

L-2-Hydroxyglutaric Aciduria

Report of Four Turkish Adult Patients

Hulya Karatas, MD,* Serap Saygi, MD,† Birgul Bastan, MD,† Amber Eker, MD,†
Oguzhan Kursun, MD,† Yavuz Ayhan, MD,‡ and Abdurrahman Ciger, MD*

Background: L-2-Hydroxyglutaric aciduria is a rare progressive neurometabolic disorder of childhood inherited as an autosomal recessive trait. Urine organic-acid screening is necessary for its diagnosis. Although it is a disorder of childhood, recently adult cases have been reported.

Cases: Here we report 4 adult patients in whom diagnoses were established in adulthood. These patients had some interesting features. First, their diagnoses were delayed until adulthood because of mild clinical symptoms. In such cases, the typical MRI findings are the best diagnostic clue for L-2-Hydroxyglutaric aciduria. Second, there was a correlation between the severity of the clinical course and the extent of MRI findings. The cerebral white-matter lesions were diffuse and confluent on the MRI of 3 of the 4 patients, who also experienced a rapidly progressive clinical decline. Third, there were different clinical presentations even within the same family.

Conclusions: For the evaluation of patients with symptoms referable to cerebellar, pyramidal, extrapyramidal, or cognitive impairment as well as seizures associated with subcortical white-matter and symmetrical dentate nuclei and basal ganglia involvement on MRI, urine organic acid analysis should be included in the evaluation, regardless of patient's age.

Key Words: L-2-hydroxy glutaric aciduria, epilepsy, MRI findings, adult cases

(*The Neurologist* 2010;16: 44–46)

L-2-Hydroxyglutaric (L-2-OHG) aciduria is a rare progressive neurometabolic disorder of childhood, which was first reported by Duran et al in 1980.¹ It is inherited as an autosomal recessive trait.² A gene on chromosome 14q22.1 encoding a putative FAD-dependent L-2-hydroxyglutarate dehydrogenase has been recently found defective in L-2-OHG aciduria.^{3,4} Clinically, the disorder is characterized by mild mental or psychomotor retardation in the initial years of life. Later on in the clinical course, seizures, pyramidal tract signs, mild extrapyramidal signs, progressive ataxia, and mental retardation become prominent. Progressive macrocephaly is present in half of the patients. Neuroimaging findings of L-2-OHG aciduria are very specific with cranial MRI images showing increased signal intensities in the basal ganglia more frequently than in the dentate nuclei and globus pallidi than caudate nuclei and putamen on T2-weighted images and cerebellar atrophy. Cranial MRI reveals characteristic scattered or diffuse subcortical white-matter abnormalities fading centripetally.⁵ The diagnosis is established by the detection of increased L-2-OHG acid levels in the urine, cerebrospinal fluid, and plasma using gas chromatography.⁶ The treat-

ment of the disease includes a protein restricted diet and riboflavin and carnitine supplements as well as symptomatic management.

Although L-2-OHG aciduria is a childhood metabolic disorder, adult cases can also be found in the recent literature.^{3,7–13} Here we report 4 Turkish patients whose diagnoses were delayed until adulthood. Their clinical course and MRI findings, which are quite different from each other, are presented.

PATIENTS

Patient 1: This 22-year-old woman was the third child of a nonconsanguineous marriage, but her parents were from the same village. After a single febrile convulsion at 18 months old, she developed generalized tonic-clonic seizures at the age of 8. After 9 years without seizures (due to phenobarbital), she developed complex partial seizures and carbamazepine (CBZ) was started. Her performance at school was below average. Her main complaint was hand tremors and gait imbalance. Her neurologic examination (NE) revealed macrocephaly (56 cm, ± 2 standard deviation), dysarthria, intentional tremor, and mild ataxia. Electroencephalography findings included slowing in background activity and generalized paroxysmal slow waves. Cranial MRI showed bilateral, symmetrical hyperintensities in dentate nuclei, globus pallidus, putamen, and caudate nuclei, and diffuse subcortical white-matter hyperintensities particularly in the frontal and temporal lobes on T2 sequences (Fig. 1A). To exclude neurometabolic diseases, the following tests were performed: a complete blood count (CBC), blood chemistry, blood and urine amino acids, lysosomal enzyme screen, lactic and pyruvic acid levels in serum and cerebrospinal fluid, copper levels in serum and urine, and ceruloplasmin level. The results were all within the normal ranges. Visual, sensory, brain stem evoked potentials and electroneuromyography were also normal. The diagnosis was based on urine organic acid analysis in which L-2-OHG acid excretion was found to be 1770 mmol/mol Cre (control range: 130 mmol/molcre). CBZ 800 mg/d, carnitine 2 g/d, and riboflavin 200 mg/d support with a protein-restricted diet were administered for management. The 7-year follow-up showed mild progression of ataxia and cerebellar symptoms but she was seizure free with minimal increases in the hyperintensities on T2 sequences on MRI.

Patient 2: This was the 31-year-old sister of patient 1, and was the family's first child. She had developed generalized tonic-clonic seizures at the age of 12 months and had been treated with antiepileptic drugs until the age 7 years. She had attended a school for mentally handicapped children. After the diagnosis of patient 1 was established, we learned that her older sister was mentally retarded and had had cervical dystonia and hand tremors for 15 years and so we started to investigate the sister. Her NE revealed macrocephaly (57 cm, ± 2 standard deviation), moderate mental-motor retardation, intentional tremor, titubation, and cervical dystonia. CBC, blood chemistry, and blood and urine amino acids were within the normal ranges. Urinary L-2-OHG acid excretion was 1020 mmol/mol Cre. Cranial MRI showed increased T2 signal intensities in dentate nuclei, putamen, globus pallidus, and caudate nuclei. Additionally, subcortical white matter hyperintensities, particularly in the temporal and frontal lobes,

From the *Hacettepe University Institute of Neurological Sciences and Psychiatry, Ankara, Turkey; Departments of †Neurology, and ‡Psychiatry, Hacettepe University Hospitals, Ankara, Turkey.

Current address of Oguzhan Kursun is Ankara Numune Education and Research Hospital, Department of Neurology 1, Ankara, Turkey.

Reprints: Hulya Karatas, MD, Hacettepe University Institute of Neurological Sciences and Psychiatry, 06100 Sıhhiye, Ankara, Turkey. E-mail: hulyak@hacettepe.edu.tr.

Copyright © 2010 by Lippincott Williams & Wilkins
ISSN: 1074-7931/10/1601-0044

DOI: 10.1097/NRL.0b013e31819d9556

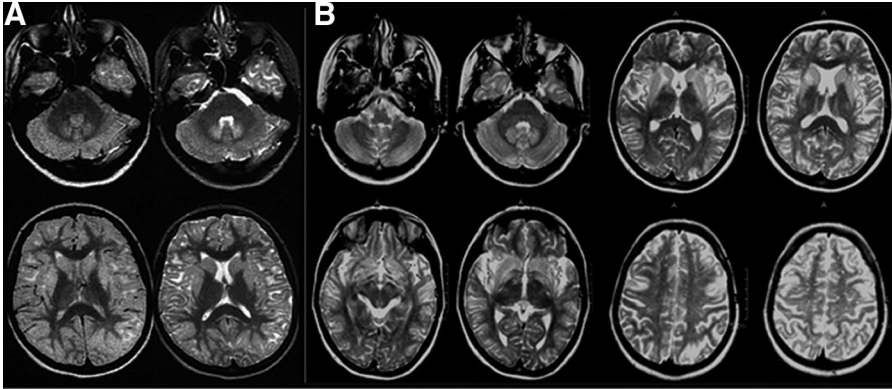


FIGURE 1. A, Cranial MRI showed bilateral, symmetrical dentate nucleus, basal ganglia, and frontal and temporal subcortical white matter hyperintensities on T2-weighted images. B, Cranial MRI showed bilateral dentate nucleus and severe basal ganglia involvement, subcortical white matter hyperintensities particularly in frontal and temporal lobes on T2-weighted images.

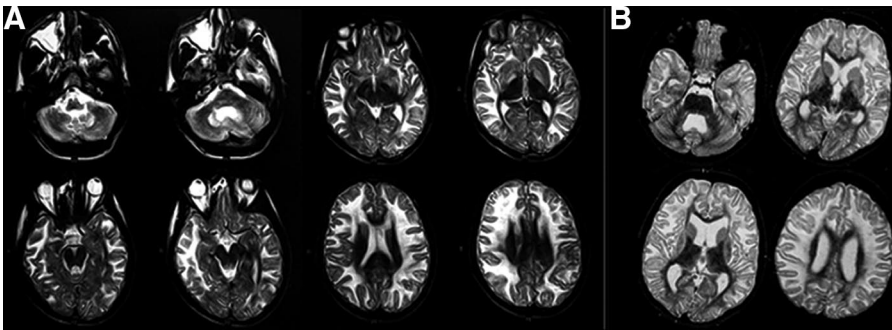


FIGURE 2. A, Cranial MRI showed bilateral dentate nucleus, cerebral white matter, globus pallidus and internal capsule hyperintensities on T2-weighted images. B, Cranial MRI showed bilateral, symmetrical hyperintensities in dentate nuclei, globus pallidus, putamen, and caudate nuclei and severe diffuse subcortical white matter hyperintensities with white matter loss and cerebellar atrophy on T2-weighted images.

were observed (Fig. 1B). Symptomatic treatment for dystonia, and carnitine and riboflavin support with a protein-restricted diet were given. Her symptoms worsened rapidly during the 5-year follow-up and currently she needs assistance with her daily activities.

Patient 3: This 20-year-old man was admitted to our clinic for seizures. His parents were first degree consanguineous. The patient had had 1 seizure at the age of 5 but seizures did not recur until the age of 18. He suffered from complex partial seizures despite CBZ treatment. NE revealed mild mental-motor retardation with mild pyramidal and cerebellar signs. Cranial MRI showed bilateral hyperintensities in the dentate nuclei, cerebral white matter, globus pallidus, and internal capsule on T2 sequences (Fig. 2A). Tandem mass spectrometry and lysosomal enzyme analysis for screening for metabolic disorders were normal. The definite diagnosis was established based on the urine organic acid analysis. Urinary L-2-OHG acid excretion was 3760 mmol/mol Cre. Visual and somatosensory evoked potentials were normal. Electroencephalography (EEG) showed slowing in background activity and bilateral independent focal epileptiform discharges in frontocentral regions. Urine organic acid analysis in the family was normal. The dose of CBZ was increased to control the seizures. Carnitine of 2 g/d and a protein restricted diet were started. During his follow-up, he suffered from status epilepticus at the age of 23 due to withdrawal of antiepileptic drugs and experienced a rapidly progressive clinical decline. After 5 years of follow-up, he can no longer communicate and is bedridden.

Patient 4: This 25-year-old woman was the first child of a first-degree consanguineous couple. At the age of 3, she developed seizures characterized by staring, loss of contact, and tonic posturing. After initial treatment with phenobarbital, she was put on valproate to which she responded better. Slowing in movements and learning difficulties were noticed at the age of 5. When she was admitted to our clinic, her main complaints were gait imbalance, difficulties in articulation and swallowing, and unintended weight loss during the previous 2 years. She had been seizure free due to valproate

treatment, but all other neurologic symptoms had progressively worsened. NE revealed mild mental retardation, severe cerebellar and extrapyramidal signs with titubation, truncal ataxia, postural instability, lid retraction, bradymimia, bilateral bradykinesia, and rigidity prominent on the left side. Additionally, she had pseudobulbar and pyramidal signs with dysphonia, dysarthria, and hyperactive deep tendon reflexes. EEG showed mild slowing in background activity, especially in the temporal lobes. Cranial MRI revealed symmetrical hyperintensities in dentate nuclei, globus pallidus, putamen, and caudate nuclei on T2 sequences and cerebellar atrophy (Fig. 2B). Laboratory tests including CBC, blood chemistry, serum lipids, thyroid functions, vitamin E level, blood and urine amino acids, and lysosomal enzyme screen were normal. Urinary L-2-OHG acid excretion was 9320 mmol/mol Cre. Then she was put on a protein restricted diet and carnitine 2 g/d supplement therapy in addition to valproate treatment. During the 1-year follow-up in our clinic, her symptoms were stable.

DISCUSSION

Different clinical presentations such as cerebellar ataxia, pyramidal signs, intellectual decline, seizures, extrapyramidal symptoms, and macrocephaly have been described for L-2-OHG aciduria. Although it is a childhood disorder, recently adult cases have been reported.^{3,7-13} Age at diagnosis in these cases varies between 18 and 57 years. Despite the wide spectrum of neurologic symptoms, the fact that the presenting symptom in almost all patients is childhood seizures is notable. Patients with mild and variable symptoms like seizure and dystonia may not be diagnosed until adulthood, as in the cases presented above. The presence of typical MRI findings must raise the suspicion of L-2-OHG aciduria.

Our patients have some outstanding features. First, their diagnoses were delayed until adulthood because of their mild clinical symptoms. Second, there was a correlation between the severity of the clinical course and extent of MRI findings. The cerebral white

matter lesions were diffuse and confluent in MRI of the second, third, and fourth patients, who also showed a rapidly progressive clinical decline. This finding is supported by previous reports.¹⁴ Third, the patients within the same family, cases 1 and 2, had different clinical presentations.

As cranial MRI findings raise suspicion of L-2-OHG aciduria, one must consider other diseases that have similar MRI findings for a differential diagnosis. These diseases include Van der Knaap disease, Canavan disease, and Alexander disease.^{15–17} In addition to bilateral dentate nucleus involvement in Van der Knaap disease, there is also involvement of the dorsal pons, mesencephalon, internal capsule, external capsule, and periventricular white matter, which is not common in L-2-OHG aciduria.¹⁵ In Canavan disease, white matter lesions are much more widespread than in L-2-OHG aciduria, the globus pallidus and thalamus are frequently involved and the disease spares brainstem structures.¹⁷ Characteristic MRI findings of Alexander disease are frontal dominant white matter lesions, the tendency to form cysts, and a peculiar pattern of contrast enhancement that is not present in L-2-OHG aciduria.¹⁶

It is unclear how L-2-OHG acid affects the central nervous system leading to MRI lesions. The exclusive involvement of the central nervous system and elevated CSF/plasma ratio of L-2-OHG acid in this disease suggest 2 hypotheses: (1) L-2-OHG acid exerts an excitotoxic effect on neurons similar to that encountered for other organic acids and amino acids.¹⁴ (2) Rzem et al demonstrated that L-2-hydroxyglutarate is normally metabolized to α -ketoglutarate (a compound amply provided by other sources) and concluded that the pathologic findings in this metabolic disorder are due to a toxic effect of L-2-OHG acid on the central nervous system.^{3,18}

In conclusion, in adult cases presenting with symptoms of cerebellar, pyramidal or extrapyramidal involvement, cognitive impairment, and seizures, L-2-OHG aciduria must be considered in the differential diagnosis based on specific findings in cranial MRI. Hence, urine organic acid analysis should be included in the etiological screening of such patients.

REFERENCES

- Duran M, Kamerling JP, Bakker HD, et al. L-2-Hydroxyglutaric aciduria: an inborn error of metabolism? *J Inherit Metab Dis*. 1980;3:109–112.
- Barth PG, Hoffmann GF, Jaeken J, et al. L-hydroxyglutaric acidemia: a novel inherited neurometabolic disease. *Ann Neurol*. 1992;32:66–71.
- Rzem R, Veiga-da-Cunha M, Noël G, et al. A gene encoding a putative FAD-dependent L-2-hydroxyglutarate dehydrogenase is mutated in L-2-hydroxyglutaric aciduria. *Proc Natl Acad Sci USA*. 2004;101:16849–16854.
- Topcu M, Jobard F, Halliez S, et al. L-2-hydroxyglutaric aciduria: identification of a mutant gene C14orf160, localized on chromosome 14q22.1. *Hum Mol Genet*. 2004;13:2803–2811.
- D'Incerti L, Farina L, Moroni I, et al. L-2-Hydroxyglutaric aciduria: MRI in seven cases. *Neuroradiology*. 1998;40:727–733.
- Barth PG, Hoffmann GF, Jaeken J, et al. L-2-hydroxyglutaric acidemia: clinical and biochemical findings in 12 patients and preliminary report on L-2-hydroxyacid dehydrogenase. *J Inherit Metab Dis*. 1993;16:753–761.
- Fujitake J, Ishikawa Y, Fujii H, et al. L-2-Hydroxyglutaric aciduria: two Japanese adult cases in one family. *J Neurol*. 1999;246:378–382.
- Goffette SM, Duprez TP, Nassogne MC, et al. L-2-Hydroxyglutaric aciduria: clinical, genetic, and brain MRI characteristics in two adult sisters. *Eur J Neurol*. 2006;13:499–504.
- Lamaout A, Hentati F, Belal S, et al. Clinical and pathological study of 3 Tunisian siblings with L-2-OHG. *Acta Neuropathol (Berl)*. 1994;88:367–370.
- Vilarinho L, Cardoso ML, Gaspar P, et al. Novel L'HGDH mutations in 21 patients with L-2-hydroxyglutaric aciduria of Portuguese origin. *Hum Mutat*. 2005;26:395–396.
- Warmuth-Metz M, Becker G, Bendszus M, et al. Spinal canal stenosis in L-2 hydroxyglutaric aciduria. *Arch Neurol*. 2000;57:1635–1637.
- Samuraki M, Komai K, Hasegawa Y, et al. A successfully treated adult patient with L-2-Hydroxyglutaric aciduria. *Neurology*. 2008;70:1051–1052.
- Periasamy V, Rudwan M, Yadav G, et al. Epilepsy in a young adult caused by L-2-hydroxyglutaric aciduria: a case report. *Med Princ Pract*. 2008;17:258–261.
- Moroni I, D'Incerti L, Farina L, et al. Clinical, biochemical and neurological findings in L-2-hydroxyglutaric aciduria. *Neurol Sci*. 2000;21:103–108.
- Van der Knaap MS, Barth PG, Stroink H, et al. Leukoencephalopathy with swelling and a discrepantly mild clinical course in eight children. *Ann Neurol*. 1995;37:324–334.
- Van der Knaap MS, Valk J. Alexander's Disease. In: *Magnetic Resonance of Myelin, Myelination, and Myelin Disorders*, 2nd edn. New York, NY: Springer, Berlin Heidelberg; 1995;259–264.
- Topcu M, Erdem G, Saatci I, et al. Clinical and magnetic resonance imaging features of L-2-hydroxyglutaric acidemia: report of 3 cases in comparison with Canavan disease. *J Child Neurol*. 1996;11:373–377.
- Rzem R, Vincent MF, Van Schaftingen E, et al. L-2-Hydroxyglutaric aciduria, a defect of metabolite repair. *J Inherit Metab Dis*. 2007;30:681–689.