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Glycogen Storage Disease Type III Presenting as Recurrent Seizure Disorder in a Second Twin: A Case Report

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Abstract

Glycogen storage diseases (GSDs) are a group of genetic autosomal recessive metabolic disorders resulting from deficiencies of enzymes of glycogen metabolism occurring in the liver, muscles or kidneys. Various types and sub-types exist based on genetic classification presenting with symptoms and signs of hypoglycaemia, hepatomegaly and myopathy depending on severity, and age of onset. A high index of suspicion is required for the diagnosis of GSDs. An eighteen-month-old girl who was apparently healthy with normal development was without any abnormality until about 12 months of age when she had the first episode of afebrile seizure which was treated with sodium valproate but continued to have occasional seizures. She had a status seizure, which was only aborted with a glucose infusion. Intra-ictal incident glucose level was 1.4mmol/L. Biochemical investigation revealed deranged liver enzymes, normal serum cortisol, C-peptide and insulin. Liver histology showed features consistent with GSD III and diagnosis of glycogen storage disease type III was made based on the liver histology and other supportive laboratory features. Following dietary management, the child responded very well, was seizure-free and off anticonvulsant therapy. This case highlights the occurrence of symptomatic seizures due to factors other than epilepsy.

Keywords: Glycogen storage Disease, Recurrent, Seizure, Disorder

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Introduction

Glycogen-storage disease (GSD) type III (GSD III) is an autosomal recessive inborn error of metabolism caused by loss of function mutations of the glycogen debranching enzyme (Amylo-1,6-glucosidase [AGL]) gene, which is located at chromosome band 1p21.2 (Goldberg and Slonim, 1993). Glycogen debranching enzyme (GDE) is also referred to as "limit dextrinosis," "Cori," or "Forbes" disease (Goldberg and Slonim, 1993; Haagsma *et al*., 1997). GDE is one of the few known proteins with two independent catalytic activities occurring at separate sites on a single polypeptide chain. The two activities are transferase (1,4-α-d-glucan; 1,4-α-d-glucan 4-α-d-glycosyltransferase) and amyloid-1,6-glucosidase (Goldberg and Slonim, 1993). Both the debranching enzyme and phosphorylase enzyme are needed for the complete degradation of glycogen. GSD is characterized by the storage of structurally abnormal glycogen, termed limit dextrin, in both liver, skeletal and cardiac muscle with greater variability in resultant organ dysfunction Haagsma *et al*., 1997). The disease has been reported in many different ethnic groups including Caucasians, Africans, Hispanics, and Asians. It has been reported that there are remarkable variations in individuals with this disease, both clinically and enzymatically (Howell and Williams, 1983; Van Hoof and Hers, 1967). Approximately 85% of patients are GDE deficient in both the liver and muscle (type IIIa) and about 15% of patients have GDE absent in the liver but retained in muscle (type IIIb) (Angelini, Martinuzzi and Vergani, 1996). The latter two are extremely rare with only a handful of cases reported (Van Hoof and Hers, 1967; Ding *et al*., 1990; Sugie *et al*., 2001). Major manifestations of GSD III

include hypoglycemia, hepatomegaly with elevated transaminases, hyperlipidemia, hyperuricemia, and skeletal myopathy/cardiomyopathy with increased creatine phosphokinase (CPK). There is no specific treatment for GSDs, but dietary therapy improves symptoms (especially hypoglycemia), reduces liver size, and improves overall growth and development (Smit, Rake, Akman and DiMauro, 2006). Rare complications of GSDIII include liver cirrhosis and failure together with secondary glucose intolerance and frank diabetes (Ismail, 2009). It is important to recognize the condition early in order to manage it effectively and to prevent potential morbidity and mortality.

Case presentation

This is an eighteen-month-old girl, second twin, who was apparently healthy with normal development and without any abnormality until the weaning process commenced at 12 months of age when she had the first episode of afebrile seizure. She was placed on sodium valproate but continued to have occasional seizures. At 18 months, she was completely weaned off breast milk. Subsequently, within one month she was noticed to have become sluggish and had less physical activity compared to her former self and her twin sister with associated repeated afebrile seizures and a slowly progressive distended Abdomen. She had a sudden onset of status seizures which was only aborted with a glucose infusion. Intra-ictal incident glucose level was 1.4mmol/l. She also continues to have low blood sugar, especially early morning but it's usually mitigated by frequent meals. Pertinent findings on examination were mainly a round face, sparse hair distribution, and underweight with stunting, distended abdomen with huge hepatomegaly. Other systems were essentially normal

Initial 8:00 am serum cortisol revealed a lower level of 150 nmol/L (200 – 600). We thought of possible Adrenal insufficiency because of the recurrent hypoglycaemia and low serum cortisol. However, ACTH stimulation test using Synacthen revealed normal cortisol secretion; Basal level 311.29 nmol/L, at 30 minutes: 926.73 nmol/L, at 60 minutes: 1088.39 nmol/L. Other tests done are; liver function tests which showed raised Gamma GT: 519(1-32), ALT: 337 (3-37), AST: 678 (16-46). Lipid profile also revealed raised cholesterol of 9.2mmol/L (2.5-6.0) and LDL 7.2 (0.8-4.3), but HDL 1.2(0.8-2.6) was normal. Serum IGF-I, IGFBP3, C-peptide, Insulin, lipase, Urea/electrolyte & creatinine, thyroid function test, serum protein and complete blood count were all normal, except for mild normocytic normochromic anaemia. The serum level of Creatinine Kinase was normal (130U/L). An abdominal ultrasound scan revealed a hepatomegaly of 14cm. Viral markers: HBsAg, Anti HCV, Anti HAV, Anti HEV were all negative, and ECG and echocardiography were normal. The child was suspected to have an inborn error of metabolism most likely glycogen storage disorder based on findings of gradual abdominal distension, round face, massive hepatomegaly, hypercholesterolemia and abnormal liver enzymes. Diagnosis of Glycogen Storage Disease (GSD) type III was made based on liver histology which showed features consistent with GSD III: Hepatocytes with vacuolated cytoplasm and central nuclei were seen. Portal areas showed inflammatory infiltrate and fibrosis, and periodic acid-Schiff stains showed an accumulation of glycogen within the hepatocytes (Fig. I). The patient was put on dietary management which consists of a high protein and frequent round-the-clock carbohydrate diet including uncooked corn starch, low fatty diet, multivitamins, calcium and Iron supplementation. In addition, she is on feeding gastrostomy to ensure adequate feeding. She is currently relatively well-controlled and has continued to be free of hypoglycemic attacks, seizure-free and off antiepileptic therapy.

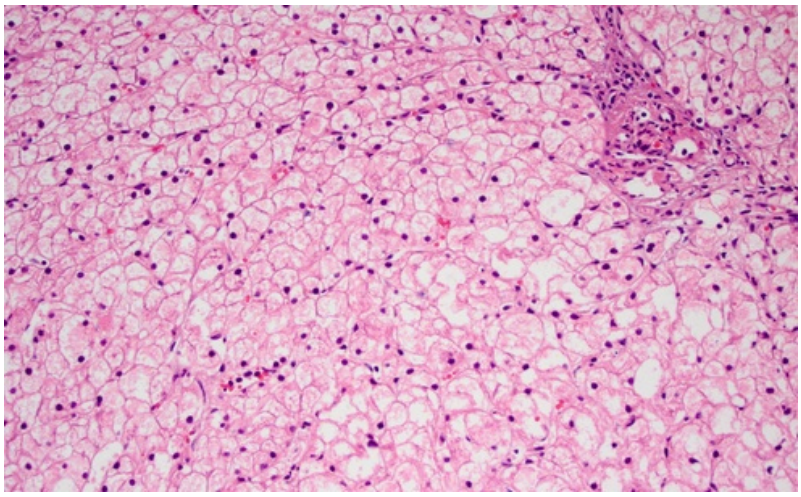

Figure I: *Swollen hepatocyte, lobular architecture is preserved with periportal fibrosis.*

Discussion

Glycogen Storage Disease type III is a metabolic disease that is inherited as an autosomal recessive disorder (Goldberg and Slonim, 1993). Major organs involved in various levels of severity are the Liver, skeletal muscle and heart (Goldberg and Slonim, 1993; Haagsma *et al*., 1997). The disease has variable presentation; poor growth, gross hepatomegaly, hypoglycemia and seizures Haagsma *et al*., 1997). Our patient also had a similar presentation.

In patients with hepatic involvement there is a protruded abdomen because of gross hepatomegaly and also have raised serum aminases and serum cholesterol. In our patient, hepatic involvement was predominant with no obvious cardiac and skeletal muscle involvement because the patient has normal serum CK levels, even though normal CK levels do not rule out muscle enzyme deficiency according to (Lee *et al*., 1995). In addition, muscle involvement in GSD IIIa is variable as some individuals have asymptomatic cardiomyopathy while some have symptomatic cardiomyopathy leading to death, and others have only skeletal muscle and no apparent heart involvement. This correlates with findings by (Hobson-Webb *et al*., 2010; Kotb *et al*., 2004). Hepatomegaly and hepatic symptoms in most individuals with type III GSD improve with age and usually resolve after puberty (Coleman *et al*., 1992). The apparent improvement may be related to a reduced relative glucose requirement. The decrease in liver size can be misleading as progressive liver cirrhosis and hepatic failure can occur, and some individuals develop end-stage liver cirrhosis, as reported by (Coleman *et al*., 1992; Labrune *et al*., 1997).

In our patient, there was frequent history suggestive of hypoglycemia, even though hypoglycemia is known to occur less frequently in GSD III as compared to type I. Patients with Glycogen storage disorder usually have normal cerebral development, and our patient has no clinical evidence of cerebral impairment.

The differential diagnosis of type III is extensive but the most common alternative diagnosis in the differential is GSD type I which initially was our diagnosis for this case. Features common to both disorders are hepatomegaly, hyperlipidemia, and hypoglycemia. These features are present in our case. However, there are some key differences between GSD I and III that helped us to differentiate these two disorders. We

thought of GSD I initially because individuals with GSD I typically present earlier (in the first few months of life) with severe fasting hypoglycemia 3 to 4 hours after a feed. In patients with GSD III, hypoglycemia is usually not as severe as in GSD I because of intact gluconeogenesis and the ability to metabolize peripheral branches of glycogen via phosphorylase (Clayton, 2003). We favoured GSD III because our patient presented at late infancy, 12 months of life, even though with symptoms of severe fasting hypoglycaemia, and there are cases of GSD III whose clinical onset is similar to that of GSD I. A similar finding was also reported by (Clayton, 2003). Laboratory features that further help us to distinguish between these two disorders are elevated uric acid and lactate concentrations in GSD I, which are typically normal in GSD III (Wolfsdorf *et al*., 1999). Our case has normal uric acid and lactate. In addition, our case has raised an AST level of 686U/L as commonly seen in GSD III patients. Individuals with GSD III have higher hepatic transaminase concentrations exceeding 500 U/L than GSD I (Wolfsdorf *et al*., 1999). Ultrasound imaging of the liver at baseline is similar in GSD I and GSD III, but the presence of nephromegaly in GSD type I can be a clue to the diagnosis (Lee *et al*., 1994). Our patient has no nephromegaly. Also, blood lactate concentrations rise rapidly in GSD type I as soon as hypoglycemia develops, whereas hyperketonemia with fasting is suggestive of GSD III. Our patient has normal serum lactate but has ketonuria (3+), even though we could not assay serum ketone.

Transaminase elevation and hepatomegaly are common to many primary hepatic diseases and other metabolic disorders but hypoglycemia is uncommon until the development of end-stage liver disease (ESLD) for most of the disorders except GSDs (Wolf and Lavine, 2000). The extent of the hepatomegaly is similar in types III, VI and IX GSD, and all of these (GSD III, VI, and IX) can have profound ketosis after an overnight fast but the extent of the hypoglycemia, transaminase elevation, and hyperlipidemia are usually more severe in GSD III. GSD type IV does not have hypoglycemia or ketone abnormalities until reaching the end stage, and liver dysfunction is usually more pronounced in GSD IV (Moses and Parvari, 2002). Other metabolic disorders such as Gaucher disease and Niemann-Pick disease may, initially, be confused with GSD because of the presence of hepatomegaly. In these storage disorders, however, splenomegaly is massive and helps in the differential diagnosis (Wolf and Lavine, 2000).

DNA mutation analysis can help confirm the diagnosis and provide information to predict the GSD III subtype, carrier testing, and prenatal or pre-implantation genetic diagnosis. Unfortunately, we could not do Enzyme analysis and DNA mutation and our diagnosis of GSD III was based on liver histology and other supportive laboratory features.

GSD III disease is a multisystem disorder best managed by a multidisciplinary team led by an experienced physician. All specialists involved in the care of the patient should have an understanding of the disease, and its challenges, including the psychological and emotional impact of the disease on patients and families. However, primary therapy is mainly dietary which should be tailored to the individual patient (Kishnani *et al*., 2010). Frequent feeds (every 3-4 hours) are needed to maintain euglycemia in infancy. Toward the end of the first year of life, several doses per day (~1 g/kg) of cornstarch may be required to avoid hypoglycemia. Protein intake of 3 g/kg is recommended; extra protein, high-class protein, and supplementation may be needed, because some amino acids serve as substrate for gluconeogenesis (Slonin *et al*., 1984). For those with night-time hypoglycemia, Glycosade® extended-release cornstarch or continuous nocturnal drip-feeding can be used. Vitamin D and calcium supplementation are important to prevent osteoporosis (Kishnani *et al*., 2010). [20]

The follow-up plan is blood glucose and ketones routinely, growth monitoring, USG, LFTs, CK, lipid profile, ECG and Echocardiogram to monitor for cardiomyopathy (Kishnani *et al*., 2010).
The cirrhosis found in some patients is of a mild degree and does not have a significant impact on the course of the disease, however progressive liver disease with liver fibrosis may occur throughout life. Prognosis is guarded but in cirrhotic cases outcome is very poor (Kishnani *et al*., 2010). Liver transplantation is reserved for those with severe hepatic cirrhosis, liver dysfunction, and/or hepatocellular carcinoma. Liver transplantation may exacerbate myopathy and cardiomyopathy.

Conclusion

This case highlights the occurrence of symptomatic seizures due to factors other than epilepsy; and the importance, in the correct clinical setting, of considering alternative, and sometimes treatable, causes of seizures other than idiopathic seizure disorder.

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