NEONATAL HYPOTONIA WITH AN ATYPICAL DIAGNOSIS

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INTRODUCTION:
❖ Glycine – the smallest amino acid also functions as a neurotransmitter.
❖ The cell and tissue-specific abundance of glycine depends on the balance between its use in biosynthetic reactions, catabolism by the glycine cleavage system (GCS) and excretion via the glycine conjugation pathway.
❖ The GCS is localised in the mitochondrial matrix and comprises of
  • Glycine decarboxylase (GLDC)
  • Amino methyltransferase (AMT)
  • GCS H-protein (GCHS)
  • Dihydrolipoyl dehydrogenase (DLD)

NON-KETOTIC HYPERGLYCINAEMIA (NKH):
❖ Classical NKH is associated with bi-allelic variants of GLDC and AMT.
❖ Typically, presentation is in the early neonatal period with hypoventilation followed by an intractable severe seizure disorder and a poor prognosis even with optimal treatment.
❖ However, the less common attenuated NKH confers residual activity of the glycine cleavage system and responds to treatment.

PATIENT:
❖ First child of a non-consanguineous Caucasian couple.
❖ Presented with hypotonia and feeding difficulties.
❖ Readmitted to hospital after normal delivery having lost 13% of birthweight.
❖ Improved clinically with sustained nutrition but had persisting hypotonia with normal deep tendon reflexes.
❖ No seizures.

AMINO ACID RESULTS:
❖ Table below shows results from plasma and CSF amino acid analysis.

<table>
<thead>
<tr>
<th>Plasma (μmol/L) (RR 131 - 530)</th>
<th>CSF (μmol/L) (RR 4 - 14)</th>
<th>Ratio (RR &lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>839H</td>
<td>85H</td>
<td>0.10H</td>
</tr>
<tr>
<td>748H</td>
<td>81H</td>
<td>0.10H</td>
</tr>
</tbody>
</table>

Plasma results were not consistent with classical NKH.
However, elevated CSF glycine and the ratio were consistent with attenuated NKH.

MOLECULAR TESTING:
❖ Rapid TRIO whole exome sequencing (WES) was undertaken due to the atypical presentation.
❖ WES identified bi-allelic variants in the GLDC gene:
  • c.698T>A, p.(Val233Asp) (likely pathogenic, paternally inherited)
  • c.806C>T, p.(Thr269Met) (pathogenic, maternally inherited)

TREATMENT:
❖ Patient treated with
  • sodium benzoate
  • dextromethorphan
❖ Plasma glycine has ranged between 250 – 350 μmol/L (< 412) since treatment.

DISCUSSION:
❖ At 18 months, she has mild delay with no seizures.
❖ This case highlights that attenuated NKH can present with a diverse range of clinical presentations.
❖ Early recognition and treatment may result in better neurodevelopmental outcomes.