Abstract

Background and aims. To describe the characteristics of patients with type I glycogenosis, the presentation types, the main clinical signs, the diagnostic criterias and also the disease outcomes on long term follow-up. Methods. The study group consisted of 6 patients (medium age 3 years 6 months) admitted in hospital between 2001 and 2005 and followed-up for 1 to 5 years. The sex ratio was 1:1. Results. The referral reasons varied from hepatomegaly incidentally discovered (3 of 6 patients) to abdominal pain (4 of 6 patients), growth failure (3 of 6 patients), symptoms of hypoglycemia (3 of 6 patients), recurrent epistaxis (1 patient). Hepatomegaly was present in all cases. Biological profile: hypoglycemia, increased transaminase values, hypertriglyceridemia, lactic acidosis, normal uric acid levels. Two patients had neutropenia and other two had increased glomerular filtration rate. Liver biopsy showed glycogen-laden hepatocytes and markedly increased fat. Four patients had type Ia and 2 patients type Ib glycogenosis. The therapy consisted of: diet, ursodeoxycholic acid, granulocyte colony-stimulating factor, broad spectrum antibiotics for those with type Ib glycogenosis. The follow-up parameters were clinical, biological, imaging. Metabolic interventions and antiinfectious therapy were necessary. All patients are alive, two of them on the waiting list for liver transplantation. Conclusions. Glycogen storage disease type I is a rare condition, but with possible life-threatening consequences. It has to be kept in mind whenever important hepatomegaly and/or hypoglycemia are present.

Key words: Glycogen storage disease type I - hypoglycemia - children - hepatomegaly

Introduction

Glycogen storage disease type I (GSD I) is part of a rare group of inherited diseases characterized by enzyme defects that affect the glycogen synthesis and degradation cycle. GSD I is more appropriately considered a defect in gluconeogenesis, as the enzyme defect blocks the formation of glucose not only from glycogen stores, but also from glucose precursors (lactate, aminoacids) (1). There are two subtypes of type I glycogen storage disease, both having autosomal recessive transmission: type Ia is the most common, characterized by a defect in glucose-6-phosphatase (an enzyme found only in the liver, kidney and intestinal mucosa) (1). There are two subtypes of type I glycogen storage disease, both having autosomal recessive transmission: type Ia is the most common, characterized by a defect in glucose-6-phosphatase (an enzyme found only in the liver, kidney and intestinal mucosa) activity, and type Ib, caused by a defect in microsomal transport of glucose-6-phosphate (2). Given the fact that there are no newborn screening programs for this disorder, there are no reliable estimates for the incidence of GSD I, but it is unlikely that it occurs more frequently than 1 case in 100 000 infants (3). Besides the clinical findings of massive hepatomegaly, enlarged kidneys and growth failure, the biologic picture of GSD I is very complex, characterized by hypoglycemia, lactic acidosis, hyperlipidemia, moderate increase in transaminase levels, hyperuricemia, and also neutropenia or neutrophil dysfunction in type Ib GSD. The hepatic and renal injury is chronic, emphasizing the need for long-term follow-up. There is a high variability in the course of the disease, including the possibility of hepatocarcinoma, making therapeutic decisions vary from simple dietary measures to liver or hepatocyte transplantation (4). Life expectancy in GSD-1 has improved considerably. Its relative rarity implies that no metabolic centre has experience of a large series of patients. Experience with long-term management and follow-up at each centre is limited (5).

The aims of this study are to establish the characteristics of patients with GSD I, to describe the presentation types and the main clinical signs, to evaluate the diagnostic criterias (clinical, biological and histological) and also the disease outcomes regarding growth, liver function and metabolic profile on long term follow-up. The importance of establishing practical guidelines for long term follow-up is
emphasized by the serious and potential life-threatening complications of the disease.

Material and methods

The study group consisted of 6 patients aged 1 year 3 months to 6 years 5 months (mean age 3 years 6 months) at diagnosis, admitted in our clinic between 2001 and 2006 and periodically reevaluated for 1 to 5 years. The sex ratio was 1:1. There was no consanguinity of the parents of these children, nor was there any known shared pedigree between the 6 cases, all of whom lived in different regions of Moldavia.

The inclusion criterias were:
1. clinical: hepatomegaly; growth failure; no muscular symptoms and signs;
2. biological: hypoglycemia early in fasting (3-4 hours after meals); normal insulin / glycemia ratio; little or no glycemic response to glucagon; lactic acidosis; normal values of creatinine kinase;
3. histological: markedly increased fat and glycogen in hepatocytes.

Results

The clinical information for each of the 6 cases is shown in Table I.

The first presentation in our clinic was due to different reasons. Two patients were referred for investigation of a hepatomegaly incidentally discovered at physical examination in the context of an acute pathologic condition. The other patients referred as follows: abdominal pain accompanied by increased abdominal girth (Fig.1) (4 cases), growth failure (3 cases), symptoms of hypoglycemia with early morning awakenings for feeding and an increased appetite, episodes of fatigue and decreased energy that improved after feeding, unexplained somnolence, sweating (2 cases), recurrent epistaxis (1 case). Two of the cases had a positive history of frequent bacterial infections ( recurrent mouth ulcers, otitides, boils, pneumonias).

The physical findings constantly included hepatomegaly of different degrees, from moderate to massive, with a liver span between 14 and 22 cm. In five cases the patients had doll-like facies, short stature, increased abdominal girth, liver span 18 cm.

Table I Clinical information for cases 1 – 6

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at diagnosis</th>
<th>Sex</th>
<th>Reason for referral</th>
<th>Physical findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 mo</td>
<td>F</td>
<td>asymptomatic hepatomegaly incidentally discovered</td>
<td>Liver span 14 cm, ketotic breath</td>
</tr>
<tr>
<td>2</td>
<td>19 mo</td>
<td>M</td>
<td>Suspected recurrent hypoglycemia; increased abdominal girth, abdominal pain</td>
<td>Liver span 16 cm, doll-like facies, ketotic breath</td>
</tr>
<tr>
<td>3</td>
<td>2 yr 1 mo</td>
<td>F</td>
<td>Asymptomatic hepatomegaly incidentally discovered</td>
<td>Liver span 18 cm, doll-like facies, short stature</td>
</tr>
<tr>
<td>4</td>
<td>4 yr 10 mo</td>
<td>F</td>
<td>Short stature; increased abdominal girth, abdominal pain</td>
<td>Liver span 18 cm, doll-like facies, short stature</td>
</tr>
<tr>
<td>5</td>
<td>4 yr 10 mo</td>
<td>M</td>
<td>Short stature, increased abdominal girth, abdominal pain, recurrent epistaxis</td>
<td>Liver span 22 cm, doll-like facies, short stature</td>
</tr>
<tr>
<td>6</td>
<td>6 yr 5 mo</td>
<td>M</td>
<td>Suspected recurrent hypoglycemia;</td>
<td>Liver span 20 cm, doll-like facies, short stature</td>
</tr>
</tbody>
</table>
Table II  Serum biochemical profile on presentation

<table>
<thead>
<tr>
<th>Case</th>
<th>Fasting glucose</th>
<th>ALP, U/L</th>
<th>AST, U/L</th>
<th>ALT, U/L</th>
<th>GGT, U/L</th>
<th>Total bilirubin (120 – 230 mg/dl)</th>
<th>Cholesterol (20-130 mg/dl)</th>
<th>Triglycerides (20-130 mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.28 g/l</td>
<td>X 1.5 NV</td>
<td>X 6 NV</td>
<td>X 5 NV</td>
<td>N</td>
<td>N 268</td>
<td>340</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.45 g/l</td>
<td>N</td>
<td>X 4 NV</td>
<td>X 5 NV</td>
<td>N</td>
<td>N 327</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.33 g/l</td>
<td>N</td>
<td>X 12 NV</td>
<td>X 11 NV</td>
<td>X 4 NV</td>
<td>N 339</td>
<td>1100</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.42 g/l</td>
<td>N</td>
<td>X 5 NV</td>
<td>X 4 NV</td>
<td>X 2 NV</td>
<td>N 275</td>
<td>570</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.38 g/l</td>
<td>N</td>
<td>X 2 NV</td>
<td>X 3 NV</td>
<td>N</td>
<td>N 324</td>
<td>740</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.44 g/l</td>
<td>N</td>
<td>X 3 NV</td>
<td>X 3 NV</td>
<td>N</td>
<td>N 306</td>
<td>620</td>
<td></td>
</tr>
</tbody>
</table>

ALP alkaline phosphatase, AST aspartate aminotransferase, ALT alanin aminotransferase, GGT gammaglutamyl transpeptidase, NV normal value

Random blood glucose levels varied between severe hypoglycemia and normal values, and the glycemic profile correlated to feeding schedule showed the occurrence of hypoglycemia within 3 to 4 hours after meals in all cases. The patients underwent fasting challenges that were concurrent with these findings. The oral glucose tolerance test showed inappropriate (small) glycemic rise in all cases. We assessed the insulin levels, correlated to the glycemia values, finding low levels of insulinemia and appropriate values of insulin/glycemia ratios in all cases. The glucagon test showed a glycemia rise of 15 – 25 % in two cases, and no glycemic response in 4 cases. This helped us to distinguish GSD I from GSD III, in which patients often have an increased serum glucose after glucagon administration, with the exception of prolonged fasting, when patients with GSD III lose their ability to respond to glucagon. Having no access to enzymatic diagnosis in our country, those analyses have been strong arguments for the clinical type of GSD. The results of the fasting challenges are shown in Table III.

Table III  Results of initial fasting challenge

<table>
<thead>
<tr>
<th>Case</th>
<th>Time to hypoglycemia</th>
<th>Fasting challenge</th>
<th>Glucagon response in fed state</th>
<th>Time to lactic acidosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.5</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>Glycemia rise of 15%</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>Negative</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3.5</td>
<td>Glycemia rise of 25%</td>
<td>Positive</td>
<td></td>
</tr>
</tbody>
</table>

The triglyceride values were elevated in all cases but at different degrees: 200 – 500 mg/dl in 2 cases, 500 – 1000 mg/dl in 3 cases, and more than 1000 mg/dl in one case, accompanied by prolonged bleeding time due to impaired platelet function as a consequence of hypertriglyceridemia (1).

Uric acid levels were normal at diagnosis in all patients. The lactate levels increased dramatically with hypoglycemia and glucagon administration and decreased following administration of glucose. Ketosis was quantified in urine at 1+ in 4 cases and 2+ in 2 cases. Four of the patients (cases 3-6) had increased glomerular filtration rate, with normal blood urea nitrogen. The youngest patients had no evidence of renal involvement at admission.

In the evaluation protocol we included the assessment of hypoglycemia consequences on the central nervous system. Clinically, all patients were within normal for age regarding psychomotor development. The EEG showed no changes consistent with brain damage. The psychological evaluation was also normal.

Imaging studies consisted of ultrasonographic evaluation and CT scan. Ultrasoundography showed marked homogeneous hepatomegaly with intense hyperechogenicity, no splenic abnormalities; the kidneys were enlarged in three cases (age between 4 and 7 years), all of them also having increased glomerular filtration rate. There were no signs of portal hypertension in any of the cases. The CT scan was performed in 3 cases, showing massive homogeneous enlargement of the liver, with low contrast enhancement.

Three cases had delayed bone maturation.

The percutaneous liver biopsy showed glycogen-laden hepatocytes in PAS staining in all cases, establishing the diagnosis of GSD (Fig.2). Sudan stain showed markedly increased fat in the liver. There was no evidence of fibrosis in the liver tissue. The bone marrow showed no pathologic elements in any of the cases.

The association of massive liver enlargement, rapid onset of hypoglycemia 3 to 4 hours after meals, elevated lactic acid levels and marked hypertriglyceridemia was considered sufficient to establish the diagnosis of GSD Ia in four cases,

Fig.2  Case 3: Liver tissue, optic microscopy: glycogen laden hepatocytes (PAS stain).
and Ib in those two cases associated with frequent bacterial infections and neutropenia (cases 4 and 6) (1,21,22). In these two cases, although they had no suggestive symptoms, we performed also colonoscopy and colonic mucous biopsies to identify the eventual changes consistent with inflammatory bowel disease that is often associated with glycogen storage disease type Ib (6,7,22). We found no such changes.

**Therapeutic approach**

The mainstay of therapy in all cases consisted of dietary measures including a pattern of frequent carbohydrate feedings; administration of 2 g/kg of uncooked cornstarch suspensions (1,8,9,20) every 6 hours was effective in avoiding hypoglycemia symptoms in all children. However, during follow-up, in spite of this measure, there were still low glycemic values in the morning, but no accompanying symptoms.

Data about the development of premature atherosclerosis in young adult GSD I patients are very scarce. Even though in familial hypercholesterolemia or familial combined hyperlipidemia, a comparable degree of hyperlipidemia is associated with cardiovascular morbidity and mortality at early age, studies showed that GSD type Ia is not associated with premature atherosclerosis, despite the longstanding dyslipidaemia and microalbuminuria (10). Little is known about possible vascular protective mechanisms against the dyslipidaemia in GSD Ia. The diminished platelet aggregation (11) can be only partly protective (12). Recently, a decreased susceptibility of in vitro oxidation of VLDL cholesterol has been found (13). The renal deleterious effects of dyslipidaemia are, however, an argument for lipid-lowering measures, including drug treatment (14,15,20). We considered it prudent to advise our patients to avoid high lipids intake, and we recommended omega-3 fatty acids supplements (fish oil) for their effect of decreasing triglycerides and VLDL levels in hypertriglyceridemic subjects, with a concomitant increase in HDL. Omega-3 fatty acids lower plasma triglycerides by inhibiting VLDL and apolipoprotein B-100 (16) synthesis, and in conjunction with transcription factors, target the genes governing cellular triglyceride production and those activating oxidation of excess fatty acids in the liver. Inhibition of fatty acid synthesis and increased fatty acid catabolism reduce the amount of substrate available for triglyceride production (17). We also recommended dietary restrictions on fructose and galactose and supplemented the diet with calcium and multivitamins (1).

All patients received treatment with ursodeoxycholic acid (15 mg/kg body weight) for its hepatoprotective effects and its intervention in cholesterol metabolism.

Those patients with type Ib GSD received also broad spectrum antibiotics, and one of them received granulocyte colony-stimulating factor (GCSF) 5 μg/kg twice per week for a period of two years, and the median neutrophil counts increased significantly to normal values and simultaneously there was a slight decrease in median leukocyte and platelet counts, and the number and severity of infections decreased. As a complication of the treatment, a mild splenomegaly occurred.

**Evolution during follow-up**

The patients were followed-up in our clinic for a period of 1 to 5 years. The follow-up parameters were clinical (the amount of catch-up growth under appropriate carbohydrate supplementation, the liver span, psychological evaluation), biological (neutrophil count, glycemic profile, transaminase levels, lipid profile, uric acid levels, renal function parameters), imaging (for early detection of focal hepatic lesions and renal changes).

One of the four patients with short stature had a satisfactory growth rate, reaching normal values for age after two years of treatment. The other three patients remained under normal values for age. Cases 1 and 2 that showed normal values of the anthropometric measurements for age at diagnosis also had a satisfactory growth rate. Liver span decreased in four cases by 10-15% and increased by 10-15% in the other two cases. There were no signs of brain damage or any deterioration in cognitive functions or delay in psychomotor achievements.

Despite the dietary measures, there was poor control of the glycemic values in cases 2 and 3, with frequent moderate hypoglycemia during the night and in the morning accompanied by sweating, tremor, irritability/apathy. In the other 4 cases there was good glycemia control, with rare episodes of hypoglycemia accompanying acute diseases with low oral intake that required intravenous glucose support and prompt metabolic intervention until resolution.

Transaminase levels remained moderately to mildly increased, with the exception of case 3 that maintained moderate to high levels for a period of one year of follow-up (Fig.3).

**Fig.3 Transaminase values during follow-up.**

Cholesterol and triglyceride values normalized in case 1 and remained slightly to moderately increased in the other 4 cases. Uric acid was high after 3 and 4 years, respectively, in cases 3 and 2, and normal in all the other cases. We used allopurinol 10 mg/kg/day divided in three doses.
There were no signs of renal function impairment in any of the patients during follow-up, and case 2 showed also renal enlargement and high glomerular filtration rate after 3 years of follow-up.

Ultrasonographic evaluation was performed during every check-up (18) and there were no focal liver changes suggestive for adenoma or hepatocellular carcinoma.

Because of the massive hepatomegaly accompanied by poor glycemic control, cases 2 and 3 are on the waiting list for liver transplantation (20-22).

As a new hope for the etiologic treatment of the disease, recent data of genetic research on animal models demonstrated that a single administration of a recombinant adenovirus vector can alleviate the clinical manifestations of GSD type Ia, suggesting that this disorder in humans can potentially be corrected by gene therapy (19).

Conclusions

Glycogen storage disease type I is a rare condition, but it has to be kept in mind for differential diagnosis whenever confronted with hepatomegaly and/or hypoglycemia. It is important to look for hypoglycemia even in the absence of suggestive clinical signs, as the high levels of lactate can serve as an alternative fuel for the brain.

The profound alteration of carbohydrate homeostasis with its consequences on acid-base balance can lead to life-threatening situations that need prompt metabolic intervention; patients with GSD type Ib require special attention because of the high risk of sepsis.

Long term complications of GSD type I require complete periodic reevaluation.

Hepatic transplantation is indicated in cases in which there is no sufficient metabolic control, in children who develop multiple adenomas and when hepatomegaly is massive.

References