

CASE REPORT

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Glycogen Storage Disease Type IIIa Presenting with Hyperglycemia: A Novel Mutation

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ABSTRACT Glycogen, the storage form of glucose in cells; plays a vital role in cellular function by providing the energy required for most metabolic processes. Defects in glycogen metabolism cause an accumulation of glycogen in the tissues. The glycogen storage diseases were categorized numerically in the order in which the enzymatic defects were identified. Glycogen storage disease type IIIa is an inherited glycogen storage disease that is an autosomal recessive transition affecting liver and muscles. It occurs as a result of mutation in the gene of glycogen debranching enzyme (AGL gene). Hypoglycemia is a common condition. In this case, we presented a case of glycogen storage disease type IIIa with a new mutation in the AGL gene presenting with hyperglycemia.

Keywords: Glycogen storage disease type IIIa; hyperglycemia; a novel mutation

Glycogen storage disease type IIIa (GSD IIIa) is an autosomal recessive disorder caused by deficiency of glycogen debranching enzyme.¹ When the debranching enzyme is defective, glycogen breakdown is incomplete.

The disorder usually involves both liver and muscle and is termed glycogen storage diseases type IIIa. However, in about 15% of patients, the disease appears to involve only the liver and is classified as type IIIb. Hypoglycemia, hepatomegaly and progressive myopathy are prominent clinical findings. The presence of a wide variety of mutations in the AGL gene causing disease has been described in the literature.²⁻⁴ This new mutation we found in the AGL gene has not been yet published. In this case, we aimed to present our case of a 44-year-old Turkish male diagnosed as glycogen storage disease type IIIa, accompanied by this new mutation with hyperglycemia associated with type 2 diabetes mellitus without hypoglycemia.

CASE REPORT

A 44-year-old male patient was admitted to our clinic with complaints of inability to walk, dry mouth, polydipsia and polyuria. There is no known family history of diabetes mellitus and glycogen storage disease.

Physical exam showed hepatomegaly, muscle weakness and atrophy of the distal extremities. The patient's height was 165 cm and weight 50 kg. When he was 20 years old, he was diagnosed with glycogen storage disease (GSD) by muscle biopsy due to myopathy but at that time the type of the disease was not determined. The patient first noticed muscle weakness of the distal extremities at the age of 20. The symptoms gradually increased, and he could no longer walk without walking stick.

In blood tests, glucose: 262 mg/dl, ALT: 74 U/L, AST: 50 U/L creatinine kinase (CK): 898 U/L HbA1c: 10.3% was detected. The laboratory results of the patient are shown in Table 1.

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TABLE 1: Laboratory values of the patient.		
Laboratory values	Result	Reference range
Glucose (mg/dl)	262	70-100
Creatinine (mg/dl)	0,67	0,5-1,4
Na (mmol/L)	138	135-145
K (mmol/L)	4,2	3,5-5,1
Ca (mg/dl)	8,8	8,4-10,2
Phosphorus (mg/dl)	3,8	2,5-4,5
ALT (U/L)	74	0-45
AST (U/L)	50	0-35
CK (U/L)	898	40-165
LDH (U/L)	288	125-220
HbA1c (%)	10,3	4-5,6
C-peptide (ng/mL)	1,24	1,1-4,4

Due to the newly diagnosed diabetes mellitus, we decided to start low dose insulin therapy. The patient was injected insulin lispro 3x4 units and insulin glargine 1x12 units.

EMG (electromyography) for the lower extremities was applied to the patient who had difficulty in walking and had elevated muscle enzymes. Sensorimotor polyneuropathy was observed on EMG. Abdominal ultrasonography revealed enlargement of liver. The muscle biopsy performed 24 years ago due to the patient’s inability to walk was consistent with the GSD but the patient has been never followed since then. Molecular genetic analysis was performed for the patient to determine the type of GSD. A ho-

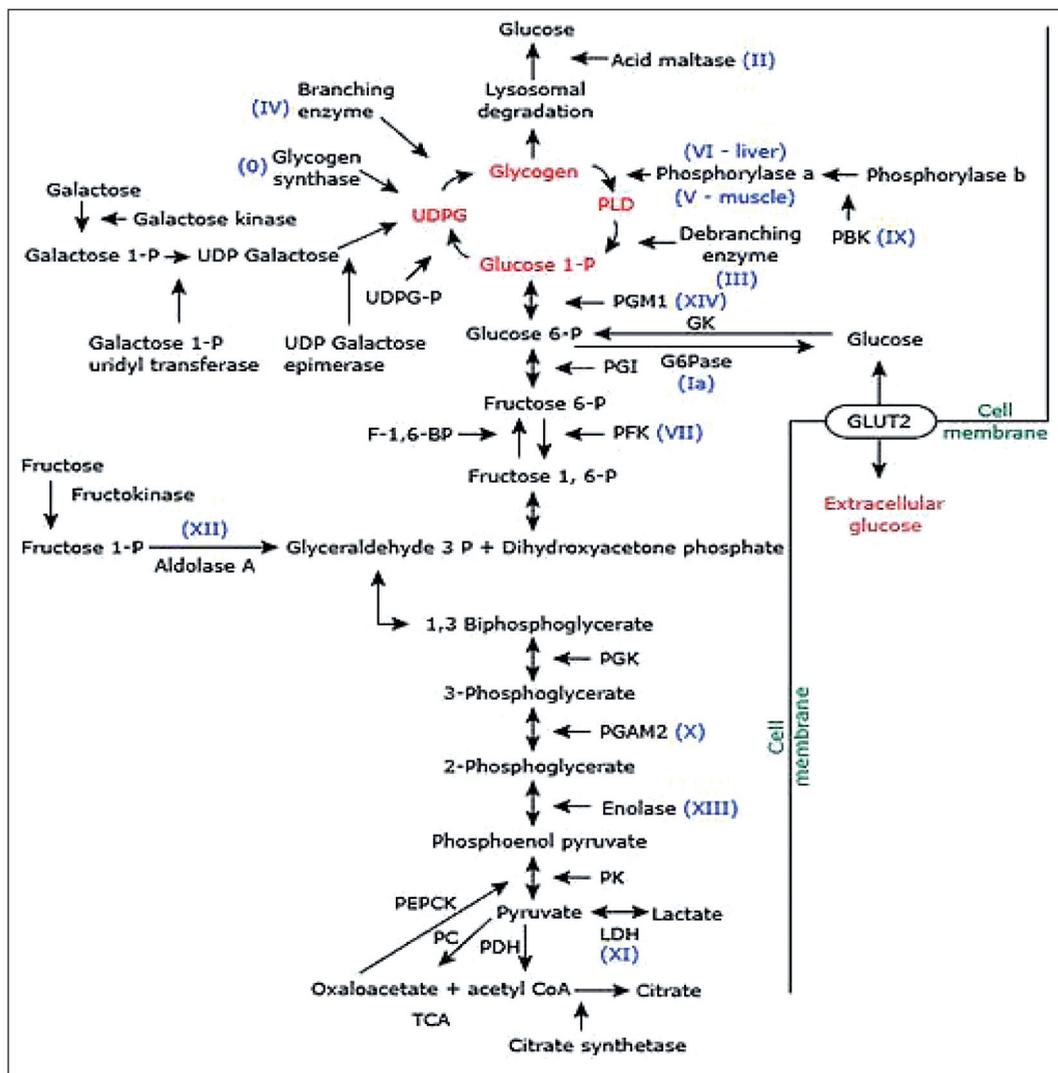


FIGURE 1: The figure shows the sites of enzymatic defects resulting in clinical glycogenoses.⁶

mozygous class 2 c.3258_3259DelAGinsCC mutation was detected in the AGL gene exon 24. This change has not been previously reported in the literature and the patient was diagnosed with glycogen storage disease type IIIa. The patient's blood glucose level was regulated and the patient was discharged with supportive treatment.

DISCUSSION

Glycogen storage disease type IIIa is an autosomal recessive transition as a result of a mutation in the AGL gene.⁵ This disease is characterized by the development of dysfunction of the organs as a result of glycogen storage in the muscle and liver due to the glycogen debranching enzyme defect.

Glycolysis by which glycogen is broken down by the action of enzyme phosphorylase to the glucose molecules. Depolymerization of glycogen by phosphorylase halts when glycogen branches have been reduced to two to four linked glucose molecules. Glycogen debranching enzyme has two catalytic activities. One of this is the cleavage of a dextrin branch from the remaining glycogen molecule (amylo-1,6-glucosidase activity). The other one is the transfer of the dextrin to the free end of a dextran polymer (oligo-1,4-1,4-glucanotransferase activity). The transferred dextrin may then be further depolymerized by phosphorylase.⁶

Clinical features and enzyme activities are highly variable in affected patients. The enzyme defects of glycogen storage diseases are shown in Figure 1.

Due to the glycogen debranching enzyme defect, patients may develop hypoglycemia, hepatomegaly, growth retardation and progressive myopathies.

Hypoglycemia, in particular, is a life-threatening complication and frequent episodes of hypoglycemia cause growth retardation in childhood. Hypoglycemia is controlled by frequent carbohydrate meals and a form of continuous carbohydrate supply overnight.⁷ The tendency toward normoglycemia as the patient grows older is considered to be due to a decrease in insulin output. He was learned to feel very hungry from time to time in childhood, but decreased as he grows older. But he had no severe hypoglycemia episodes since diagnosed GSD.

Hypoglycemia is common in GSD. However, hyperglycemia was detected in this case due to the diagnosis of diabetes mellitus. Hyperglycemia, on the other hand, has been rarely reported in patients with GSD IIIa. Diabetes mellitus in GSD IIIa is difficult to treat due to predisposition to hypoglycemia. After careful consideration, we decided to start low dose insulin therapy. After the insulin therapy, the patient did not develop hypoglycemia.

Depending on the affected organ, elevation in liver and muscle enzymes can be seen. Our patient who was admitted to our hospital complained of muscle weakness. Level of creatinine kinase (CK) and liver enzymes were high. Serum CK levels can be useful for muscle involvement; however, normal CK levels do not rule out muscle enzyme deficiency.⁸ Our patient had previously (24 years ago) been diagnosed with GSD in Gülhane Military Medical Academy in Turkey but not diagnosed with disease type. GSD Type IIIa diagnosis was considered because of muscle and liver involvement. 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.⁹ However hepatic failure was not observed.

Clinically relevant myopathy with slowly progressive muscle weakness typically develops later.¹⁰ Myopathy usually becomes prominent in the third or fourth decades of life, manifesting as slowly progressive muscle weakness involving the proximal muscles, that is, the larger muscle groups of the shoulders and hips. He first noticed muscle weakness of the distal extremities at the age of 20. Then his symptoms gradually increased, and he could no longer walk without walking stick.

The human AGL gene located on chromosome 1 (1p21) has 35 exons and covers about 85 kb of genomic DNA.¹¹ A wide variety of AGL gene mutations have been described which cause disease today. Molecular genetic analysis of the AGL gene was performed by DNA sequencing to determine the type of GSD of this patient. The AGL gene exon 24 was detected homozygous class2 c.3258_3259Del AGinsCC mutation. This type of mutation was a new type that was not previously described in the literature. In

this case of Turkish race, the cause of glycogen storage disease type IIIa with hyperglycemia may be due to this new mutation. As new patients with this mutation are found, the association may perhaps be better explained.

As a result, this new mutation type detected in the Turkish population and the presence of hyperglycemia without underlying chronic liver disease in the patient is a rare condition for GSD type IIIa.

Informed Consent

The patient has given written consent for this case report.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that pro-

vides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Mehmet Güven; **Design:** Müslüm Güneş; **Control/Supervision:** Selahattin Tekeş; **Data Collection and/or Processing:** Mehmet Güven; **Analysis and/or Interpretation:** Mehmet Şimşek; **Literature Review:** Mehmet Güven; **Writing the Article:** Mehmet Güven; **Critical Review:** Müslüm Güneş; **References and Fundings:** Mehmet Güven; **Materials:** Mehmet Güven.

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