

SHORT COMMUNICATION

NON-KETOTIC HYPERGLYCINEMIA - A TYPICAL CASE DETECTED IN A SCREENING PROGRAM FOR INBORN ERRORS OF METABOLISM

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ABSTRACT

We present a typical case of neonatal non-ketotic hyperglycinemia (NKH; McKusick 23830) detected in a screening program for inborn errors of metabolism (IEM) carried out in Rio de Janeiro and confirmed by analyses which characterize the specific findings of this disorder. Clinical symptoms and biochemical characteristics are described and compared to cases previously reported.

INTRODUCTION

Non-ketotic hyperglycinemia (NKH) is a rare autosomal recessive metabolic dysfunction. It is considered a primary disorder of glycine metabolism and is characterized by the finding of large amounts of glycine in plasma, urine, cerebrospinal fluid (CSF) and brain. NKH is distinguished from ketotic hyperglycinemia syndrome, which occurs in propionic acidemia and other organic acid metabolism disorders, by the absence of ketoacidosis, hyperammonemia and propionic or methylmalonic acidemia

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(Benson and Fensom, 1987; Hayasaka *et al.*, 1987; Nyhan, 1989; Toone and Applegarth, 1989).

The molecular defect of NKH was found to be in the cleavage system of glycine. The deficient multienzymatic complex in this disease is mitochondrial and consists of four protein components: P-protein (a pyridoxal phosphate-dependent glycine decarboxylase), H-protein (a lipoic acid-containing protein), both required for the formation of CO₂ from glycine, T-protein (a tetrahydrofolate (FH₄) requiring enzyme) and L-protein (a lipoamide dehydrogenase).

Beside the typical neonatal NKH, considered the classic phenotype of the disease, there is also an atypical form with late onset of symptoms (Hayasaka *et al.*, 1987; Nyhan, 1989; Leuzzi *et al.*, 1990; Tada *et al.*, 1990).

The neonatal disfunction is very severe and primarily affects the brain. More than 120 patients have been reported (Hayasaka *et al.*, 1987). In most cases, neurological manifestations progress rapidly, followed by muscular hypotonia, seizures, lethargy, coma and apneic episodes. The patients who survive the neonatal period present severe neurological impairment (Hayasaka *et al.*, 1987; Nyhan, 1989; Tada *et al.*, 1990).

Some cases with relatively mild retardation have been reported, suggesting that the disorder is probably heterogeneous.

In this study we present a case of typical non-ketotic hyperglycinemia, identified in the neonatal period through a screening program for IEM, and its follow-up until the age of one year.

METHODS

Plasma, urine and CSF were collected from the patient at different ages. Qualitative tests were performed on occasional urine samples, according to Buist (1968), Perry *et al.* (1966) and Wannmacher *et al.* (1987), with some adaptations added by the authors. Circular paper chromatographic technique, a method developed for food proteins (Pinto *et al.*, 1976) and adapted for biological fluids by the authors (Oliveira, 1991), was used to separate plasma and urine amino acids into seven groups (Table I). Plasma and urine were previously deproteinized by ultrafiltration.

The data obtained in the amino acid chromatography are shown on a histogram, which presents the mean value of each group together with the normal range corresponding to the patient's age (Figures 1 and 2). The normality range is expressed by the mean value of each group in control individuals, ± 2 SEM (standard error of the mean).

Amino acids were quantified on an automatic amino acid analyser. Ultrasonography, electroencephalogram (EEG), computed tomography (CT) and nuclear magnetic resonance imaging (NMR) of the brain were also performed.

Table I - Circular paper chromatography: distribution of the amino acids in 7 groups.

Group	Composition
1	ammonia, cystine
2	arginine, hystidine, lysine, ornithine
3	glycine, serine, aspartic acid, citrulline, asparagine, glutamine, hydroxyproline, homocystine
4	glutamic acid, threonine
5	proline, alanine, tyrosine, tryptophan, GABA, β -alanine
6	valine, methionine, phenylalanine
7	leucine, isoleucine

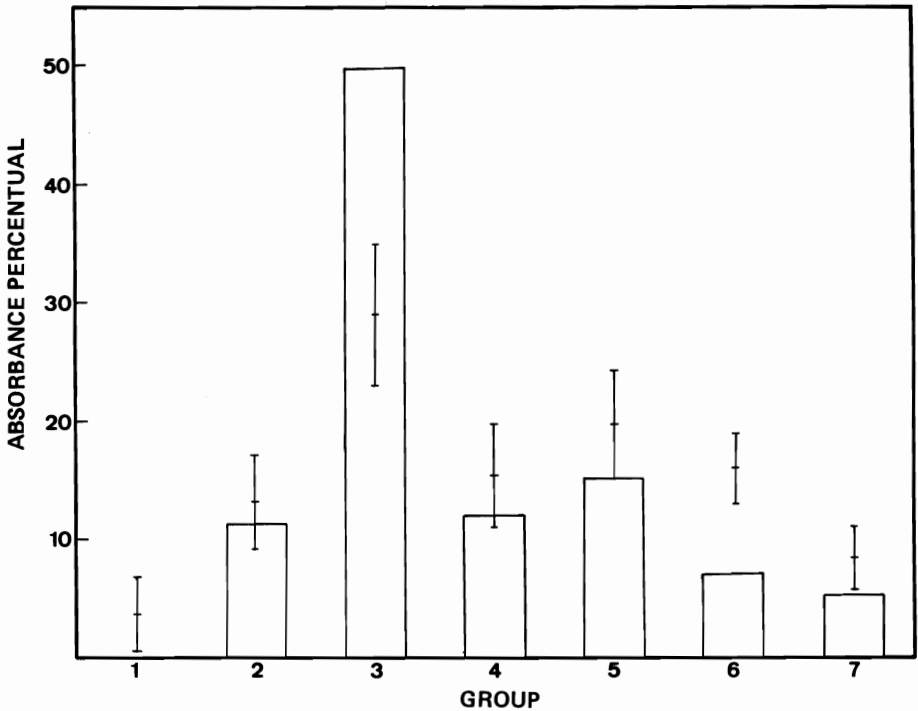


Figure 1 - Plasma amino acid pattern by circular paper chromatography (age: 8 days).

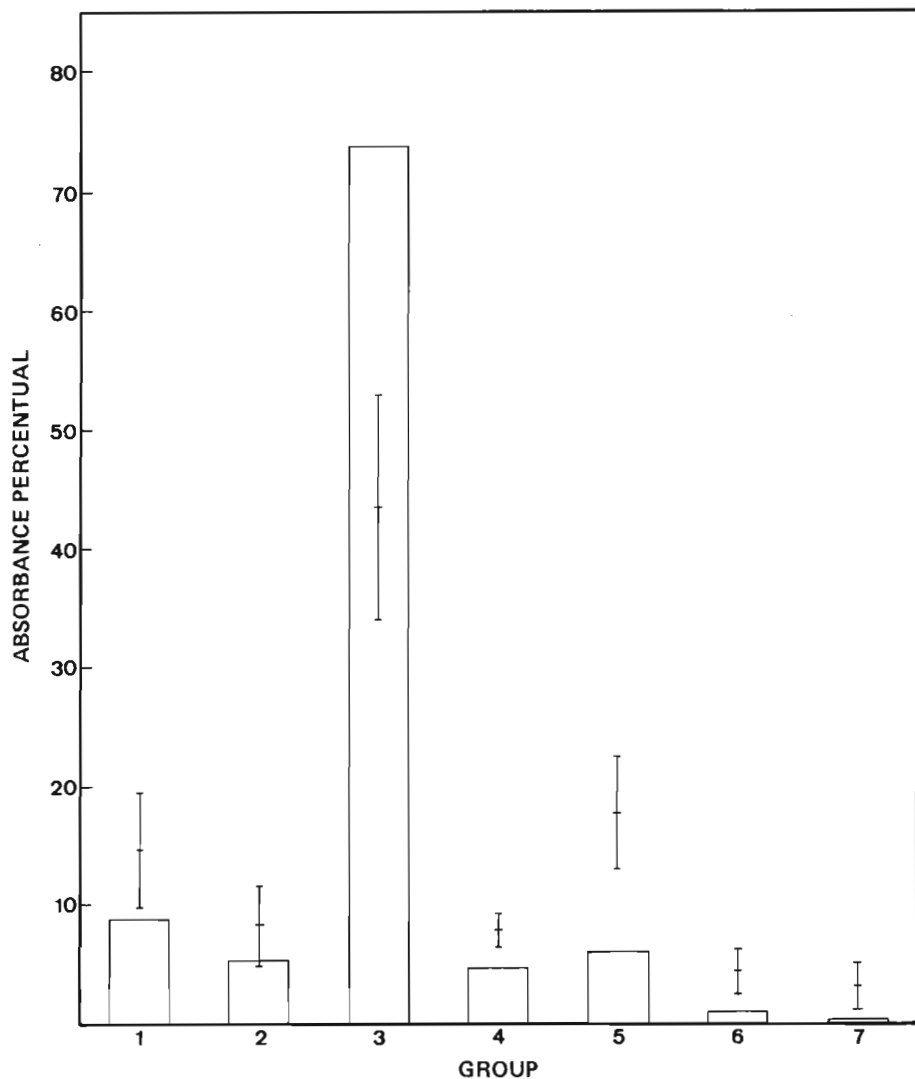


Figure 2 - Urine amino acid pattern by circular paper chromatography (age: 8 days).

CASE REPORT

A.G.M., a white Brazilian boy, is the second child of non-consanguineous parents. The first gestation was voluntarily interrupted by abortion. A child of the father's first marriage is healthy. The infant was delivered by cesarean section; birthweight was

3400 g, length 48 cm, head circumference 34 cm and apgar scores were 7 and 9 at 1 and 5 minutes respectively.

The newborn showed progressive hypoactivity and poor suckling. At two days of age he deteriorated to a superficial coma with loss of reflexes and respiratory failure and on the 17th day he developed convulsions. At 26 days he presented severe flexion and extension spasms and tonic-clonic seizures, and at 65 days severe spasms and myoclonus.

Initially the patient received phenobarbital. When seizures became more severe, he was given pyridoxine and clonazepam. He became hypoactive, hypotonic and sleepy. Adrenocorticotrophic hormone (ACTH) was introduced but caused adverse effects. Treatment with diazepines, diphenylhydantoin and phenobarbital led to progressive improvement of seizure activity. Due to the somnolence, primidone was started and diazepam/phenobarbital were reduced. The child was dismissed at the age of 3 months, with convulsive seizures under control.

At one year the patient was re-examined, weighing on this occasion 8800 g. There was no improvement in his general condition. He presented poor sucking, poor reflexes, convergent strabismus and brief focal convulsive seizures several times a day. He also was incapable of following objects and showed no head or body control, thus demonstrating the severe neurological impairment of patients that survive the neonatal period.

LABORATORY RESULTS

At eight days of age, an increased amino acid excretion was the only altered result shown by the chemical screening tests on urine. Circular paper chromatography of plasma and urine amino acids revealed a significant increase of the third group, which comprises glycine (Figure 1 and 2). Based on these findings, and the clinical features, the possibility of NKH was raised. Plasma, urine and CSF, analysed by an automatic ion-exchange amino acid analyser, showed high concentrations of glycine (Table II).

Gasometry, plasma ammonia, muscle biopsy and renal function were normal. Transfontanelle ultrasonography (TFUS) indicated no abnormality at first, but when repeated after 28 days, showed cortical atrophy. At 56 days of age areas of demyelination were revealed by brain NMR and at two months EEG showed generalized abnormality. Analyses made at the ages of 65 days and one year, confirmed the elevation of the third group of amino acids (data not shown) and the increased plasma and urine glycine levels.

Table II shows the results, which are perfectly consistent with the glycine concentrations observed in previously reported patients.

Table II - Glycine levels in physiological fluids.

Parameter	Normal level ^a	Levels in previously reported patients	Our patient		
			8 days	65 days	1 year
Plasma (mg/dL)	1.82 ± 0.15	6.9 - 9.3 ^a 7.5 ± 3.4 ^a 6.44 - 12.78 ^b 8.4 (range 2.1 - 23.2) ^c	7.7	5.5	3.01
Urine (mg/mg creatinine)	0.1 - 0.2		4.67	1.0	0.66
CSF (mg/dL)	< 0.1	0.98 - 2.7 ^a 0.58 - 1.96 ^b 1.87 (range 0.75 - 4.27) ^c 0.698 (mean value) ^a	1.30	n.d.	n.d.
CSF: plasma ratio	0.02	0.17 ± 0.09 ^a 0.10 - 0.39 ^a 0.22 ^a	0.168	n.d.	n.d.

n.d. = not determined.

^a - Nyhan, 1989.

^b - Hayasaka *et al.*, 1987.

^c - Saudubray *et al.*, 1989.

COMMENTS

The data obtained (including the absence of ketoacidosis and hyperammonemia), evaluated together with the clinical findings, suggested that the patient has a typical form of neonatal NKH. The results stress the efficiency of the screening program and the sensitivity of the circular paper chromatographic method used to evaluate the imbalance of amino acids in physiological fluids. The complementary analyses confirmed the diagnosis, characterizing the specific findings of this disease.

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RESUMO

Apresentamos um caso típico de hiperglicinemia não-cetótica neonatal (McKusick 23830) detectado em um programa de triagem para erros inatos do metabolismo realizado no Rio de Janeiro e confirmado por análises que caracterizam os sintomas específicos desse distúrbio.

Dados clínicos e características bioquímicas são descritos e comparados com casos previamente relatados.

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