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HYPERGLYCINURIA: A FAMILY REPORT

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ABSTRACT

A 3-year-old girl with mental retardation and a cleft palate disclosed hyperglycinuria. Serum glycine concentration was within the normal limits and renal clearance of glycine was elevated. Oral loading test of glycine showed that the intestinal absorption of glycine seemed to be normal. With intravenous loading of glycine, maximum tubular reabsorption rate (Tm) for glycine could not be obtained. Intravenous infusion of L-proline indicated that the Tm for proline was about half the normal value and that the impaired glycine reabsorption was further depressed. The patient's mother also had a reduced Tm for proline although she did not exhibit distinct hyperglycinuria. It seems likely that the patient and her mother have a heterozygous trait for iminoglycinuria.

INTRODUCTION

Hyperglycinuria is a rare hereditary disorder characterized by an excessive urinary excretion of glycine. It is caused by an impairment of glycine transport in the renal tubule. The hyperexcretion of glycine was first described in 1957 by de Vries et al. (5) in a family where four members exhibited hyperglycinuria, three of whom had renal stones of calcium oxalate. Hyperglycinuria has been reported at times in association with glucosuria (7), pancreatitis (1), cataract (14), hypophophatemic rickets (4, 12), or mercury intoxication (3). Isolated hyperglycinuria is also seen in heterozygotes with one form of iminoglycinuria (9) where homozygotes excrete excessive amounts of proline, hydroxyproline and glycine in the urine but heterozygotes exhibit a hyperexcretion of glycine only.

This report describes a patient with mental retardation, a cleft palate and hyperglycinuria, and her family.

CASE REPORT

Hyperglycinuria was found in this 3-year-old girl. She was a child of healthy nonconsanguineous parents and had one sibling aged 13 months. She was born by normal delivery at term after a normal pregnancy with a birth weight of 3220 g. She was in good condition at birth but had a cleft palate. She started to smile at six months, stand up at twenty months and walk at twenty-three months. Because of the delayed development the girl was examined in the hospital at the age of two years.

Her height and weight were normal. She had mental retardation but no corresponding abnormality in the neurological examination was found. The results of routine urinary analysis and blood examinations for hemoglobin, red and white blood cells were normal.

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The serum sodium was 139 mEq/l; potassium, 3.8 mEq/l; chloride, 101 mEq/l; calcium, 4.8 mEq/l and phosphorus, 4.3 mg/dl. The blood urea nitrogen was 12.0 mg/dl; creatinine, 0.7 mg/dl; S-GOT, 45 units; S-GPT, 25 units; LDH, 260 units and alkaline phosphatase, 14.4 units. Chromosomal analysis, bone radiographs and electroencephalogram had no abnormal findings.

METHODS

Random urine samples were collected early in the morning before breakfast. Short-term amino acid clearance tests were carried out by a modification of the method of Scriver and Davies (11). Oral glycine loading tests were performed in the morning under fasting conditions. 200 mg glycine per kilogram of body weight was given orally in water. Blood samples were collected at 0, 1, 2, 3 and 4 hours after loading.

Intravenous loading tests of L-proline and glycine were performed in the morning after an overnight fast. Before and during the procedures, water was given orally to produce a diuresis exceeding 5 ml per minute. Following a 30-minute control clearance period, 120 to 150 mg per kilogram of 1 mol L-proline or glycine solution was infused intravenously within a period of three minutes. After infusion, urine specimens were collected during three consecutive clearance periods of 30 minutes. Blood samples were drawn at the midpoint of each clearance period. In each period, endogenous creatinine clearance was measured simultaneously to estimate the glomerular filtration rate.

Urine specimens were kept frozen until analyzed. Blood samples were drawn from the antecubital vein. Serum was separated immediately and deproteinized by adding 4% sulfosalicylic acid at a ratio of 1:3. The supernatant was stored at −20°C. Amino acids in urine and serum were estimated by an automatic amino acid analyzer according to the method of Spackman et al. (15). Urinary and serum creatinine was measured by the method of Bonsnes and Taussky (2).

Control subjects who applied for the amino acid clearance and loading tests were seven healthy children (four males and three females) ranging in age from 6 to 13 years. Informed consent was obtained from the children's parents or guardians.

RESULTS

The patient excreted excessive amounts of glycine, and her mother and sister excreted a little increased glycine, but glycine excretion of her father was normal (Table 1). Fasting serum concentrations of glycine in the patient and her mother were within the normal range (Table 1). The patient had elevated renal clearance and impaired tubular reabsorption of glycine, but the mother had no elevation of glycine clearance (Table 2). Oral loading tests showed that intestinal absorption of glycine seemed to be normal in the patient (Fig. 1).

In both the patient and her mother the maximum tubular reabsorption rate (Tm) for proline, which was obtained by increasing the filtered load of proline with an intravenous infusion, was about half the normal value and glycine reabsorption was further depressed by proline infusion (Fig. 2). Tm for glycine could not be attained by the loading of glycine both in the girl and in the controls (Fig. 3).

Table 1. Urinary and serum concentration of glycine in the family members

Subject	Age	Urinary concentration (mg/g creatinine)	Serum concentration (mg/dl)
Patient	3Y	674*	1.46
Father	27Y	76.3**	
Mother	25Y	202**	1.39
Sister	13M	287**	
Normal		48.3-156#	0.879-1.67##

* Mean of five samples
** Mean of three samples
# Range from ten normal subjects
##From Scriver and Davies (11)

Table 2. Renal clearance and tubular reabsorption of glycine in patient and her mother.

Subject	Renal clearance (ml/min/1.73 m^2)	Tubular reabsorption (%)
Patient	24.1	72.8
Mother	7.32	91.7
Normal*	1.2-8.6	93-99

*From Scriver (9)

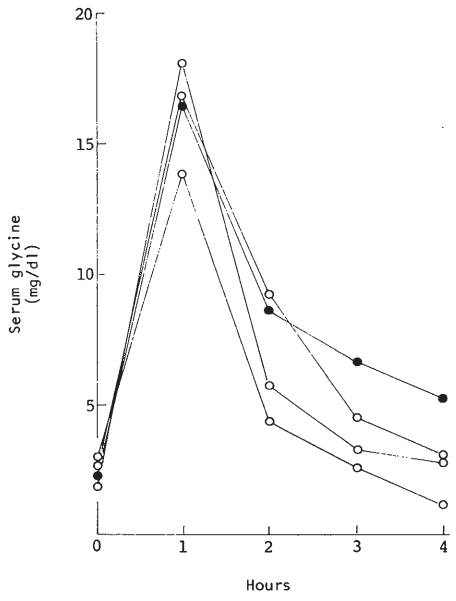

Fig. 1. Serum glycine concentration before and after oral ingestion of 200 mg of glycine per kilogram of body weight in patient (●) and three controls (○).

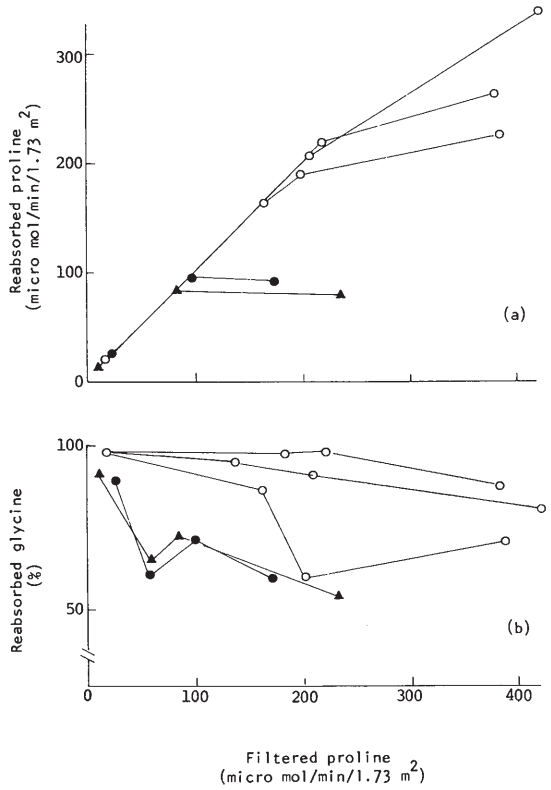

Fig. 2. Tubular reabsorption rate of proline (a) and percentage tubular reabsorption of glycine (b) before and after intravenous L-proline infusion in patient (●), her mother (▲) and three controls (○).

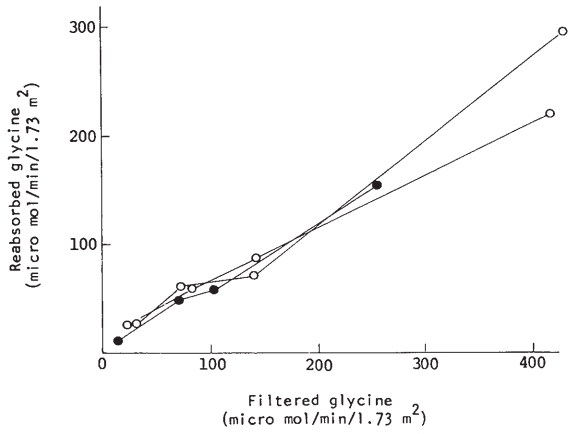

Fig. 3. Tubular reabsorption rate of glycine before and after intravenous glycine infusion in patient (●) and two controls (○).

DISCUSSION

This 3-year old girl with mental retardation and a cleft palate disclosed hyperglycinuria in the presence of normal blood levels of glycine, and elevated renal clearance of glycine, that indicates that she has an impairment of renal transport of glycine. But the transport defect appears to be limited to the kidney because intestinal absorption of glycine was not impaired. Other members of her family did not exhibit distinct hyperglycinuria. Her mother and sister excreted only a little increased glycine. However, the mother had a decreased Tm for proline which showed approximately half the normal value. Therefore, the parent as well as the patient is thought to have an impaired tubular transport of glycine and it may be possible that the sister also has a slight impairment of glycine transport. The patient, however, appears to have a more severe transport defect than the other two because she had more increased urinary excretion and renal clearance of glycine.

Hyperglycinuria is sometimes associated with several clinical disorders mentioned earlier. The present family does not appear to have any such disorders. This patient had delayed mental development and a cleft palate. Some patients with iminoglycinuria have mental retardation but others not, and iminoglycinuric heterozygotes who display hyperglycinuria have no mental disorder (9). Thus, the association between the retardation and hyperglycinuria in this patient is probably fortuitous.

Intravenous infusion of L-proline in the present patient and her mother revealed that they had a reduced Tm for proline and that their impaired tubular reabsorption of glycine was further depressed by the loading of proline. The renal handling bore a resemblance to that characterized by the heterozygous iminoglycinurics (10). Therefore, it seems very likely that these subjects have a heterozygous trait for iminoglycinuria. Intravenous loading of glycine indicated that Tm for glycine could not be obtained both in this patient and in the control subjects. The Tm for glycine in dogs has been shown to be about 20 mg/min (8), but Scriver et al. (13) indicated that a Tm for glycine in the human kidney could not be measured because of the toxicity of a large glycine infusion.

A particular type of hyperglycinuria has been described by Greene et al. (6) in a family where one patient showed a normal Tm for proline but there was marked splay in the proline titration curve. Moreover, no further depression of glycine reabsorption was shown by proline infusion in the patient. It was postulated that the family has a homozygous trait for an unusual type of iminoglycinuria. Whether other hyperglycinuric families have relation to iminoglycinuria or not remains obscure because proline infusion studies have not been done in these families and some of the families (1, 7, 14) have combined some specific clinical conditions unrecognized in iminoglycinuria.

It is of interest that the present subjects showed irregular excretion patterns of glycine and that the patient's mother had a reduced Tm for proline although she did not exhibit distinct hyperglycinuria. This study suggests that hyperglycinuria can be a heterozygous trait for iminoglycinuria.

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