CASE REPORT

Glycogen Storage Disease Type VI With a Novel Mutation in *PYGL* Gene

BARATH JAGADISAN AND *PRAJNYA RANGANATH

*From the Department of Pediatrics, JIPMER, Puducherry; and *Diagnostics Division, Centre for DNA Fingerprinting & Diagnostics, Department of Medical Genetics, Nizam's Institute of Medical Sciences, Hyderabad; India.*

Correspondence to: Dr Barath Jagadisan, Associate Professor, Department of Pediatrics, JIPMER, Puducherry 605 006, India. barathjag@yahoo.com
Received: December 03, 2016; Initial review: March 02, 2017; Accepted: July 05, 2017.

Background: Glycogen storage disease type VI (GSD-VI) presents with failure to thrive and also fibrosis in some cases, without cirrhosis. **Case characteristics:** 2½-year-old girl presented with short stature, transaminase elevation and significant fibrosis, suggesting GSD-III. **Observation:** A pathogenic mutation in *PYGL* gene suggested GSD-VI. **Message:** GSD-VI should be a differential diagnosis whenever GSD-III is suspected.

Keywords: *Chronic liver disease, Mutation analysis, Storage disorders.*

Glycogen storage disease type VI (GSD-VI) (OMIM # 232700) is an inherited disorder of glycogen metabolism. It has an autosomal recessive pattern of inheritance and is caused by homozygous or compound heterozygous mutations in the *PYGL* gene on chromosome 14q22.1, that codes for liver glycogen phosphorylase [1]. It has an estimated world-wide prevalence of 1 in 1,00,000. We report here a mutation-confirmed case of GSD VI with significant fibrosis.

CASE REPORT

A 2-year-5-month-old, developmentally normal female child was brought with complaints of progressive abdominal distension noticed since one year of age. There was no history of fever, vomiting, loose stools or constipation. Jaundice or bleeding manifestations were absent. Poor weight- and height-gain were noticed since infancy. There were no seizures, altered sensorium, early morning lethargy or earlier hospital admissions. The child was the first-born of second-degree consanguineous parents. There was no similar illness in the family. She had a cherubic facies. There was no pallor, icterus or clubbing. The height (74 cm) and weight (8.45 kg) were less for the age (weight-for-age z-score was -3.4; height-for-age z-score was -4.7). A firm hepatomegaly was palpable 12 cm below the costal margin. The spleen was not palpable.

The haematological workup, serum electrolytes, bilirubin, creatinine, International Normalized Ratio, uric acid, and Creatinine phospho kinase (and its MB component) were within normal range. The child had serum aspartate trans-aminase of 445 IU/L, serum alanine aminotransferase of 484 IU/L, serum alkaline phosphatase of 813 IU/L, serum albumin of 4.2 g/dL, serum total protein of 7 g/dL. Serum triglycerides were 854 mg/dL and serum cholesterol was 249 mg/dL. Fasting blood glucose was 60 mg/dL and serum bicarbonate was 23 meq/L. Ultrasound showed hepatomegaly without any adenoma or nodularity and normal-sized kidneys. Liver biopsy showed mildly distorted architecture. Hepatocytes were swollen with rarefaction of cytoplasm, prominent cell membrane and centrally placed nucleus. Portal tracts showed mild to moderate inflammatory infiltrate composed predominantly of lymphocytes and few neutrophils. There was fibrous expansion of portal tracts with porto-portal bridging and occasional incomplete nodule. Periodic-Acid-Schiff staining positivity with diastase-sensitivity was present. Esophago-gastroduodenoscopy did not show varices. Type-III GSD was suspected. Uncooked cornstarch fourth hourly with high protein diet and restriction of refined sugars was advised.

Molecular genetic testing was done through Next generation sequencing-based multigene panel testing for the GSD-related genes. Following targeted gene capture using a custom capture kit, sequencing was done with the Illumina sequencing platform (Illumina Inc., San Diego, California, United States). A homozygous nonsense variation c.1297 G>T (p.Glu433Ter) was identified in exon 11 of the *PYGL* gene. Sanger sequencing of exon 11 of the *PYGL* gene confirmed the presence of this homozygous pathogenic variant in the proband and heterozygous carrier status in her father; her mother was not available for testing. The p.Glu433Ter mutation in the *PYGL* gene is a variant, not previously reported in

mutation databases such as the Human Gene Mutation Database (*http://www.hgmd.cf.ac.uk/ac/*. Accessed November 10, 2016) and ClinVar (*https://www.ncbi.nlm.nih.gov/clinvar/*. Accessed November 10, 2016), which is expected to result in a stop codon and premature truncation of the protein at the 433rd amino acid position. This variant was not present in the 1000 Genome (*http://phase3browser.1000genomes.org/*. Accessed November 10, 2016) and Exome Aggregation Consortium databases (*http://exac.broadinstitute.org/*. Accessed November 15, 2016), thereby confirming that it was not a known polymorphism. The pathogenicity of this variant was inferred based on the results of the mutation prediction software Polyphen-2 (*http://www.ngrl.org.uk/Manchester/page/polyphen-2-polymorphism-phenotyping-version-2*. Accessed November 15, 2016), Mutation Taster (*www. mutationtaster.org*. Accessed November 15, 2016) and SIFT (*http://sift.jcvi.org/*. Accessed November 15, 2016).

The child was continued on the above diet and after a year the weight was 9.9 kg and height 80.5cm. There was no adenoma at 1-year follow-up.

DISCUSSION

GSD VI presents with hepatomegaly, failure to thrive and short stature as seen in the index case. Hypoglycemia may be mild to moderate; it is present only in 5% of larger cohorts and was absent in the child. The heart and skeletal muscles are usually normal [2]. The intellectual ability and development is found to be normal, as in the propositus. Around 86-90% of GSD VI patients have serum transaminase elevation [2]. Hyper-cholesterolemia and hypertriglyceridemia was present in the girl as in 67%, and 76%, respectively of a cohort of 21 patients reported from Canada. Incomplete nodules were already present in liver biopsy in the propositus. Even though fibrosis is known to be present in GSD VI, cirrhosis is uncommon. In the cohort reported by Roscher, *et al*. [2], GSD VI and GSD IX were mistaken for GSD III and also GSD IV which usually presents with significant inflammation and fibrosis. The child needs further follow-up over years to assess the progression of the fibrosis.

Uncooked cornstarch and restriction of refined sugars is essential in managing these children. The prognosis is usually good. Failure to thrive or short stature have been shown to normalize in 84% of treated patients even though 93% do not show improvement in hepatomegaly [2]. GSD.VI is known to develop hepatic adenoma in follow-up and in some cases hepatocellular carcinoma and focal nodular hyperplasia [2-4].

Around 40 different mutations in the *PYGL* gene have been reported world-wide, including point mutations, splice site mutations and deletions [2]. Mutations in the intron 13 splice donor site of the *PYGL* gene have been detected in upto 3% of chromosomes in a Mennonite population, based on which targeted mutation testing is used to detect the disease and carrier state in this population [5]. The mutation reported in our patient has not been reported earlier.

GSD VI, an important differential diagnosis of GSD III, has not been reported from India possibly because GSD VI can be mistaken for type III on liver biopsy [2]. With the easier availability of genetic testing in India, this case underscores the need for mutation analysis in all cases for correct diagnosis, accurate prognostication and management along with appropriate genetic counseling and prenatal diagnosis.

Contributors: Both authors contributed to the manuscript and approved the final manuscript.
Funding: None; *Competing interest*: None stated.

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