Fits, pyridoxine, and hyperprolinaemia type II

Valerie Walker, Graham A Mills, Sheila A Peters, W Louis Merton

Abstract

The rare inherited disorder hyperprolinaemia type II presents with fits in childhood, usually precipitated by infection. A diagnosis of hyperprolinaemia type II and vitamin B_{6} deficiency was made in a well nourished child with fits. It is thought that pyridoxine deficiency was implicated in her fits and was the result of inactivation of the vitamin by the proline metabolite, pyrroline-5-carboxylate.

Case report

A previously well girl had a febrile convolution at 18 months. She recovered completely. At 20 months she became sleepy, lethargic, and fed poorly in association with pneumonia. She had three convulsions within 15 hours, two lasting more than five minutes and one 20 minutes. After these, she was encephalopathic with back arching and purposeless movements, areflexic, but breathing normally. An electroencephalogram (EEG) six hours after her fits did not show any discharges; slow activity was quite prominent with spindles appropriate for sleep. On full arousal, low activities were seen with no excess of slow activity to indicate an overt encephalopathy. However, 24 hours later, when she was awake and not fitting, the EEG was very abnormal (fig 1). Large irregular slow activities (2–3 Hz, 200 µV) mixed with rather repetitive sharp/polyspikes and occasional spikes were seen over both hemispheres with variable localisation. Computerised brain tomography was normal. She recovered slowly over five days. The EEG became normal. Three months later she had a severe nappy rash for three to four weeks, which was resistant to local treatment. There have been no more fits (see addendum). After demonstrating pyridoxine deficiency, she was treated with 50 mg pyridoxine orally daily from 32 months of age for five weeks, reducing to 10 mg daily long term. At 3 years of age, she is growing along the 50th centile for height, 25th centile for weight, and is neurologically normal except for slight speech delay. She has a good, mixed diet and there have never been feeding or intestinal problems.

Biochemical investigations

Hyperprolinaemia type II was diagnosed from persisting amino acid and organic acid abnormalities when she presented with fits and encephalopathy. We speculate that pyridoxine deficiency was implicated in her fits and that it was caused by inactivation of the vitamin by the proline metabolite pyrroline-5-carboxylate. This would be a unique cause of increased vitamin dependency. It would account for the fits in hyperprolinaemia type II, which are currently unexplained.

Table 1 Diagnostic biochemical investigations

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Value (µmol/l or µmol/mmol creatinine)</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolin (µmol/l) n = 5</td>
<td>6.90</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>Hydroxyproline (µmol/l)</td>
<td>131–145</td>
<td>27–103</td>
</tr>
<tr>
<td>Urine (µmol/mmol creatinine) (n = 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolin</td>
<td>3700–4750</td>
<td>&lt; 13</td>
</tr>
<tr>
<td>Hydroxyproline</td>
<td>85–420</td>
<td>&lt; 13</td>
</tr>
<tr>
<td>Glicine</td>
<td>1432–4055</td>
<td>&lt; 356</td>
</tr>
<tr>
<td>Ornithine</td>
<td>18–33</td>
<td>&lt; 8</td>
</tr>
<tr>
<td>N-(pyrrole-2-carboxyl)-glycine</td>
<td>Present</td>
<td>Not detected</td>
</tr>
<tr>
<td>Vitamin B_{6} deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma (µmol/l) n = 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridoxal phosphate</td>
<td>1.0; 2.7</td>
<td>10.9–27.3</td>
</tr>
<tr>
<td>Pyridoxic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine (µmol/mmol creatinine) (n = 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyridoxic acid</td>
<td>0.4</td>
<td>0.5–2.3</td>
</tr>
</tbody>
</table>

Plasma vitamin B_{6} was measured by high performance liquid chromatography (Dunn Nutrion Centre, Cambridge; department of clinical biochemistry, Glasgow Royal Infirmary). Tryptophan metabolites and pyridoxic acid were measured in urease treated extracted urine by gas chromatography mass spectrometry with single ion monitoring. Basal values are compared with in house paediatric reference ranges.


deficiency from amino acid and organic acid abnormalities when she presented with fits and encephalopathy. We speculate that pyridoxine deficiency was implicated in her fits and that it was caused by inactivation of the vitamin by the proline metabolite pyrroline-5-carboxylate. This would be a unique cause of increased vitamin dependency. It would account for the fits in hyperprolinaemia type II, which are currently unexplained.

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Biochemical investigations

Hyperprolinaemia type II was diagnosed from persisting amino acid and organic acid abnormalities (table 1). DNA analysis has excluded the mutation present in a large Irish kindred.3 Further DNA studies are planned. A skin biopsy for fibroblast enzyme confirmation is not justifiable at present. Novel findings in the acute urine sample were two metabolites of tryptophan: xanturenic acid and a volatile degradation product of kynurenine, 2-aminoacetoephone. These abnormalities suggested vitamin B_{6} deficiency.4 Plasma
analysed by two laboratories when the child was well at 22 months and 28 months showed marginally low pyridoxal phosphate and greatly reduced pyridoxic acid, to concentrations that were barely detectable. Pyridoxic acid is the end product of vitamin B₆ catabolism and low values indicate a deficiency. An oral L-tryptophan loading test (100 mg/kg body weight) was carried out at 28 months of age to stress vitamin B₆ metabolism. Random urine samples were collected for 7.5 hours after loading. Basal excretion of xanthurenic acid was increased and the response to loading was excessive, confirming vitamin B₆ deficiency. In a follow up test after five weeks of 50 mg pyridoxine orally daily, basal urine xanthurenic acid was normal (1.1 μmol/mmol creatinine), as was the post load excretion (9.8 μmol/mmol creatinine). Co-incubation of pyridoxal, pyridoxal phosphate, and pyridoxamine with pyrroline-5-carboxylate at physiological pH in vitro produced new compounds demonstrable with gas chromatography mass spectrometry and nuclear magnetic resonance spectroscopy. Studies to characterise these are in progress (see addendum).

### Discussion

Because vitamin B₆ occurs widely in food, symptomatic deficiency is rare. Nutritional deficiency in infants aged 6 weeks to 6 months fed autoclaved cows' milk caused irritability and generalised convulsions with EEG abnormalities. Adults treated with vitamin B₆ antagonists and low pyridoxine diets also had epileptiform convulsions and sometimes a red scaly rash involving the eyes, nose, and perineum. Vitamin B₆ deficiency would explain the fits in our child and might have contributed to the severe nappy rash. The unusual EEG abnormalities in her acute illness resemble those in pyridoxine dependent epilepsy.

Nutritional deficiency was not the explanation here. Alternatives are antagonism or inactivation of one of the physiological forms of vitamin B₆ (pyridoxal, pyridoxine, or pyridoxamine, or their phosphates). Antagonists are generally structural analogues of the B₆ vitamins or agents that complex with them. Pyrroline-5-carboxylate is a reactive compound that accumulates in hyperprolinaemia type II. We propose that it links covalently with one of the B₆ vitamins and inactivates it. Pyridoxal or pyridoxal phosphate are likely candidates because they have a very reactive aldehyde group. Our preliminary studies in vitro indicate that such an interaction is possible. We know of no other instance of an endogenous metabolite causing similar vitamin dependency.

We intend to treat our patient with pyridoxine (10 mg/day) until she is 10 years old when the risk of fits should have decreased. Other children with the defect might also benefit from supplements and their plasma pyridoxal phosphate and pyridoxic acid should be measured.

We thank Professor D Valle, The Johns Hopkins University School of Medicine, Baltimore, USA for undertaking DNA mutation analysis.

### Addendum

The child was admitted in December 1999 (aged 4 years 7 months) with a lower respiratory tract infection. She had fits, which was unrousable, and encephalopathic as before. She had not been receiving vitamin B₆ at home. She was given 110 mg pyridoxine intravenously in divided doses. She was responsive within 16 hours and was back to normal within 36 hours. We have now characterised the conjugate of pyridoxal phosphate and pyrrol-5-carboxylate, and are preparing a further [analytical] publication.

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