GLUTARIC ACIDURIA TYPE 1: TWENTY-FOUR CASES IN BRAZIL OVER A TEN-YEAR PERIOD EXPERIENCE

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Introduction and Objectives

Glutaric aciduria type I (GA1) is an autosomal recessive inborn error of metabolism caused by the deficiency of the mitochondrial matrix enzyme glutaryl-coenzyme A dehydrogenase, which affects the catabolism of lysine, hydroxylysine and tryptophan [1]. Untreated, most patients suffer an acute encephalopathic crisis, characterized by hypotonia and seizures, which lead to the gradual development of a complex movement disorder. In some patients, the movement disorder develops insidiously, in the absence of an encephalopathic crisis [1]. In symptomatic patients, quantitative urinary organic acids, and plasma or dried blood spot (DBS) and urinary acylcarnitine analyses are the preferred methods of diagnosis [2,3]. We report the biochemical findings of a series of symptomatic patients that were diagnosed with GA1 in a Brazilian reference laboratory.

Methodology

Urine and DBS were obtained from 6024 patients with a clinical suspicion of an IEM. Urinary organic acids were identified by gas chromatography/mass spectrometry (GC-MS), and acylcarnitines in DBS and urine by electrospray ionization tandem mass spectrometry (ESI-MS/MS).

Results

The diagnosis of GA1 was made in 24 patients, 11 females and 13 males, with ages varying from 7 months to 20 years. Most of the patients were diagnosed in the chronic neurodegenerative phase after an encephalopathic crisis. Three patients presented the insidious or the late forms of the disease. Suggestive clinical signs included epilepsy (9 in 24), extrapyramidal manifestations (9 in 24), macrocephaly (6 in 24), neuroradiologic abnormalities (4 in 24) [Figure 1], and truncal hypotonia (4 in 24). Parental consanguinity was reported in four patients. A urinary peak of glutaric acid and a less conspicuous peak of 3-hydroxyglutaric acid (high excretor phenotype) were found in 22 patients [Figure 2]; in eight of them, excretion of glutaconic acid was also observed. Two patients with a low excretor phenotype had undetectable or trace urinary levels of these acids [Figure 3]. The diagnosis in these patients was accomplished by the finding of a urinary and/or DBS glutarylcarnitine peak - C5DC [Figure 4]. In all patients with a high excretor phenotype, in which acylcarnitines could be analyzed (12 in 22), it was possible to find a C5DC peak.

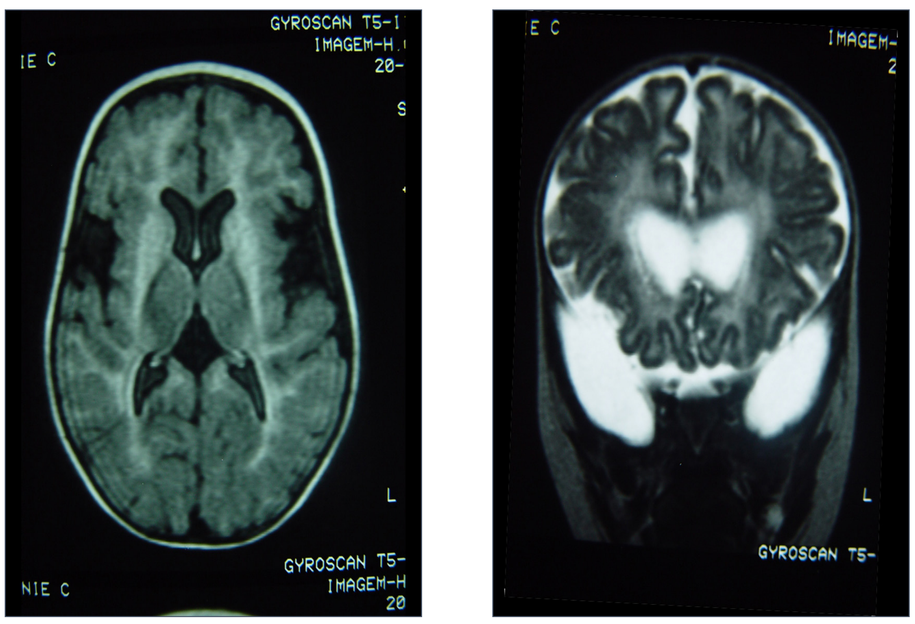

Figure 1. Brain magnetic resonance imaging of an infant with glutaric aciduria type I at 10 months of age.

A. Axial FLAIR image: Abnormal bilateral increased signal intensity (hyperintensity) of the putamen, globus pallidus and caudate nucleus, and bilateral symmetrical widening of the Sylvian fissures.
B. Coronal T2-weighted image: Hypoplasia of the frontotemporal regions of the cerebral hemispheres, with prominence of the lateral ventricles.

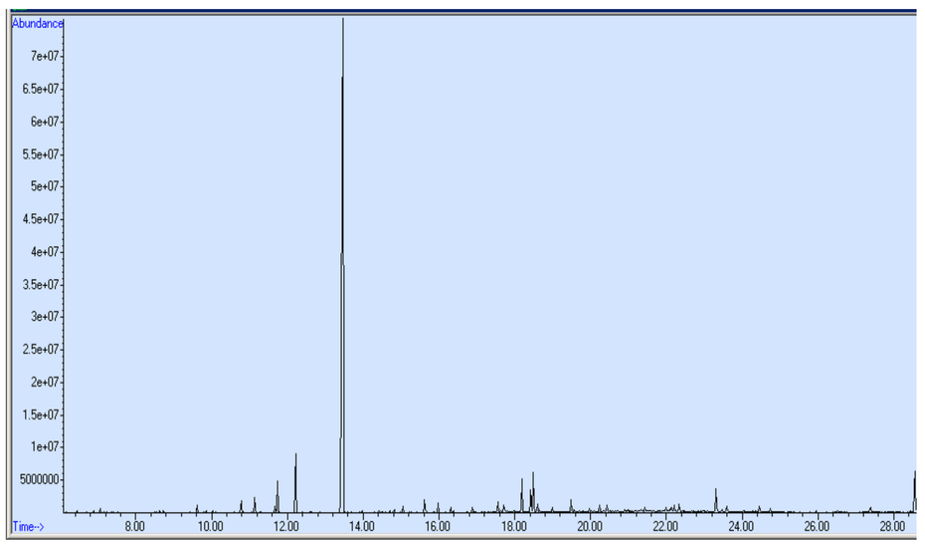

Figure 2. GC-MS urinary organic acid chromatogram of a school-age girl showing the characteristic profile of glutaric aciduria type I. Daughter of a c onsanguineous couple (3rd degree cousins), her sample was referred because of psychomotor delay and metabolic acidosis.
3-Hydroxyglutaric acid = 17.26 mmol/mol creatinine (Normal range: <4,6)
G lutaric acid > 4,514 mmol/mol creatinine (Normal range: <13)

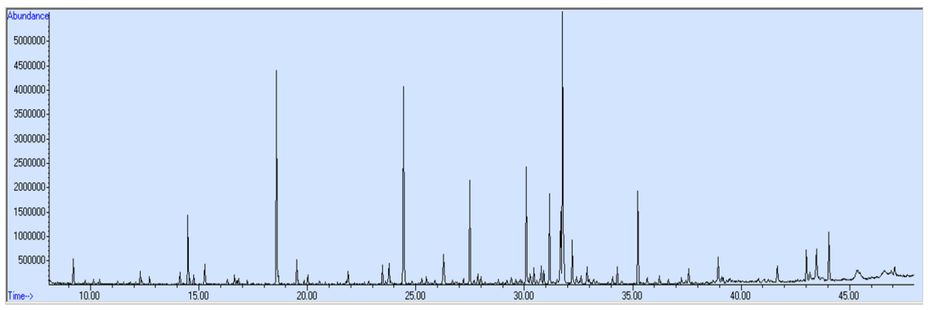

Figure 3. Twenty-year-old male patient presenting growth and psychomotor delay, receiving riboflavin and L-carnitine supplements.
3-Hydroxyglutaric acid = 5.23 mmol/mol creatinine (Normal range: ND)
Glutaric acid = 8.13 mmol/mol creatinine (Normal range: <2.6)

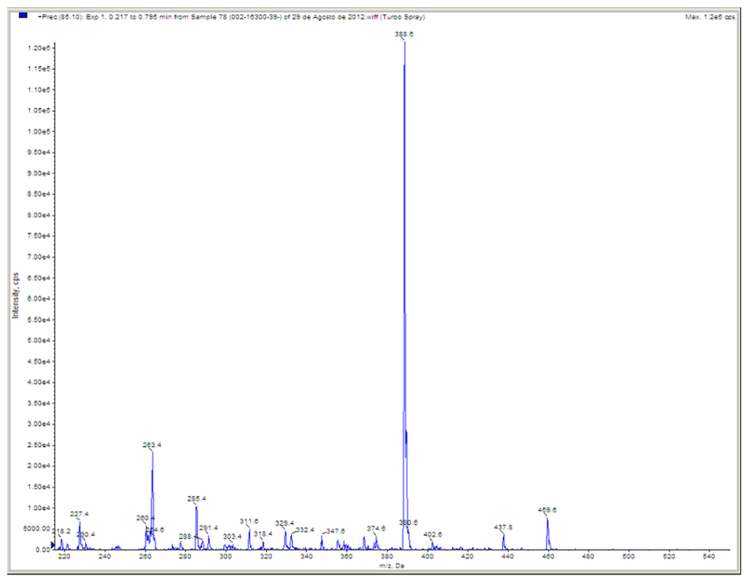

Figure 4. Urinary glutarylcarnitine (C5DC) outstanding peak in the same low excretor patient whose organic acid profile is shown in Figure 3.

Discussion and Conclusions

The profiles of urinary organic acids and DBS acylcarnitines are indicated for all patients with macrocephaly, acute encephalopathic crisis, abnormal movements, or neuroradiologic studies revealing white matter abnormalities or frontotemporal hypoplasia, for which no other etiology has been established [3]. Multiple acyl-CoA dehydrogenation deficiency (MADD), or glutaric aciduria type II, which also results in elevated DBS C5DC and urinary glutaric acid excretion, can easily be differentiated from GA1 by the presence of blood isovalerylcarnitine (C5), medium (C6 and C8) and long chain (C14 and C14:1) acylcarnitines, and increased urinary excretion of ethylmalonic and 2-hydroxyglutaric acids [4,5].

References

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