Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2016:

<table>
<thead>
<tr>
<th>Name of the enterprise / Nature of the interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nothing to declare</td>
</tr>
</tbody>
</table>
Case 6

Sophie Stenton
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Sheffield Children’s Hospital
Clinical History

- 9 year old male
- Third child to consanguineous first cousin parents
- Abdominal pain, weakness in lower limbs, dizzy spells and ‘clammy episodes’ at school
- General examination was unremarkable
- Mildly deranged transaminases
- Ultrasound confirmed fatty liver and hepatomegaly
Summary of histology report

- Adequate core of hepatic tissue with 10 portal tracts
- Diffusely abnormal parenchyma
- Enlarged hepatocytes with pale, flocculent cytoplasm
- Micro- and macrovesicular steatosis
- Scanty periportal and lobular infiltrate of mixed inflammatory cells
- There is no excess of iron or copper deposition
Summary of EM Report

- Excessive glycogen content of hepatocytes
- Unremarkable hepatocyte organelles
- Absent smooth endoplasmic reticulum
- Unremarkable kupffer cells and cholangiocytes
Impression from histological and ultrastructural findings

• Metabolic disorder
• Disorder of glycogen metabolism
• The histological and ultrastructural features were not suggestive of GSD 2 (Pompe’s) or GSD 4 (Anderson’s disease)
Glycogen Storage Disorders

- Glycogen storage disorders (GSD) are a group of inherited metabolic disorders of glycogen metabolism, estimated to affect 1/20,000 – 1/43,000 live births.

- The main subtypes are classified based on enzymatic defect and affected tissues.

- Clinical features vary with the most severe cases presenting in infancy with acute hypoglycaemic crisis or severe cardiomyopathy.

- The combination of clinical features with the histological and ultrastructural findings can enable partial distinction in glycogenosis.
## Glycogen Storage Disease

### Table 21.1 Glycogen-storage diseases

<table>
<thead>
<tr>
<th>Type</th>
<th>Defective enzyme</th>
<th>Organ affected</th>
<th>Glycogen in the affected organ</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Glucose 6-phosphatase or transport system</td>
<td>Liver and kidney</td>
<td>Increased amount; normal structure.</td>
<td>Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.</td>
</tr>
<tr>
<td>II</td>
<td>α-1,4-Glucosidase (lysosomal)</td>
<td>All organs</td>
<td>Massive increase in amount; normal structure.</td>
<td>Cardiorespiratory failure causes death, usually before age 2.</td>
</tr>
<tr>
<td>III</td>
<td>Amylo-1,6-glucosidase (debranching enzyme)</td>
<td>Muscle and liver</td>
<td>Increased amount; short outer branches.</td>
<td>Like type I, but milder course.</td>
</tr>
<tr>
<td>IV</td>
<td>Branching enzyme (α-1,4 → α-1,6)</td>
<td>Liver and spleen</td>
<td>Normal amount; very long outer branches.</td>
<td>Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.</td>
</tr>
<tr>
<td>V</td>
<td>Phosphorylase</td>
<td>Muscle</td>
<td>Moderately increased amount; normal structure.</td>
<td>Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.</td>
</tr>
<tr>
<td>VI</td>
<td>Phosphorylase</td>
<td>Liver</td>
<td>Increased amount.</td>
<td>Like type I, but milder course.</td>
</tr>
<tr>
<td>VII</td>
<td>Phosphofructokinase</td>
<td>Muscle</td>
<td>Increased amount; normal structure.</td>
<td>Like type V.</td>
</tr>
<tr>
<td>VIII</td>
<td>Phosphorylase kinase</td>
<td>Liver</td>
<td>Increased amount; normal structure.</td>
<td>Mild liver enlargement. Mild hypoglycemia.</td>
</tr>
</tbody>
</table>

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.

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*Table 21.1*  
*Biochemistry, Seventh Edition*  
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Enzyme studies

Reduced total phosphorylase (+AMP):
1.76 umol/hr/mg ptn (2.7-8.32)

- Phosphorylase a (-AMP),
- Phosphorylase a/total ratio
- Glycogen debrancher
- Phosphorylase b kinase normal
DNA sequencing by a panel of genes associated with liver glycogen storage disease

Homozygous for the c.1228A>T, p(Lys410*) pathogenic mutation in exon 10 of the PYGL gene.

This mutation has not previously been described but is predicted to result in a premature termination codon.

Confirms a diagnosis of GSD type VI (Hers)

Future pregnancies are at a ¼ risk of same
What affect does this mutation have?

- The mutation results in isolated hepatic accumulation of glycogen due to a deficiency of glycogen phosphorylase.

- This enzyme is involved in the initial phase of the glycogen metabolism pathway.

- Glycogen phosphorylase catalyzes the degradation of glycogen to glucose-1-phosphate by the phosphorylytic cleavage of α-1,4-glycosidic bonds.
GSD Type 6 is caused by a primary deficiency in glycogen phosphorylase.
Hers Disease

- Primary deficiency in glycogen phosphorylase.

- Type 6 now encompasses other GSDs due to abnormalities of the phosphorylase cascade system (GSD 8, 9 and 10)

- Increased glycogen content of hepatocytes on EM

- Follows a similar, albeit milder clinical course to GSD I (Von Gierke’s)
Hers Disease

- Autosomal Recessive
- 30% of all GSD
- Mild clinical course in childhood with many asymptomatic for long periods
- Mild growth impairment, hepatomegaly, hypotonia, hypoglycaemia
Hers Disease

• Normal growth and intellectual parameters in adulthood

• A subset of individuals with abnormality of phosphorylase kinase are at an increased risk of cirrhosis

• These are the PHKA2, PHKB and PHKG2 genes which encode the alpha, beta subunits and activating enzyme component of phosphorylase kinase.

• Only one documented case of hepatocellular carcinoma in GSD VI
Summary

- Hers disease is a uncommon form of GSD
- Mild clinical course and may go undetected
- Histological and ultrastructural findings are distinctive for a glycogen storage disorder
- Genetic investigations are needed for confirmation of subtype of GSD
Thank you
Questions?