Type II hyperprolinemia: a case report

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Hyperprolinemia type II (HP II) is a rare inherited metabolic disease due to the deficiency of pyroline-5-carboxylate dehydrogenase. It is generally believed to be a benign condition although some patients have neurological problems such as refractory convulsions. Here we report a six-year-old girl with HP II who admitted to our hospital with recurrent seizure refractory to multiple antiepileptic drugs. She was the third child of healthy, consanguineous parents. The family history was negative for neurological and renal disorders. On physical examination, she had no facial dysmorphism; the anthropometric measurements, and systemic and neurological examinations were normal. Mental and motor development was appropriate for her age.

Laboratory findings revealed elevated levels of proline, glycine, and ornithine in serum and pyrroline-5-carboxylate and hydroxyproline in urine. Cerebral computerized tomography and magnetic resonance imaging were both normal. Electroencephalogram showed a very active epileptic abnormality; partial control of seizures was achieved by two antiepileptics.

Increased plasma glycine and ornithine levels are the unique features of our case when compared to the other HP II cases reported in the literature.

Key words: hyperprolinemia.

Case Report

A six-year-old girl was admitted to our hospital with recurrent convulsions, which started at the age of three years during a febrile illness. The seizures were first myoclonic and of absence type and characterized by falling of the head. They lasted 3-5 seconds and recurred 20-40 times in a day. Despite antiepileptic therapy given in another hospital in multiple combination (sodium valproate, carbamazepine) seizures continued and changed to generalized tonic-clonic type.

She was the third child of healthy, consanguineous parents. Patient’s grandmothers were first-degree cousins. The family history was negative for neurological and renal disorders except for grandmal epilepsy in a second-degree cousin. Pregnancy and delivery were uneventful. She achieved normal developmental milestones for her age. On physical examination, she looked well and had no
facial dysmorphism. The anthropometric measurements were as follows: weight: 16.2 kg (10-25%), height: 113 cm (25-50%), and head circumference: 51 cm (50%). Systemic and neurological examinations were completely normal. Mental and motor development as appropriate for her age.

In laboratory examination, all biochemical parameters were within normal limits. The following metabolic investigations were normal: serum ammonia, lactate, pyruvate, ketones and urinary organic acids. Chromatography of urinary and plasma amino acids revealed hyperprolinemia, hyperornithinemia, hyperlysinemia, hyperprolinuria, hyperhydroxyprolinuria, and hyperglycinunira (Table I). Her mother, father, and brother had normal chromatography of plasma and urinary amino acids. Chromosomal analysis showed a 46, XX karyotype.

Table I. Serum and Urine Proline, Hydroxyproline, Glycine, and Ornithine Levels in Our Patient, and in HP I, and HP II Patients, and Normal References Values

<table>
<thead>
<tr>
<th>Plasma</th>
<th>Reference value</th>
<th>HP-I</th>
<th>HP-II</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proline</td>
<td>59-369 mol/ml</td>
<td>500-2500</td>
<td>500-3700</td>
<td>2624</td>
</tr>
<tr>
<td>Hydroxyproline</td>
<td>3-45 nMol/ml</td>
<td>1-46</td>
<td>1-46</td>
<td>34</td>
</tr>
<tr>
<td>Glycine</td>
<td>127-341 nMol/ml</td>
<td>378</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ornithine</td>
<td>10-163 nMol/ml</td>
<td></td>
<td></td>
<td>202</td>
</tr>
<tr>
<td>Urine Proline</td>
<td>0-9 mol/mol creatinine</td>
<td>2102-40215</td>
<td>2912</td>
<td></td>
</tr>
<tr>
<td>Hydroxyproline</td>
<td>0-13 mol/mol creatinine</td>
<td>84-3769</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>91-246 mol/mol creatinine</td>
<td>1347-15052</td>
<td>192</td>
<td></td>
</tr>
</tbody>
</table>

HP: Hyperprolinemia.

Discussion

There are three different inherited errors of proline metabolism. HP I and HP II are due to the deficiencies of two enzymes in proline catabolism. The third one is due to the deficiency of an enzyme in proline synthesis, called pyroline synthetase. In addition to these disorders, plasma proline levels increase in severe lactic acidosis, type II glutaric aciduria, and in DiGeorge and Shprintzen syndromes. Disorders of amino acid metabolism are believed to be benign conditions; however, several reports have pointed to renal problems in HP I and neurological problems such as refractory convulsions in HP II1-6.

Generally, in HP II, an infectious disease or fever is the triggering factor for seizures. Despite recurrent convulsions, mental-motor and physical development are not affected. In almost all patients seizures disappear in adulthood1. Our patient had numerous of refractory seizures, first starting during a febrile episode. She had a normal developmental pattern. Recently, Bellet et al7 reported a new form of HP II with renal dysfunction but without neurological disorders.

Laboratory findings of our patient confirmed the diagnosis of HP II. Unlike in the classical presentation of this disorder, our patient had increased levels of glycine and ornithine. There are three other reported cases with an elevation...
of glycine. Significance of increased plasma glycine and ornithine levels in this disorder is not known.

In conclusion, as hyperprolinemia is a rare inherited metabolic disorder we report our case and discuss it in the light of the literature.

REFERENCES