Known and a novel mutation in PHKA2 expand the phenotype of glycogen storage disease IXa to include idiopathic ketotic hypoglycaemia

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Conclusion: Patients with idiopathic ketotic hypoglycaemia may have a mild form of glycogen storage disease. Genetic analysis is encouraged to improve precision of treatment and prognosis, and to diagnose affected family members.

Background

• Idiopathic ketotic hypoglycaemia (IKH) is the most common cause of hypoglycaemia in childhood. It is an exclusion diagnose when thorough investigations have been made
• Glycogen Storage disease (GSD) type IX is due to a deficiency in phosphoralyse kinase and comprises one quarter of all GSD’s. GSD IXa, encoded by \textit{PHKA2}, is the most frequent subtype with a majority of private mutations (>100)
• Clinical features in children with GSD IXa include hepatomegaly, elevated liver enzymes, short stature and ketotic hypoglycemia. Wide variations in symptoms and severity exist without any known genotype-phenotype correlation

Methods

• Retrospective chart evaluation in three families with IKH patients
• Genetic analysis by whole exome sequencing or 29 gene GSD panel

Results

• Six children in three families were diagnosed with IKH (Table 1.) and were reclassified to have GSD IXa

<table>
<thead>
<tr>
<th>Patient</th>
<th>Onset</th>
<th>Sex</th>
<th>GSD IXa (mmol/L)</th>
<th>Ketosis (&gt;1.0 mmol/L)</th>
<th>Hepatomegaly (ultrasound or clinical)</th>
<th>Liver dysfunction (≤2 SD)</th>
<th>Growth retardation</th>
<th>Normal hormonal and metabolic investigations</th>
<th>Gene</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PHKA2</td>
<td>p.Pro869Arg</td>
</tr>
<tr>
<td>II:1</td>
<td>17 mo.</td>
<td>F</td>
<td>2.5</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II:1</td>
<td>19 mo.</td>
<td>M</td>
<td>1.9</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Elevated lactat + pyruvat</td>
<td>PHKA2</td>
<td>p.Pro498Leu</td>
</tr>
<tr>
<td>II:2</td>
<td>20 mo.</td>
<td>M</td>
<td>2.1</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Elevated lactat + pyruvat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PHKA2</td>
<td>p.Arg2Gly</td>
</tr>
<tr>
<td>III:2</td>
<td>6 y.</td>
<td>F</td>
<td>2.2</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III:3</td>
<td>8 mo.</td>
<td>M</td>
<td>1.8</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes (subnormal GH values)</td>
<td>PHKA2</td>
<td>p.Arg2Gly</td>
</tr>
<tr>
<td>III:4</td>
<td>3 y.</td>
<td>M</td>
<td>2.3</td>
<td>nd</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>nd</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textit{nd=} no data, \textit{mo=} month, \textit{y=} year, \textit{F=} female, \textit{M=} male

Table 1. Clinical details in IKH patients

Genetic investigations

• In family A and B Whole Exome Sequencing were made
• Two previously reported mutations in PHKA2 were found: c.2606C>G, p.Pro869Arg and c.1493C>T, p.Pro498Leu

Family history and the knowledge from family A and B prompted reevaluation of the IKH diagnosis in family C
• A novel GSD IXa mutation (HGMD, ClinVar and literature) c.4C>G, p.Arg2Gly in PHKA2, maternal was found
• Allele frequency 4/100,000 (genomAD)
• \textit{In} silico analysis: Deleterious (PolyPhen-2), deleterious (SIFT), disease-causing (Mutaster)
• Classification according to ACMG guidelines was likely pathogenic

Discussion

• IKH and GSD IXa can clinically overlap, as suggested by our report, why GSD IXa may be under-diagnosed
• We hypothesize that IKH may represent milder variants of GSD, Figure 2.
• GSD gene panel and family testing is encouraged in IKH

Figure 1. Pedigree of three families with IKH
Dark grey: Symptoms
Hachured: Symptoms in childhood
White: No symptoms

Figure 2. Hypothesis: Mild affected children with GSD IXa may be misdiagnosed as IKH. The same may be true for other GSDs.