ASYMPTOMATIC TYPE II HYPERPROLINEMIA ASSOCIATED WITH HYPERGLYCINEMIA IN THREE SIBLINGS

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Type II hyperprolinemia is a rare metabolic disorder associated with mental retardation, seizures, and EEG anomalies.
The authors describe a Sicilian family, detected screening for aminoacidopathies by the method of Scriver, in which three siblings have high levels of serum proline and urinary pyrroline-5-carboxylic acid, without any signs of associated anomalies.

Hyperprolinemia is an inborn error of aminoacid metabolism characterized by elevated plasma proline concentration and by urinary excretion of proline, hydroxyproline, and glycine. Efron (1966) distinguished two types of hyperprolinemia: type I, characterized by deficiency of proline-oxidase which catalyses the oxidation of proline into Δ1-pyrroline-5-carboxylic acid (PC); and type II, probably due to deficiency of the enzyme pyrroline-5-carboxylic acid dehydrogenase, which transforms glutamic acid-γ-semialdehyde into L-glutamic acid.

Type II hyperprolinemia shows plasma levels of proline more elevated than type I and increased urinary excretion of PC (Scriver and Efron 1972). There are also important clinical differences between the two types of hyperprolinemia: type II is associated with mental retardation, seizures, and EEG alterations, while type I is often associated with hereditary nephropathy and inconstantly with deafness, photogenic epilepsy, mental retardation, and EEG anomalies. Both types of hyperprolinemia can occur without clinical or EEG signs (Fontaine et al. 1970; Mollica et al. 1970; Goodman, cited by Scriver and Efron 1972; Applegart, cited by Scriver and Efron 1972).

In 1970, in occasion of the 3rd Congress of Neurogenetics and Neuroophthalmology, we reported a family, several members of which were affected by type I hyperprolinemia not associated with clinical anomalies (Mollica et al. 1970) Now, we report another family in which three siblings showed type II hyperprolinemia without clinical symptoms. The hyperprolinemia of this family was constantly associated with hyperglycinemia.

CASE REPORT

The proband in whom hyperprolinemia was noted, is an 8 year-old girl, born after a full-term and uneventful pregnancy. She had not suffered from any particular illnesses and, at present, is completely

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asymptomatic. Routine laboratory examinations, performed after the detection of the hyperprolinemia, including BUN, intravenous urography, hearing and ophthalmologic examinations, karyogram, and IQ, gave normal results.

The parents, who come from a small village in the province of Ragusa (Sicily), are first cousins. Clinical examination was extended to the parents and to two siblings of the girl: all appeared healthy. The routine laboratory findings, hearing examination, and EEG, were normal. All the members of the immediate family were submitted to metabolic study.

RESULTS

Both the proband and her two siblings showed a marked increase in plasma proline by paper chromatography, while the mother was normal. The analysis of serum aminoacids, performed by ion-exchange column chromatography, confirmed the increase of proline in the three siblings and demonstrated also a marked increase of glycine. Only in one of the three siblings was there also a slight increase in ornithine (mg 2.43/100 ml; normal values 0.66-1.95). These serum aminoacids, on the other hand, were normal in the mother.

All three hyperprolinemic subjects showed a marked urinary excretion of proline, hydroxyproline, and glycine, while aminoaciduria was normal in the parents.

The urinary excretion of PC was markedly increased in the three siblings, moderately increased in the mother, and normal in the father.

DISCUSSION

Apart from the rarity of the anomaly, this family deserves particular attention with regard to its clinical and metabolic aspects. Clinically, our studies have confirmed the possibility that high levels of plasma proline can be present in completely healthy subjects. From the metabolic point of view, characteristic of this family is the elevated serum level of both proline and glycine.

The considerable urinary loss of glycine, proline, and hydroxyproline, attributable to a tubular system that these three aminoacids have in common (Scriver et al. 1961), should result in a low level of serum glycine. In our patients, on the contrary, the level of plasma glycine is even higher than we have observed in patients with nonketotic and ketotic hyperglycinemia. Hyperglycinemia has also been observed by us in some members of the family with type I hyperprolinemia (Mollica et al. 1971): in the father (mg 5.1/100 ml) and in a 10 year-old sister of the proband (mg 4.2/100 ml). Even the proband of the family with type I hyperprolinemia described by Efron (1965) had hyperglycinemia. In the mother and in two twin sisters of the patient reported by Similä and Visakorpi (1967), there was a slight increase of urinary excretion of glycine not associated either with hyperprolinemia or with hyperprolinuria.

We believe that the association between hyperglycinemia and hyperprolinemia cannot be fortuitous. Since there is no known direct metabolic relationship between glycine and proline (apart from the common tubular system), this association could be the expression of two different metabolic anomalies, due to a single gene with pleiotropic effects or to two linked genes.

The consanguinity of the parents and the slight increase of the urinary excretion of PC in the mother supports a hereditary transmission of autosomic recessive type.

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