

# A patient with glycogen storage disease type 0 and a novel sequence variant in *GYS2*: a case report and literature review

Journal of International Medical Research  
48(8) 1–8

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DOI: 10.1177/0300060520936857

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## Abstract

Glycogen storage disease type 0 (GSD0) is an autosomal recessive disorder caused by a sequence variant in the *GYS2* gene, leading to decreased or absent activity of hepatic glycogen synthase. With a frequency of less than 1 in 1,000,000 individuals, GSD0 represents only around 1% of all glycogen storage disease cases but it might be underrecognized. A 13-month-old girl of reportedly unrelated parents presented with a decreased level of consciousness, twitching in her left cheek, and munching. During a fasting test, hyperketotic hypoglycemia was found. A novel homozygous *GYS2* gene sequence variant p.Thr445Arg was later confirmed by next-generation gene sequencing. After establishing a cornstarch- and protein-rich diet, the hypoglycemic episodes subsided and the patient's neurocognitive development was normal. To date, only 39 patients with 24 disease-causing gene variants have been identified in GSD0, and we review their characteristics. Because of the heterogeneous phenotypes, GSD0 is an underdiagnosed disorder. In patients with hyperketotic hypoglycemia and postprandial hyperglycemia, *GYS2* gene analysis should be performed.

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## Keywords

Glycogen storage disease type 0, GYS2, GSD, hyperketotic hypoglycemia, hepatic glycogen synthase, gene sequence variant

Date received: 23 December 2019; accepted: 2 June 2020

## Introduction

Glycogen storage disease type 0 (GSD0) is an autosomal recessive disorder caused by a deficiency of hepatic glycogen synthase, which participates in the production of glycogen.<sup>1</sup> Glycogen storage diseases (GSD) affect approximately 1 in 20,000 to 25,000 people, with GSD0 representing only around 1% of all GSD cases, although it might be underrecognized.<sup>2</sup>

The deficiency is caused by a mutation in the *GYS2* gene located on chromosome 12p12.2, which encodes the hepatic isoform of glycogen synthase. Twenty-three sequence variants are reported.<sup>3-7</sup> As a result of mutation, enzymatic activity is decreased or absent in the liver but normal in muscle.<sup>1,8-10</sup> The outcome of inadequate production of hepatic glycogen is fasting hypoglycemia, usually with a rapid onset.<sup>11</sup> The disease manifests with symptoms of fasting ketotic hypoglycemia and postprandial hyperglycemia and hyperlactatemia.<sup>5</sup> Fasting ketotic hypoglycemia is accompanied by low levels of alanine and lactate. Unlike other GSDs, patients with GSD0 usually do not develop hepatomegaly.<sup>1,8,10</sup>

The diagnosis is confirmed by genetic analysis of the *GYS2* gene.<sup>9</sup> Before the availability of molecular analyses, liver biopsies were used to diagnose GSD0.<sup>8</sup> With the help of genetic analysis, a relatively simple diagnostic tool, we are now able to screen symptomatic patients for the disease.<sup>9</sup> The goal of treatment is to prevent hypoglycemic episodes during fasting with

regular protein-rich meals and uncooked cornstarch before bed.<sup>8,12</sup> As patients grow older, they usually tolerate fasting better, but dietary support is still required.<sup>11-13</sup>

## Case report

The fourth female child of healthy reportedly unrelated Caucasian parents was born 12 days before term by cesarean section and weighed 3580 g. Her older sister had an episode of cerebral paroxysms at 13 years of age, the underlying cause of which was unclear. The other two siblings, both older, are healthy. The patient's mother had gestational diabetes. Written informed consent was obtained from the patient's parents for publication of this case report.

At 13 months of age, the patient presented with a decreased level of consciousness, twitching in the left cheek, and munching during a 7-hour fast, having missed the morning meal. The episode of decreased level of consciousness lasted 1 hour, finishing 20 minutes after breastfeeding. A few days after the episode, she was admitted to our department for evaluation of her condition. Her hemoglobin A1c was 4.7%, and her height and weight were at the 14th and 60th percentiles, respectively.

During a fasting test, hyperketotic hypoglycemia without hyperlactatemia [ $\beta$ -OH-butyrate: 1473  $\mu$ mol/L; serum glucose: 1.1 mmol/L (19.8 mg/dL); lactate: 0.8 mmol/L] was observed. Adrenal insufficiency was excluded (Synacthen test: serum

cortisol after 60 minutes: 922 nmol/L). Electroencephalogram results were normal. An implanted continuous glucose monitoring device detected a few isolated events of postprandial hyperglycemia [up to 12 mmol/L (216 mg/dL)].

Nonfasting lactate levels during follow-up were within normal range (0.96–2.2 mmol/L; normal range: 0.5–2.2 mmol/L). Borderline elevations in triglycerides (up to 2.7 mmol/L; normal range: 0.6–1.7 mmol/L) and cholesterol (up to 6.2 mmol/L; normal range: 4–5.2 mmol/L) were noted. Levels of transaminases were in the upper normal range during follow-up (aspartate transaminase: up to 0.81  $\mu$ kat/L, normal range up to 0.78  $\mu$ kat/L; alanine transaminase: up to 0.69  $\mu$ kat/L, normal range up to 0.48  $\mu$ kat/L). All amino acid levels tested in the blood were within reference ranges.

Genomic DNA of the patient and her parents was isolated from peripheral blood samples using the FlexiGene DNA isolation kit (Qiagen, Hilden, Germany). Targeted next-generation sequencing was conducted in the patient using the TruSightOne Sequencing Panel on the MiSeq platform desktop sequencer coupled with MiSeq Reagent kit v3 (Illumina Inc., San Diego, CA, USA). Further evaluation of variants was restricted to a GSD gene panel (*GYS1*, *GYS2*, *G6PC*, *SLC37A4*, *GAA*, *AGL*, *GBE1*, *PYGM*, *PYGL*, *PFKM*, *PHKA2*, *PGAM2*, *LDHA*, *ALDOA*, *ENO3*, *PHKB*, *PHKA1*, *PGM1*, *GYG1*, and *PRKAG2*). A homozygous novel sequence variant c.1334C>G (NM\_021957.3) was found in exon 11 of *GYS2*, changing threonine to arginine at codon 445 (NP\_068776: p.Thr445Arg).

This variant had not previously been reported in patients or apparently healthy populations although *in silico* tools predicted it to be pathological (Mutation taster, <http://www.mutationtaster.org/>; CADD score 27.9). According to the

American College of Medical Genetics/Association for Molecular Pathology 2015 guidelines,<sup>14</sup> the variant was classified as pathological based on the following grades: PS1 (strong, same amino acid change as a previously established pathogen), PM2 (absent from general population), PP1 (co-segregation with the disease in multiple affected family members in a gene definitely known to cause the disease), and PP3 (multiple lines of computational evidence supporting the deleterious effect). Additionally, Sanger sequencing revealed that both parents were heterozygous for this variant.

The patient was put on a diet with frequent meals to prevent hypoglycemic episodes. Initially, she was prescribed 20 g (2 g/kg) of uncooked cornstarch in the evening, two times during the night, and 10 g (1 g/kg) before the daytime nap. The parents were instructed to monitor blood glucose levels using the implanted continuous glucose monitoring device, with a desired range between 4 and 8 mmol/L (72–144 mg/dL). The cornstarch meals were adjusted based on these measurements. The dietitian advised them to increase the amount of complex carbohydrates and proteins in the meals to reduce daily calorie intake while avoiding simple carbohydrates. With this dietary regimen, the patient experienced fewer episodes of hypoglycemia over time. After the nightly cornstarch meals were introduced, her height progressed very well. The patient was in the 14th percentile for height at her first visit (before the introduction of cornstarch) and gradually increased to the 88th percentile at the last visit at the age of 5 years (her predicted adult height range, based on parental heights, was between the 75th and 99th percentile). The patient had been overweight at her first visit, with body mass index ranging from the 97th percentile at the first visit to the 99th percentile at the last visit; however, in the last 2 years,

the patient's weight excess has been slowly decreasing.

Owing to poor appetite and frequent vomiting, especially during swinging motions, some meals with uncooked cornstarch were replaced with a modified cornstarch product (Glycosade, Vitaflo USA, Bridgewater, NJ, USA) at 2 years of age, but after a further 1.5 years, the patient was switched back to the former cornstarch meals. In the 3 years since the first episode of hypoglycemia, the relative size of uncooked cornstarch meals has decreased (18% reduction of g/kg of body weight in nighttime dosages and 5% reduction in daily dosages).

At 2 years of age, the patient had normal motor development, a normal physical examination, and good cognitive development.

## Discussion

Since the first description of GSD0 in 1963,<sup>1</sup> there has been a small but increasing number of reports of patients with GSD0 symptoms of varying severity. Our patient first presented with hypoglycemia at the age of 14 months, which correlates the time of diagnosis in most reported cases. Patients most often develop symptoms when they stop nighttime feedings, presenting with drowsiness, lack of attention, pallor, disorientation, or even convulsions before the first meal of the day.<sup>1,8,10,13</sup> The disease presents with phenotypes of different severity, probably correlating with the degree of hepatic enzyme activity.<sup>15</sup> Hepatic enzyme activity was not measured in our patient, but based on previous assumptions and the degree of her symptoms, enzyme activity was likely greatly reduced. With the exception of twins in Lewis et al.,<sup>1</sup> previously reported patients, like our patient, did not have any physical or neurocognitive developmental abnormalities.<sup>9</sup> The reported abnormalities in the twins

could also be related to pre- or perinatal history.<sup>10</sup>

Some asymptomatic patients are diagnosed incidentally, having been hospitalized for another illness or after their siblings had been diagnosed. Laboratory results may show random hypoglycemia without any clinical symptoms and, in some cases, postprandial hyperglycemia on further testing.<sup>4,9,15,16</sup> Because the liver is unable to synthesize glycogen, blood glucose levels spike after a carbohydrate-rich meal.<sup>12</sup> Postprandial hyperlactatemia occurs because excess glucose is shunted toward the glycolytic pathway, resulting in hyperlactatemia and hyperlipidemia.<sup>1,8,10</sup> During fasting, the patient develops hyperketonemia.<sup>12</sup> Gluconeogenesis and fatty acid oxidation prevent a rapid decrease of blood glucose levels in the postabsorptive period; however, those processes are not sufficient to prevent hypoglycemia during fasting.<sup>17</sup> Because of variable responses to glucagon in the fasting and fed states, a glucagon test cannot be used to rule out or confirm a diagnosis of GSD0.<sup>8,18,19</sup>

After nightly cornstarch meals were introduced to our patient, the parents reported frequent vomiting and nausea, especially after meals. Consequently, we approved the mother's wish to switch to modified cornstarch (Glycosade). After introduction of Glycosade in the diet, the intervals between meals had to be shortened to prevent hypoglycemic episodes; therefore, the patient switched back to uncooked cornstarch. There are reports of using modified cornstarch in only two patients with GSD0,<sup>20</sup> although modified cornstarch has been tested in other types of GSD. The literature suggests that physically modified cornstarch prolongs the time between meals because of altered digestibility, but it is not approved for use in children under the age of 5 years in the United States because of the lack of trials in the age group. The reason for lower tolerance

**Table 1.** Review of patients' age, clinical characteristics, and mutations [missense and nonsense mutations are described on the protein level (NP\_068776), splicing mutation on the cDNA level (NM\_021957.3) and frameshift mutations on both levels].

Study	No. of patients, age at presentation	Comments, clinical characteristics	Mutations
Lewis et al. (1963) <sup>1</sup>	2 (2, 7 months)	First reported case; slow neurocognitive development	/ <sup>*</sup>
Dykes and Spencer-Peet (1972) <sup>13</sup>	3 ( <sup>*</sup> )	Asymptomatic relatives	/ <sup>*</sup>
Aynsley-Green et al. (1977) <sup>8</sup>	1 (7 years)	NNR	/ <sup>*</sup>
de Kremer et al. (1990) <sup>26</sup>	1 (21 months)	NNR	/ <sup>*</sup>
Gitzelmann (1996) <sup>10</sup>	2 (2, 3.5 years)	NNR	/ <sup>*</sup>
Orho et al. (1998) <sup>9</sup>	9 (3, 4, 5, 3.5, 2 years)	Slow neurocognitive development	p.Arg246Term, c.941 + IG>T (splice), p. Pro479Gln, p.Ala339Pro, p.Met491Arg, p.Asn39Ser, p.Ser483Pro, p.His446Asp
Rutledge et al. (2001) <sup>19</sup>	1 ( <sup>*</sup> )	NNR	/ <sup>*</sup>
Bachrach et al. (2002) <sup>18</sup>	2 (5, 9 years)	NNR	p.Arg5Term, p.Gln183Term, 73 nucleotide deletion (11E2-8-+65), p.Arg246X
Laberge et al. (2003) <sup>27</sup>	1 (7 years)	NNR	/ <sup>*</sup>
Weinstein et al. (2006) <sup>12</sup>	6 ( <sup>*</sup> )	NNR	c.495 + IG>T, p.Thr445Met, p.Arg582Lys, p.Asp668Asn
Spiegel et al. (2007) <sup>15</sup>	2 (8, 14 months)	NNR	p.Thr445Met, p.Lys286Asp
Soggia et al. (2010) <sup>23</sup>	1 (6 months)	NNR	p.Arg246Term, c.996_967delGAinsC (p.Lys322Asnfs*22)
Miwa et al. (2010) <sup>28</sup>	1 (2.5 years)	NNR	p.Gly449Asp
Nessa et al. (2012) <sup>5</sup>	1 (soon after birth)	NNR	p.Leu601Term
Szymańska et al. (2015) <sup>16</sup>	1 (7 years)	NNR	p.Phe574Leu
Kasapkara et al. (2017) <sup>4</sup>	2 (15 months, 4 years)	NNR	p.Arg246Term, p.Gly382Glu
Hachimdioglu et al. (2018) <sup>7</sup>	1 (5 years)	NNR, short stature	c.1081delA (p.Thr361Glnfs*2)
Ghosh et al. (2017) <sup>6</sup>	1 (1-11 years)	Mild developmental delay	p.Cys243Term, p.Glu518Ala

<sup>\*</sup>Data missing; <sup>#</sup>Genetic analysis not performed.

NNR, normal neurocognitive development.

in younger patients is probably rapid growth and gastrointestinal immaturity.<sup>20–22</sup> We suggest more trials on the use of modified cornstarch in younger children before clinical use.

According to the literature, 39 patients with GSD0 and with 24 different disease-causing gene variants have been identified to date, including the present case.<sup>4–7</sup> We review the reported patients, their age at onset, and the location of sequence variants (Table 1). Our patient experienced her first symptoms at 14 months of age, consistent with the majority of patients, who experience their first symptoms by the age of 3.5 years on average. The sequence variant found in our patient has not previously been reported.<sup>9,12,15</sup> In two reports, sequence variants were identified in the same codon (p.Thr445Met) but with a different nucleotide change (c.1334C>T).<sup>12,15</sup> This is one of only two sequence variants in *GYS2* that is not unique to a particular family.<sup>4,15</sup> The other sequence variant that has been reported in several families is the p.Arg246Term sequence variant, found in five patients from four families<sup>4,9,18,23</sup> and first reported by Orho et al.<sup>4,9,23</sup> There is no firm evidence of genotype–phenotype correlation; the clinical picture varies from asymptomatic to reports of short stature in patients with the same mutation.

Because some patients are asymptomatic,<sup>9,15,16</sup> GSD0 is probably more common than previously thought. The symptoms of GSD0 are variable and frequently subtle and can be confused with early diabetes mellitus. Compared with cases of other types of GSD, a review of the literature shows that patients with GSD0 do not present with hepatomegaly. A recent study by Kaplowitz and Sekizkardes<sup>24</sup> suggests that other types of GSD can, on rare occasions, also present without hepatomegaly. We believe this could be one factor that explains why GSD0 is still an underdiagnosed and late-diagnosed disorder.

This opens the question of when to consider screening patients for GSD0 and which tests to use. The findings of Nessa et al.<sup>5</sup> and the test results in our patient suggest a higher likelihood of GSD0 in patients with hyperketotic hypoglycemia in a fasting state and concomitant postprandial hyperglycemia. According to Brown et al.,<sup>25</sup> GSD panel analysis is not recommended in patients with hyperketotic hypoglycemia if elevated morning ketones are not demonstrated.

We believe that in patients with hyperketotic hypoglycemia and supporting laboratory data (postprandial hyperglycemia and hyperlactatemia, hyperlipidemia, fasting hypoalaninemia, mildly elevated serum transaminases), GSD should be considered and genetic analysis performed to exclude GSD0. Genetic analysis is increasingly available around the world and therefore should be used when exploring the cause of hyperketotic hypoglycemia.

To summarize the learning points from this case report, (1) GSD0 should be considered in patients with hyperketotic hypoglycemia and possible concomitant postprandial hyperglycemia; (2) genetic analyses in hyperketotic hypoglycemia would facilitate the diagnostic process in GSD0; and (3) physically modified cornstarch should not be used in children younger than 5 years.

### Author contributions

U. Groselj and J. J. Arko conceptualized and designed the study, performed clinical work, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. M. Debeljak and U. Groselj performed clinical work, designed the data collection instruments, and reviewed and revised the manuscript. T. Battelino and M. Z. Tansek performed clinical work, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and

agree to be accountable for all aspects of the work.

### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

### Funding

The study was partly funded by the Slovenian Research Agency program (P3-0343).

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