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Hypercholesterolemia in a GSD III patient with a novel genotype

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Introduction

Glycogen storage disease III or Cori-Forbes disease (MIM# 232400) is an autosomal recessive metabolic disorder caused by deficiency of the glycogen debrancher enzyme (amylo-1,6-glucosidase, EC 3.2.1.33). It is associated with accumulation of abnormal glycogen with short outer chains. Most patients are enzyme-deficient in both liver and muscle (IIIa), but about 15% are enzyme-deficient in liver only (IIIb) (1). These subtypes have been explained by differences in tissue expression of the deficient enzyme (2). In rare cases, selective loss of only 1 of the 2 debranching activities, glucosidase or transferase, results in type IIIc or IIId, respectively (3).

Clinically, patients with GSD III present in infancy or early childhood with hepatomegaly, hypoglycemia, and growth retardation. Muscle weakness in GSD III is minimal in childhood but can become more severe in adults; some patients develop cardiomyopathy (1). We report a GSD III patient with a novel genotype. In early infancy the patient presented in a classical way with hypercholesterolemia.

Case report

A boy of 1 year and 7 months old presented with a retarded growth (weight 7845 g (p < -2.5 SD) and length 69 cm (p <– 3.5 SD)). He was the second child of non-consanguineous healthy Dutch parents born after uncomplicated pregnancy and birth. At birth, he had a normal height and weight (0 SD) which changed after 3 months to < -2.5 SD. His mental development was normal but his motor development was delayed. He was hypotonic and coordination problems were noticed; no further neurological problems were reported. At the age of 8 months, he was able to roll over and at 10 months of age, he could sit independently. Noteworthy, his parents stated that the patient had a constant demand for food and ate every 2 hours. Physical examination revealed a dystrophic child with protuberant abdomen due to hepatomegaly. Echo abdomen showed a homogeneous liver with normal bile ducts and veins. Normal kidneys were seen. Cardiomegaly was excluded by a normal ECG and echo cor.

Initial lab tests showed a very high cholesterol of 14.1 mmol/l (ref. 18 m-3 y of 1.1-4.5 mmol/l) with a LDL-cholesterol of 11.8 mmol/l (ref. 3.5-4.4 mmol/l), HDL-cholesterol of 0.5 mmol/l (0.9-1.7 mmol/l) and triglycerides of 3.9 mmol/l (0.8-2.0 mmol/l). Both parents had normal plasma cholesterol concentrations of 4.3 and 5.0 mmol/l respectively. In addition, liver enzymes were increased with gamma-glutamyltransferase of 365 IU/l (ref. < 50 IU/l), ASAT of 657 IU/l (ref. <35 IU/l), ALAT of 389 (ref. < 45 IU/l) and LD of 1020 IU/l (ref. < 480 IU/l). With exception of one low fasting glucose (1.9 mmol/l) normal concentrations of blood glucose and lactate were found. Uric acid values in plasma were found normal as well. Metabolic screening of urine showed tetraglucose $(Glc)_4$ in oligosaccharide analysis (figure 1), a compound seen in some GSD subtypes.

The activity of the debrancher enzyme in erythrocytes was 1.9 nmol/24h/mg Hb (ref. 8-34 nmol/24h/mg Hb) which confirmed the diagnosis of GSD III. The reference enzyme phosphorylase kinase (GSD IX) was normal (15 nmol/24h/mg Hb; ref. 6-19 nmol/24h/mg Hb). Mutation analysis revealed compound heterozygosity for p.Arg408X, c.1222C>T mutation in exon 11 and the p.Lys707fs, c.21202121delAA mutation in exon 17 of the amyloglucosidase (*AGL*) gene. The mother is carrier of c.1222C>T mutation and the father is carrier of c.21202121delAA mutation.

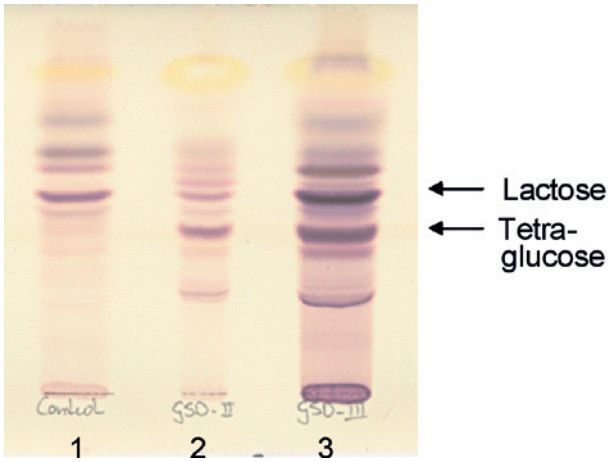

Figure 1. Thin layer chromatogram of urinary oligosaccharides of a young control person (lane 1), a GSD II patient (lane 2) and the GSD III patient (lane 3).

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At first presentation, a hyperlipidemia/hepatomegaly dietary therapy, consisting of frequent meals with high carbohydrate intake (200-250 g/day) and fat restriction (only 5-energy%; normally 35-energy%), was initiated. Total daily energy intake was 1100 kcal. After diagnosis of GSD III, fat intake was increased from 5 to 22 energy-% with an increase in protein intake and continuation of high carbohydrates intake (65-energy%). In addition, continuous drip feeding during the night was started (400 kcal; 60-energy% carbohydrates; 20-energy % fat).
Initial high cholesterol concentrations decreased dramatically from 14.1 mmol/l to 2.3 mmol/l within two months, after start of therapy with concomitant improvement of liver functions. Hepatomegaly was still noticeable. Upon start of dietary therapy, clear catch-up of growth was noticed and motor development progressed adequately.

Discussion

This paper describes a young GSD III patient with hepatomegaly, growth retardation and high plasma cholesterol. Upon onset of dietary therapy, the latter decreased dramatically to (low-) normal concentrations. This may be considered as a temporal derangement in the cholesterol metabolism.
In GSD III, degradation of glycogen to glucose is defective due to genetic changes in the *AGL* gene encoding a bifunctional enzyme with two catalytic sites which has both oligo-1,4→1,4-glucantransferase as well as amylo-1,6-glucosidase activity (4).
Due to stagnation in the glycogenolysis, increased β-oxidation of fatty acids is postulated in GSD III patients during fasting. This results in increased fatty acid flux from adipose tissue to the liver (5). Fatty acids serve as alternative source of fuel and the fatty acid flux explains high triglyceride concentrations in the GSD III patient. The origin of the high initial cholesterol concentration remains unexplained.
Hypercholesterolemia with markedly decreased HDL-cholesterol and increased LDL-cholesterol levels in combination with a mild hypertriglyceridemia has been reported in GSD III patients. It is more common in children younger than 3 years of age with GSD III (5) than in older patients in whom abnormalities of plasma lipid and lipoprotein profiles are not often observed (6).
In GSD I patients (defect in glucose-6-phosphatase), normally presenting with quite high triglycerides and moderately elevated cholesterol, hyperlipidemia is postulated to develop because of an increase of acetyl-CoA and increased synthesis of fatty acids and cholesterol in the liver (7). We speculate that increased acetyl-CoA due to enhanced beta-oxidation together with liver dysfunction could explain the initial high cholesterol values. Prevention of fasting by continuous feeding with high carbohydrate and fat restriction probably improved liver function. This contributes to normalization of plasma cholesterol concentrations in the GSD III patient.
One of the mutations described in the patient is the c.1222C>T mutation that has been described in 6 children with GSD IIIa, with liver and muscle involvement. The mutation was not detected in 198 German newborns. However, on the Faroe Isles, 9 of 272 newborns were heterozygous, predicting a carrier frequency of 1 in 30 and a calculated prevalence of 1 per 3,600 in the Faroese population (8).
The other mutation, c.21202121delAA, has not been previously reported. We suggest it to cause premature truncation of the protein and hence to be pathogenic. Compound heterozygosity of the patient for these mutations in AGL gene led to classical GSD III phenotype with hepatomegaly and childhood onset growth retardation.
Furthermore, hyperlipidemia, normal blood glucose, lactate and uric acid were found. So far, no clear myopathic features have been noticed. Remarkable was normalization of plasma cholesterol upon dietary therapy. It is uncertain how the disease will further develop. After all, in patients with GSD III progressive liver cirrhosis and failure in addition to cardiomegaly have been described to occur even in childhood (9, 10).

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