Hyperprolinemia Type IA: Benign Metabolic Anomaly or a Trigger for Brain Dysfunction?

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Abstract

Objective: Hyperprolinemia type 1 (HPI) is a rare and inherited autosomal recessive disorder caused by proline oxidase deficiency. Hyperprolinemia type 1 is biochemically defined as high plasma proline levels without urinary Δ-1-pyrroline-5-carboxylate excretion. Hyperprolinemia type 1 has been considered a benign metabolic disorder, but a relationship with neurological disorders has recently been suggested. **Study Design:** We retrospectively analyzed plasma amino acid values obtained by amino acid analysis from 10 030 children admitted for neurological reasons during the years 1996 to 2010 at the Regional Sicilian Centre for Metabolic Diseases. Patients with proline levels above the normal range of 129 to 245 µM were identified. **Results:** Only 2 children showed high levels of proline (450-480 µM and 380-470 µM, respectively), but their disorders (tubercular neuroencephalitis and progressive mitochondrial encephalopathy) did not seem to be related to hyperprolinemia as a causative factor. **Conclusion:** The question of HPI as benign metabolic anomaly or as a direct cause of brain damage is still open. Since HPI is rare, other observations on this regard are necessary.

Introduction

Hyperprolinemia is a rare and inherited autosomal recessive disorder with 2 different phenotypic forms.[1] Hyperprolinemia type 1 (HPI) results from a deficiency in proline oxidase (POX) caused by mutations in the proline dehydrogenase (*PRODH*) gene (OMIM: 606810) on chromosome 22q11.2. Hyperprolinemia type 2 (HPII) is associated with a deficit of pyrroline-5-carboxylate dehydrogenase caused by mutations in the delta-1-pyrroline-5-carboxylate dehydrogenase (*P5CDH*) gene (OMIM: 606811) on chromosome 1p36. Proline is a nonessential amino acid that plays an inhibitory function in a subset of glutamatergic synapses, in addition to the role as a substrate for protein synthesis and as a precursor for glutamate.[2]

For some time, there has been debate as to whether HPI is a metabolic disorder without clinical effects or if it can cause clinical manifestations in both the central nervous system and other areas of the body, like other aminoacidopathies. For this purpose, we investigated the plasma levels of proline in a large group of patients with neurological manifestations.

Among several quantitative determinations of plasma amino acids, we found hyperprolinemia only in 2 patients, in whom there was no evidence of a direct correlation between hyperprolinemia and brain damage. The debate of HPI as a benign metabolic anomaly or a trigger of brain damage is still ongoing.

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Materials and Methods

Between 1996 and 2010, we tested 10 030 patients by quantitative determination of plasma amino acids at the Regional Centre for Metabolic Diseases of the Unit of Clinical Paediatrics of the University of Catania, Italy. Patients were seen for diagnostic tests to determine the cause of their neurological diseases, including metabolic diseases and particularly mental retardation and/or epilepsy. The age of the patients ranged from 6 months to 18 years (average: 7 years) and the male to female ratio was 1:1.2. The determination of proline was performed by chromatographic separation using ion exchange resins according to the method of Stein and Moore.[3]

Results

Among the patients examined, 10 028 showed plasma levels of proline in the normal range, with values ranging between 129 and 245 μM. Two patients were affected by tubercular meningoencephalitis and progressive mitochondrial encephalopathy and showed high levels of proline in the ranges of 450 to 480 μM and 380 to 470 μM, respectively. The values of proline in these 2 patients remained elevated during a 1-year follow-up.

Discussion

Proline levels among 10 030 patients with different neurological disorders were normal, ranging from 129 to 245 μM, with the exception of 2 patients who presented with specific diagnoses not related to HPI. One of these patients had a diagnosis of tubercular meningoencephalitis, and the other was diagnosed with mitochondrial encephalopathy. Plasma amino acid analyses of these patients during a 1-year follow-up continued to show proline elevations.

The first cases of familiar hyperprolinemia were published in the 1960s and 1970s, yet the role of HPI as a cause of neurological damage is still debated. Scriver et al and Schafer et al described some HPI cases associated with brain dysfunction and nephropathy.[1,4] Subsequently, Perry et al reported HPI cases with renal anomalies in children of consanguineous parents in the span of 2 generations of families of American Indian descent.[5] They noticed that high levels of proline appeared in homozygous patients, while normal or slightly increased values were present in heterozygotes.

Fontaine et al and Mollica et al reported cases of hyperprolinemia in normal patients with neither neurological disorders nor other defects. They hypothesized that HPI was a metabolic disorder not associated with any clinical manifestations.[6,7] A questionnaire survey and a study of previous reports in Japan identified only 2 cases of HPI and 1 of HPII. The first patient with HPI had chromosomal abnormalities, and the second showed photosensitive epilepsy.[8] In the 1990s, the theory of HPI as a benign metabolic disorder continued. Ishikawa et al, Shivananda et al, and Humbertclaude et al reported cases of HPI in which neurological disorders were not related to the metabolic defect.[9-11] Phang et al[2] reported prospective studies of patients with HPI identified through neonatal screening, which did not show a correlation between the metabolic disturbance and clinical manifestations, so they regarded HPI as a benign finding. More recently, Jacquet et al, Afenjar et al, and Di Rosa et al again called into question the relationship between HPI and neurological disorders.[12-14] Overall, 12 patients were described with clinical features of severe psychomotor retardation, delayed speech, autistic traits, and seizures. A genetic survey showed either *PRODH* mutations or deletions involving chromosome 22q11, and very high levels of proline were correlated with the clinical manifestations of the patients. Bender et al raised the possibility that a deficiency of POX may play a cooperative role rather than a causative one, especially after the discovery of the *PRODH* gene on chromosome 22q11.2.[15] Studies of this gene and the assessment of residual function of POX enzyme have allowed for the subdivision of *PRODH* mutations into 3 groups based on whether they lead to an average (<30%), moderate (30%-70%), or severe (> 70%) reduction in the function of the enzyme. This correlated the serum levels of proline to the severity of the enzyme deficiency.[15] Guilmatre et al report on genotype/phenotype correlations in HPI and hypothesized that *PRODH* mutations cause hyperprolinemia through decreased POX activity or involving other biological parameters.[16] van de Ven et al investigated serum amino acids in 16 720 blood samples. They found 4 patients with hyperprolinemia type 2 and only 1 with hyperprolinemia type 1 who showed seizures and behavioral problems.[17] Clelland et al compared fasting plasma proline in 90 control patients and 64 patients with schizophrenia and hypothesized that mild to moderate hyperprolinemia may represent a significant risk for the development of schizophrenia.[18] Studies on rats have shown that acute and chronic hyperprolinemia induce significant oxidative damage to proteins, lipids, and DNA, and this effect may be prevented by adjuvant therapy with antioxidants (vitamins E and C).[19,20] Brain damage and spatial memory deficit in hyperprolinemic animal models have been related to the negative effects produced by an energy metabolism deficit, Na(+), K(+)-adenosine triphosphatase activity, kinase creatine, oxidative stress, excitotoxicity, lipid content, the purinergic and cholinergic systems, adenosine triphosphate levels, and increased lipoperoxidation.[21]

Studies on patients with hyperprolinemia and on animal models have relevant results, but they are not enough to clearly show whether hyperprolinemia plays a cooperative role rather than directly causing brain damage. The causal relationship between deficiency of POX in HPI and clinical symptoms is difficult to prove for two reasons. First, the majority of patients in which HPI is found have been identified retrospectively or in the course of investigations for other clinical problems, which implies a sampling bias. Second, cerebral injury has rarely been reported in cases of hyperprolinemia, and a direct cause–effect relationship has not been demonstrated. In addition, prospective studies of patients with HPI identified by neonatal screening indicate that the metabolic disorder is not necessarily associated with clinical manifestations.[2]

The surveys of our patients with various neurological diseases led to the following conclusions:

1. Hyperprolinemia type I is a very rare anomaly. In the 10 030 cases screened, we identified only 2 patients with proline levels above the normal range.
2. We have not observed a causal relationship between the metabolic deficit and brain damage. In fact, in both cases, there were clear causal factors (tubercular meningoencephalitis and progressive mitochondrial encephalopathy).
3. Reports describe hyperprolinemia in patients with neurological problems such as mental retardation and epilepsy, and indeed, most of these cases have been genetically characterized as showing mutations in the *PRODH* gene. However, it remains to be demonstrated that the hyperprolinemia was directly associated with the primary neurological problems.
4. In the literature, HPI has been reported as a benign metabolic anomaly or as a causative trigger of neurological impairment. However, since HPI is rarely found, no clear conclusion may be drawn on this topic. The different results reported by the authors may be related to the differences in the populations' genetics, even if a direct pathogenetic effect of HPI cannot be ruled out.

Authors' Note

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Declaration of Conflicting Interests

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