications include portal vein thrombosis requiring a surgical porto-systemic shunt (17), terminal renal failure related to focal glomerulosclerosis (3) and unilateral optic atrophy leading to unilateral blindness (8). Even if few reports are available, the long-term outcomes in such patients are characterized by severe complications. Progressive renal failure was reported as a result of azathioprine administration, but it was not reported with more recent immunosuppressive drugs. However, some concern remains because of the use of nephrotoxic immunosuppressive drugs in patients with potential glomerulopathy. For this reason, some Authorities have proposed combined liver-kidney transplantation, especially in patients with more severe kidney involvement.

In GSD type Ib, liver transplantation also results in metabolic improvement. However, it seems that neutropenia may persist after transplantation, increasing the risk of infection as well as of inflammatory bowel disease (18). Recently, the liver transplantation in two GDS Ib patients led to clinical improvement, with fewer recurrent infections despite persistent neutropenia, and with normalization of the diet and a decreased frequency of hospital admissions (19).

Age plays a role in the indications to liver transplantation. In infancy, liver transplantation can be indicated because of the unresponsiveness to medical therapy, of insufficient metabolic control or of poor quality of life. In adolescence and adulthood, the main indication to liver transplantation is to control the potential malignant degeneration of adenomas and severe bleeding. Because of the absence of reliable biochemical markers to detect early malignant transformation, ultrasound (every 3-4 months) and NMR (at least one per year) examinations of the liver are mandatory in the follow-up.

In the retrospective European registry, 95% of patients over 20 years of age had renal involvement. In addition to a Fanconi-like syndrome, clinical and laboratory manifestations including glomerular hyperfiltration, hypertension, microalbuminuria and albuminuria and progressive renal failure. Pathological findings include focal segmental sclerosis with interstitial fibrosis. The aetiology of renal involvement is unclear. It seems that the expression of renal disease is negatively correlated with metabolic control and dyslipidaemia (21). More than ten GSD I patients have received renal transplants but only two have been reported (22,23). In both cases, renal transplantation failed to improve glucose metabolism. To date, two GSD Ia patients have undergone combined liver and kidney transplantation (5,17).

Hepatocyte transplantation

Because the metabolic alterations appear to derive from selective deficiency of a hepatic enzyme, this disease has been proposed as a possible target for hepatocyte transplantation (24) . Regression of the hepatic adenomatosis, reported to occur after correction of the metabolic imbalance, and rarity of malignant transformation of the adenomas (3) add further support to this therapeutic concept. We have described transplantation of allogenic hepatocytes into the liver of a 47-year-old woman with GSDIa (25). At age 3 years, she presented with hepatomegaly, hypoglycaemia and lactic acidosis. The diagnosis of GSDIa was subsequently confirmed on the basis of undetectable glucose-6-phosphatase activity in liver biopsy tissue. Despite management with frequent meals, nocturnal nasogastric feedings and uncooked corn starch meals every 3 hours, she was unable to maintain blood glucose constantly above 3.5 mmol/l, as required for optimal metabolic control of the disease. Other biochemical abnormalities included hypertriglyceridemia (up to 20 mmol/l), lactic acidosis (3-5.5 mmol/l) and hyperuricemia (0.50-.75 mmol/l). Liver function tests were normal. Several hepatic adenomas were demonstrated on ultrasound, CT scan and NMR. Compliance with dietary treatment became increasingly difficult because of the poor quality of life resulting from the required feeding regimen. The patient felt that her quality of life was very poor mainly due to dietary schedule but she did not accept the idea of liver transplantation. She was lacking confidence in the future and tended to delay night meals, resulting in worse metabolic control. However, she accepted enthusiastically the idea of an alternative treatment based on cell therapy. She received two billion freshly isolated viable hepatocytes from an ABO compatible donor liver. The total number of cells infused was limited because of pre-existing portal hypertension due to hepatic glycogen storage disease. Portal pressure increased from 15 mm Hg up to 31 mm Hg during cell infusion, but it returned to baseline within 24 hours. A triple immunosuppression therapy was initiated. Methylprednisolone (1 g i.v.) was administered during cell infusion, then tapered from 200 mg to 4 mg per day over the next 16 weeks and finally discontinued. Oral tacrolimus adjusted to maintain serum levels of 7 to 8 ng per ml were also administered, together with Mycophenolate mofetil 1 g per day for 12 weeks mycophenolate mofetil for 12 weeks, in order to enhance immunosuppression during the early post-transplant period. Due to the lack of experience with immunosuppression in hepatocyte transplantation (even animal studies are lacking) the inclusion of mycophenolate mofetil in the protocol was entirely empirical. Following the procedure, the patient was initially able to tolerate at least 7 hours of fasting while maintaining blood glucose levels above 3.5 mmol/l. When compared to the pre-transplant condition, a more sustained postprandial elevation of blood glucose was observed, in

parallel with a more profound and persistent inhibition of lactate. Blood triglycerides dropped to 7 mmol per litre on the day after transplantation, and thereafter fluctuated between 10 and 15 mmols/L. Blood uric acid levels were not affected. Both ultrasound and NMR showed no change in liver adenomas for four years after the procedure.

Approximately 18 months following cell transplantation, the patient experienced an episode of nocturnal hypoglycaemia, associated with reduced tolerance to fasting in the next few days. Blood tacrolimus levels were 5 ng/ml. The drug dosage was increased in order to reach 8 ng/ml, and the metabolic control improved, although it was not as good as previously. Because of the possible hyperglycaemic effect of tacrolimus, we hypothesized a possible relationship between tacrolimus and blood glucose levels but we found no correlation between the two parameters during the whole period following hepatocyte transplantation. Thereafter the patient slowly deteriorated, and presently, four years after cell transplant, her clinical conditions are similar to those observed prior to cell transplantation. Possible therapeutic options currently include a second cell infusion or orthotopic liver transplantation. However, the latter procedure is relatively contraindicated by the presence of pulmonary hypertension, which was documented during hepatocyte infusion.

In conclusion, the experience suggests that hepatocyte transplantation can allow a regular diet in GSDIa, with considerable improvement in the quality of life. The problems we encountered with this individual patient can be summarised as follows.

1. The presence of portal hypertension and possibly of pulmonary hypertension should be considered before hepatocyte transplantation, since such complications can limit the procedure and increase the risk of side effects.
2. The problem of identifying rejection, common to all procedures involving allogenic cell transplantation, was particularly troublesome in our patient. We cannot exclude that rejection played a role in the decreased metabolic control observed over time. Specific immunosuppressive protocols for cell transplantation, diagnostic tools to monitor rejection and ideally protocols to induce tolerance to transplanted cells would greatly improve the applicability of the procedure.
3. Monitoring hepatic adenomas remains a major concern due to the possibility of malignant transformation. Indeed, this possibility was the most critical problem we had to consider before deciding to perform hepatocyte transplantation in GSD1a, and the patient was informed about this risk. We were encouraged to proceed not only because malignant transformation of the adenomas is extremely rare (only 5 cases of transition from adenoma to hepatocellular carcinoma have been described in literature) (26), but also because adenomas seem to benefit from improved metabolic balance, as they have a tendency to regress after continuous nocturnal nasogastric feeding (6, 26, 27). A conservative approach to hepatic adenomatosis is usually recommended in GSD1a (27), and successful treatment of rapidly growing adenomas with percutaneous ethanol injections was recently reported (28). However, a description of HCC development in a renal transplant patient with GSD1a ten years after transplantation was published by Gossmann et al. (2001). Indeed, we cannot exclude that immunosuppression could favour the development of HCC in our patient. To minimize this risk, we have been performing serial α-fetoprotein determinations and liver ultrasound (every 3-4 months) in order to detect any change in tumour size. In case of suspicious growth, we were prepared to perform surgical resection. Should a malignant transformation have been documented, we would have immediately withdrawn immunosuppressive treatment. Indeed, it should be stressed that hepatocyte transplantation is not an irreversible procedure, and thus immunosuppression can be withdrawn, resulting at most in restoration of pre-transplant metabolic conditions. Surveillance of hepatic nodules in our patient was further intensified by serial NMR (every 6 months), a procedure with high sensitivity for detecting malignant transformation of hepatic lesions (29).
4. Enrolment of glycogenosis patients for hepatocyte transplantation should include a plan of actions to be implemented in case of insufficient metabolic control, such as listing for whole liver transplantation.

Clearly, the long term results of this treatment on the natural history of the disease remain to be established.

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