ECRONICON OPEN ACCESS

EC NEUROLOGY
Case Report

Type 1 Glutaric Aciduria: About a Case of Insidious Presentation Interpreted as a Childhood Cerebral Palsy

Linares María Andrea and Cruz Daniel*

Neurólogo Pediatra, Hospital General del Norte de Guayaquil, IESS Ceibos, Guayaquil, Ecuador

***Corresponding Author:** Cruz Daniel, Neurólogo Pediatra, Hospital General del Norte de Guayaquil, IESS Ceibos, Guayaquil, Ecuador.

Received: January 27, 2020; **Published:** February 17, 2020

Abstract

The first reported national case of glutaric aciduria type I is presented. This pathology is part of the congenital errors of metabolism; It is produced by deficiency of the enzyme glutaryl coenzyme A dehydrogenase involved in the catabolism of L-lysine, L-hydroxylysine and L-tryptophan, which causes the storage of glutaric and 3 hydroxyglutaric acids in the central nervous system. A clinical case with late diagnosis is described and corresponding to a form of insidious presentation of the disease. The clinical, imaging and metabolic integration allowed to establish a diagnosis of type I glutaric aciduria.

Keywords: *Inborn Errors of Amino Acid Metabolism; Glutaric Aciduria Type I; Dystonic Tetraparesis*

Abbreviations

AGI: Type I Glutaric Acid; C5DC: Glutaryl-Carnitine; FLAIR: Fluid Attenuated Resolution

Introduction

Type I glutaric aciduria (AGI) is an autosomal recessive disease with an estimated prevalence of 1 in 30,000 to 100,000 newborns [1]. It is caused by the congenital deficiency of glutaryl coenzyme A dehydrogenase, responsible for the degradation of L-lysine, L-hydroxylysine and L-tryptophan, resulting in the accumulation of glutaric acid, 3-hydroxyglutaric acid, to a lesser extent glutaconic acid, glutarylcarnitine and the subsequent cerebral depletion of carnitine [2]. It is a genetic-based condition with mechanism of autosomal and recessive inheritance [3].

It was described by Goodman and collaborators in 1975 and currently more than 500 cases are reported worldwide [4].

This disorder is expressed with acute encephalopathy, chronic dystonic tetraparesis and a bilateral and posterior striatal lesion is identified in neuroimaging. Less frequently, its clinical presentation is insidious. In more than two thirds of the cases the AGI debuts in the first three years of life; a nonspecific infection with fever or dehydration triggers an acute encephalopathic crisis that is accompanied by deep hypotonia or generalized stiffness, neurological depression, irritability, epileptic seizures, dystonia and dyskinesia. Dystonic movements can often be confused with epileptic seizures [1,5,6].

Imaging findings on brain magnetic resonance include frontotemporal atrophy called "bat wings", in the FLAIR sequence (Fluid attenuated resolution) hyperintensity of the caudate nucleus, rot and white matter is identified, in other sequences ventricular dilation can be evidenced, cerebral atrophy, communicating hydrocephalus, hygromas or subdural hematomas [6,7].

The biochemical diagnosis is based on the detection of high levels of glutaric and 3-hydroxyglutaric acids, as well as glutarylcarnitine in body fluids. Some patients, however, can excrete normal levels of glutaric acid and 3 hydroxyglutaric acid and may have normal levels of glutarylcarnitine in the blood [1]. Detection of elevated concentrations of glutaryl-carnitine (C5DC) by tandem mass spectrometry in neonatal screening of metabolic diseases establishes a suspicion of AGI [8]. The diagnosis is confirmed by highlighting the pathogenic variants in gene [3].

The treatment consists of a diet low in lysine and tryptophan, carnitine supplements and intensive emergency treatment during catabolic states. The treatment is effective and improves the neurological outcome in those individuals diagnosed early; however, treatment after the onset of symptoms is less effective [3].

The first nationally reported case of AGI is presented, which was initially interpreted as a dystonic-type infantile cerebral palsy of unclear etiology.

Presentation of the Case

Two-year-old and eight-month-old preschooler, afro descendant, female, daughter of non-consanguineous parents, with family history of intellectual disability. It is the product of second pregnancy, previous abortion, complicated pregnancy in the first trimester of pregnancy with placenta previa and partial placental detachment, intrauterine growth retardation. Born by caesarean section, late premature, not vigorous, birth weight 1740 grams, height at birth 44 cm, the cephalic perimeter measurement is unknown. In the first hours of life he presented a respiratory distress syndrome, receiving support from mechanical ventilatory assistance for two days, course with sepsis, multifactorial jaundice and grade IV intraventricular hemorrhage. In his clinical evolution he presented a global delay in psychomotor development, a perimeter cephalic in the 97th percentile and chronic malnutrition. It was interpreted as a dystonic-type infantile cerebral palsy of unclear etiology (Figure 1).

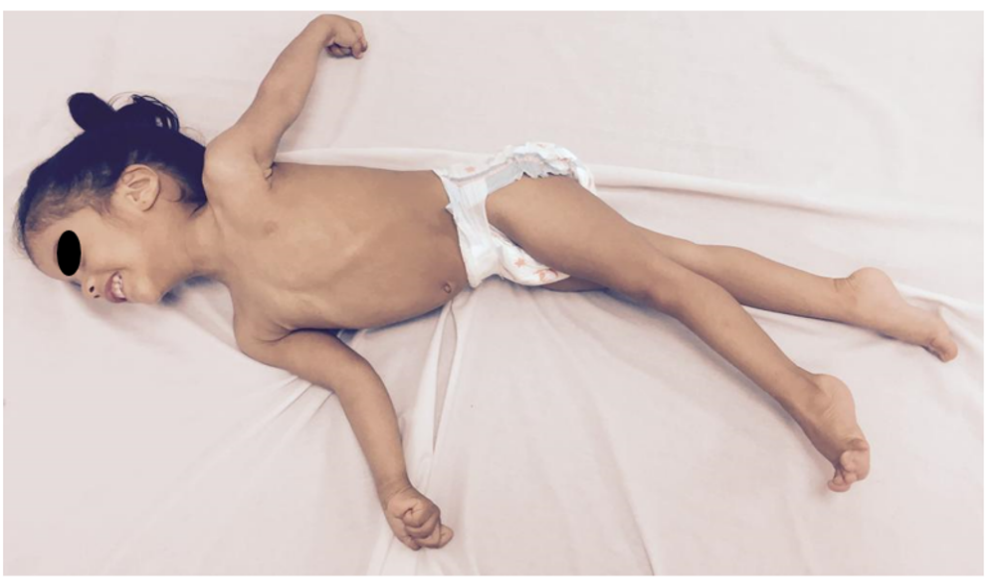

Figure 1: *Female patient of two years and eight months, there is evidence of cranio-body disproportion and dystonic posture.*

He has a history of multiple hospitalizations due to metabolic decompensation from the year of age: sustained metabolic acidosis, hypoglycemia 15 mg/dl, hyperammonemia 99 µmol/L (5.87 - 46.98 umol/L), lactic acid 3.6 mmol/L (less than 2.2 mmol/L), GAP anion elevated by 29, in the context of catabolic states such as respiratory and digestive infections.

Once the case has been reconsidered, it is oriented towards an inborn error of metabolism, initiating the diagnostic approach. In the study of Cerebral Magnetic Resonance, an increase in the subarachnoid space is identified as elements of a probable cerebral atrophy of bilateral temporal frontal predominance, thinned corpus callosum and in FLAIR sequence a bilateral hyperintensity of basal ganglia (Figure 2).

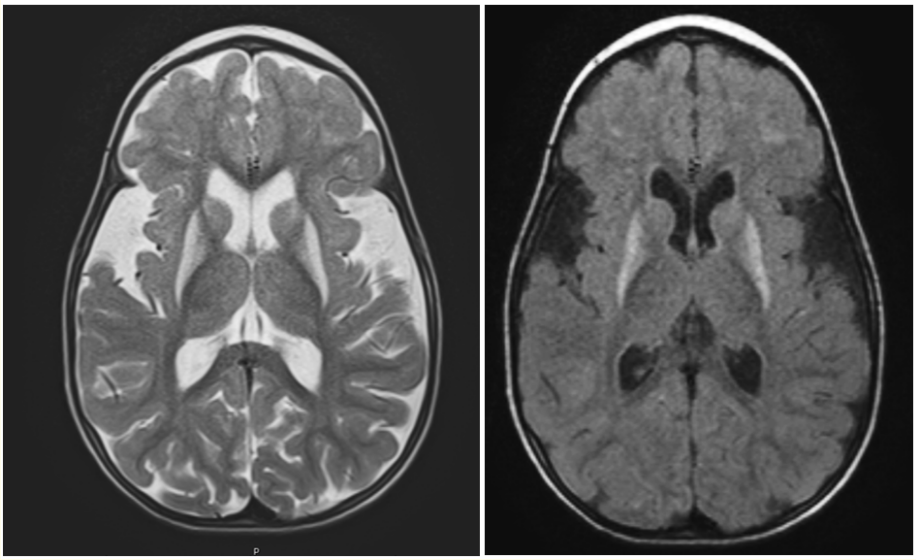

Figure 2: *A. Axial section in T2, increase in the temporal frontal subarachnoid space "bat wings", bilateral hyperintensity of basal ganglia. B. Axial section in FLAIR, hyperintensity of bilateral basal ganglia.*

The electroencephalogram provided elements of cortical dysfunction. In the study of blood acylcarnitines by tandem mass spectrometry (MS/MS), high values of glutarylcarnitine 0.96 (0.0 - 0.3 umol/l), glutarylcarnitine/palmitoylcarnitine 3.4 (0.0 - 0.18 umol/l), glutarylcarnitine/acetylcarnitine were determined 0.38 (0.0 - 0.1 umol/l). With a support in clinical, imaging and metabolic integration, a diagnosis of AGI is established. The beginning of a diet low in lysine and tryptophan is proposed in multidiscipline, with a contribution of carnitine and riboflavin. In the evolution, improvement of the nutritional state is evidenced. It is currently maintained without metabolic decompensation five months after the start of the diet.

Discussion

The history of infantile cerebral palsy of dystonic type, of unclear etiology, accompanied by a cephalic perimeter in 97th percentile and multiple metabolic decompensations, were the basis for clinical suspicion of AGI. It is a condition described by some authors in the group of "cerebral" organic acidosis, and often misdiagnosed as a childhood cerebral palsy of dystonic type [3,9].

Due to the clinical presentation and case evolution, an insidious presentation was proposed; This form of presentation is the most difficult to diagnose. The typical clinical picture is evident after an acute encephalopathy crisis, which causes regression in neurodevel-

opment, generalized hypotonia and dystonic movements. In these patients, macrocephaly can be found and some have a mild delay in psychomotor development and can be confused with a dyskinetic cerebral palsy [8,10].

In relation to macrocephaly in the medical literature, it is referred to as a frequent finding (75%) but not specific and is present at or shortly after birth [11]. In our patient, the head circumference was established at the 97th percentile.

The imaging findings were decisive for the approach to diagnostic suspicion. In the AGI, typical images of bilateral temporal fronto atrophy referred to as "bat wings" explained by dilatation of the insular cistern, hyperintensity of the lenticular nuclei, can also be seen increase in cerebrospinal fluid at the level of the temporal lobes and frontal as well as commitment of the white substance [8,9].

The finding of elevated glutarylcarnitine levels in the metabolic study was the last integrative element in a clinical, imaging and biochemical diagnosis of AGI. These findings are accepted in the medical literature as sufficient for the definitive diagnosis [1,8].

Unfortunately, the identification of the disease was late, the neurological damage is irreversible. Neonatal screening is essential for the early diagnosis and improvement of the prognosis of this disease [11].

The treatment is aimed at preventing cerebral degeneration in cases of presymptomatic diagnosis. When a late diagnosis is made as in the present case, the therapeutic impact is limited and is aimed at the prevention of progressive neurological deterioration [12]. Without treatment, about 90% of patients will suffer from acute encephalopathy crisis, which is associated with high morbidity and mortality [13].

The estimated prevalence of neonatal screening for AGI based on data from several countries is 1: 106,900. In Ecuador the prevalence is unknown [14].

Conclusion

AGI is a treatable disease with a better prognosis when it is identified in time or in its presymptomatic form as it is by neonatal screening. A late diagnosis makes us reflect on the need not to ignore it and suspect it in the patient with dystonia-type infantile cerebral palsy of an unclear type with or without macrocephaly. Parents are advised about the high risk of recurrence of the same condition in future pregnancies, regardless of fetal sex.

Contribution of the Authors

Daniel Cruz, María Andrea Linares: Conception and work design, Information gathering. Daniel Cruz, María Andrea Linares: Writing the manuscript. Daniel Cruz, María Andrea Linares: Critical revision of the manuscript. All authors read and approved the final version of the article.

Data Availability

Free and limited use bibliographic resources were used. The information collected is available under the lead author.

Informed Consent

The publication is pending approval by the Editorial Board of the General Hospital of the North of Guayaquil, IESS Los Ceibos.

Financing

We worked with the authors own resources.

Interest Conflict

The authors report no conflicts of interest.

Acknowledgement

To the Teachers: Aida Lemes and Gabriel Gonzalez (Montevideo- Uruguay), Professor of Neuropediatria, University of the Oriental Republic of Uruguay.

Bibliography

1. Cerisola A., *et al*. "Seizures versus dystonia in encephalopathic crisis of glutaric aciduria type I". *Pediatric Neurology* 40.6 (2009): 426-431.
2. Forero Sánchez., *et al*. "Acidemia glutárica tipo 1: presentación de un caso y revisión de la literature". *Iatreia* 28.2 (2015): 193-197.
3. Barreiro A., *et al*. "Aciduria glutárica tipo I. Descripción del primer caso clínico nacional". *Revista Médica del Uruguay* 20.3 (2004): 221-227.
4. Goodman SI., *et al*. "Glutaric aciduria: a new inborn error of amino acid metabolism". *Biochemia Medica* 12 (1975): 12-21.
5. McClelland VM., *et al*. "Glutaric aciduria type 1 presenting with epilepsy". *Developmental Medicine and Child Neurology* 51.3 (2009): 235-239.
6. Hedlund GL., *et al*. "Glutaric acidemia type 1". *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics* 142C.2 (2006): 86-94.
7. Brismar J and Ozand PT. "CT and MR of the brain in glutaric acidemia type I: a review of 59 published cases and a report of 5 new patients". *American Journal of Neuroradiology* 16.4 (1995): 675-683.
8. Ortiz A., *et al*. "Glutaric aciduria type 1". *Acta Neurológica Colombiana* 28 (2011): 157-165.
9. Sarangi PK., *et al*. "Glutaric Aciduria Type I: A Rare Metabolic Disorder Mimicking as Choreoathetoid Cerebral Palsy". *Journal of Pediatric Neurosciences* 12.1 (2017): 85-86.
10. Heringer J., *et al*. "Use of guidelines improves the neurological outcome in glutaric aciduria type I". *Annals of Neurology* 68.5 (2010): 743-752.
11. Boy N., *et al*. "Proposed recommendations for diagnosing and managing individuals with glutaric aciduria type I: second revision". *Journal of Inherited Metabolic Disease* 40.1 (2017): 75-101.
12. Wang Q and Yang YL. "[Complex heterogeneity phenotypes and genotypes of glutaric aciduria type 1]". *Zhongguo Dang Dai Er Ke Za Zhi* 18.5 (2016): 460-465.
13. Tsai FC., *et al*. "Experiences during newborn screening for glutaric aciduria type 1: Diagnosis, treatment, genotype, phenotype, and outcomes". *Journal of the Chinese Medical Association* 80.4 (2017): 253-261.
14. Lindner M., *et al*. "Neonatal screening for glutaryl-CoA dehydrogenase deficiency". *Journal of Inherited Metabolic Disease* 27 (2004): 851-859.

Volume 12 Issue 3 March 2020