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IMINOGLYCINURIA: A BENIGN TYPE OF INHERITED AMINOACIDURIA*

*Turgay Coşkun MD***, İmran Özalp MD***, Ayşegül Tokatlı MD*****

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The diagnosis of iminoglycinuria was established in two patients on the basis of increased urinary excretion of proline, hydroxyproline and glycine in the presence of normal plasma concentrations of these respective compounds. Routine metabolic screening was performed in these infants in order to find the cause for the developmental delay observed in one infant and the siblings deaths noted in the family of the other. These two patients gave further support to the previous suggestion that renal iminoglycinuria is a benign disorder with no recognizable clinical pattern. Its detection, therefore, requires screening programs or aminoacid studies. *Key words: glycinuria, iminoaciduria.*

Iminoglycinuria is a rare inborn error of metabolism associated with increased urinary excretion of glycine and the iminoacids, proline and hydroxyproline. It occurs because of a defect in the renal tubular transport mechanism shared by these three aminoacids[1,2].

Lack of a typical clinical picture peculiar to iminoglycinuria restricts the number of reported cases. The purpose of this paper is to describe the clinical and laboratory findings of the first two patients reported in Turkey afflicted with this disorder.

Case Reports

Case 1

A ten-day-old male infant was admitted to Hacettepe University Children's Hospital because of a family history of sibling deaths due to unknown causes. He was the seventh child born to parents who were first degree relatives. The pregnancy and delivery had been uneventful. Three other male children had died at around three months of age, and three females were alive.

* From the Pediatric Nutrition and Metabolism Unit, Department of Pediatrics, Hacettepe University Institute of Child Health, Ankara.

** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.

*** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

**** Associate Professor of Pediatrics, Hacettepe University Institute of Child Health.

Physical examination revealed a normal, healthy infant with a body weight of 4200 g and length of 53 cm.

The results of urine analyses and blood examinations for hemoglobin, white blood cells, urea, electrolytes, alkaline phosphatase, proteins, glucose and pH were within normal limits. Paper chromatographic amino acid analysis of the urine sample demonstrated a marked increase in proline and glycine concentrations. A quantitative amino acid analysis of the serum and urine specimens was performed at the age of six (Table I).

Table I: Plasma Concentrations and Urinary Excretion of Glycine, Proline and Hydroxyproline in Two Patients

	Cases		
	1	2	Normal Values
Plasma (μmoles/L)			
Glycine	315	305	125 - 318
Proline	320	87	40 - 332
Hydroxyproline	Trace	23	-
Urinary excretion (μmoles/24 h)			
Glycine	8430	8802	165 - 1420
Proline	8960	19126	-
Hydroxyproline	1336	1820	-

The patient was doing well when seen for the last time at the age of six. His physical, mental and motor development was normal.

Case 2

A fourteen-month-old male infant was referred to the Hacettepe University Children's Hospital for evaluation of developmental delay. He was the product of consanguineous parents. Pregnancy and delivery had been uncomplicated. The parents had two older healthy children. The patient had experienced a seizure ten days prior to admission.

Physical examination revealed an infant with a weight of 11,700 g and a length of 79 cm. He had no contact with his surroundings and was unable to speak, stand unsupported or walk.

Routine metabolic screening was performed in order to ascertain the cause for the developmental delay observed in this patient. Results of paper chromatog-

raphy revealed that large quantities of proline and glycine were being excreted in the urine. At the age of two, a quantitative analysis of plasma and urine amino acids was performed, the results of which are presented in Table I. The EEG showed a bioelectric abnormality in the posterior part of the right hemisphere of the brain.

Material and Methods

Plasma and urine amino acid screening was performed by paper chromatography (butanol: acetic acid: water)[3]. Plasma and urine samples were then analyzed quantitatively by ion exchange chromatography on a LKB Alpha Plus Model 4151 amino acid analyzer using the standard method.

Results

In all the urine samples of the patients screened by paper chromatography, markedly increased concentrations of proline, hydroxyproline and glycine were detected. These findings were confirmed by quantitative amino acid analyses done using the amino acid analyzer. The plasma concentrations of the respective amino acids were within normal limits (Table I). The urinary excretion of iminoacids and glycine was normal in parents and sibs of patients.

Discussion

Iminoglycinuria is characterized by an abundant urinary excretion of glycine and the iminoacids, proline and hydroxyproline presumably due to a defect in the high capacity, low affinity group specific membrane transport system of the brush border membrane shared by these three amino acids while the plasma levels of these compounds are normal. Large amounts of iminoacids and glycine excretion have been described in premature and term newborn infants between 6 to 12 months of age and in patients with hyperprolinemia[1,2]. The latter two possibilities were unlikely in our patients because quantitative amino acid analyses were performed after age one and at the ages of six and two, respectively. The analyses we performed revealed increased urinary excretion of proline, hydroxyproline and glycine when the plasma levels of these three compounds were within normal limits (Table I).

There is no typical clinical picture attributed to iminoglycinuria[1,2]. While most patients with this disorder can live normal lives, others are observed to have mental retardation[4-8], convulsions[4,9], blindness[10], achromatopsia[11], deafness[10,12], failure-to-thrive[13] and transient hematuria with metopic suture[14].

It is not certain whether the iminoglycinuria caused the developmental delays in our patients, or if it was just a coincidental occurrence. Our patients were

diagnosed as having iminoglycinuria following routine screening which was carried out because of a family history of sibling deaths in the first case and developmental delay in the second. Since a developmental delay was only seen in Case 2, we drew the conclusion that the association of iminoaciduria with mental retardation and with some of the other clinical conditions mentioned above were only coincidental, and a consequence of the selection of subjects screened. Iminoglycinuria, therefore, appears to be a "harmless" inborn error of metabolism assuring a normal life span[1,2,10,14].

The occurrence of multiple cases with this defect in the same family, the presence of consanguinity in some of the reported families and hyperglycinuria without iminoaciduria in some of the parents indicate that iminoglycinuria is inherited as an autosomal recessive trait[1,2]. The parents of our two patients were first degree relatives, but we were unable to demonstrate an increase in glycine excretion in the urine samples of the parents or find any other affected siblings. Due to the possible genetic heterogeneity of the defect resulting from the existence of several allelic genes, there may be an associated impairment of intestinal amino acid transport in iminoglycinuria as seen in other inherited diseases such as cystinuria and Hartnup's disease, which involve renal tubular transport[1,2,7]. Fecal amino acid analysis was not available in our cases.

The present report is in accord with previous suggestions to the effect that iminoglycinuria of renal origin is a benign disorder with no clinical abnormality and that its detection depends on screening programs or amino acid studies. The link between iminoglycinuria and the accompanying clinical manifestations still remains controversial. There is need for additional case reports and studies in affected individuals at the cellular level in order to determine whether these are two separate defects, one leading to a benign condition, while the other to a symptomatic disease, as hypothesized[15].

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