Improvement of cholestasis in MPV17-related hepatocerebral mitochondrial DNA depletion syndrome with meticulous glycaemic management

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Background

MPV17-related hepatocerebral mitochondrial DNA depletion syndrome causes a variable disorder comprising progressive liver disease and fluctuating encephalopathy, and a later-onset form with neuropathy. Early-onset forms often progress to liver failure with high mortality rate independent of liver transplant. Management of hypoglycaemia is reportedly imperative but detail of infantile treatment is sparse (Spinazzola et al 2006). This case report describes how dietary management was implemented for infantile-onset MPV17 deficiency.

Presentation

Neonatal background

Third child to non-consanguineous Caucasian parents, older siblings were reportedly well. No significant family history.

Patient born at term, birth weight 3.49kg (50-85th %tile), length 50cm (50-75th %tile), head circumference 33.5cm (15-50th %tile), weight for length 50-85th %tile.

Mild neonatal jaundice, well until 3 months old – presented and admitted with non-bilious persistent vomiting, cholestatic liver disease and 10% weight loss.
Medical investigations

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated bilirubin (IU/L)</td>
<td>46 (H)</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase (IU/L)</td>
<td>680 (H)</td>
<td>&lt; 45</td>
</tr>
<tr>
<td>Plasma lactate (mmol/L)</td>
<td>2-6 (H)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>1131 (H)</td>
<td>10 – 100</td>
</tr>
<tr>
<td>Ammonia (µmol/L)</td>
<td>152 (H)</td>
<td>10 – 0</td>
</tr>
<tr>
<td>Blood glucose (mmol/L)</td>
<td>Numerous lows (&lt;2.6)</td>
<td>3.1 – 10</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>15.3 (H)</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>Alpha fetoprotein</td>
<td>46340 (H)</td>
<td>0 – 77</td>
</tr>
</tbody>
</table>

Growth

- Weight: 4.14kg (<3rd %tile, Z-score -3.06)
- Length: 58.5cm (10-25th %tile)
- Head circumference: 38.5cm (3rd-15th %tile)

Brain MRI

- Normal

Urine metabolic screen

- 3-methylglutaconate – slight increase
- Creatine – increase

Abdominal ultrasound

- Mild hepatomegaly (9cm) with diffuse increased echogenicity. Liver edge smooth.

Neurological exam

- Disconjugate eye movements. No encephalopathy. Intermittently increased upper left limb tone

Trio whole exome sequencing (at 6 months of age)

- Compound heterozygous pathogenic variants in MPV17- c.293C>T p.(Pro98Leu) and c.135del p.(Glu45Aspsfs*8)

Table 1: Initial investigations and findings at presentation of a 3 month old with vomiting, weight loss and cholestatic liver disease

Initial management

3mo

- Inpatient: Nasogastric continuous feeds of expressed breast milk + extensively hydrolysed infant formula
- Discharge: overnight continuous; day time bolus. High energy (147kcal/kg, 1kcal/ml)

5mo

- Continuous glucose monitor (CGM) commenced, used 24/7 to titrate day time bolus feeds against blood glucose level (BGL) → minimise hypoglycaemia

7mo

- Gastrostomy inserted (oral aversion – gagging, vomiting)
- Formula changed to extensively hydrolysed infant formula + glucose polymer

10mo

- Initial metabolic dietitian review: formula changed to stage 2 infant formula + glucose polymer
- Carbohydrate (CHO) provision: 0.45g/kg/hr

12mo

- Regular vomiting resolved, liver function improved, nerve conduction normal
- Uncooked corn starch (UCCS) introduced 1/day at 0.34g/kg/dose: initial abdominal discomfort (resolved), ↓ appetite for oral food, ↑ time between day bolus feeds.

Figure 1: Initial and subsequent feeding management of an infant with recurrent hypoglycaemia in the context of MPV17-related hepatocerebral mitochondrial DNA depletion syndrome.
Current management

Feeding Management from 15 mo

- Oral feeding minimal; consistent exposure encouraged
- Gastrostomy
- UCCS 1g/kg/dose x4 /day
- Standard paediatric formula, 1kcal/ml
- Continuous overnight feeds 11/24 0.37g/kg/hr CHO
- Daytime bolus feeds x4-5 q2–3.5h 0.4g/kg/hr CHO
- CGM 24/7 Finger prick x4/day Aim BGL >3.2mmol/L
- Illness: ↓ volume; ↑ frequency (q2.5h)
- Hypo rescue solution 0.35–0.4g/kg CHO

Current management

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Figure 2: Current feeding management of a 15 month old with MPV17-related hepatocerebral mitochondrial DNA depletion syndrome

Weight

Figure 3: Weight of an infant with MPV17-related hepatocerebral mitochondrial DNA depletion syndrome (WHO charts)
Continuous Glucose Monitoring

Figure 4: CGM trend over a week for a 15 month old with MPV17-related hepatocerebral mitochondrial DNA depletion syndrome

At 18 months of age

- No regular hypoglycaemic events
- Normal development – ambulatory, climbing, using single words
- No oral intake – likely related to intensive gastrostomy feeding regimen
- Mild hepatocellular liver dysfunction without cholestasis
  - Alanine transaminase (ALT) 77 U/L (<36)
  - Aspartate transaminase (AST) 130 U/L (<66)
  - Gamma-glutamyltransferase (GGT) 181 U/L (<45)

Conclusion

Continuous glucose monitoring has been paramount in titration of gastrostomy feeds for this case study with MP17-related hepatocerebral mitochondrial DNA depletion syndrome. Meticulous glycaemic control has correlated with improved liver function and promoted normal growth and development, although long term clinical outcomes remain uncertain.