Avicenna Anatolian Journal of Medicine

Case Report

L-2-Hydroxyglutaric Aciduria: A Case Report with Clinical, Radiological, and Genetic Insights

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Submitted at: 06.12.2024 - Accepted at: 28.12.2024 - Published at: 30.12.2024
Avicenna Anatol J Med. Year; 2024, Volume: 1, Issue: 1

doi 10.5281/zenodo.14574051

Abstract

L-2-hydroxyglutaric (L-2-OHG) aciduria is a rare, autosomal recessive inherited neurodegenerative disease. It can present with varying degrees of mental dysfunction, macrocephaly, febrile and afebrile seizures, pyramidal and extrapyramidal symptoms, and cerebellar ataxia. Typical magnetic resonance imaging (MRI) findings include bilateral symmetric subcortical white matter, basal ganglia, and dentate nucleus involvement. The brainstem, corpus callosum, and periventricular white matter are usually spared. Besides clinical and neuroimaging findings, the diagnosis can be made by detecting an elevated level of L-2-OHG acid in the blood, cerebrospinal fluid (CSF), and urine. Here, we present a 26-year-old patient diagnosed with L-2-OHG aciduria with an onset of gait disorder in his late teens. For contributing to the literature, clinical and typical imaging findings and differential diagnosis of this rare syndrome are discussed.

Keywords: L-2-hydroxyglutaric aciduria, spongiform degeneration, macrocephaly, mental retardation, ataxia

INTRODUCTION

L-2-hydroxyglutaric aciduria (L-2-OHG) is a rare autosomal recessive, progressive neurometabolic disorder caused by pathogenic variants in the 14q22.1 gene encoding mitochondrial 2-hydroxyglutarate dehydrogenase. The age of onset and severity of the disease are variable. In the slowly progressive course of the disease can usually observed with cerebellar ataxia, dysarthria, seizures, macrocephaly, pyramidal and extrapyramidal signs, and growth stunting (1-3).

Magnetic resonance imaging (MRI) findings are pivotal in diagnosing L-2-OHG. They unveil characteristic patterns of spongiform degeneration in subcortical white matter, basal ganglia, and the dentate nucleus while typically sparing the periventricular white matter and brainstem (3-5). Specific diagnostic tests, including urine and plasma levels of L-2-hydroxyglutaric acid and genetic examinations, can then confirm the diagnosis (2,6-8).

This report presents a 26-year-old male with progressive gait disturbance and multiple neurological impairments, ultimately diagnosed with L-2-OHG aciduria based on clinical and radiological findings. The case highlights the diagnostic challenges, clinical progression, and potential management strategies during managing this rare disorder.

CASE

A man, 26-year-old applied to a neurology clinic due to a progressive gait disorder for the last seven years. He is one of 11 siblings from a first-cousin marriage. Two brothers were reported to have died at 27 and 16 years, while another brother and sister were at 1 and 9 months, respectively (**Figure 1**). Twenty-seven-year-old brother who has similar symptoms to our patient died from an accident. The cause of death of other siblings was also not clear. In our patient, who had a history of difficult vaginal delivery after an average pregnancy period, the first symptom was a delay in walking. Over time, he had learning difficulties and deterioration in his hand skills and had to drop out of school. He had no history of attention-deficit/hyperactivity disorder (ADHD) or epilepsy, and his functionality was good in adolescence. His gait disorder has progressed over the last seven years, and swallowing difficulties and speech impairment were added to his symptoms.

A neurological examination of the patient revealed dysarthric and slow speech with a poor vocabulary, impaired repetition, and naming. He had ocular apraxia, head and body titubation, truncal ataxia, dysmetria,

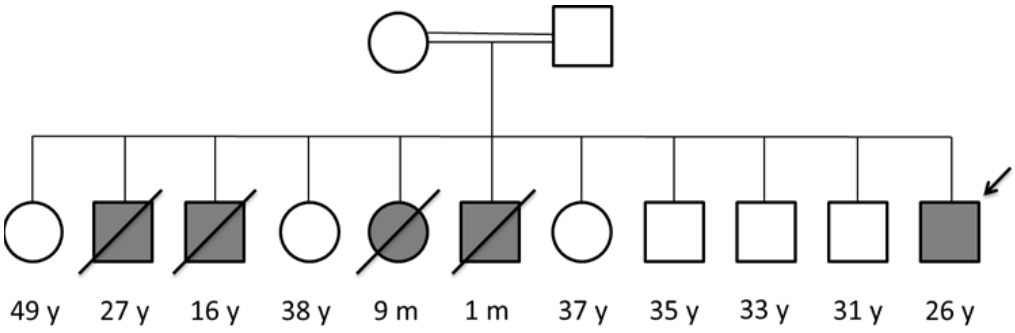

Figure 1. Pedigree of family [y: years, m: month(s)]

and dysdiadochokinesia. Dystonia, especially in hands, spasticity in lower extremities, and impaired fine and gross motor skills were also present. He was dependent on a wheelchair.

Electromyography and electroencephalography examinations were normal. The visual evoked potential examination detected prolonged bilateral prechiasmatic optic nerve latencies (Right P100 latency: 130, Left P100 latency: 145). Cerebral MRI revealed cerebral and cerebellar atrophy, enlargement of lateral and third ventricles, hyperintensity in T2-weighted and fluid-attenuated inversion-recovery (FLAIR) sections in a bilateral diffuse symmetric subcortical white matter, basal ganglia, and dentate nucleus. The thalamus, corpus callosum, periventricular white matter, and brain stem were spared (**Figure 2**). Routine laboratory tests revealed no abnormality except B12 deficiency (B12: 155.9 pg/mL). In the organic acid screening of urine, 2-OHG (2-Hydroxyglutaric) aciduria was detected, but D- and L- isoforms could not be evaluated due to technical limitations. Genetic tests and cerebrospinal fluid analyses could not be performed due to the patient not volunteering. However, according to the onset age of the disease and clinical and neuroradiological findings, he was diagnosed with L-2-OHG (L-2-Hydroxyglutaric) aciduria.

DISCUSSION

Two different clinical entities in 2-OHG aciduria are determined by increased L- and D- isoforms. L-2-OHG aciduria is usually associated with slow progressive encephalopathy, which develops with the degradation of L-2-OHG acid dehydrogenase enzyme activity due to gene mutation localized in chromosome 14p22. D-2-OHG aciduria has a neonatal onset, progressing

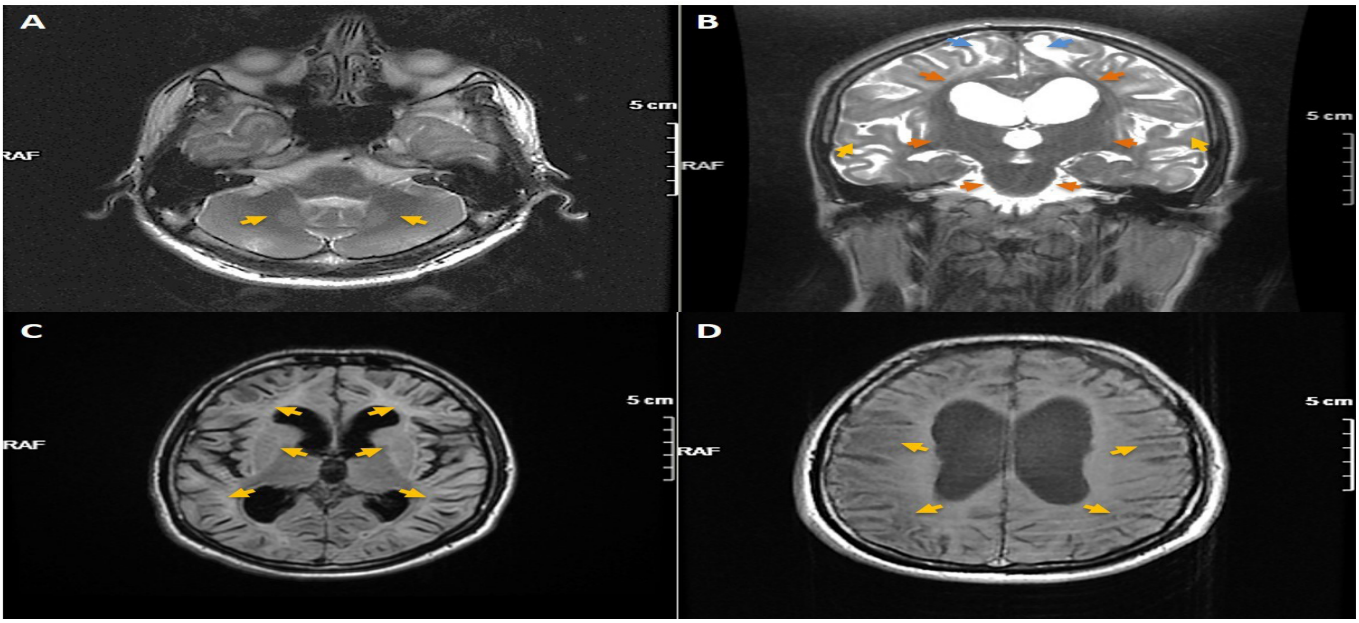

Figure 2. 26-year-old male with L-2-OHG aciduria. A; The T2-weighted axial section of the brain MRI demonstrates symmetrical hyperintensity in the bilateral dentate nucleus (yellow arrows). B; The T2-weighted coronal section demonstrates symmetrical hyperintensity in bilateral subcortical white matter, especially the subcortical U-fibers (yellow arrows) and dilatation of the ventricles. There is cystic degeneration in the anterior frontal lobes, the most prominent (blue arrows). Also, it is noteworthy that the cortex, periventricular white matter, thalamus, and brain stem are preserved (orange arrows). C; The FLAIR axial section demonstrates symmetrical hyperintensity in bilateral subcortical white matter and basal ganglia (yellow arrows). D; In contrast to what is seen in the T2-weighted section, in the T1-weighted axial section, symmetrical hypointensity in bilateral subcortical white matter (yellow arrows) is noticed.

with severe neurological symptoms such as early infantile encephalopathy, growth retardation, and severe hypotonia (1,2).

L-2-OHG aciduria is a rare autosomal recessive, neurodegenerative disease (1). Patients with L-2-OHG have varying mental dysfunction, pyramidal and extrapyramidal symptoms, seizures, macrocephaly, growth retardation, dysarthria, and cerebellar ataxia (1,3). As seen in our patient, mild psychomotor retardation later, combined with learning and attention problems, are observed in the first years of life. Pyramidal findings such as clonus and spasticity, dysarthria, and truncal ataxia were also prominent features (4). Patients with L-2-OHG aciduria usually have dystonia in the upper extremities, as in our patient. The patient was also observed with mental motor retardation and slow progressing accompanying dysarthria, truncal ataxia, pyramidal findings, dystonia, and cerebellar impairment without metabolic acidosis or acute deterioration periods. Besides these symptoms, he did not have macrocephaly, seizures, or extrapyramidal symptoms.

MRI findings show a quite characteristic pattern of spongiform degeneration of bilaterally symmetric subcortical white matter, globus pallidus, and dentate nucleus, along with preservation of the periventricular white matter and brainstem. Progression of spongiosis in MRI correlating with clinical deterioration is observed (3-5). The significant MRI finding, scattered or diffusely localized subcortical white matter abnormality with centripetal progression, was present in our patient (Figure 2). Similar MRI findings, including spongiform degeneration, can be seen in Canavan disease, Kearns-Sayre syndrome, and other organic acidurias (9).

Nevertheless, in L-2-OHG aciduria, periventricular white matter and corpus callosum are preserved in almost all cases, while subcortical white matter is more affected [4,5,10]. Macrocephaly is a finding in the early stage of the disease, which should warn the physician about organic aciduria. However, as in our patient, macrocephaly may not be seen with age progression secondary to white matter atrophy. Similar spongiform progressive leukodystrophy is seen in Canavan disease, but unlike L-2-OHG aciduria, it has typical brainstem involvement and white matter abnormalities (5).

Diagnosis of L-2-OHG aciduria is difficult because of its rarity, slow progression, and differences in clinical presentation between individuals. Typical MRI findings give clues, and the demonstration of a 90% increase in the L-isoform of 2-OHG acid in the urine, blood, and cerebrospinal fluid provides a diagnosis (2,6,7). We could not demonstrate L-isoform in our patient, but we detected 2-OH glutaric aciduria and MRI findings supported our diagnosis.

There is no specific treatment for the disease yet. In addition to Riboflavin 100 mg/day and L-carnitine 50-100 mg/kg/day, symptomatic treatments such as levodopa-benserazide in the presence of dystonia, atomoxetine in the presence of ADHD or antiepileptics can be administered (3,11). Additional supportive treatments include botulinum injection, special training programs, physical therapy for spasticity, and a low-lysine diet (12). In addition to diet, we applied botulinum injection for spasticity and started trihexyphenidyl for dystonia for our patient. We also referred our patient to physical therapy for gait disorder.

Although there is no specific treatment, it is vital to identify patients regarding supportive treatment applications and genetic counseling. Prenatal diagnosis is possible by detecting the L-2-OHG ratio in amnion fluid, allowing for earlier diagnosis (13). Genetic counseling is critical to detecting other suspected individuals and controlling genetic inheritance (8,11).

TEACHING POINT

Macrocephaly is a finding that should warn the physician about organic aciduria in the early stage of the disease. MRI findings of patients with L-2-OHG show a quite characteristic pattern of spongiform degeneration of bilaterally symmetric subcortical white matter, globus pallidus, and dentate nucleus, along with preservation of the periventricular white matter and brainstem. The

Table 1. Summary of key characteristics and management of the disease

Etiology	Gene mutation localized in chromosome 14p22.1
Incidence	<1/1000000
Gender ratio	Unknown
Age predilection	Diagnosis is in late childhood to early adolescence.
Risk factors	Consanguineous marriages
Treatment	There is no specific treatment for the disease yet. In addition to Riboflavin 100 mg/day and L-carnitine 50-100 mg/kg/day, symptomatic treatments in the presence of dystonia, atomoxetine in the fact of ADHD, or antiepileptics can be administered. Additional supportive treatments include botulinum injection, special training programs, physical therapy for spasticity, and low-lysine diet.
Prognosis	The prognosis depends on how severe the condition is, and it is usually poor.

ADHD: Attention-deficit/hyperactivity disorder

other characteristics are summed up in Table 1.

DECLARATIONS

Ethics Committee Aproval: Not available since this is a case report.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Informed consent form: Verbal consent was taken from the patient and the patient's first-degree relatives.

Funding source: No funding was received for the research.

Artificial Intelligence: Not apllied.

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