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Case Report

GYS2 gene Variant Leading to Glycogen Storage Disease Type 0 in an Adolescent Patient with an Unusual Presentation

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Abstract ***Introduction:*** Glycogen storage disease type 0 (GSD 0) is a rare congenital metabolic disorder that occurs due to the deficiency of glycogen synthase enzyme, caused by loss-of-function mutations of *GYS2*. We present an unusual case of GSD 0. ***Case presentation:*** Sixteen-year-old male was admitted due to elevated transaminase levels, hepatomegaly, and hepatosteatosis. He did not reveal any history of hypoglycaemia. Medical history revealed the death of two siblings due to unknown aetiology. Severe ketonuria was present at fasting. Metabolic tests were inconclusive. Molecular genetic analysis was performed to unravel the underlying aetiology that revealed a previously reported homozygous c.736C>T; p.(Arg246Ter) variant in *GYS2* (NM_021957), that is known to cause GSD type 0. ***Discussion:*** GSD type 0 is a very rare metabolic disorder that may be overlooked, mostly due to unspecific symptoms. No special diagnostic laboratory tests are available, and definitive diagnosis can only be made by molecular genetic analyses.

Key words Developmental delay; Glycogen storage disease type 0; *GYS2*; Hypoglycaemia; Ketosis

Introduction

Glycogen storage disease type 0 (GSD 0), is an autosomal recessively transmitted congenital metabolic disorder, that occurs due to the deficiency of glycogen synthase (GS) enzyme, caused by loss-of-function mutations of *GYS2* gene located on chromosome 12p12.2. Although the exact incidence is not known, it is considered to be rare, with nearly 30 cases reported worldwide.[1]

The deficient activity of GS leads to disruption of glycogen synthesis in liver, thus hepatic glycogen stores diminish. Main clinical signs are fasting hyperketotic hypoglycaemia and postprandial hyperglycaemia that become apparent in late infancy, when overnight feeds are ceased. In contrast to other types of GSDs, hepatomegaly (HM) and lactic acidemia is not observed. Attacks of hypoglycaemia may lead to seizures. Mild growth delay may occur. The disease may be overlooked, since the disorder may be asymptomatic. No special diagnostic laboratory tests are available, and definitive diagnosis can only be made by molecular genetic analyses. Treatment consists of frequent meals along with high protein intake, to prevent fasting.[2]

We present an usual case of GSD 0.

Case Presentation

A sixteen-year-old male patient was admitted due to elevated transaminase levels, HM, and hepatosteatosis. He was the 4th child of consanguineous parents of Syrian origin. His mother had a history of type 2 diabetes mellitus,

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hypertension, and hepatosteatosis that was considered to be related with obesity. His father had a diagnosis of Behçet's disease. The second, third, and fourth children of parents had died at age 5, due to unknown aetiology. They were both male and had hepatosteatosis and HM. The second child was a 23-year-old woman with nonspecific hepatic disease (Figure 1). The presented patient's previous medical history was also unclear.

He was initially evaluated in the paediatric gastroenterology clinic of an external centre. Alpha-1-antitrypsin, celiac markers, ceruloplasmin, and autoimmune markers were normal. Brucellosis was ruled out. Viral markers for TORCH and hepatitis, and reducing substance of urine were negative. Amlodipine treatment was initiated due to hypertension. He was referred to our centre to exclude underlying metabolic disease. He did not reveal any history of hypoglycaemia. He could fast as religious duty, since the age of 10, and did not have any complaints indicative of hypoglycaemia. No data of glucose and ketone levels during fasting were available, since he was asymptomatic during fasting. His only complaint was fatigue during prolonged exercise. Physical evaluation at the time of admission showed HM (liver was palpable 2 cm at mid-clavicular region). Weight and height were within normal centiles. His mental evaluation and physical development were normal. Initial laboratory analyses were as follows: Complete blood count, renal function tests, creatine kinase, insulin, lactate, and serum lipids were normal. Fasting blood glucose was detected 85 mg/dl (NR: 70-110). Ketonuria was present at fasting. Transaminases were elevated (Aspartate aminotransferase 78 U/L, Normal range-NR: <29), alanine aminotransferase 134 U/L, NR: 0-27, γ-glutamyl transferase 54 U/L (NR <45). Metabolic tests including ammonia, lactate, acylcarnitine profile, urine organic acids, plasma and urine amino acid analyses, and very long chain fatty acids were inconclusive. Postprandial hyperglycaemia and hyperlactataemia were ruled out by an oral galactose loading test. Abdominal ultrasonography showed HM and grade 2 hepatosteatosis. Lysosomal enzyme analysis of lysosomal acid lipase was found within normal limits, which ruled out acid-lipase deficiency. Echocardiography revealed normal cardiac findings. The ophthalmologic examination was normal.

Due to inconclusive findings of metabolic tests, molecular genetic analysis was performed to unravel the underlying aetiology. Targeted sequencing using SOPHIA hereditary disorder solution™ panel covering 569 genes revealed a previously reported homozygous c.736C>T; p.(Arg246Ter) variant in *GYS2* (NM_021957), that is known to cause GSD type 0 (ACMG criteria; PVS1, PM2, PP3, PP5) (Figure 2).

Frequent feeds with high protein intake were initiated, to prevent hypoglycaemia.

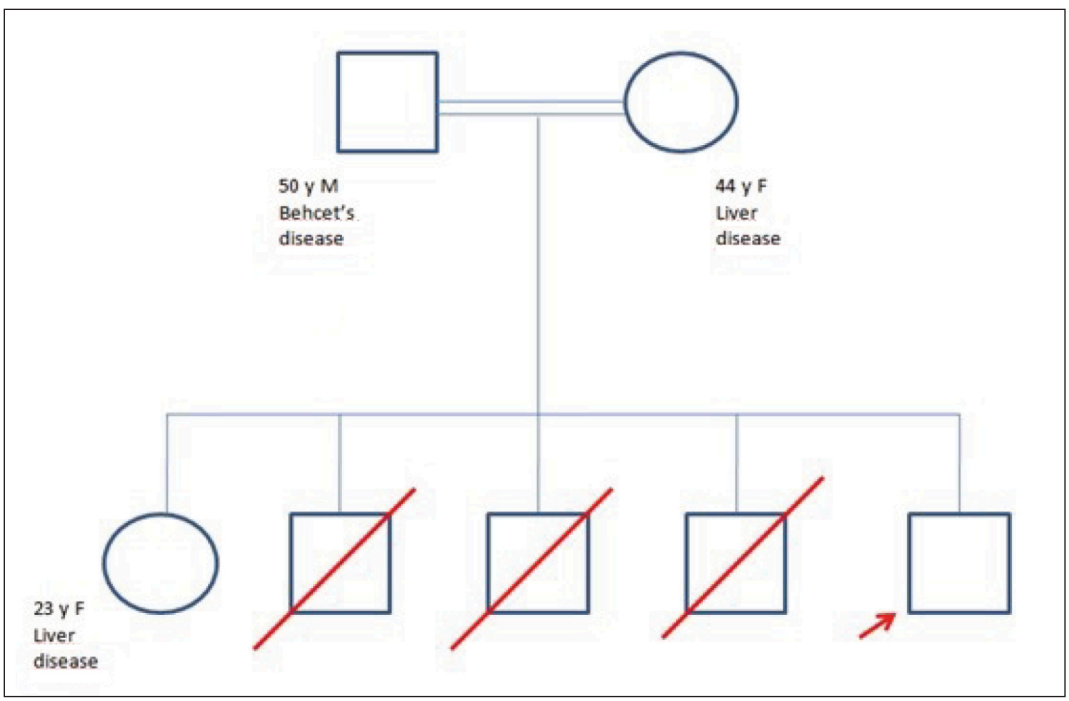

Figure 1 Pedigree of the presented case.

Discussion

GS catalyses the formation of α-1,4-linkages that elongate chains of glucose molecules to form glycogen. In GSD 0, only glycogen synthesis in the liver is impaired.[2] No specific clinical sign exists. Short stature may be suggestive.[1] Patients are prone to attacks of ketotic hypoglycaemia, especially at times of prolonged fasting. Transaminases are elevated. In contrast to other types of GSDs, other biochemical disturbances, including elevated lactate, uric acid, or lipids are not encountered. Hypoglycaemia is usually milder than other forms of GSDs since gluconeogenesis and fatty acid oxidation are intact. Hyperglycaemia and hyperlactataemia may be detected in the fed state, due to the shunting of dietary glucose from glycogenesis to the glycolytic pathway. A diminished response to the glucagon test is seen. Muscle, liver, and kidney pathologies seen in other types of GSDs have not been reported.[2]

Iijima et al have summarised the clinical and biochemical features of 33 patients with GSD 0a, and concluded that nonspecific fasting symptoms (lethargy, drowsiness, nausea, and irritability) were found in 39% of patients. All patients had a combination of fasting ketotic hypoglycaemia and postprandial hyperglycaemia/hyperlactataemia. Hepatomegaly and hepatic steatosis were reported in 12% and 73% of patients, respectively.[3] We believe this is the main factor contributing to the delayed diagnosis in our case. A notable peculiarity in our patient is the absence of hypoglycaemia throughout childhood.

Fatty liver has rarely been reported in GSD 0. de Kremer et al have presented a boy of Italian ancestry with hepatic deficiency with mild clinical symptoms contrasted with a remarkable fatty liver degeneration.[4] Unfortunately, genetic analysis of this patient is unavailable. Irimia et al have shown insulin resistance and hepatosteatosis in a mouse model of GSD 0, and have suggested the cause of fatty liver to be the diversion of glucose towards fat synthesis, correlating with impaired hepatic insulin signaling and glucose disposal.[5]

Liver biopsy may be inconclusive, since glycogen level is only moderately decreased, with a normal structure. Molecular genetic analysis of *GYS2* provides a simple and quick diagnosis to GSD 0.[2]

Prolonged fasting may lead to severe hyperketonaemia and increased free fatty acids that inhibit the release of alanine from skeletal muscle which is a gluconeogenic precursor.[4] Interestingly, the presented case does not have a laboratory finding of proven hypoglycaemia. He even can fast as a part of a religious practice for 16-18 hours. This finding is consistent with the literature, where

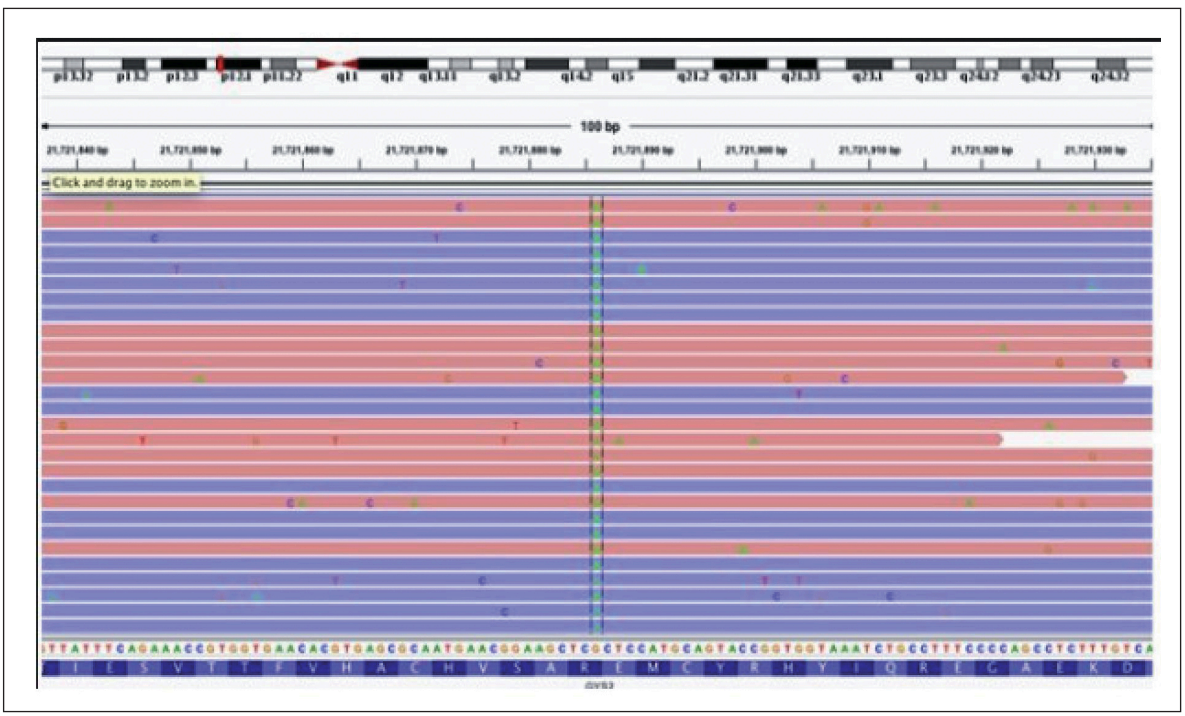

Figure 2 The image of molecular genetic analysis of *GYS2*.

children over 7 years of age have been reported to tolerate an overnight fast without hypoglycaemia, and fasting for up to 18 hours has been reported in teenagers. This may be explained by the asymptomatic nature of the disease and the tolerance of patients to sustained hypoglycaemia.[4] Nevertheless, since the risk of hyperglycaemia exists during a catabolic state, frequent feeds should be recommended.

In glycogen storage disease type 0, no clear genotype–phenotype correlation has been demonstrated. This reflects the rarity of the disorder and the predominance of private mutations, together with variable residual enzyme activity, compensatory metabolic pathways, dietary and hormonal influences, and possible genetic modifiers, all of which contribute to marked interindividual variability.[6] A mild mutation may lead to some residual enzyme activity that causes asymptomatic hyperglycaemia or ketotic hypoglycaemia during an acute illness and poor enteral intake.[4] The homozygous p.R246* variant is previously reported in GSD 0 patients of Italian and Turkish origin.[7-10] This variant leads to a premature stop codon that causes the loss of 65% of the COOH-terminal part of the protein, and the catalytic and the allosteric glucose-6-phosphate binding sites. It is initially defined in a 4-year-old Turkish boy with short stature and ketotic hypoglycaemia by Orho et al, who had practically normal glycogen concentrations and the least severe reduction in the GS activity, while this variant was shown to cause complete loss of GS activity in animal models.[6] None of the patients with the defined mutations have been reported to have HM and fatty liver.

Treatment includes frequent feeds with complex, low glycaemic index carbohydrates to prevent hypoglycaemia and ketonuria, and protein supplementation, to provide gluconeogenic precursors to support gluconeogenesis. This not only reduces systemic acidosis, but prevention of hyperketonaemia also enhances gluconeogenesis since more alanine can be released from skeletal muscle. Glucose supplementation is known to improve fatigue during exercise.[2]

Our reported case is a mild form of GSD 0, who probably had attacks of hypoglycaemia during childhood, but was missed due to being asymptomatic. He was evaluated in detail due to a history of liver disease and child death in the family, and molecular genetic panel testing led to a definitive diagnosis. Although the aetiology of the liver disease of his siblings remains unknown, an overlapping viral infection or an accompanying metabolic disease may be the most probable explanation. Our patient is still being followed up in our clinic for any further symptoms that may reveal family history.

Genetic panels are important diagnostic tools to unravel metabolic disorders with unspecific signs, and GSD 0 should be kept in mind in patients with ketotic hypoglycaemia and elevated transaminase levels. Our case report emphasizes that genetic panels are important diagnostic tools to unravel metabolic disorders with unspesific signs, and GSD 0 should be kept in mind in patients with ketotic hypoglycemia and elevated transaminase levels.

Declarations

Ethics Approval and Consent to Participate

Not applicable

Consent for Publication

Written informed consent has been received from the mother of the patient for this case report and the figures to be presented.

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