

Glycogenosis type I or von Gierke's disease

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Abstract

Glycogenoses type I (von Gierke's disease) are caused by a dysfunction in the glucose-6-phosphate (G6P) system, a key step in the regulation of glycemia. The deficit concerns the catalytic subunit (type Ia) or the G6P transporter (type Ib). Their incidence is around 1/100,000 births and transmission is autosomal recessive. The patients have poor tolerance of fasting; severe hepatomegaly; growth retardation (small stature and late puberty), generally improved by an appropriate diet; osteoporosis; full-cheeked, round face; hypotonia with delayed acquisition of motor skills; enlarged kidneys; and platelet dysfunctions. In type Ib, the following are also present: a tendency towards infections associated with neutropenia, relapsing aphthous gingivostomatitis, and inflammatory bowel disease. The biological diagnosis of these diseases is suspected based on abnormal basal values and functional test results, and is confirmed by the demonstration of the deficit responsible in a liver biopsy, preferably fresh rather than frozen. The genes for types Ia and Ib have been localized to chromosomes 17 and 11, respectively and cloned. Mutations have been identified, thereby enabling prenatal diagnosis of these glycogenoses. The dietary treatment aims at avoiding hypoglycemia (frequent meals, nocturnal enteral feeding through a nasogastric tube, later oral addition of uncooked starch), acidosis (restricted fructose and galactose intake) and hepatic complications (adenomas). Liver transplantation, performed on the basis of the rare but possible transformation of adenomas into hepatocarcinoma, corrects hypoglycemia.

Keywords

glucose 6 phosphate deficiency, glycemia dysfunction, fasting intolerance, hepatomegaly, growth retardation, osteoporosis, locus 17, locus 11, liver transplantation

Name of the disease and its synonyms

Glycogenosis type I or von Gierke's disease

main diagnostic criteria are: hepatomegaly, hypoglycemia and hyperlacticacidemia. Its transmission is autosomal recessive.

Diagnostic criteria/Definition

Glycogenosis type I is a hepatic glycogen storage disease (GSD) resulting from a defect in the glucose-6-phosphate (G6P) system. The

Incidence

Glycogenoses type I (GSD I) are rare diseases whose incidence is estimated to be around 1/100,000 births. Representing approximately one-fourth of the hepatic glycogenoses, they are the most severe form (Chen, 2000).

Clinical description

(Chen, 2000)

The disease becomes manifest as of the first weeks of life with the discovery of marked hepatomegaly. This latter is soft during the first years of life and hardens or becomes nodular later on (Pizzo, 1980). Tolerance of fasting is very limited. Hypoglycemia capable of causing convulsions and hyperlacticacidemia giving rise to severe metabolic acidosis explain the initial gravity of this disease. The full-cheeked, round face, due to subcutaneous fat deposits (also causing cutaneous xanthomas), and a protruding abdomen contrast with the thin limbs. Small stature, osteopenia (Lee *et al.*, 1995) and late onset of puberty (Nuoffer *et al.*, 1997) constitute the constant signs. The kidneys are enlarged and symmetrical. Platelet dysfunctions explain the tendency for ecchymoses and bleeding.

Long-term complications (de Parscau *et al.*, 1988; Smit, 1993; Talente *et al.*, 1994) can be delayed by good metabolic control in these patients. The main ones are: hepatic adenomas (towards the 2nd and 3rd decades) with a risk of malignant transformation (Bianchi, 1993), anemia, osteopenia and/or fractures, ovarian cysts. Renal complications start with silent glomerular hyperfiltration before the development of proteinuria, which can progress to renal insufficiency. Hypercalciuria is common, as are renal calculi and/or nephrocalcinosis. Hyperuricemia (Cohen *et al.*, 1985) must be treated because it can lead to gout and, above all, it participates in the constitution of stones, nephrocalcinosis, renal insufficiency (Reitsma-Bierens, 1993, Restaino *et al.*, 1993) and hypocitraturia (Weinstein *et al.*, 2001). Pulmonary hypertension is a rare complication and its prognosis is very poor (Pizzo, 1980; Furukawa *et al.*, 2001). Dyslipidemia seems to increase the risk of pancreatitis (Kikuchi *et al.*, 1991) but the risks of atherosclerosis and early cardiovascular complications do not seem to be higher (Trioche *et al.*, 2000).

Fertility is normal and a certain number of pregnancies have been reported in affected women. The risk of aggravating the renal involvement, the enhanced danger of hemorrhages and the need to assure a metabolic equilibrium for the fetus requires particularly close monitoring of these pregnancies (Ryan *et al.*, 1994).

Type Ib has a similar evolution. In addition to the type Ia signs, patients are generally neutropenic (only rarely absent: Kure *et al.*, 2000) with functionally abnormal monocytes (Bashan *et al.*, 1988), held responsible for recurrent infections (Seger *et al.*, 1984); they often have oral and intestinal mucosal ulcerations, and inflammatory intestinal diseases suggestive of Crohn's disease (Ambruso *et al.*, 1985; Roe *et al.*, 1992; Visser *et al.*, 2000).

Management including treatments

(Chen, 2000)

Treatment is essentially dietary, aimed at circumventing the metabolic disorders so as to avoid neurological involvement, assure normal growth and limit, as much as possible, long-term complications (hepatic, renal ...).

Treatment consists of frequent meals, continuous nocturnal enteral feeding rate (Greene *et al.*, 1976; Fernandes *et al.*, 1989; Wolsdorf *et al.*, 1999), ingestion of slow-absorption carbohydrates (Chen *et al.*, 1984), and restricted intake of fructose and galactose which can aggravate hyperlacticacidemia.

Caloric intake per day must be strictly monitored: insufficient intake does not correct the metabolic disorder (hypoglycemia, hyperlacticacidemia and hyperuricemia) and leads to retarded growth, whereas excessive intake increases the glycogen overload, hepatomegaly and hyperlipidemia, and cause obesity. The diet is high in carbohydrates (60–65% of caloric intake) and low in lipids (20–25% of caloric intake).

For newborns and infants

Frequent meals are recommended (5 meals per day) and continuous nocturnal feeding via a nasogastric tube (providing 8–10 mg of glucose/kg/min then 5–7 mg/kg/min).

After 18 months

Uncooked cornstarch in 1 or 2 doses of 1–2 g/kg/dose per night can replace the continuous nocturnal feeding (Chen, 2000).

Therapeutic adjuvants include vitamin supplements, calcium to prevent osteopenia and allopurinol when hyperuricemia is present (Chen, 2000). Efficacy of angiotensin-converting enzyme (ACE) inhibitors in preventing renal complications remains to be demonstrated.

Treatment efficacy is evaluated by monitoring clinical (growth curve, degree of hepatomegaly, blood pressure, ...) and biological parameters: preprandial glycemia (> 3.5 mmol/L), urinary lactates (< 0.6 mmol/L in urine night and day), triglyceridemia, cholesterolemia, uricemia, proteinuria and complete blood count (anemia is common).

Portocaval shunts were recommended in the past but accorded very limited clinical benefit and have been abandoned. Treatment of complications consists of liver transplantation should dietary control fail or hepatic adenomas undergo malignant transformation but no explanted liver has ever been shown to have confirmed hepatocarcinoma (Faivre *et al.*, 1999). Liver grafting corrects the hypoglycemia and the other biochemical anomalies (Koestinger *et al.*, 2000), but not the neutropenia observed in type Ib, and it has not been proven that it can prevent renal involvement. Kidney transplantation, performed in the case of severe renal insufficiency, does not correct the hypoglycemia (Emmett and Narins, 1978). Should grafting be indicated, the possibility of a dual liver–kidney graft has been discussed but not performed to date.

For glycogenosis type Ib, granulocyte and granulocyte–macrophage colony-stimulating factors (G- and GM-CSF) are able to correct the neutropenia (Schroten *et al.*, 1991), reduce the severity of bacterial infections and attenuate inflammatory intestinal disease (Roe *et al.*, 1992).

Etiology

Glycogenoses type I are caused by a defective glucose-6-phosphatase (G6Pase), which catalyzes the hydrolysis of G6P into phosphate and glucose. This reaction plays a key role in the regulation of glycemia because it controls the ultimate step of glycogenolysis and neoglucogenesis.

GSD I was first described by von Gierke in 1929. Cori and Cori showed, in 1952, that the disease was caused by a deficit in G6Pase, an enzyme expressed mainly in the liver and kidney and, to a lesser degree, in the intestine and pancreas. Subsequently, it was found that some patients are not deficient in G6Pase, even though a number of functional tests demonstrated their inability to degrade G6P *in vivo*: this condition was called glycogenosis Ib by Senior and Loridan (1968). To explain this defect, Arion *et al.* (1975) hypothesized that G6P hydrolysis required the participation of several membrane proteins: a catalytic unit (G6Pase) capable of hydrolyzing several phosphate esters (G6P, mannose-6-phosphate, carbamylphosphate and pyrophosphate) and a G6P-specific bidirectional translocase (G6PT1), which would assure its entry into the lumen of the endoplasmic reticulum, where G6Pase exerts its action. A G6Pase deficiency is responsible for glycogenosis type Ia ([MIM 232200](#)) and a G6PT1 deficit causes glycogenosis type Ib ([MIM 232220](#)). Nordlie *et al.*, (1983) described a

patient with glycogenosis type Ic ([MIM 232240](#)), who had a deficit in a bidirectional translocase specific to phosphate (G6PT2) which allowed phosphate to leave the endoplasmic reticulum resulting in G6P hydrolysis outside the endoplasmic reticulum. The existence of this glycogenosis type Ic was put in doubt when mutations in the gene encoding G6PT1 were identified in some of these patients (Veiga-da-Cunha *et al.*, 1998). Indeed, Lin *et al.*, (1999) did not find any mutation in the gene encoding G6PT1 in the patient originally described by Nordlie *et al.*, thereby suggesting that another protein was responsible in this patient. The existence of glycogenosis type Id, attributed to a deficit in a translocase (G6PT3), enabling glucose to exit the endoplasmic reticulum, has never been proven and the hypothesis that the cDNA of the glucose transporter GLUT7 would code for this transporter was shown to be incorrect.

G6Pase (EC: 3.1.3.9): This enzyme has never been sufficiently purified to allow its molecular characterization. The cDNA of murine G6Pase was isolated first (Shelly *et al.*, 1993), then the highly homologous human G6Pase (Lei *et al.*, 1993). The gene is around 12.5 kb long, includes 5 exons and was localized on chromosome 17 at 17q21. Its promoter contains several response elements for glucocorticoids, cyclic AMP and insulin, and is regulated by hepatocyte nuclear factors that control its expression (van de Werve *et al.*, 2000). According to the amino-acid sequence, the predicted structure is that of a highly hydrophobic protein, 357 amino acids long and containing 9 transmembrane helices, whose N-terminal end is situated in the endoplasmic reticulum lumen and whose C-terminal end is in the cytoplasm (Chou and Mansfield, 1999).

G6P translocase (G6PT): Identification of its gene combined two approaches: linkage studies (Annabi *et al.*, 1998; Fenske *et al.*, 1998) and the use of probable homology with bacterial transporters of monophosphate esters to isolate cDNA (Gerin *et al.*, 1997), before determining the complete structure of the gene (Marcolongo *et al.*, 1998; Gerin *et al.*, 1999). The gene is 4.5 kb long and contains 9 exons, 8 of which are expressed in the liver, and it was localized on chromosome 11 at 11q23 (Annabi *et al.*, 1998).

Unlike the gene encoding G6Pase, the *G6PT1* gene is expressed in many adult and fetal tissues, but it is expressed later (at least in animal models: Pan *et al.*, 1998). This expression is particularly important in the liver, pancreas, kidney and hematopoietic progenitor cells (Ihara *et al.*, 2000). Tissue-specific splicing can explain 6 variants, but their significance has not yet been elucidated (Middlewirth *et al.*, 1998;

Gerin *et al.*, 1999); the SV5 variant, expressed in the brain, heart and skeletal muscles contains exon VII which codes for 22 extra amino acids not present in the liver enzyme. *G6PT1* gene expression in hepatic cells is affected, like that of G6Pase, by glucose, insulin and cyclic AMP (van de Werve *et al.*, 2000). G6PT is a highly hydrophobic protein, 429 amino acids long in the liver, consisting of 10 transmembrane domains and whose N- and C-terminal extremities are both situated in the lumen of the endoplasmic reticulum. Its role, in addition to that in the G6Pase system, has not yet been elucidated (Mechin and van de Werve, 2000): its much weaker expression in peripheral blood cells than in hematopoietic progenitor cells suggests a role in the differentiation of neutrophils, which are abnormal in GSD Ib (Ihara *et al.*, 2000). Finally, the new diagnostic test proposed by Verhoeven *et al.* (1999) shows that the stimulation of oxidative stress induced by extracellular glucose in the presence of phorbol myristate acetate (PMA) is defective in the neutrophils of patients with GSD Ib.

Biological methods of diagnosis (Maire *et al.*, 1991)

The basic work-up

The basic work-up of fasting blood analyses reveals hypoglycemia, hyperlacticacidemia, hypertriglyceridemia, hypercholesterolemia and hyperuricemia in about half of the patients.

Indirect tests

Indirect tests show the absence of a glycemic response and an aggravation of hyperlacticacidemia after injection of glucagon (1 mg/m² of body surface) in a fasting patient or 2 hours after a meal rich in carbohydrates. Galactose injection (1 g/kg) neither corrects the hypoglycemia nor induces hyperglycemia.

Study of the G6Pase system in a liver biopsy

The biochemical diagnosis of GSD I requires a liver biopsy (ideally fresh not frozen), sufficiently large to enable the analysis of the different constituents of the G6Pase system. A homogenate is prepared under conditions maintaining or not microsomal membrane integrity and hydrolytic activity is measured using several substrates: mannose-6-phosphate (to evaluate microsomal membrane integrity), G6P and pyrophosphate.

In type Ia

In type Ia, hydrolytic activity is defective, regardless of the substrate used and the status of microsomal membranes.

In type Ib

In type Ib, G6P activity is defective when microsomal membranes are intact.

Molecular studies

GSD Ia

(Rake *et al.*, 2000; Janecke *et al.*, 2001)

About 350 unrelated patients affected with GSD Ia have been studied worldwide and more than 60 mutations have been identified, the majority of which are missense mutations. Several could not be identified. Only some of the mutations have a significant frequency:

- In the Caucasian population, R83C and Q347X are found in 55–63% of the GSD Ia alleles in most studies.
- In Hispanic Americans, the 459 insTA mutation appears relatively frequently.
- In Chinese, the Q347X mutation has never been found and R83C only once, however, R83H is present in around 40% of the mutated alleles (Lee *et al.*, 1996).
- In Japanese, the Q347X and R83C mutations have never been found, R83H is very rare, but the silent nucleotide change 727G-->T, responsible for the deletion of 91 nucleotides in exon V in the cDNA, is present in > 92% of the GSD Ia alleles in this population (Akanuma *et al.*, 2000).

Some of these mutations were expressed (Bruni *et al.*, 1999; Chou and Mansfield, 1999): missense mutations that affect the active site (R83) or transmembrane helices almost always abolish enzymatic activity (only the G222R mutation retains approximately 4% residual activity), while some of those affecting the two large intraluminal loops conserve residual activity (E110Q: 18%; and W236R: 4%).

Genotype–phenotype correlations could not be established based on the results of molecular studies.

It should be noted that the subject considered to have variant GSD IaSP, which supposes the existence of a stabilizing protein (SP) for the catalytic unit (Burchell *et al.*, 1990), was shown to be homozygous for the R83C mutation, typical of type Ia.

GSD Ib

In the major transcript exon VII is missing and a 5' part of exon I and a 3' portion of exon IX are not expressed: no *GSD Ib* mutation was found there.

More than 70 patients have been studied to date and more than 50 mutations have been identified (Veiga-da-Cunha *et al.*, 1999; Santer *et al.*, 2000). Among the patients previously reported to have GSD Ic or Id, 8 of the 11 mutations

identified were also present in patients with GSD 1b and a ninth had a mutation affecting an extremely well-conserved arginine, R300 (Veiga-da-Cunha *et al.*, 1998). It is probable that certain patients diagnosed as having type 1c or 1d indeed belong to the same allelic group as those with type 1b. Nevertheless, no mutation in the G6PT1 protein was found in the first patient described by Nordlie *et al.* (Lin *et al.*, 1999).

Molecular heterogeneity varies widely but several mutations predominate and vary according to the population. W188R is present in more than 55% of the Japanese patients' GSD 1b alleles (10/18) (Kure *et al.*, 1998), whereas 1211delCT and G339C are the most common in the Caucasian population, where they represent half of the GSD 1b genes studied (Veiga-da-Cunha *et al.*, 1999).

Testing the most common G6Pase and G6PT mutations can provide the diagnosis in the majority of patients thereby eliminating the need for a liver biopsy, which nonetheless remains necessary in approximately 30% of the cases.

Genetic counseling

Identification of the mutations in a given family enables the diagnosis of heterozygous members of the extended family and facilitates their genetic counseling. The rarity of the disease in the general population and the good response of most patients to dietary control render recourse to prenatal testing rare. Nonetheless, some children respond poorly to the diet and require a liver transplant. In addition, glycogenosis type 1b is often accompanied by severe infections and intestinal inflammatory syndrome.

Prenatal diagnosis

Of glycogenosis type 1a

Previously, biochemical diagnosis was needing a sufficiently large fetal liver biopsy which could only be obtained with difficulty and late during the pregnancy (Golbus *et al.*, 1988): indeed, studies on the ontogeny of the G6Pase system in rat and mouse liver and kidney demonstrated its weak expression in the fetal liver (Pan *et al.*, 1998), thereby explaining the biochemical diagnosis errors. The identification of mutations in the family henceforth enables less-invasive, early and reliable molecular diagnosis (Qu *et al.*, 1986; Wong, 1996).

Of glycogenosis type 1b

This diagnosis was impossible until the discovery of the gene. Molecular studies have made it reliable and easy to perform when the familial mutations have been identified (Lam *et al.*, 2000).

Unresolved questions and comments

Surgery requires special precautions in these patients at increased risk of hemorrhages and metabolic imbalances (hypoglycemia and hyperlactacidemia): glycemia must be maintained (perfusions of 10% glucose, before, during and after the intervention) and solutions containing lactate should be avoided (Ringer's, for example).

The existence or not of glycogenosis type 1c remains incompletely resolved at this time.

Finally, it remains to elucidate the nature of the interactions between G6Pase and G6PT, and the G6PT functions other than G6P transport. The creation of animal models, made possible by the identification of the gene coding for G6Pase and G6PT, should provide answers to these questions and improve our understanding of the pathophysiology of these diseases. Lastly, these animal models serve as indispensable tools for therapeutic trials.

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