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CASE REPORT

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A Case of Glycogen Storage Disorder With a Novel Mutation

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Keywords

Glycogen storage disease type 3, *AGL* gene, hepatosteatosis, hypoglycemia

ABSTRACT • Glycogen storage disorder (GSD) type III is an inborn error of glycogen storage leading to abnormal glycogen deposition in various tissues that lead to hepatic pathologies including hepatomegaly, hypoglycemia, elevated transaminases, and hyperlipidemia. There are two major GSD type III subtypes: GSD type IIIa in which the liver and muscle is affected (80% of all GSD III cases) and GSD type IIIb, where only liver disease is seen. 1 year old boy was referred to our clinic due to hepatomegaly. No history of hypoglycemia was present. Laboratory examinations revealed elevated transaminases, creatine kinase and triglycerides. Liver biopsy was performed that showed accumulation of PAS positive material and cirrhotic changes that suggested an underlying glycogen storage disease. A multi-gene panel testing for the known genes of GSDs listed in OMIM, was performed that revealed a novel homozygous c.3971_3972delAT (p.Tyr1324Ter) mutation in the *AGL* gene. GSD type III is a rare inborn error of metabolism caused by the defects in *AGL* gene, and diagnosis may be difficult. Next generation sequencing is a practical alternative to invasive procedures such as liver biopsy and leads to most accurate diagnosis of GSDs.

INTRODUCTION

Glycogen storage disorders (GSDs) are a group of inborn errors of metabolism with abnormal storage or processing of glycogen. Different types of GSDs are classified according to the deficient enzymes and affected tissues (1,2). GSD type III (GSD III) is caused by the deficiency of glycogen debrancher enzyme (amylo-1,6-glucosidase) leading to accumulation of 'abnormal' glycogen mainly in the liver and other tissues (2). There are two major GSD III subtypes: GSD type IIIa in which the liver and muscle is affected (80% of all GSD III cases) and GSD IIIb, where only liver disease is seen. With the advances in next-generation sequencing (NGS) technologies, mutation analysis has become a preferred method for diagnosing GSDs (3).

We present a case of a 2 year old boy with GSD type III caused by a novel mutation.

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CASE PRESENTATION

1 year old boy was referred to our clinic due to hepatomegaly. He was the second child of consanginous parents (Second degree cousins) with a healthy elder sister. He was born at term with cesarean section after an uncomplicated pregnancy, and was admitted to the NICU because of respiratory distress. Mechanical ventilation was applied for 2 days. His general condition improved gradually and was discharged after 10 days of hospitalisation. His physical and mental development was normal during his follow-up and he did not have had any health problems until age one when he had an afebrile seizure during an episode of viral upper airway infection and was admitted to the emergency department of an external clinic. He was fully conscious upon admisson and physical examination was normal except hepatomegaly. Laboratory examinations including complete blood count, biochemistry, blood gas analysis were normal except elevated transaminases [Aspartate aminotransferase (AST): 646 U/L (Normal range, NR: 10-40), alanine aminotransferase (ALT): 586 U/L (NR: 10-40)], creatine kinase (CK) (450 U/L, NR: 0-200) and slightly elevated GGT (86 U/L, NR: 7-49). His seizures did not recur and he was discharged and referred to the pediatric gastroenterology department of a tertiary care hospital, where he was evaluated due to hepatomegaly. Laboratory examinations were performed in detail showing elevated triglyceride (366 mg/dl, NR: 30-130) and slightly elevated PT (13.8 sec, NR: 11-13) and lactate (2.4 mmol/L, NR: 0.5-1.6) with normal alpha-fetoprotein (AFP), alfa-1 antitrypsin and ceruloplasmine. Viral markers were negative. Liver biopsy was performed that showed accumulation of PAS positive material and cirrhotic changes that suggested an underlying GSD. He was referred to our clinic for further evaluation. Upon admission, he was in good condition with height and weight being within normal centiles. Heptomegaly was detected (9 cm below the lower costal margin). Abdominal ultrasonography showed hepatomegaly and stage I hepatosteatosis. Metabolic screening tests including acylcarnitine analysis from dried blood spot, urine organic acid analysis and plasma amino acid analysis were normal. Cardiac examination including echocardiogram showed normal findings.

Since there was strong suspicion of a glycogen storage disorder, a multi-gene panel testing for the known genes of GSDs listed in OMIM, was performed using Next Generation DNA Sequencing (NGS) (Thermo Fisher Ion S5). A novel homozygous c.3971_3972delAT (p.Tyr1324Ter) mutation in the AGL gene was detected (Figure-1). Parents were shown to carry the mutation heterozygously.

High protein diet and elimination of simple sugars was initiated. He is now doing well and is under close follow up in our clinic with annual cardiological check-ups for any cardiac involvement.

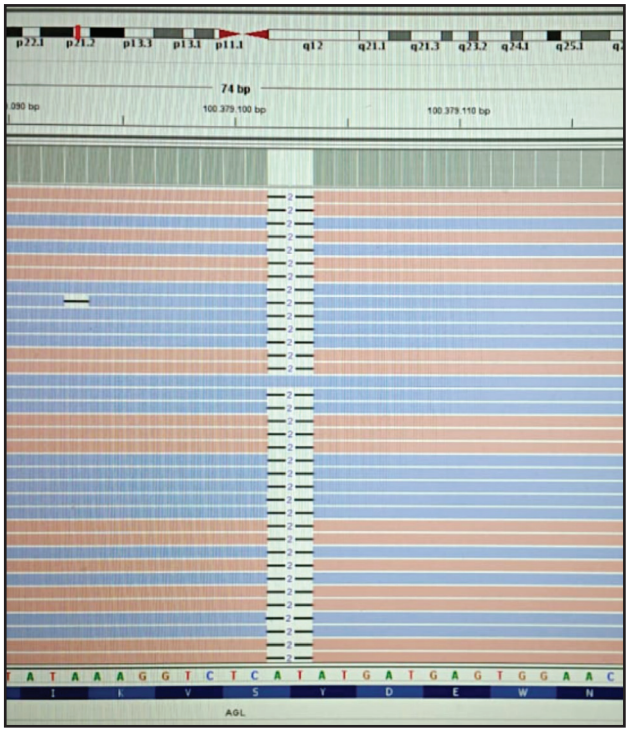

Figure 1 The mutation analysis of *AGL* gene.

DISCUSSION

GSD type III is an inborn error of glycogen storage leading to abnormal glycogen deposition in various tissues that lead to hepatic pathologies including hepatomegaly, hypoglycemia, elevated transaminases, and hyperlipidemia. Also, severe complications including cirrhosis or hepatic adenomas can ocur rarely. Muscle involvement is another significant feature of GSD type IIIa that usually occur in adults. Hypertrophic cardiomyopathy and arrhythmias that are mainly related with impaired energy metabolism of muscle may also develop (4). Serum CK may not be elevated at the time of the diagnostic work up, but the absence of lactic acidosis and markedly elevated transaminases may provide clues to the diagnosis. Diagnosis is most accurately made by molecular genetic analysis of AGL gene. The NGS approach is preferable, since a group of candidate genes can be sequenced simultaneously and liver biopsy can be avoided. Management includes the prevention of hypoglycemia by frequent carbohydrate meals and using high protein/fat diet as a source of energy since gluconeogenesis is sustainable (5).

The involvement of skeletal muscle is used to differentiate GSD IIIa from GSD IIIb, where serum CK, which is a nonspecific marker of muscle breakdown, can be helpful. Although the correlation between the level of CK and the severity of muscle involvement is not known yet, most patients with GSD IIIa have been reported to have CK levels above 1000 IU/L (6,7).

GSD III occurs as a result of the genetic changes in AGL gene that encodes glycogen debrancher enzyme (amylo-1,6-glucosidase). AGL gene is located on chromosome 1p21.2, having a length of 85 kb with 35 exons. To date, more than 200 mutations have been reported of the AGL gene many of them being novel (www.hgmd. org) (6). The majorities are nonsense, deletion, insertion and splicing mutations (8). Great phenotypic diversity is observed with variable severity of the clinical course (1). The exact genotype–phenotype correlation is difficult to assess due the heterogenous nature of the AGL gene (6). The prevalent mutations of AGL in GSD III vary among the ethnic groups (9).

The genetic changes in our patient, c.3971_3972delAT (p.Tyr1324Ter) causes an early stop codon in exon 30 that leads to premature termination of protein synthesis. HGMD (http://www.hgmd.cf.ac.uk) and Clinvar (https://www.ncbi.nlm.nih.gov/clinvar) evaluated this premature stop codon (PTC) mutation to be “Likely pathogenic”. The clinical findings of our patient, along with the fact that parents are carriers, supports the pathogenicity of the mutation. We predict this mutation to cause a severe clinic due to functional deficiency of the glycogen debranching enzyme. Since it is not previously reported in literature, clinical progress of our patient during follow up will demonstrate the long term effects of this genetic change.

The clinical findings of our patient is correlated with the patients previously reported in literature (5-9), besides hypoglycemia, which is an expected symptom of GSD III, that was never detected in our patient. We believe that hypoglycemia might have been overlooked in our patient and since he has a history of afebrile seizure during the time he had an upper airway infection, the etiology of seizure may be hypolycemia due to diminished oral intake.

According to the largest series reported to date that from China with 51 different mutations from 43 patients and 31 novel mutations, the majority of patients with PTC mutations, as in our patient, had elevated CK levels (9). Lu et al also observed a possible association between the age and the serum CK level, where patients equal to or older than 10 years old had a higher serum CK value than normal. Our patient’s CK levels have been found moderately increased, but is under close follow up, since we are still unable to predict the subtype of GSD III.

CONCLUSION

GSD type III is a rare genetic disease, with nonspesific findings, that may lead to severe complications. It is important to realize the symptoms of this disease and appropriate genetic testing should be performed immediately to ensure initiation of early treatment. NGS is a practical alternative to invasive procedures such as liver biopsy and leads to most accurate diagnosis of GSDs.

Informed consent has been obtained from patients fort he publication of this case report providing that patient identity will not be disclosed.

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