Type II hyperprolinemia: a case report

Neslihan Önenli-Mungan[1], Bilgin Yüksel[1], Mürüvet Elkay[2], Ali Kemal Topaloğlu[1] Tolunay Baykal[3], Güler Özer[1]

Departments of [1]Pediatric Endocrinology and Metabolism, and [2]Pediatric Neurology, Çukurova University Faculty of Medicine, Adana, and Deparment of [3]Pediatric Metabolism and Nutrition, İstanbul University İstanbul Faculty of Medicine, İstanbul, Turkey

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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 dysmorphy; 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 hydroxproline 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.

Hyperprolinemia (HP) is a rare autosomal recessive inborn error of proline metabolism due to deficiencies of two enzymes in the proline degradation system. In type I (HP I) proline oxidase and in type II (HP II) Δ'-pyrroline-5-carboxylate (5-P-C) dehydrogenase enzymes are insufficient. The metabolic abnormalities are a 3-5-fold increase in plasma proline in HP I, while in HP II there is a 10-15-fold increase in plasma proline, accumulation of pyrroline-5-carboxylate and increased excretion of urinary proline, hydroxyproline and glycine[1,2]. Molecular analysis of 5-P-C dehydrogenase gene revealed four mutant alleles, two with frame shift mutations and two with missense mutations[3]. Clinically both forms of hyperprolinemia are thought to be benign conditions although renal involvement in HPI and nerological problems like mild mental retardation and convulsions in HP II have been reported in the literature[1,4,5].

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 grand-mal 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 dysmorphy. 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.

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 II[1,4,6].

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 adulthood[1]. Our patient had numerous of refractory seizures, first starting during a febrile episode. She had a normal developmental pattern. Recently, Bellet et al[7] reported a new form of HP II with renal dysfunction but without neurological disorders.

Laboratoıy 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

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

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

HP: hyperprolinemia.

Cerebral computerized tomography and magnetic resonance imaging were both normal. Electroencephalogram (EEG) showed a very active epileptic abnormality, which was provocated by hyperventilation.

The diagnosis of hyperprolinemia type II was made based on a 13-fold increase in plasma proline and a 200-fold increase in urinary proline together with author increase in urinary hydroxyproline, glycine, and the accumaliton of 5-P-C. A partial control of seizures was achieved by two antiepileptics: clonazepam (0.20 mg/kg/day) and sodium valproate (30 mg/kg/day).

of glycine. Significance of increased plasma glycine and ornithine levels in this disorder is not known[8].

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

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