Rash in Methylene Tetrahydrofolate Reductase (MTHFR) deficiency: The Eastern Australian Experience


Introduction: MTHFR deficiency is a disorder of folate-dependent homocysteine remethylation, with wide phenotypic variation. We report two infants presenting with rash in addition to classical features of failure to thrive, apnoeas and microcephaly.

**Patient 1.** Female - current age 8 months

Clinical Features
- Presentation: 4 weeks of age
- Poor weight gain
- Preceding two-week history of lethargy, poor feeding and periodic breathing
- Examination: Rash (patchy, erythematous, crusting), hypothermia, encephalopathy, acquired microcephaly, apnoeas, severe hypotonia, hyporeflexia and paucity of spontaneous movement

**Patient 2.** Female - current age 13 years

Clinical Features:
- Presentation: three weeks of age
- Poor weight gain
- Examination: desquamating skin eruption, hypothermia, lip smacking suggestive of seizures and hypotonia
Pathology Results

<table>
<thead>
<tr>
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<th>Patient 1</th>
<th>Patient 2</th>
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<tbody>
<tr>
<td>Initial total homocysteine micromol/L</td>
<td>200 (RR&lt;15)</td>
<td>110 (RR 3-19)</td>
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<tr>
<td>Initial plasma Methionine micromol/L</td>
<td>3 (RR 10-40)</td>
<td>2 (RR 14-47)</td>
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<tr>
<td>Methylmalonate</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Full blood count abnormalities</td>
<td>Low haemoglobin Low platelets No macrocytosis</td>
<td>Result not available</td>
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<tr>
<td>Biotinidase enzymology</td>
<td>Normal</td>
<td>Result not available</td>
</tr>
<tr>
<td>Pathogenic Variant MTHFR</td>
<td>Bi-allelic pathogenic variants (c.1699C&gt;T and c.1013T&gt;C)</td>
<td>Homozygous pathogenic synonymous variant affecting splicing (c.1530G&gt;A)</td>
</tr>
</tbody>
</table>

Treatment: associated with rapid biochemical and clinical response
- Betaine
- Folinic acid
- Intramuscular hydroxocobalamin
- In patient 1., plasma homocysteine reduced to 65micromol/L and plasma methionine increased to 19 micromol/L within 4 days of initiation of treatment. Resolution of the described rash within the first 7 days of treatment.

Complications:
Patient 1. Seizures, nystagmus, microcephaly
Patient 2. Hydrocephalus and mild intellectual disability

Discussion: Desquamating, diffuse, erythematous rash has been reported in severe MTHFR deficiency previously in three individuals. Early diagnosis is known to be associated with better outcome in this condition. These additional two cases from different centres in Eastern Australia highlight the importance of quantifying plasma homocysteine levels in infants with encephalopathy in association with rash to facilitate early diagnosis and treatment of severe MTHFR deficiency.

References: