Glycogen-Storage Disease Type VI in a girl presenting with Recurrent Ketotic Hypoglycaemia but no Hepatomegaly

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Background
Glucose homeostasis:
• Glycogen, the stored form of glucose, is formed in periods of dietary carbohydrate loading, and broken down during fasting to maintain euglycaemia.
• This process is called glycogenolysis and relies on numerous enzymes, including glycogen phosphorylase.
• Inborn errors of metabolism resulting from mutations in genes involved in glycogen synthesis, degradation or regulation cause a group of conditions called Glycogen Storage Diseases.
• Glycogen is most abundant in liver and muscle, the organs most affected by glycogen storage diseases (GSDs).
• Ketotic hypoglycaemia is a relatively common diagnosis in children presenting with hypoglycaemia, but it is a diagnosis of exclusion.

Glycogen Storage Disease type VI (GSD VI):
• Autosomal recessive
• Deficiency of the liver isoform of glycogen phosphorylase
• Results in abnormal accumulation of glycogen
• Typical presentation - early childhood with growth retardation, hepatomegaly, hypoglycaemia and ketosis

Fasted state

Case
• 3-year-old girl, born at term, birth weight 3.14kg
• Presented with episodes of recurrent hypoglycaemia not associated with intercurrent illness
• Non-consanguineous Caucasian parents
• Uneventful past medical history
• Height SDS -2.5
• Normal examination with no dysmorphic features or hepatomegaly

1. Investigations:

<table>
<thead>
<tr>
<th>Glucose (mmol/L)</th>
<th>Insulin (pmol/L)</th>
<th>C-peptide (pmol/L)</th>
<th>Free fatty acids (µmol/L)</th>
<th>B-hydroxybutyrate (µmol/L)</th>
<th>Bedside blood Ketones (mmol/L)</th>
<th>Cortisol (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4</td>
<td>&lt;14</td>
<td>51</td>
<td>3640</td>
<td>3965</td>
<td></td>
<td>2.5</td>
</tr>
<tr>
<td>2.3</td>
<td>&lt;24.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1065</td>
</tr>
</tbody>
</table>

• Plasma amino acids, lactate, blood ammonia, blood spot acylcarnitine profile and urine organic acids - no abnormalities
• Suggestive of ketotic hypoglycaemia

2. Further results:
• IGF1 5.4 (2.3-32 nmol/L)
• Prolactin 77 (0-500 mU/L)
• TSH 1.04 (0.3-3.8 mu/L)
• T4 14.3 (9.9-19 pmol/L)
• Normal bone profile
• 46XX karyotype

3. Glucagon stimulation test:

<table>
<thead>
<tr>
<th>Glucagon Stimulation Test</th>
<th>Free</th>
<th>KB</th>
<th>EBR</th>
<th>ALD</th>
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<tbody>
<tr>
<td>8</td>
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<td>334</td>
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<tr>
<td>98</td>
<td>3.77</td>
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<tr>
<td>128</td>
<td>8.99</td>
<td>586</td>
<td>2.70</td>
<td></td>
</tr>
</tbody>
</table>

• Committed on growth hormone

4. Continued to have symptomatic ketotic hypoglycaemic episodes
• Not triggered by intercurrent illness
• Further genetic analysis undertaken

5. Metabolic mutation analysis:

Heterozygous PYGL mutation
• Suggests a diagnosis of probable GSD VI with an unidentified second mutation
• Presence of exonic deletions or deep intronic variations in the PYGL gene cannot be ruled out as these were not analysed

Conclusion
• We report a case of probable GSD VI who presented with recurrent ketotic hypoglycaemia without hepatomegaly.
• Ketotic hypoglycaemia is a diagnosis of exclusion.
• It is important to consider alternative diagnoses especially in the presence of recurrent hypoglycaemic episodes with atypical features for ketotic hypoglycaemia.
• Genetic evaluation may be warranted in selected cases of ketotic hypoglycaemia.

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Alder Hey Children’s
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