

Glycogen storage disease type 0 due to a novel frameshift mutation in glycogen synthase 2 (GYS2) gene in a child presenting with fasting hypoglycemia and postprandial hyperglycemia

Bülent Hacıhamdioğlu¹, Gamze Özgürhan², Bahar Çaran², Evrim Meydan-Aksanlı², Ece Keskin³

Departments of ¹Pediatric Endocrinology, ²Pediatrics and ³Medical Genetics, University of Health Sciences, Suleymaniye Women Maternity and Child Diseases Training and Research Hospital, İstanbul, Turkey. E-mail: hacihamdi@yahoo.com.tr

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SUMMARY: Hacıhamdioğlu B, Özgürhan G, Çaran B, Meydan-Aksanlı E, Keskin E. Glycogen storage disease type 0 due to a novel frameshift mutation in glycogen synthase 2 (GYS2) gene in a child presenting with fasting hypoglycemia and postprandial hyperglycemia. Turk J Pediatr 2018; 60: 581-583.

Glycogen storage disease type 0 (GSD0) has been considered a rare disorder, it is characterized with ketotic hypoglycemia after prolonged fasting and postprandial hyperglycemia. Herein, we report a novel mutation in the *glycogen synthase 2* gene in a Turkish child, as well as her clinical characteristics and 12-month follow-up. We evaluated a 5-year-old girl for asymptomatic fasting ketotic hypoglycemia with postprandial hyperglycemia diagnosed with glycogen storage disease type 0. We identified a novel frameshift mutation, c.1081delA (p.Thr361Glnfs*2) in exon 8 on *glycogen synthase 2* gene. Children with GSD0 may have a mild phenotype and GSD0 may be underdiagnosed due to subclinical or asymptomatic hypoglycemia. The diagnosis of GSD0 should be considered in a child with ketotic fasting hypoglycemia with postprandial hyperglycemia but without hepatomegaly.

Key words: ketotic hypoglycemia, glycogen storage disease type 0, glycogen synthase 2 gene.

Low blood glucose accompanied by ketosis is the most common type of hypoglycemia in children and may be caused by rare metabolic diseases.¹ Ketotic hypoglycemia is a major clinical feature of some types of glycogen storage diseases such as types 0, VI, and IX.¹ Glycogen storage disease type 0 (GSD0) is characterized with deficiency of hepatic glycogen synthase encoded by the *glycogen synthase 2* (GYS2) gene. The major clinical finding is fasting ketotic hypoglycemia with postprandial hyperglycemia and hyperlactatemia, but without hepatomegaly.^{1,2}

Glycogen synthase normally catalyzes the formation of α -1,4-linkages, which elongate chains of glucose molecules to form glycogen. In GSD0, glycogen synthesis in the liver is impaired,

which renders the patient prone to develop ketotic hypoglycemia and low lactatemia after fasting. After the ingestion of a carbohydrate-containing meal, hyperglycemia is common because glycogen cannot be synthesized. Excess glucose is converted anaerobically to lactate and can cause hyperlactatemia.^{1,2}

Herein, we report a novel mutation in the GYS2 gene in a child, as well as her clinical characteristics and 12-month follow-up.

Case Report

A 5-year-old girl was referred to the department of pediatric endocrinology with the complaint of short stature. During routine investigation of short stature, fasting blood glucose was

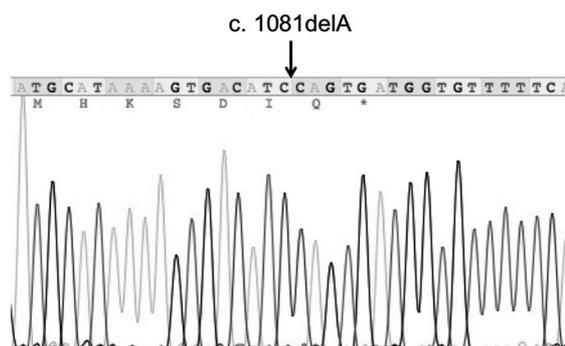
Table I. Results of Critical Samples at the Time of Hypoglycemia.

Glucose	43 mg/dL
Beta hydroxybutyrate	5.1 mmol/L
Lactate (0.7-2.0 mmol/L)	1.5 mmol/L
Insulin	<2 IU/L
Cortisol	24 mcg/dl
Growth hormone	11 ng/ml

detected at 34 mg/dl with 3 (+) ketonuria without clinical symptoms. She was born from consanguineous parents at full-term without complications weighing 3,200 g with normal psychomotor development. Her physical examination was normal. Her height standard deviation score (SDS) was -2.5 (97.5 cm) and relative body weight was 85% (12.9 kg). Her mid-parental height was 151.5 cm (-1.97 SDS).

The patient's glucose profile during hospitalization revealed frequent fasting hypoglycemia with postprandial hyperglycemia (220 mg/dl) and hyperlactatemia (5 mmol/L). Her lipid profile was normal. A critical sample was obtained at the time of hypoglycemia (Table I). We observed a rapid glycemetic response to glucagon administration at the time of fasting hypoglycemia (from 40 to 70 mg/dl). Glycohemoglobin (HbA1c) level was measured and an oral glucose tolerance test (OGTT) was performed because of postprandial hyperglycemia (Table II).

GYS2 gene analysis showed that a novel frameshift mutation c.1081delA (p.Thr361Glnfs*2) leading to a premature termination codon was identified in exon 8 (Fig. 1). Genetic analysis of the parents demonstrated that both were carriers of the same mutation. Her parents did not have hypoglycemia based on the fasting test, but OGTT revealed that her father was classified as glucose intolerant (Table II). Her parents were non-obese and did not have any other risk factor for glucose

**Fig. 1.** Homozygous molecular variant c.1081delA (p.Thr361Gln) in the *GYS2* gene.

intolerance.

Her initial dietary prescription consisted of three meals and three to four snacks (last one at bedtime) and avoidance of fasting for longer than 8 h (we determined this time during the follow-up in the hospital). Uncooked cornstarch (bedtime, 1 g/kg) was recommended. In addition, simple carbohydrates were limited. Morning hypoglycemia (< 50 mg/dl) and exaggerated postprandial hyperglycemia (> 180 mg/dl) resolved with this regimen. She was followed regularly for one year, and her last height is 104.5 cm (-2.0 SDS) and weight is 15.4 kg. Her growth rate was 7 cm in 12 months.

Written consent of parents has been obtained.

Discussion

In this report, we describe a child who was diagnosed as GSD0 with a novel mutation in the *GYS2* gene. GSD0 is a very rare disease¹⁻⁸ that presents with a wide phenotypic spectrum, including seizures, fasting ketotic hypoglycemia, hyperglycemia, glucosuria, short stature, and failure to thrive.^{2,5} Our patient presented with short stature, but there were no specific signs of hypoglycemia.

Although short stature is common in inappropriately managed children with GSD, it is rare as a presenting complaint.² Previously, it

Table II. Results Glycohemoglobin (HbA1c) and Glucose Response During Oral Glucose Tolerance Test.

	HbA1c	Basal glucose	30 min glucose	60 min glucose	120 min glucose
Patient	4.8%	74	200	126	154
Mother	5.2%	85	-	100	113
Father	6.1%	94	-	148	162

*Glucose levels were given in mg/dl.

was shown that short stature can be improved by preventing hypoglycemia, lactic acidosis, and ketosis.^{2,9}

In our patient, we observed a normal glycemic response to glucagon administration at the time of fasting hypoglycemia. This observation was also reported previously.⁸ We presume that glycogen stores were not completely depleted despite the presence of hypoglycemia, and pharmacological amount of glucagon were able to stimulate their breakdown.⁸ This would be a reasonable explanation for positive glycemic response to glucagon administration which is unlikely in GSD.

Treatment of liver glycogen synthase deficiency consists of frequent protein-rich meals and avoidance of prolonged fasting. Uncooked cornstarch acts as a “slow release” form of glucose and may prevent morning hypoglycemia. Low glycemic index carbohydrates should be preferred to avoid hyperlactatemia and hyperglycemia. It is also known that tolerance to fasting improves with age.^{2,8} We observed the usefulness of this treatment approach in our patient.

To date, 20 different mutations have been documented in the *GYS2* gene.¹⁻⁷ A novel homozygous molecular variant c.1081delA (p.Thr361Gln) in the *GYS2* gene was identified in our patient. This frameshift mutation leads to a premature stop codon in exon 8. MutationTaster software analysis revealed that this mutation may be associated with the disease.

GYS2 is an important gene for glucose homeostasis. In the present report, the father was a carrier of the mutation and did not develop fasting hypoglycemia. However, he was diagnosed as prediabetic according to the HbA1c and OGTT. This was reported by Soggia AP et al.⁶ A previous linkage study did not identify this as a major gene contributing to type 2 diabetes susceptibility, but it may be associated with impaired glucose tolerance.⁸ Thus, further studies on heterozygote *GYS2* mutation carriers are required.

GSD0 has been considered a rare autosomal recessive disease, but it may be more common where consanguineous marriage is prevalent. Children with GSD0 may have a mild phenotype and GSD0 may be underdiagnosed due to subclinical or asymptomatic hypoglycemia. Appropriate dietary intervention is sufficient for the management of this rare disease. Overall, the diagnosis of GSD0 should be considered in a child with ketotic fasting hypoglycemia with postprandial hyperglycemia but without hepatomegaly.

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