From Shadows to Diagnosis: Unraveling L-2 Hydroxyglutaric Aciduria in Adulthood

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Abstract

L-2-hydroxyglutaric aciduria (L2HGA) is a rare autosomal recessive metabolic disorder that causes central nervous system dysfunction. We present the case of a 33-year-old woman with macrocephaly, developmental delay, cerebellar ataxia, pyramidal signs, and seizures. Despite typical clinical features and suggestive magnetic resonance imaging findings, the diagnosis was not made. Genetic analysis revealed a homozygous missense mutation in the L-2-hydroxyglutarate dehydrogenase (*L2HGDH*) gene. Treatment with riboflavin and L-carnitine was initiated. L2HGA should be considered in the differential diagnosis, even in adults, when suggestive imaging findings are present. Early diagnosis is crucial for better outcomes.

Keywords: Epilepsy, L2-hydroxyglutaric aciduria, cranial MRI, genetic mutation

INTRODUCTION

L-2-hydroxyglutaric aciduria (L2HGA) is an autosomal recessive inborn metabolic error. It occurs because of a deficiency in the L-2-hydroxyglutarate dehydrogenase (L2HGDH) enzyme.[1] It is a type of cerebral organic aciduria that causes central nervous system dysfunction. Psychomotor developmental delay, intellectual disability, cerebellar dysfunction, pyramidal-extrapyramidal signs, macrocephaly, and seizures are the hallmarks of the disease.[2] The age of symptom onset may be heterogeneous. Like many other inborn errors of metabolism, milder or juvenile forms can be diagnosed in late adulthood.[3] Although many patients are diagnosed in infancy or childhood, diagnosis in some cases may be considerably delayed because of vague symptoms. Here we present a 33-year-old female patient with macrocephaly, developmental delay, cerebellar ataxia, pyramidal signs, and seizures. Despite typical clinical features and suggestive magnetic resonance imaging (MRI) findings, the diagnosis was overlooked.

CASE PRESENTATION

A 33-year-old right-handed female patient, born to a consanguineous marriage, was admitted to our clinic for seizure control. Her medical history revealed that her generalized onset tonic-clonic seizures had started at the age of 3 years and ceased after anti-seizure medication (ASM) treatment. Two years later, her ASM was discontinued, and she was seizure-free until 22 years of age when generalized onset tonic-clonic seizures reappeared. She was put on 3000 mg/day levetiracetam (LEV). Phenytoin and topiramate were also prescribed, but she could not continue because of side effects such as dizziness and somnolence. Her parents noticed that infections precipitated her seizures. Otherwise, she was seizure-free.

Personal history revealed macrocephaly and delayed motor and language skills, in addition to seizures. The patient underwent surgery for congenital cataract and congenital dysplasia of the hip. She was diagnosed with cerebral palsy and treated symptomatically. Family history was unremarkable. Her physical examination revealed dysmorphic features such as a long face, deeply located eyes, up-slanting palpebral fissures, thin lips, and macrocephaly. The metacarpophalangeal and interphalangeal joints were rigid. On neurological examination, the

patient had cognitive impairment, scarce verbal output, dysarthria, and extremity ataxia. She also had mild motor deficit and spasticity and could not walk independently.

Her routine blood tests were normal. There was mild diffuse background slowing in the EEG. Brain MRI demonstrated symmetric T2 and FLAIR high signal intensity and T1 low signal intensity of the subcortical and deep white matter (U-fibers) with relative sparing of the periventricular regions and brain atrophy. White matter involvement had a centripetal pattern, starting in the U-fibers and extending to the deeper white matter (see Figure 1 for detailed description).

Basic metabolic scans were ordered because of highly suggestive cranial MRI findings. Urine organic acid analysis by gas chromatography-mass spectrometry showed a 5-fold increase in 2-hydroxy glutaric acid (2HGA) excretion. We performed *L2HGDH* gene analysis, which revealed a homozygous missense c.164G>A (p. Gly55Asp) mutation in exon 2 of the *L2HGDH* (NM_024884.3) gene. Riboflavin and levo-carnitin were added to her ASM and supportive therapy.

DISCUSSION

L2HGA is a rare genetic metabolic disorder that mainly affects the central nervous system. The first case was reported by Duran et al.[4] in 1980. Mutations in the L2HGDH enzyme, which is involved in the oxidation of L-2-hydoxyglutarate (L2HG) to alpha-2-ketoglutarate, cause the disease. In 2004, Topçu et al.[5] mapped the disorder to chromosome 14q22.1 by homozygosity mapping in Turkish families. This gene is primarily expressed in the central nervous system. Mutations in the *L2HGDH* gene result in the accumulation of L-2HGA in the cerebrospinal fluid (CSF), plasma, and urine.[6] This leads to white matter toxicity via myelin vacuolation.

Macrocephaly must alert clinicians to the possibility of cerebral organic aciduria, especially in epilepsy clinics, as status epilepticus might be the first symptom of the disease.[7] Seizures are usually well controlled with ASMs. EEG may show irregular background activity and slowing, focal or generalized spikes, and slow wave discharges.[2] Radiological hallmarks of the disease are predominant subcortical white matter abnormalities and involvement of dentate nuclei and basal ganglia. These findings become symmetrical, and atrophy ensues with increasing disease duration.[8] Subependymal pseudocysts, delayed cerebral maturation, callosal agenesis, and enlargement of the lateral ventricles are other clues suggesting L2HGA.[9] It can be diagnosed with increased levels of 2-HGA in blood, CSF, or urine via gas chromatography-mass spectrometry or genetic analysis. In Turkey, the most common variants in the *L2HGDH* gene are c.164G>A (p. Gly55Asp) and c.1115delT (p. Met372fs). The c.164G>A mutation was previously reported only in Turkish patients.[10] Thus far, there has been no definitive treatment. Some patients may benefit from Riboflavin and L-carnitine (even in adulthood), physical therapy, and rehabilitation.[11]

MAIN POINTS

- Epileptic seizures may be the first sign of metabolic disorders.
- L-2-hydroxyglutaric aciduria is a rare genetic disorder affecting the central nervous system that presents with intellectual disability, developmental delay, and seizures.
- Here, we present a case of a patient diagnosed with L-2-hydroxyglutaric aciduria at the age of 33 years and emphasize the need for heightened awareness in adults.

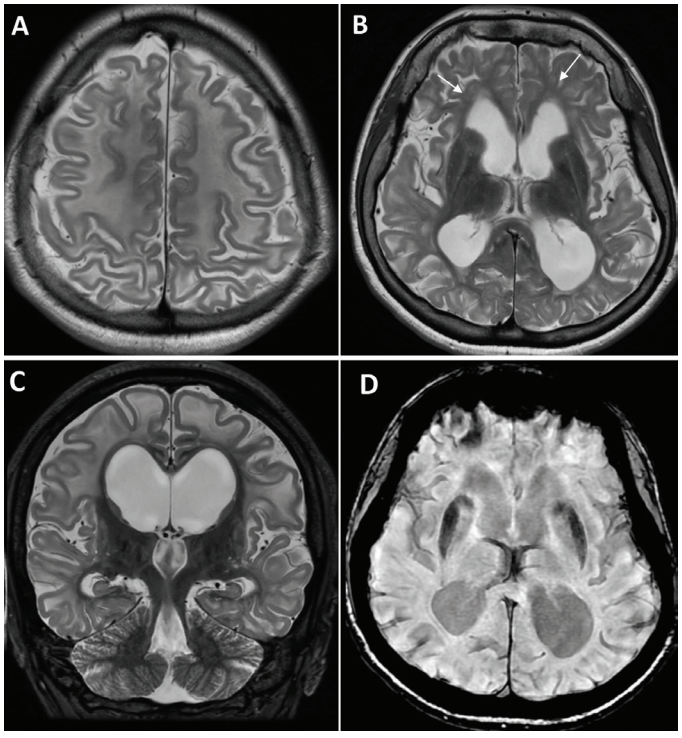

Figure 1. A-D) Brain magnetic resonance ımaging. Axial (A, B, D) and coronal (C) sections. T2-weighted images show high signal intensity of the subcortical white matter (U-fibers) (A), with relative sparing of the periventricular white matter (B, C) and hypointense and atrophic basal ganglia. Susceptibility-weighted image (D) reveals susceptibility effects in the caudate and putamen

L-2HGA has a chronic progressive highly variable clinical course and lacks acute exacerbations, unlike other organic acidurias.[11] Therefore, diagnosis is often delayed. In milder forms, subtle clinical findings may not be noticed until adulthood. Several publications have reported delayed diagnosis in adult patients in their late 40s and 50s.[3] Cases diagnosed in the third and fourth decades of their lives were also reported in the studies of Zübarioğlu et al.[12] from Turkey.

CONCLUSION

In conclusion, patients with epilepsy, developmental delay, and cognitive impairment should be examined carefully, and cranial MRI should be performed without delay. If the imaging findings are suggestive, inborn errors of metabolism should be considered in the differential diagnosis, even in adult patients.

Ethics

Informed Consent: The consent form was filled out by the parent of the patient.

Authorship Contributions

Surgical and Medical Practices: E.D.Ö., J.N., H.T.A., A.D., R.G., N.D., Concept: N.D., Design: N.D., Data Collection or Processing: E.D.Ö., J.N., D.Y.Y., A.D.,

Analysis or Interpretation: E.D.Ö., H.T.A., D.Y.Y., A.D., R.G., N.D., Literature Search: E.D.Ö., H.T.A., N.D., Writing: E.D.Ö., H.T.A., D.Y.Y., N.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Kranendijk M, Struys EA, Salomons GS, Van der Knaap MS, Jakobs C. Progress in understanding 2-hydroxyglutaric acidurias. *J Inherit Metab Dis*. 2012;35(4):571-587. [Crossref]
2. Topçu M, Aydin OF, Yalçinkaya C, et al. L-2-hydroxyglutaric aciduria: a report of 29 patients. *Turk J Pediatr.* 2005;47(1):1-7. [Crossref]
3. Fujitake J, Ishikawa Y, Fujii H, et al. L-2-hydroxyglutaric aciduria: two Japanese adult cases in one family. *J Neurol.* 1999;246(5):378-382. [Crossref]
4. Duran M, Kamerling JP, Bakker HD, van Gennip AH, Wadman SK. L-2-Hydroxyglutaric aciduria: an inborn error of metabolism? *J Inherit Metab Dis.* 1980;3(4):109-112. [Crossref]
5. Topçu 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(22):2803-2811. [Crossref]
6. Zhang Y, Wang C, Yang K, Wang S, Tian G, Chen Y. A novel compound heterozygous mutation of the L2HGDH gene in a Chinese boy with L-2-hydroxyglutaric aciduria: case report and literature review. *Neurol Sci.* 2018;39(10):1697-1703. [Crossref]
7. Işikay S. L-2 hydroxyglutaric aciduria presenting with status epilepticus. *BMJ Case Rep.* 2013;2013:bcr2013010164. [Crossref]
8. Steenweg ME, Salomons GS, Yapici Z, et al. L-2-Hydroxyglutaric aciduria: pattern of MR imaging abnormalities in 56 patients. *Radiology*. 2009;251(3):856-865. [Crossref]
9. Muthusamy K, Sudhakar SV, Christudass CS, Chandran M, Thomas M, Gibikote S. Clinicoradiological Spectrum of L-2-Hydroxy Glutaric Aciduria: Typical and Atypical Findings in an Indian Cohort. *J Clin Imaging Sci.* 2019;9:3. [Crossref]
10. Bozaci AE, Er E, Ünal AT, et al. Glutaric aciduria and L-2-hydroxyglutaric aciduria: Clinical and molecular findings of 35 patients from Turkey. *Mol Genet Metab Rep*. 2023;36:100979. [Crossref]
11. Ahmed S, Siddiqui A, DeBerardinis RJ, et al. L-2-hydroxyglutaric aciduria - review of literature and case series. *Ann Med Surg (Lond).* 2023;85(4):712-717. [Crossref]
12. Zübarioğlu T, Yalçınkaya C, Oruç Ç, et al. L-2-hidroksiglutarik asidüri hastalarında klinik, nöroradyolojik ve genetik bulguların değerlendirilmesi. *Turk Pediatri Ars*. 2020;55(3):290-298. [Crossref]