

L-2-hydroxyglutaric aciduria. A case report

Aciduria L-2-hidroxiglutárica. A propósito de un caso

Valentina Múnera[1]
Carlos Alberto Hinestroza Perea[1]
Stephanie Sánchez Villa[2]
Angélica Arteaga Arteaga[3]
Ana Carolina Sierra Montoya[3]
Santiago Vargas Arango[4]
Sergio Vargas[5]

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Summary

L-2-hydroxyglutaric aciduria (AL2HG) is a rare autosomal recessive neurometabolic disorder. It is characterized by elevated of L-2-hydroxyglutarate and lysine in urine, cerebrospinal fluid and plasma. Patients usually have neurological manifestations including mild to moderate psychomotor developmental delay, cerebellar ataxia, macrocephaly and epilepsy. Magnetic resonance imaging (MRI) has shown abnormalities in the signal intensity of the subcortical cerebral white matter, putamen and dentate nucleus. This article reports a case to demonstrate the classically described imaging findings.

Resumen

La aciduria L-2-hidroxiglutárica (AL2HG) es un raro trastorno neurometabólico de tipo autosómico recesivo. Se caracteriza por niveles elevados de L-2-hidroxiglutarato y lisina en orina, líquido cefalorraquídeo y plasma. Los pacientes suelen tener manifestaciones neurológicas que incluyen retraso en el desarrollo psicomotor de leve a moderado, ataxia cerebelosa, macrocefalia y epilepsia. En resonancia magnética (RM) se han descrito anormalidades en la intensidad de señal de la sustancia blanca cerebral subcortical, el putamen y el núcleo dentado. En este artículo se presenta un caso para demostrar los hallazgos por imagen que se describen clásicamente.

Introduction

2-hydroxyglutaric aciduria (A2HG) is a rare, inherited, metabolic disorder that includes D2-hydroxyglutaric aciduria (AD2HG), L2-hydroxyglutaric aciduria (AL2HG) and combined AD-2HG/AL2HG (Figure 1). AL2HG is an autosomal recessive disorder caused by mutations of the L2HGDH gene on chromosome 14q22. The gene encodes a mitochondrial protein, which has been termed duranin with homology to FAD (Flavin Adenine Dinucleotide) dependent oxidoreductases (1, 2). It was first reported in 1980 in a Moroccan child with psychomotor retardation; since that time approximately 90 cases have been described worldwide (3).

Patients with this disorder present with mild-to-moderate motor retardation (presenting mainly as ataxia), macrocephaly and sometimes febrile seizures during the first year of life. Neurodevelopmental delay (of variable severity) usually manifests during the second year of life, sometimes followed by dystonia and pyramidal signs. Rarely, the disease may result in infant death. Pathological analysis of brains with this pathology shows spongiform degeneration of the cerebral and cerebellar white matter with gliosis and vacuolization of the neuropil. The subcortical white matter contains numerous hyperplastic astrocytes and is severely demyelinated with cystic cavities. The basal ganglia and cerebellum are less affected, with spongiosis, but with mild neuronal loss and no cavitation (1-3).

Magnetic resonance imaging (MRI) findings are virtually pathognomonic for the disease. There is prolongation of the relaxation times visible in sequences with T1 and T2 information in basal ganglia and in the cerebellar dentate nucleus. The cerebral white matter abnormality exhibits a very characteristic centripetal and anteroposterior gradient (with initial frontoparietal compromise); the subcortical white matter is more affected and the basal ganglia are also affected, especially the putamen and the cerebellar dentate nucleus); whereas the periventricular white matter and, particularly, the central corticospinal tracts (internal capsule) and the corpus callosum are preserved. The extreme and external capsules are abnormal (Figure 2).

The cerebellar white matter is usually not altered. The thalami are normal, but the cerebellar dentate nuclei are always abnormal. Over time, much more

[1]Resident of Radiology and Diagnostic Imaging, Universidad Pontificia Bolivariana. Medellin, Colombia. [2]Residente de Pediatría de la Universidad de Antioquia. Medellín, Antioquia.

[2]Resident of Pediatrics, Universidad de Antioquia. Medellin, Antioquia.

[3]Child Neurologist, León XIII-IPS University Clinic. Professor of Child Neurology, Universidad de Antioquia. Medellin, Colombia.

[4]Physician, CES University. Medellin, Colombia.

[5]Neuroradiologist CediMed. Professor of Neuroradiology, Universidad de Antioquia, CES, Bolivariana. Medellin, Colombia.

extensive involvement of the white matter is observed and the affected areas usually atrophy, but even in advanced stages the periventricular white matter, internal capsule and corpus callosum are preserved. In newborns, T2-weighted images may show high cerebellar signal in the first days of life. Eventually, this may progress to mild to severe cerebellar atrophy, particularly involving the vermis. In the acute phase, asymmetric water diffusion restriction occurs in the basal ganglia and subcortical white matter. Spectroscopy shows that NAA (N-acetyl aspartate) is slightly decreased due to axonal loss secondary to spongiosis. Increased myoinositol, choline, lactate-lipid peak and glutamate/L2HG have been documented, but these alterations are not consistent in the different published series, so they are non-specific and change in acute and chronic stages (1-6).

Regarding laboratory diagnostic markers, they are considered when there is an increase in lysine levels in plasma, urine and cerebrospinal fluid (1).

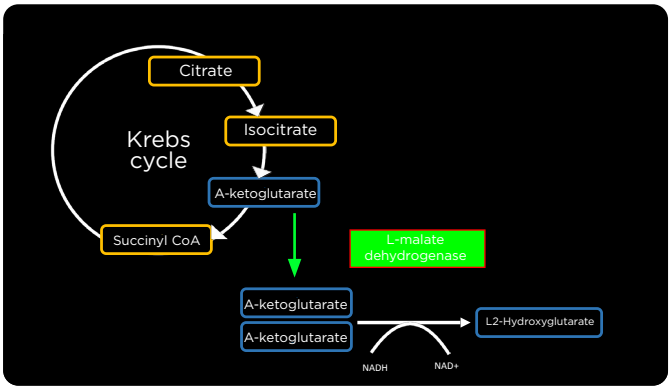


Figure 1. Undesired secondary reaction of L-malate dehydrogenase in the Krebs cycle (tricarboxylic acid cycle). A moderate elevation of lysine probably reflects a low mitochondrial availability of 2-α-ketoglutarate. The exact pathogenesis of leukodystrophy is poorly understood, although oxidative stress may play an important role.

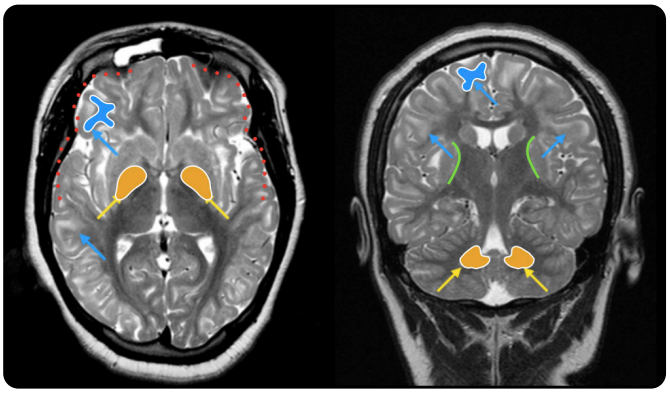


Figure 2. Graphic representation of the pathognomonic involvement of hydroxyglutaric aciduria, with involvement of the subcortical white matter (blue) with anteroposterior gradient (frontotemporal predominance: red), alteration of the basal ganglia and dentate nucleus (yellow) and involvement of the external and extreme capsule (green).

Clinical case

A 14-year-old female patient, daughter of non-consanguineous parents, with no relevant history, who at 7 months of age started a clinical picture of paroxysmal events characterized by activity arrest, ocular deviation to the right, cyanosis and loss of tone. These symptoms became repetitive. An electroencephalogram was performed, showing diffuse cortical theta slowing -slowing due to white matter damage, disconnection between cortex and subcortex or loss of corticosubcortical coherence-, and a simple brain MRI, which showed high signal in sequences with subcortical T2 information in the supratentorial region. Focal epilepsy was diagnosed and treatment was started with valproic acid, 250 mg every 12 hours. He had no recurrence of seizures for five years and the antiepileptic was discontinued, but two years after discontinuation he had a relapse, so it was necessary to use it again.

At the age of 12 years (she had been asymptomatic for two years), she was evaluated again with the following results: neurodevelopmental delay and cognitive compromise, she could not read or write, she did not recognize vowels or body parts and she counted numbers only up to 20. A new MRI was performed describing leukoencephalopathy with involvement of U-shaped fibers that respected the central white matter, involvement of the globus pallidus and dentate nuclei. With these findings, valproic acid was discontinued and carbamazepine was started.

With suspicion of organic aciduria, urine organic acid test was requested, with a result of significant increase in L2-hydroxyglutaric acid. In 2019 and age 14 years, mild left hemiparesis, generalized hyperreflexia, independent gait with tremor and dysmetria, and puerile behavior and language were found. MRI showed increased signal in T2-information sequences of the bilateral and symmetric globus pallidus and high signal in the subcortical white matter (Figure 3), U-fibers and both dentate nuclei in T2-information sequences (Figure 3 and Figure 4) (Figure 5).

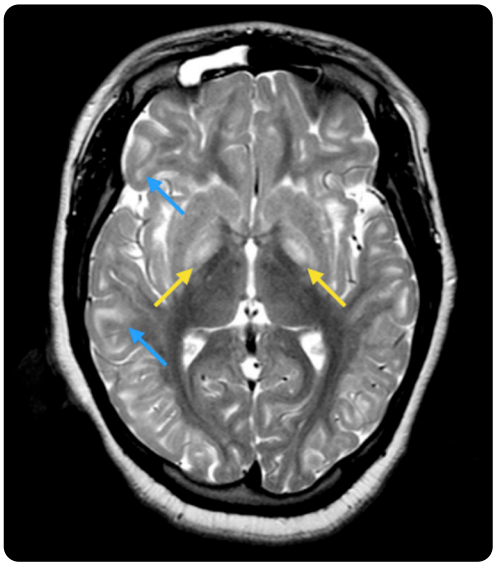


Figure 3. MR, axial image with T2 information: increased signal of the bilateral and symmetrical globus pallidus (yellow arrows). High signal of the subcortical white matter (blue arrows), with cystic morphology.

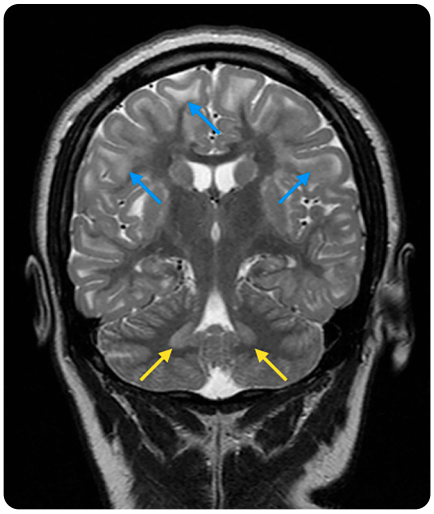


Figure 4. MRI, coronal image with T2 information: high signal of the supratentorial subcortical white matter affecting the cystic U-shaped fibers (blue arrows). High signal of both dentate nuclei (yellow arrows).

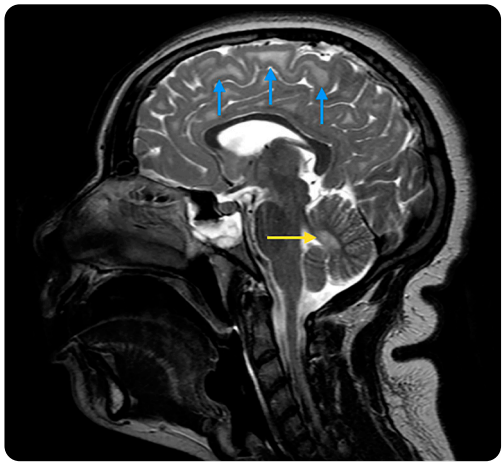


Figure 5. MRI, sagittal image with T2 information: involvement of the dentate nucleus of the cerebellum (yellow arrow). High signal of the subcortical white matter of cystic appearance (blue arrows). Pathognomonic findings of the disease.

Discussion

White matter diseases correspond to a huge group of disorders, among which AL2HG is a rare organic aciduria with a gradual clinical course and pathognomonic imaging findings (2, 6). Characteristically, high frontal subcortical white matter signals are observed with preservation of periventricular, commissural, brainstem and cerebellar white matter (6). The basal ganglia and dentate nucleus are involved in almost all patients, while the thalamus is usually spared (1, 6). Cerebellar volume loss is common. Clinically, it manifests with neurodevelopmental delay, seizures, progressive ataxia, spasticity and pyramidal signs. Treatment with riboflavin (vitamin B2) can decrease L-2-hydroxyglutaric acid levels (4).

Several authors have demonstrated an increased risk of malignant brain tumors, speaking of oncometabolites (2-hydroxyglutarate, succinate and fumarate), such as astrocytomas, oligodendrogliomas, ependymomas, medulloblastomas and Wilms' tumor (7, 8).

It is necessary to take into account the main differential diagnoses with other disorders that may simulate the involvement given by AL-2HG (5, 6). These include diseases with macrocranial involvement: Canavan disease, which shows diffuse and confluent compromise of the subcortical white matter, involvement of the globus pallidus and thalamus, but the caudate nucleus, putamen and dentate nucleus are spared, with a characteristic increase of the NAA on spectroscopy. In Kearns-Sayre syndrome, in which lesions are also located in the subcortical white matter, globus pallidus and caudate nucleus, but also involve the thalami and brain stem. Succinyl semialdehyde dehydrogenase deficiency involves the globus pallidus and dentate nucleus only, sparing the subcortical white matter. HMG-CoA Lyase deficiency where there is greater involvement of the posterior white matter, and the periatrial white matter may be affected, with signal abnormalities in the caudate nuclei and dentate nuclei (3, 6).

In conclusion, AL2HG is an aciduria occurring in both sexes, which has a characteristic imaging pattern encompassing a spectrum of alterations: predominantly involving the supratentorial subcortical white matter with anteroposterior gradient, the caudate nucleus, globus pallidus and putamen, and the dentate nuclei of the cerebellum (1, 5). With the progressive course, these abnormalities increase and manifest with greater signal intensity in sequences with MR T2 information and their final evolution will be diffuse atrophy of the cerebral white matter (1, 3, 6).

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Correspondence

Valentina Múnera Orozco
CediMed Centro de Imágenes Diagnósticas
Medellín, Colombia
valentina.muneraorozco@gmail.com

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