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Reversal of glycogen storage disease type IIIa-related cardiomyopathy with modification of diet

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Summary

Glycogen storage disease type III (GSD III) is caused by a deficiency in debranching enzyme, which leads to an accumulation of abnormal glycogen called limit dextrin in affected tissues. Muscle and liver involvement is present in GSD type IIIa, while the defect is limited to the liver only in GSD type IIIb. Besides skeletal muscle involvement, a cardiomyopathy resembling idiopathic hypertrophic cardiomyopathy is seen. Management consists of maintaining normoglycaemia by supplementation with cornstarch therapy and/or protein. While studies are lacking regarding the best treatment for skeletal muscle disease, a high-protein diet was previously reported to be beneficial. No cases of improvement in cardiomyopathy have been reported. Our patient presented in infancy with hypoglycaemia and hepatomegaly. His prescribed management consisted of cornstarch supplementation and a high-protein diet providing 20% of his total energy needs. At 16 years of age, he developed a severe cardiomyopathy with a left ventricular mass index of 209 g/m². The cardiomyopathy remained stable on a protein intake of 20–25% of total energy. At age 22 years, the diet was changed to increase his protein intake to 30% of total energy and minimize his cornstarch therapy to only what was required to maintain normoglycaemia.

Dramatic improvement in the cardiomyopathy occurred. Over one year, his left ventricular mass index decreased from 159.7 g/m² to 78 g/m² (normal 50–86 g/m²) and the creatine kinase levels decreased from 455 U/L to 282 U/L. Avoidance of overtreatment with carbohydrate and a high-protein diet can reverse and may prevent cardiomyopathy.

Introduction

Glycogen storage disease type III (GSD III) is caused by a deficiency of debranching enzyme. The debranching enzyme is a single polypeptide with two catalytic sites, amylo- α -1,6-glucosidase (EC 3.2.1.33) and 4- α -glucanotransferase (EC 2.4.1.25) (Bates et al 1975; Liu et al 1991). During glycogenolysis, the glycogen phosphorylase enzyme (E.C. 2.4.1.1) cleaves the peripheral glucosyl residues until four residues remain before the α -1,6 branch point. The terminal three residues are then transferred to another branch by the transferase component of the debranching enzyme. The glucosidase component of the debranching enzyme then cleaves the α -1,6 branch point. When the debranching enzyme is deficient, only the peripheral glucosyl residues can be cleaved and an abnormal glycogen called limit dextrin accumulates (Chen 2001). Deficiency of the enzyme in liver and muscle is seen in 85% of patients and is designated as type IIIa; about 15% are enzyme-deficient in liver only and are designated as type IIIb (Bao et al 1997; Shen et al 1996).

GSD III is characterized by variability in enzyme activity and clinical heterogeneity. Hepatomegaly and hypoglycaemia predominate in childhood as seen in GSD I (Wolfsdorf and Weinstein 2003). However, in GSD III, hyperuricaemia and lactic acidosis are not prominent, hyperlipidaemia is not as significant, and serum hepatic transaminase concentrations are higher. Liver size and transaminase levels decrease in adolescence (Coleman et al 1992). Liver failure and cirrhosis can occur and both adenomas and hepatocellular carcinoma have been reported (Fellows et al 1983; Momoi et al 1992). In type IIIa, muscle weakness is minimal in childhood and gradually progresses into adulthood (DiMauro et al 1979; Talente et al 1994). Creatine kinase (CK) levels usually become elevated once children are active (Talente et al 1994). Besides skeletal muscle involvement, cardiomyopathy that resembles idiopathic hypertrophic cardiomyopathy on echocardiogram may be seen (Labrune et al 1991; Lee et al 1997; Moses et al 1989). The clinical significance of the cardiomyopathy is unclear. While most patients are usually asymptomatic (Lee et al 1997), severe cardiac dysfunction, congestive heart failure, arrhythmias, and sudden death have been reported (DiMauro et al 1979; Miller et al 1972; Olson et al 1984; Rossignol et al 1979).

There is no consensus regarding management of GSD III. Treatment consists of maintaining normoglycaemia by cornstarch therapy or continuous night-time feeds with oligosaccharides and protein. A high-protein diet is recommended as gluconeogenesis is intact. It is commonly believed that there is no treatment for the myopathy, which is often considered irreversible. Slonim and colleagues (1982, 1984) and Kiechl and colleagues (1999) have reported improvement in muscle strength and electromyographic findings on a high-protein diet. To our knowledge, there are no cases of improvement in GSD III-related cardiomyopathy in the literature. In this report, we present a case of reversal of severe cardiomyopathy after initiation of a high-protein diet with avoidance of overtreatment with carbohydrate.

Case report

Our patient is a white male born to non-consanguineous parents after an uncomplicated pregnancy. Delivery was via Caesarean section owing to decelerations noted during labour. His nursery course was complicated by a generalized seizure with reportedly normal

electroencephalogram and glucose levels. He experienced another seizure at week 2 of life and was started on phenobarbital, which was later discontinued at 3 months of life. At 6 months of age on a routine 'well child' visit, the patient was noted to have a protuberant abdomen and hepatomegaly extending down to the iliac crest. The blood glucose was 27 mg/dl, and he had markedly elevated hepatic transaminase concentrations with AST 1599 U/L and ALT 906 U/L. Additional evaluation included normal lactic acid and mildly elevated uric acid at 8.4 mg/dl. Dietary modifications including four-hourly feeds with soy-based formula supplemented with a glucose oligosaccharide resulted in significant improvement in the liver size as well as liver enzymes (AST 285 U/L, ALT 404 U/L) over 2 months. Diagnosis of GSD III was confirmed on the basis of retention of limit dextrin in cultured fibroblasts exposed to media lacking in glucose.

As he progressed through childhood, his hypoglycaemia became less problematic, but he experienced poor growth, persistent hepatomegaly, and elevated liver and muscle enzymes along with hypertriglyceridaemia (Table 1). Management during childhood consisted of cornstarch supplementation with a high-protein diet formulated to provide 20% of total energy. The high-protein diet was not always adhered to because of aversion to high-protein foods and resistance to night-time tube feeds.

During adolescence, his hypoglycaemia resolved, and his liver size improved from 9 cm below the left costal margin to 2 cm below the costal margin. No muscle weakness was reported by the patient. Laboratory tests showed continued elevation in CK concentrations, less prominent hepatic transaminase elevations, and improved triglycerides (Table 1).

At 16 years of age, an echocardiogram was obtained after a new murmur was identified, and he was found to have hypertrophic cardiomyopathy. The initial echocardiogram showed a left ventricular mass index of 209 g/m² with otherwise normal cardiac anatomy and normal biventricular systolic function. Based on the prior reports by Slonim and colleagues (1982, 1984), the patient was prescribed a diet providing 25% of energy from protein, but compliance was not optimal. At age 20 years, the patient's protein intake improved to the recommended target. The cardiomyopathy remained stable but no improvement was noted on his annual echocardiograms (Table 2).

At 22 years of age, we increased his protein intake to provide 30% of total energy, and his cornstarch intake was decreased to a minimum amount required to maintain normoglycaemia (from 2.95 g/kg divided three times a day to 1.36 g/kg divided twice a day). This dietary change led to a dramatic improvement in the cardiomyopathy over one year, with the left ventricular mass index decreasing from 159.7 g/m² to 78 g/m² (normal 50–86 g/m²) and the CK level decreasing from 455 U/L to 282 U/L (Fig. 1; Table 2).

Discussion

GSD III-related cardiomyopathy is common. Cardiomyopathy in GSD III is representative of a storage process and glycogen accumulates between the myofilament bundles (Olson et al 1984). Focal fibrosis has also been reported in a patient with GSD III who developed dilated phase of hypertrophic cardiomyopathy (Akazawa et al 1997).

Echocardiographic evidence of cardiomyopathy is seen in 31–65% of patients with GSD III based on several series (Carvalho et al 1993; Labrune et al 1991; Lee et al 1997; Miller et al 1972; Moses et al 1989). Most patients are asymptomatic and the clinical significance is uncertain. Clinically evident cardiac involvement is believed to be rare in childhood and adolescence, but cases of cardiac decompensation in childhood have been reported (DiMauro et al 1979; Lee et al 1997; Miller et al 1972; Moses et al 1989; Olson et al 1984; Rossignol et al 1979). Lee and colleagues (1997) showed that GSD III patients with

cardiomyopathy have relatively normal response to thallium scintigraphy and exercise stress test as compared to non-GSD patients with idiopathic hypertrophic cardiomyopathy in spite of the similar appearance of the two on echocardiography.

Treatment in GSD III remains controversial. While some have advocated a high-protein diet in this condition with protein providing 25% of the energy, this recommendation is based upon limited data and has only demonstrated improvement with the skeletal myopathy. With our case, we provide evidence that cardiomyopathy may also be reversible with appropriate dietary management. It should be noted, however, that no histological studies were performed to confirm the echocardiographic evidence of improvement.

In GSD III, gluconeogenesis is intact and protein may be used as a precursor for glucose. Overtreatment with cornstarch can cause deposition of glycogen, which cannot be broken down, leading to accumulation. This case report demonstrates that a diet providing 30% of energy from protein and avoidance of over-treatment with carbohydrate can stabilize and even reverse cardiomyopathy.

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Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
CK	creatine kinase
GSD	glycogen storage disease

Fig. 1. Graphical representation of left ventricular mass indices and CK levels. *Represents protein intake of 2.5 g/kg. §Represents protein intake of 3 g/kg with restriction of cornstarch

Table 1
Laboratory data over time. Range of values for AST, ALT, CK and triglycerides in childhood and adolescence

Age	AST (U/L) (Normal 0–37)	ALT (U/L) (Normal 0–41)	CK (U/L) (Normal 30–170)	Triglycerides (mg/dl) (Normal 45–149)
Initial	1599	906	Not obtained	Not obtained
Childhood (1–12 years)	132–493	118–610	467–1394	134–1233
Adolescence (13–19 years)	73–199	108–197	391–1223	93–210

Table 2
Echocardiographic parameter values from age 17 to 23 years

	Age (years)				
	17	19	21	22	23
Left ventricular mass (g)	315.9	343.2	278.8	284.2	142.9
Left ventricular mass index (g/m ²)	235.8	190.0	157.5	159.7	78.0