CASE REPORT

A MALAYSIAN CASE OF GLYCOGEN STORAGE DISEASE TYPE VI

Rabiatul Adawiyyah Mohamad Noor1, Noor Azlin Azraini Che Soh @ Yusof1, Julia Omar1, Rowani Mohd Rawi2, Noorazliyana Shafii1

Abstract

Glycogen storage disease (GSD) type VI is one of the rare GSD variants characterised by PYGL mutation. It leads to liver phosphorylase deficiency, thus causing glycogenolysis disorder. Classic manifestations are mild hypoglycaemia, abdominal distension, growth retardation, hepatomegaly, elevated liver transaminases, hyperlipidaemia, and normal lactate and uric acid. This proband is a 14-year-old Malay girl who was the second child of non-consanguineous parents. At four years old, she was referred for the incidental finding of hepatomegaly with deranged liver enzymes. Clinically, there was hepatomegaly (4 cm below the right costal margin) without any growth retardation. Subsequently, at 11 and 13 years old, she experienced a twisted left ovarian cyst and acute colitis, respectively. Biochemically, there was significantly increased transaminases, hypertriglyceridaemia, and mild hypoglycaemia. The liver biopsy result was consistent with GSD. Next-gene sequence analysis test revealed compound heterozygous mutations identified on the PYGL gene: splicing site c.772+2_772+3del and missense c.2071G>C (p.Gly691Arg). Biochemical parameters were normalised except for persistent hypertriglyceridaemia after treatment with uncooked corn starch four times daily. Family screening of mother and younger brother exhibits both are carriers of a missense mutation at c.2071G>C(p.Gly691Arg). Genetic testing helps patients better understand their conditions and serve as a guide for future pregnancy planning.

Keywords: Glycogen storage disease; GSD type VI; ovarian cyst; PYGL gene

DOI: 10.51407/mjpch.v29i3.267

Introduction

Glycogen storage disease (GSD) is a group of inherited metabolic diseases that disturb glycogen synthesis or breakdown due to congenital enzyme abnormalities. Hers’ disease, also called Glycogen Storage Disease type VI (GSD VI, MIM #232700), is inherited in an autosomal recessive pattern that is caused by mutations in the PYGL (MIM *613741) gene, which is located on chromosome 14q21-q22 that codes for hepatic phosphorylase [1,2]. PYGL is the only gene known to be associated with GSD type VI. It primarily affects the liver. It is less frequent than other types of GSD, with an incidence of 1/60 000 to 1/85 000 [2]. Here is a report of one patient with GSD type VI and a summary of her clinical symptoms, laboratory examinations, liver biopsy, and genetic test.

Case presentation

This is a case of a 14-year-old Malay girl, the second child of three siblings, a product of a non-consanguineous marriage. She was born at full-term with the birthweight of 2.4 kilograms. At four years old, she was referred for the incidental findings of hepatomegaly with liver transaminitas. The proband complained of abdominal discomfort for the previous three months. The symptom was neither related to meals nor altered bowel habits. There was no known genetic disorder in the family. Physical examination showed average growth, no dysmorphism, and no jaundice; per abdomen showed hepatomegaly (4 cm below the right costal margin). Other systemic examinations were unremarkable.

She was further investigated for hepatomegaly and liver transaminitas. Laboratory data showed an elevation of liver transaminases (alanine

Received: 4 July 2023; Accepted revised manuscript: 4 September 2023; Published online: 5 Nov 2023

1Department of Chemical Pathology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia
2Department of Paediatric, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia
*Corresponding Author:
Dr Noor Azlin Azraini Che Soh @ Yusof, Department of Chemical Pathology, School of Medical Sciences, Universiti Sains Malaysia Health Campus, 16150 Kota Bharu, Kelantan, Malaysia
Telephone: +609-7676477 Email: noorazlin79@usm.my
aminotransferase [ALT] (117 U/L; normal range: 0-31), aspartate aminotransferase [AST] (88 U/L; normal range: 0-32). There was low average fasting blood glucose (3.8 mmol/L; normal range: 4.1-5.5), hypercholesterolaemia (6.6 mmol/L; normal range: 5.2-6.2) and hypertriglyceridaemia (3.9 mmol/L; normal range: 0.0-2.3). The blood urea, electrolytes, ammonia, lactate, copper, ceruloplasmin, and alpha-fetoprotein were within normal range. She also was screened negative for TORCHES (toxoplasmosis, syphilis, hepatitis B, rubella, cytomegalovirus, herpes simplex) and viral hepatitis B and C. The autoantibodies like anti-nuclear antibody (ANA), smooth muscle antibody (SMA), and anti-liver-kidney microsomal antibody (LKM) were tested negative, thus ruling out autoimmune hepatitis. Screening tests for inborn error of metabolism were negative (dry blood spots, plasma amino acid, and urine organic acid). Haematological investigations such as full blood count, full blood picture, and haemoglobin analysis were normal. Liver ultrasonography showed a homogenous liver with normal echogenicity, smooth outline, and hepatomegaly with no focal lesion. A liver biopsy depicted the hepatocytes are swollen and mainly clear, with some showing eosinophilic granular cytoplasm, peripherally located round nuclei and thick cell membrane. The special stain highlighted intracytoplasmic glycogen (PAS positive, PAS-D digested), and the result was consistent with GSD. Next-gene sequencing analysis employing the targeted gene panel for GSD revealed compound heterozygous mutations identified on the PYGL gene: splice site c.772+2_772+3del and missense c.2071G>C (p.Gly691Arg).

She was diagnosed with GSD type VI and was followed up by the Genetic department in our hospital. The progression of her disease was monitored 3-6 monthly via biochemical investigation such as liver function test, fasting blood sugar, lipid profile and serum lactate, and annual abdomen ultrasonound. Family screening of mother and younger brother exhibits both are carriers of a missense mutation of c.2071G>C(p.Gly691Arg). Molecular testing for the father was sent but had a preanalytical issue.

At 10, she developed several episodes of symptomatic hypoglycaemia, such as sweatiness, trembling, and lightheadedness. These episodes occur at night or while performing moderate physical activities. However, blood glucose was not taken during these events, and they resolved by taking simple sweet drinks. Since then, she has been on corn starch four times daily. Hypoglycaemic episodes have improved post-treatment.

Laboratory results post-treatment showed normalised transaminases (ALT 23-28 U/L, AST 21-22 U/L), normoglycaemia (fasting blood glucose 3.9-4.6 mmol/L), normal lactate 1.15 mmol/L and persistent hypertriglyceridaemia (triglyceride 2.7-5.1 mmol/L) (Table 1). Per abdomen, the liver was not palpable, and recent liver ultrasonography showed the liver was homogenous with normal echogenicity and smooth outline. Subsequently, at 11 years old, she presented with left abdominal pain and was diagnosed with a left ovarian cyst. She underwent left salpingo-oophorectomy, appendicectomy, and exploratory laparotomy. The histopathology examination was consistent with a twisted ovarian cyst, and she had a follow-up at the gynaecology clinic. At 13 years old, she developed rectal bleeding, lower abdominal pain, constipation, and no constitutional symptoms. The colonoscopy showed multiple pseudo polyps, and the biopsy showed acute colitis features. She has a follow-up with the surgical clinic. Otherwise, she did not have a pubertal delay issue.

**Table 1. Series of biochemical parameter**

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>4</th>
<th>5</th>
<th>8</th>
<th>10</th>
<th>11</th>
<th>Reference ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>117</td>
<td>151</td>
<td>158</td>
<td>23</td>
<td>28</td>
<td>0-31 (U/L)</td>
</tr>
<tr>
<td>AST</td>
<td>88</td>
<td>160</td>
<td>122</td>
<td>21</td>
<td>22</td>
<td>0-32 (U/L)</td>
</tr>
<tr>
<td>Fasting</td>
<td>-</td>
<td>3.8</td>
<td>-</td>
<td>4.6</td>
<td>3.9</td>
<td>4.1-5.5 (mmol/L)</td>
</tr>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>3.9</td>
<td>2.0</td>
<td>2.7</td>
<td>5.1</td>
<td></td>
<td>0-2.3 (mmol/L)</td>
</tr>
<tr>
<td>Lactate</td>
<td>-</td>
<td>-</td>
<td>2.88</td>
<td>2.16</td>
<td>1.15</td>
<td>0.5-2.2 (mmol/L)</td>
</tr>
</tbody>
</table>

**Discussion**

GSD type VI occurs due to a liver phosphorylase activity defect leading to excessive glycogen accumulation in the liver. Hepatomegaly, poor growth, elevated liver transaminases, hyperlipidaemia, ketosis, and hypoglycaemia are common phenotypes in patients with GSD type VI [1–3]. Less frequently, severe phenotypes like pre- and post-prandial lactic acidosis, recurrent hypoglycaemia, or marked hepatomegaly have also been reported [3]. Clinically, the proband manifested hepatomegaly since the age of 4, and as she grew up, she developed symptomatic hypoglycaemia. The critical outcome of impaired glycogenolysis is hepatomegaly because of increased glycogen storage and mild hypoglycaemia since gluconeogenesis is intact to meet glucose demand in
the fasting state [3,4]. Later, the proband had a left ovarian cyst and per rectal bleeding. The presentation of haematochezia was similar to two cases reported in China diagnosed with inflammatory bowel disease [2]. However, we do not know whether these symptoms are related to GSD type VI, thus requiring more data about ovarian cysts and haematochezia in GSD type VI. Biochemically, liver transaminases are frequently increased upon presentation but reduce with time, suggesting that they may be linked to better metabolic regulation or the progression of liver disease [4]. In this case, the liver transaminases return to normal as the proband ages and begins treatment. If non-invasive testing is inconclusive in patients with hepatomegaly, liver biopsy should be considered [4]. Proband’s liver biopsy showed glycogen accumulation in hepatocytes, consistent with GSD. Next-gene sequencing has been regarded as a better diagnostic approach in GSD as it can bypass invasive liver biopsy [5]. Through the targeted GSD gene panel, we identified compound heterozygous mutations on the PYGL gene: splice site c.772+2_772+3del and missense c.2071G>C (p.Gly691Arg). These two mutations align with the literature review mentioned that 63 PYGL variations were discovered in GSD type VI, including 12 splice site variants, 7 deletions, 36 missense mutations, 7 stop mutations, 7 stop mutations, and 1 insertion [6]. Moreover, according to the Human Gene Mutation Database, there are around 50 mutations associated with GSD type VI, predominantly by a missense mutation of the PYGL gene [2]. Alternatively, enzyme assays can be performed to measure the hepatic glycogen phosphorylase activity. However, a normal test may not always rule out the diagnosis; phosphorylase activity may be normal in the blood cells of persons with GSD type VI [4].

Family screening (Figure 1) revealed that the younger brother and mother are carriers of this disease as a similar missense mutation was identified at c.2071G>C (p.Gly691Arg). Unfortunately, the genetic test for the father wasn’t repeated due to financial constraints. Knowing the father’s status is crucial, as there is a 25% recurrence risk if both parents are carriers [7]. The elder brother passed away on day seven of life due to complications of prematurity. No genetic test was performed on him.

Conclusions
Here, we present a rare case of GSD type VI with a left ovarian cyst and acute colitis. Due to the non-specific and broad spectrum of disease phenotypes, GSD type VI is usually underdiagnosed and presents late. Haematochezia and ovarian cysts may enrich the clinical manifestation of the disease. Thus, it is important to educate health workers to recognise genetic diseases earlier to prevent complications, thus reducing the morbidity and mortality of patients. Genetic counselling is equally vital to help patients better understand their conditions and encourages family members to take screening tests and predict recurrence risk for future pregnancies.

References
