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Neurological manifestations in glutaric acidemia type 1 and the impact of expanded neonatal screening in Brazil

Ada Maria Farias Sousa Borges[1]*; Romina Soledad Heredia Garcia[2]

[1]Department of Pediatrics, Hospital Materno Infantil de Brasília (HMIB), Brazil.

[2]Department of Genetics, Hospital Materno Infantil de Brasília (HMIB), Brazil.

***Corresponding Author: Ada Maria Farias Sousa Borges**

Department of Pediatrics, Hospital Materno Infantil de Brasília (HMIB), Brazil.

Tel: 55-61-994334564; Email: amfsb@hotmail.com

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Abstract

Glutaric acidemia type 1 (GA1) is an inborn error of metabolism caused by the deficiency of the enzyme glutaryl-CoA dehydrogenase, with consequent accumulation of the aminoacids lysine, hydroxylsine and tryptophan. About 1 in every 100,000 individuals are affected by the disease. Neurological manifestations are variable and include acute and chronic encephalopathic crises, dystonia, motor and cognitive deficits, as well as neuroimaging findings such as brain hypoplasia, striatal, white matter and subdural effusions. Early diagnosis is crucial for specific therapy, which includes a diet with restricted amino acids and carnitine replacement. The present work describes the variability of neurological manifestations in four patients with glutaric acidemia type 1, diagnosed in different age groups, through mass spectrometry, technology of the expanded neonatal screening available in the Ministry of Health program in Federal District, Brazil. Complications of GA1 were more severe in cases with later diagnosis, which justifies the use of the enlarged neonatal screening as an important resource in the early diagnosis and treatment of inborn errors of metabolism.

Keywords: Glutaric Acidemia Type 1; Glutaryl-Coa-Dehydrogenase; Acidosis; Carnitine; Dystonia; Inborn Errors Of Metabolism; Neonatal Screening.

Introduction

Glutaric acidemia type 1 (GA1) was first described by Goodman et al. in 1975 and consists of a neurological disease of metabolic etiology, caused by deficiency of the mitochondrial enzyme glutaryl-CoA dehydrogenase, a flavoprotein whose deficiency leads to alteration in the metabolism of the aminoacids lysine, hydroxylisin and tryptophan. The result of enzyme deficiency is the accumulation of 3-hydroxy-glutaric acid, glutaric acid and glutaconic acid [1-5].

The disease affects about 1 per 100,000 individuals, has an autosomal recessive inheritance and the GCDH gene, located in 19p13.2, is related to this acidemia [2,6].

The present work describes the variability of neurological manifestations in four patients with glutaric acidemia type 1, diagnosed in different age groups. The presence of an encephalopathic crisis was described in two of the four cases. In three cases, diagnosis and treatment were late, outside the neonatal period and after the appearance of neurological manifestations; these three patients were born outside the Federal District and had the result of Neonatal Screening (NS) without changes.

Cases series

Four cases of patients with GA1 were followed up in the outpatient department of Hospital Materno Infantil de Brasília (HMIB).

Case 1 is of an 8-year-old girl, born in Ipiaú, Bahia, the first daughter of non-consanguineous parents, born by normal delivery, at term, without neonatal complications. He was diagnosed with GA1 at the age of 1 during prolonged hospitalization for investigation of malnutrition and initial clinical practice of severe vomiting.

On physical examination, disproportionate incomplete hemiparesis was observed on the right, with brachial predominance. In the evolutionary neurological examination according to Funayama, 1996 there was a delay or failure in the execution of motor milestones, with impairment in static and dynamic balance, without jumping and clapping before touching feet on the ground, as well as the poise foot-heel.

Case 2 is of a 7-year-old girl, born in Ipueiras, Ceará, born by normal delivery, at term, maternal report of exacerbated irritation in the neonatal period. First daughter of non-consanguineous parents, these with a history of two previous abortions. He was diagnosed with GA1 at 4 years of age, after encephalitis, initially conducted as viral.

The evolutionary neurological examination did not show any motor impairment, however, in an evaluation according to Funayama, 1996, there was a delay in the psychic and social milestones for age, it was not located in time and space, it did not recognize the right and left, it did not identify the main colors, it changed letters when speaking. Parents also brought complaints of learning difficulties in the school environment.

Case 3 is an infant aged 1 year and 10 months, born by normal delivery, term, without neonatal complications. Born in Buritis, Minas Gerais, the first child of non-consanguineous parents. He was diagnosed with GA1 at 8 months of age, during prolonged hospitalization. Admitted with motor delay of neurological milestones (partial cephalic sustenance, he did not have voluntary hand grip), dorsal oculo-facial dystonia and fluctuation of the level of consciousness (alternating irritability with periods of drowsiness), he was initially treated with Acyclovir due to the hypothesis of viral encephalitis.

Case 4 is a 9-month-old infant, born in Federal District, the first daughter of non-consanguineous parents, with a history of prematurity, gestational age of 35 weeks. He presented alteration suggestive of GA1 in expanded neonatal screening and initiation of treatment on the 11th day of life, asymptomatic on admission and appropriate neurological marks for corrected age.

Discussion

Clinical presentation

Glutaric acidemia type 1 affects around the world, about 1 in every 100,000 children, macrocephaly is an important feature, is present in about 75% of cases and may already be present at birth, which shows intrauterine expression. Clinical manifestations appear until the second year of life and present in an acute or chronic form [3,6,7].

Table 1: Percentile of head circumference of the cases presented.

Cases	Head circumference (HC) measurement	Percentile (p) for age group
1	52 cm	p25 < HC < p50
2	55.3 cm	HC > p97
3	47 cm	p25
4	44.6 cm	p50 < HC < p75

Table 2 shows the measurement of the head circumference of the cases presented. Only case 2 presented measurements above the percentile for age.

In the acute form and without specific treatment, metabolic stress, such as dehydration, surgery, adverse effects to vaccines and febrile illnesses, can lead, in children between 3 and 36 months of life, the encephalopathic crisis, whose clinic is similar to that of encephalitis, which results in acute striatal injury, retinal hemorrhage, dystonia, dyskinesia, hypotonia, choreoathetosis, spastic paralysis, epileptic seizures, acidosis and hyperammonemia, which can progress to permanent neuropsychomotor deficits [2,3,8,9].

Chronic renal failure has also been described in adolescents and adults with GA1, which shows the need for follow-up, as the clinical characteristics have not yet been fully elucidated with the possibility of affecting multiple systems [7].

Neuroimaging

Main radiological findings include: Hypoplasia or frontotemporal atrophy, delayed myelination, chronic subdural hematoma or hygroma, atrophy of the thalamus, degeneration of the basal ganglia, which can be evidenced by atrophy or hyperintensity in T2 of the pale, caudate and putamen globe, dilation cystic silvian fissure [2,10,11].

Cases 1 and 3 underwent cranial Computed Tomography (CT), which showed in the first case, with bilateral cerebral atrophy predominating in the perinsular temporal region with widening of the silvian fissures, asymmetric ventricular widening, most predominant on the left. In case 3, the CT showed significant frontotemporal atrophy. Those are classic radiological findings of glutaric acidemia type 1.

In case 2, nuclear magnetic resonance imaging of the skull showed diffuse hypersignal of periventricular and subcortical cerebral white matter, with involvement of the corpus callosum, pale globe, accentuation of cortical grooves and cerebral fissures, enlargement of silvian fissures and ectasia of the supra and ventricular system infratentorial; it also corresponded to the radiological description of acidemia.

In case 4, a transfontanelle ultrasound was performed, which showed multissepted cystic formations, with bilateral periventricular location, areas of bilateral subependymal hyperechogenicity, most evident on the left. This can be attributed to the manifestation of this disease, but requires confirmation and follow-up by MRI.

Diagnosis and neonatal screening

The first line for the diagnosis of organic acidemias includes analysis of urinary organic acids through gas chromatography and mass spectrometry, in the case of GA1, the main organic acids elevated in the urine are 3-hydroxyglutaric acid and glutaconic acid. Confirmatory tests are based on the measurement of enzyme deficiency in lymphocytes or culture of fibroblasts and / or molecular genetic tests [12].

The screening tests for GA1 are based on the detection of an increase in glutaryl-carnitine in the blood, quantified using tandem mass spectrometry [13].

Early diagnosis and treatment, not the genotype, are associated with better patient prognosis, which emphasizes the importance of neonatal screening. The analysis of the GCDH gene is heterogeneous, with no well-established genotype-phenotype correlation. Mutation research is useful for diagnostic confirmation when enzyme assay is not possible, to assist genetic counseling and prenatal diagnosis [14].

Except for case 4, the only individual born in Federal District, who underwent enlarged initial NS, the other 3 cases were only diagnosed after the appearance of neurological manifestations. All had neonatal screening from other states, without changes.

After performing tandem mass spectrometry and an increase in C5DC (glutaryl-carnitine), a urinary sample was collected for analysis of organic acids through gas chromatography, which resulted in an increase in glutaric and 3-hydroxy-glutaric acid. Table 2 shows the values of metabolite and organic acids found in each case.

Table 2: Quantification of serum metabolite and urinary organic acids from cases of GA1 at diagnosis.

Cases	**Glutaryl-carnitine dosage (C5DC) serum** (Ref: < = 0,38 mmol/L)	**Dosage of urinary glutaric acid** (Ref: < 13 mmol/mol de creatinine)	**Dosage of urinary 3-hydroxy-glutaric acid** (Ref: < 1 mmol/mol de creatinine)
1	0,51 umol/L	80,4 mmol/mol de creatinine	11,2 mmol/mol de creatinine
2	1,16 umol/L	5.000,0 mmol/mol de creatinine	46,5 mmol/mol de creatinine
3	1,05 umol/L	9.508,0 mmol/mol de creatinine	110,0 mmol/mol de creatinine
4	7,9 umol/L	> 5.000,0 mmol/mol de creatinine	21 mmol/mol de creatinine

Treatment

GA1 is part of a select group of treatable inborn errors of metabolism. The therapeutic protocol is based on dietary lysine restriction and carnitine supplementation to minimize the risk of neuronal damage after diagnosis, includes a multi and interdisciplinary team, and has a direct effect on prognosis, quality of life and reduction of morbi and mortality [12,13,15].

The acute treatment in the encephalopathic crisis follows the basic principles of intoxication due to metabolic disease, which includes the prevention or reversion of catabolic state through the increase of the caloric rate (or administration of insulin in the case of hyperglycemia); restriction of natural protein for 24 to 48 hours; prevent carnitine depletion (through supplementation at a dose of 100 mg/kg/ day), and correct hydroelectrolytic disorders [15].

In the exposed cases, only one had the possibility to start treatment in the neonatal period (case 4) due to enlarged NS and, thus, better perspective of prognosis and reduction of neurological complications.

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