INTRODUCTION:
Orotic acid is a key intermediary metabolite in pyrimidine synthesis, and can be detected by urine organic acid analysis. Urine orotic acid accumulation is commonly associated with the X-linked urea cycle defect ornithine transcarbamylase (OTC) deficiency (OMIM #311250). However, elevations may also be associated with:

- Lysinuric protein intolerance (LPI)
- Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome
- Other distal urea cycle defects
- Mitochondrial disease
- Liver damage/high cell turnover secondary to chemotherapeutics
- Uridine monophosphate synthase (UMPS) deficiency (or carrier status)

Given the varying clinical spectrum of these diagnoses ranging from benign to life-threatening, identifying the etiology of orotic aciduria is of substantial clinical importance.

FAMILIAL INHERITANCE OF POTENTIAL CAUSES OF OROTIC ACIDURIA

MOLECULAR ANALYSIS:
Sanger sequencing and MLPA Analysis of the OTC gene:
Chr1 (GRCh37/hg19): g.([7_38,211,840]_[38,240,707_38,260,608]dup)[c.] = p.[?] =
Sanger sequencing of the UMPS gene:
UMPS (NM_000373.4): c.[869G>C]; p.([Arg230Pro]) =

CONCLUSION:
Overall, this case highlights the importance of considering alternative aetiologies to orotic aciduria (beyond urea cycle disorders), particularly in patients who are clinically asymptomatic. This case report is also an excellent example of the interdisciplinary approach required to achieve a diagnosis. The patient is currently receiving no active treatment and dietary modification has been ceased. She is growing and developing normally and has remained asymptomatic.

CASE REPORT:
History:
• A six-week-old female with a history of failure to thrive was referred to clinic with elevated urinary orotate
• Whilst being investigated for OTC deficiency, a small amount of protein-free formula was commenced with a plan to increase the quantity during periods of potential metabolic decompensation
• The failure to thrive resolved and the patient remained asymptomatic (even during an intercurrent illness*) with persistent orotic aciduria as demonstrated below

<table>
<thead>
<tr>
<th>Age</th>
<th>Plasma Glutamine (µmol/L)</th>
<th>Plasma Citrulline (µmol/L)</th>
<th>Plasma Arginine (µmol/L)</th>
<th>Plasma Lysine (µmol/L)</th>
<th>Serum Aminoacid (µmol/L)</th>
<th>Urine Orotate (µmol/CRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 weeks</td>
<td>312 ± 826</td>
<td>5 ± 43</td>
<td>24 ± 127</td>
<td>65 ± 271</td>
<td>10 – 50</td>
<td>0 – 10</td>
</tr>
<tr>
<td>7 weeks</td>
<td>647 ± 19</td>
<td>97</td>
<td>275</td>
<td>14</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>8 weeks</td>
<td>603 ± 17</td>
<td>89</td>
<td>228</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 weeks</td>
<td>716 ± 15</td>
<td>77</td>
<td>147</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 months</td>
<td>1</td>
<td></td>
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</tbody>
</table>

* Subsequent parental urine screening showed orotate levels within the reference range

<table>
<thead>
<tr>
<th>Relation to proband</th>
<th>Urine Orotate (µmol/CRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>7</td>
</tr>
<tr>
<td>Mother</td>
<td>1</td>
</tr>
</tbody>
</table>

Sanger sequencing and multiplex ligation-dependent probe amplification (MLPA) analysis of the OTC gene was performed to investigate if OTCD was the cause of the orotic aciduria

Sanger sequencing of the UMPS gene was also subsequently performed

DISCUSSION:
Despite identifying variants in two separate genes associated with orotic aciduria in our proband, carrier status for UMPS deficiency appears to be the most likely cause of her persistently elevated urinary orotate. The proband’s asymptomatic father is hemizygous for the duplication in the OTC gene which suggests the duplication may be benign. Furthermore, the proband’s plasma amino acid levels remained normal at the time of illness, providing additional evidence that the duplication is benign and most likely is not the cause of her orotic aciduria.

The proband’s asymptomatic father is also a carrier of the UMPS variant, but it is important to note that reduced penetrance has been reported4 which can explain the absence of orotic aciduria. However, given there are other genes associated with orotic aciduria that have not been sequenced, it is difficult to definitively attribute this patient’s biochemical abnormality to this particular UMPS variant.

Whole genome sequencing may elucidate the exact coordinates and pathogenicity of the duplication in the OTC gene4. More than likely, this duplication is located in tandem or elsewhere in the genome (where it would be unlikely to disrupt OTC transcription). However, it could also be intragenic (where it may disrupt the reading frame) and cause disease.

References:

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