Asymptomatic type II hyperprolinaemia associated with hyperglycinaemia in three sibs

LORENZO PAVONE, FLORINDO MOLlica, and HARVEY L. LEVY
From the Paediatric Clinic, University of Catania, Italy; State Laboratory Institute, Massachusetts Department of Public Health; Neurology Service, Massachusetts General Hospital; and Department of Neurology, Harvard Medical School, Boston, Massachusetts

Pavone, L., Mollica, F., and Levy, H. L. (1975). Archives of Disease in Childhood, 50, 637. Asymptomatic type II hyperprolinaemia associated with hyperglycinaemia in three sibs. Three clinically normal sibs were discovered to have type II hyperprolinaemia in a routine serum amino acid screening programme in Sicily. In addition to the basic biochemical features of type II hyperprolinaemia, all 3 children had marked hyperglycinaemia, whereas their parents had both normal blood proline and glycine concentrations. Clinical normality in individuals with hyperprolinaemia may suggest that these two metabolic disorders (types I and II) are benign entities. Furthermore, the absence of clinical abnormality in these sibs, despite the presence of marked hyperprolinaemia and hyperglycinaemia, may suggest that neither of these findings alone causes brain damage. The hyperglycinaemia in these sibs is unexplained and is an unusual if not unique finding in association with hyperprolinaemia.

Hyperprolinaemia is a result of at least two inborn errors of amino acid metabolism (Fig. 1). Each of these disorders is characterized by raised plasma proline concentrations and by increased urinary excretion of proline, hydroxyproline, and glycine (Scriver and Rosenberg, 1973). In hyperprolinaemia type I liver proline oxidase activity is deficient and thus proline cannot be normally oxidized to \( \Delta^1 \)-pyrroline-5-carboxylic acid (PCA) (Efron, 1965). In type II hyperprolinaemia, \( \Delta^1 \)-pyrroline-5-carboxylic acid dehydrogenase activity is deficient, resulting in the accumulation of PCA and its excretion in urine (Valle, Phang, and Goodman, 1974). In both disorders the hyperprolinaemia seems to be a specific hyperalphaacidemia.

Urinary measurement of PCA has served to distinguish these two disorders. In addition, type II hyperprolinaemics usually have had a greater degree of hyperprolinaemia than those with type I (Scriver and Rosenberg, 1973). Clinical differences have also been described. Among these are the nephropathy, deafness, photogenic epilepsy, mental retardation, and electroencephalographic (EEG) abnormalities in type I individuals, and mental retardation, seizures, and EEG aberrations in association with type II. However, several clinically normal individuals with type I disorder have been described (Scriver and Rosenberg, 1973; Fontaine, Farriaux, and Dautrevaux, 1970; Mollica, Pavone, and Antener, 1971; Potter and Waichman, 1973; Perry et al., 1967/1968; Holton, 1973), and recently a girl with type II disorder was described as being normal (Goodman et al., 1974).

Type II hyperprolinaemia seems to be a rare metabolic disorder. To our knowledge only 11 cases in nine different families have been described (Table I). An additional 2 cases, not including those in this report, are known to us (Shih, Levy, and Coulombe, unpublished data), and are included in Table I. Thus the full range of clinical and biochemical findings in this disorder has not yet been ascertained. Indeed, it is not at all certain that clinical abnormalities occur at all as a consequence of the disorder since those individuals discovered to have type II hyperprolinaemia have been studied precisely because of some known clinical abnormality.

In 1971, we reported a family in which several
members had type I hyperprolinaemia unassociated with clinical abnormalities (Mollica et al., 1971). Now we report a family in which 3 sibs have type II hyperprolinaemia without clinical abnormalities. The hyperprolinaemia in this family is also associated with hyperglycinaemia, an unusual finding in any of the hyperprolinaemic disorders.

**Case report**

As in the case of type I hyperprolinaemia already reported (Mollica et al., 1971), this family with type II hyperprolinaemia was identified while screening for aminoacidopathies in the infant population of Eastern Sicily (Mollica et al., 1970). The proband in whom hyperprolinaemia was noted is now an 8-year-old girl. She was born after a term, uneventful pregnancy, has not suffered from any particular illnesses, has been on a normal diet throughout life, and is presently clinically normal. Hearing, ophthalmological examinations, and electroencephalogram (EEG) were normal. Her intelligence quotient determined by the Wechsler Intelligence Scale for Children was 105. Laboratory examinations, including blood urea nitrogen and intravenous urography, were also normal. Chromosome count and karyotype were normal. Results of plasma amino acid screening showed a marked increase in proline.

The parents, who come from a small village in the province of Ragusa (Sicily), are first cousins (Fig. 2). Clinical examinations of the parents and 2 sibs of the proband were normal. Routine laboratory findings, hearing examination, and EEG were normal. All members of the immediate family were screened for amino acids and the 2 sibs were also found to have hyperprolinaemia.

**Methods**

Semiquantitative amino acid analysis of plasma was by the unidimensional paper chromatographic techniques of Scrivener, Davies, and Cullen (1964), and of urine by the unidimensional and two-way sequential paper chromatographic techniques of Efron et al. (1964) and Efron (1968). Plasma and urine amino acids were

**Table 1**: Pertinent clinical and biochemical characteristics of patients

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Studies</th>
<th>Age</th>
<th>Sex</th>
<th>Origin</th>
<th>Consanguinity of the parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Efron (1967)</td>
<td>10yr</td>
<td>M</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Emery et al. (1968)</td>
<td>18yr</td>
<td>F</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>Selkoe (1969)</td>
<td>19m</td>
<td>M</td>
<td>Italy</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Similà (1970)</td>
<td>2yr</td>
<td>M</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Similà (1970)</td>
<td>—</td>
<td>M</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Jeune et al. (1970)</td>
<td>18m</td>
<td>M</td>
<td>France</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Jeune et al. (1974)</td>
<td>6m</td>
<td>F</td>
<td>France</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Goodman et al. (1974)</td>
<td>9yr</td>
<td>F</td>
<td>Spanish</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>Applegarth et al. (1974)</td>
<td>5yr</td>
<td>M</td>
<td>—</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>Cooke and Raine (1973)</td>
<td>23m</td>
<td>M</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>V. E. Shih et al. (unpublished)</td>
<td>1yr</td>
<td>F</td>
<td>U.S.A (Irish)</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>H. L. Levy et al. (unpublished)</td>
<td>15yr</td>
<td>M</td>
<td>U.S.A (Irish)</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>Our proband</td>
<td>5yr</td>
<td>F</td>
<td>Italy</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>Her brother</td>
<td>10yr</td>
<td>M</td>
<td>Italy</td>
<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>Her sister</td>
<td>2yr</td>
<td>F</td>
<td>Italy</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Normal values: proline 0·11-0·44; glycine 0·12-0·31.*
Asymptomatic type II hyperprolinaemia associated with hyperglycinaemia in three sibs

![Family tree](image.png)

**FIG. 2.—Family tree showing those with biochemical abnormalities related to proline metabolism and lack of clinical signs.**

quantitated by ion-exchange column chromatography (Efron, 1966). Urinary excretion of PCA was measured by a colorimetric assay (Efron, 1965).

**Results**

Analyses were performed on plasma obtained in the fasting state and on aliquots of 24-hour urine collections of the proband, both sibs, and the parents while on a normal diet. The proband and both of her sibs showed a marked increase in plasma proline by paper chromatography, while the parents were normal. The result of quantitative plasma amino acid analyses (Table II) confirmed the marked increase in proline in all 3 sibs and also showed a marked increase in glycine. The magnitude of the hyperglycinaemia, however, was not proportional to the magnitude of the hyperprolinaemia. The proband, for instance, had the most marked hyperprolinaemia but not the most extreme hyperglycinaemia (Table II). All other amino acids, including hydroxyproline, were normal. All serum amino acids were normal in both parents.

All 3 hyperprolinaemic subjects showed a markedly increased urinary excretion of proline, hydroxyproline, and glycine (iminoglycinuria) while the urinary amino acid excretion was normal in the parents.

Urinary excretion of PCA was markedly increased in the 3 sibs, slightly increased in the mother, and normal in the father (Table II).

**Discussion**

Table I summarizes the major clinical and biochemical findings of individuals known to have type II hyperprolinaemia, including those reported here. These cases include 15 individuals in 11 different families. At least 4 have been of Italian origin.

Type II hyperprolinaemia has been associated with mental retardation, seizures, and EEG abnormalities, though not always (Table I). The convulsions have generally been grand mal in type, though in the patient described by Emery, Goldie, and Stern (1968) the seizures changed from grand...
mal to petit mal at the age of 11 years. EEG has either been normal or had diffuse nonspecific aberrations, the single exception again being the case with petit mal seizures showing the characteristic 3 per second spike and wave pattern (Emery et al., 1968).

In addition to the case described by Goodman et al. (1974), there are other cases of type II disorder in which biochemical findings are accompanied only by equivocally abnormal clinical signs. One of two type II hyperprolineaemic brothers (Similä, 1970) showed only EEG abnormalities and no clinical signs. The subject studied by Applegarth et al. (1974) was clinically healthy though he had had a febrile convulsion and abnormal EEG. In our family the affected members showed neither clinical signs nor EEG abnormalities. The mental level in each was quite high. These data suggest that high levels of plasma proline even when accompanied by accumulations of PCA may not cause clinically apparent alterations of the brain. As in the other published cases of type II hyperprolineaemia, the 3 sibs we report had a marked increase in urinary PCA. A slight increase of urinary PCA was also present in the mother, perhaps as a reflection of the heterozygotic state. However, the father, who is also an obligate heterozygote, had normal urinary PCA concentrations.

A striking characteristic of the family we describe is the markedly increased plasma glycine in those members with hyperprolineaemia. This is apparently a unique finding in type II hyperprolineaemia (Table I), though it has been noted in a much less severe degree in one family with type I hyperprolineaemia (Mollica et al., 1971). The hyperglycinemia is a peculiar finding and cannot readily be explained on the basis of the known metabolic pathway for proline, and distinct from the marked hyperglycinuria (but normal blood glycine concentration) noted in conjunction with the prolinuria and hydroxyprolinuria (iminoglycinuria) seen in individuals with hyperprolineaemia. The level of plasma glycine is even higher than has been observed in most patients with disorders that clearly result in a specific hyperglycinemia, either ketotic or non-ketotic type (H. L. Levy, V. E. Shih, and I. T. Lott, unpublished data). Since almost all of these latter cases have manifested mental retardation or other signs of brain damage not readily attributable to the hyperglycinemia, it is of interest that our patients were clinically normal.

We believe that the association between hyperglycinemia and hyperprolineaemia is not coincidental, since the hyperglycinemia was present in each of our hyperprolineaemic cases and not present in the parents who had normal proline concentrations. However, since there is no known direct metabolic relation between glycine and proline, a plausible explanation is difficult. These different findings could conceivably be an expression of two different metabolic abnormalities due to a single gene with pleiotropic effects or to two linked genes. In this context may be cited the cases of Jeune et al. (1970) in which type II hyperprolineaemia was accompanied by hyperleucinoleucinaemia and which were interpreted as sibs with double amino-acidopathy. However, precise interpretation of hyperglycinemia in our cases awaits further definition of the mechanisms for hyperglycinemia in general, a definition which could show an interrelation between proline and glycine degradation.

There is a further important point regarding hyperglycinemia. Individuals with hyperglycinemia have generally suffered brain damage when not treated. In ketotic hyperglycinemia the basic defect is one of organic acid metabolism (Nyhan, Ando, and Rasmussen, 1972) and thus brain damage is usually ascribed to the resulting organic acid
Asymptomatic type II hyperprolinaemia associated with hyperglycinaemia in three sibs


Correspondence to Dr. L. Pavone, Paediatric Clinic, University of Catania, Catania, Italy.

REFERENCES


