

A Rare Case Of Glycogen Storage Disorder Type VI Due To Novel Homozygous PYGL Variant With Coexisting RPGRIP1-Related Leber Congenital Amaurosis: A Dual Monogenic Disorder In A Child.

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ABSTRACT

INTRODUCTION:

Glycogen storage disorder type VI is a disorder of glycogenolysis caused by deficiency of hepatic glycogen phosphorylase. The critical enzyme catalyzes the rate limiting step in glycogen degradation and deficiency of the enzyme in the untreated child is characterised by hepatomegaly, poor growth, ketotic hypoglycaemia & elevated hepatic transaminases, hyperlipidemia and low pre albumin level

CASE REPORT:

This case report describes a 3 year old female child presented with delayed achievement of milestones and abnormal eye movements. Clinical examination revealed hepatomegaly with failure to thrive with gross developmental delay with hypotonia. History of hypoglycaemia episodes present.

CONCLUSION:

This case highlights the clinical severity and prognosis of Glycogen storage disorder type VI. The findings emphasise the need for evaluation in cases of hepatomegaly with poor growth velocity as well as the importance of early diagnosis and multidisciplinary planning. Genetic counselling is essential for families with a suspected or confirmed.

KEYWORDS: Dual Monogenic disorder, Glycogen storage disorder type VI, PYGL variant, RPGRIP1, Leber Congenital Amaurosis.

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INTRODUCTION

Glycogen storage disease (GSD) type VI, also known as Hers disease, is a rare autosomal recessive metabolic disorder caused by deficiency of hepatic glycogen phosphorylase or its activating system. [1] This enzyme plays a critical role in glycogenolysis by catalyzing the rate-limiting step of glycogen breakdown to glucose-1-phosphate in hepatocytes. Deficiency results in impaired glycogenolysis, leading to accumulation of glycogen within the liver and consequent hepatomegaly, mild fasting hypoglycemia, and growth retardation. [2,3] The estimated incidence of hepatic phosphorylase deficiency is approximately 1 in 65,000–85,000 live births, though the true prevalence may be underestimated due to its mild and often subclinical course. Unlike the more severe hepatic GSD types (such as types I and III), type VI generally presents with a benign clinical course, with most patients achieving normal growth and metabolic control with dietary management alone. [4] Nevertheless, early recognition remains important to differentiate it from other causes of hepatomegaly and to prevent complications such as fasting intolerance and hyperlipidemia. [5] Here, we report a case of

GSD type VI diagnosed on the basis of clinical presentation, biochemical profile, and confirmatory genetic testing, highlighting its distinguishing features and favorable long-term outcome.

CASE PRESENTATION

A 3-year-old female child, product of a non-complicated full-term delivery, presented with progressive abdominal distension and poor weight gain since infancy. Developmental milestones were delayed. There was history of third-degree consanguinity in the parents and no similar illness in siblings. On examination, the child appeared undernourished with short stature. The abdomen was distended, and the liver was palpable 7 cm below the costal margin, firm and non-tender, extending to the right iliac fossa. No splenomegaly or ascites was noted.

Laboratory evaluation revealed elevated serum transaminases (AST—6400 U/L, ALT—5238 U/L), normal bilirubin, recurrent fasting hypoglycemia (blood glucose—34 mg/dL), and mild hypertriglyceridemia. Serum lactate and uric acid were within normal limits. Ultrasound abdomen showed hepatomegaly with coarse, altered

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echotexture and no biliary abnormality. Liver biopsy demonstrated marked glycogen accumulation in hepatocytes with preserved architecture, consistent with glycogen storage disease. Whole-exome sequencing (WES) detected a homozygous mutation in the PYGL gene confirming GSD type VI. Additionally, WES revealed a likely pathogenic variant in a gene associated with cone-rod dystrophy / Leber congenital amaurosis-6, explaining the child's abnormal ocular movements and visual deficits.

The child was started on frequent complex-carbohydrate meals with uncooked cornstarch supplementation and avoidance of prolonged fasting. On follow-up, hypoglycemic symptoms reduced, growth velocity improved, and liver size gradually decreased. Ophthalmologic follow-up was advised for visual monitoring.

DISCUSSION:

Hers published the first worldwide report on the Glycogen storage disease (GSD) type VI in 1959.^[6] Atsushi Ogawa described a GSD VI case with localized nodular hyperplasia.^[7] Hepatic phosphorylase deficiency causes glycogen storage disease type VI, a hereditary illness of sugar metabolism. The only gene that is now known to be directly linked to GSD VI is the PYGL gene. Growth retardation, hepatomegaly, mild hypoglycemia, ketosis, hyperlipidemia, increased transaminases, and normally normal lactate and uric acid are examples of classic symptoms.^[8] Some researchers had found that liver glycogen accumulated excessively over time to increase the risk of liver injury, inflammation and fibrosis by constructing PYGL gene mutation mouse model.^[9]

The child did not have mild to moderate hypoglycemia. Skeletal muscles and the heart are typically normal. As in the propositus, the intellectual capacity and growth are determined to be normal. Serum transaminase increase is present in 86–90% of GSD VI patients. A liver biopsy revealed incomplete nodules in the propositus. While cirrhosis is rare in GSD VI, fibrosis is known to occur. GSD VI and GSD IX were misidentified as GSD III and GSD IV, which typically exhibits severe inflammation and fibrosis, in the cohort described by Roscher et al. In order to evaluate the fibrosis's progression, the youngster need additional follow-up over several years.^[10]

Restricting processed sugars and using uncooked cornstarch are crucial. Usually, there is a positive prognosis. While 93% of patients do not exhibit improvement in hepatomegaly, 84% of treated patients have showed normalization of failure to thrive or short stature. In follow-up, GSD VI has been documented to develop localized nodular hyperplasia, hepatocellular cancer, and hepatic adenoma.^[11] The PYGL gene has over 40 distinct variants, including deletions, splice site mutations, and point

mutations, that have been documented globally. Targeted mutation testing is utilized to identify illness and carrier states in a Mennonite community because mutations in the PYGL gene's intron 13 splice donor site have been found in up to 3% of chromosomes. Perhaps because GSD VI can be confused with type III on liver biopsy, this crucial differential diagnosis of GSD III has not been reported from India.^[12] This instance emphasizes the necessity of mutation analysis in all cases for proper diagnosis, accurate prognosis, and care, together with adequate genetic counseling and prenatal diagnosis, given the easier access to genetic testing in India.

CONCLUSION

Glycogen storage disease type VI is a rare but important cause of hepatomegaly and growth failure in early childhood. Although it usually follows a benign course with good response to dietary therapy, the presence of additional systemic manifestations should prompt further genetic evaluation. This case highlights the utility of whole-exome sequencing in identifying not only the primary metabolic defect but also a coexisting retinal dystrophy phenotype in a child from a consanguineous family. Early diagnosis and multidisciplinary management can significantly improve outcomes and help identify novel genotype–phenotype correlations in rare metabolic disorders.

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