



L-2 hydroxyglutaric aciduria: report of a Mexican-Mayan patient with the mutation c.569C>T and response to vitamin supplements and levocarnitine

CASE REPORT

ROBERTO LEAL-ORTEGA

LUIS ENRIQUE PARRA-MEDINA

LIZBETH JOSEFINA GONZÁLEZ-HERRERA

*Author affiliations can be found in the back matter of this article

ubiquity press

ABSTRACT

Background: L-2-hydroxyglutaric aciduria (L2HGA) is a rare inherited autosomal recessive neurometabolic disorder caused by pathogenic variants in the *L2HGDH* gene which encodes mitochondrial 2-hydroxyglutarate dehydrogenase. Here, we report a case of L2HGA in a Mexican-Mayan patient with a homozygous mutation at *L2HGDH* gene and clinical response to vitamin supplements and levocarnitine.

Case report: A 17-year-old, right-handed female patient with long-term history of seizures, developmental delay and ataxia was referred to a movement disorders specialist for the evaluation of tremor. Her brain MRI showed typical findings of L2HGA. The diagnosis was corroborated with elevated levels of 2-hydroxyglutaric acid in urine and genetic test which revealed a homozygous genetic known variant c.569C>T in exon 5 of *L2HGDH* gene. She was treated with levocarnitine and vitamin supplements, showing improvement in tremor and gait.

Discussion: To our knowledge this is the first report of a Mexican patient with L2HGA. This case adds information about a rare condition in a different ethnic group and supports the findings of other authors which encountered symptomatic improvement with the use of flavin adenine dinucleotide (and its precursor riboflavin), and levocarnitine.

Highlights: We report the first case of Mexican-Mayan patient with L2HGA showing a missense homozygous mutation in *L2HGDH* gene, and improvement of symptoms with vitamin supplements and levocarnitine.

CORRESPONDING AUTHOR:

Roberto Leal-Ortega, MD

Calle 20 # 119, Colonia
Altabrisa. C.P. 97130. Mérida,
Yucatán, México
drleal13@gmail.com

KEYWORDS:

L-2 hydroxyglutaric aciduria;
L2HGDH; cerebellar ataxia;
tremor; T2-hyperintensities;
riboflavin; L-carnitine

TO CITE THIS ARTICLE:

Leal-Ortega R, Parra-Medina
LE, González-Herrera LJ. L-2
hydroxyglutaric aciduria: report
of a Mexican-Mayan patient
with the mutation c.569C>T
and response to vitamin
supplements and levocarnitine.
*Tremor and Other Hyperkinetic
Movements*. 2024; 14(1):
12, pp. 1-6. DOI: [https://doi.
org/10.5334/tohm.854](https://doi.org/10.5334/tohm.854)

BACKGROUND

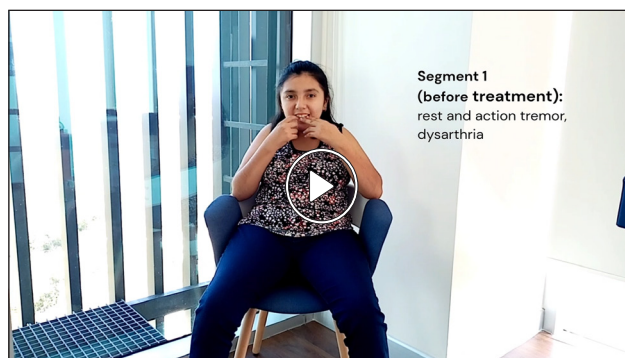
L-2-hydroxyglutaric aciduria (L2HGA) is a rare inherited autosomal recessive neurometabolic disorder caused by pathogenic variants in the *L2HGDH* gene (14q.22.1) which encodes mitochondrial 2-hydroxyglutarate dehydrogenase [1]. To date, very few cases (around 150) have been reported worldwide of this condition [2]. L2HGA is a slowly progressive illness starting in childhood with symptoms including cognitive delay, seizures, macrocephaly, and movement disorders such as tremor, dystonia, and cerebellar ataxia [3]. Often, patients remain undiagnosed until adolescence or adulthood. Brain MRI of patients with L2HGA can provide important clues to diagnosis. T2 hyperintensities with centripetal extension predominantly in the anterior white matter involving the subcortical U-fibers and sparing the brainstem and corpus callosum are typical; cerebellar atrophy and hyperintensities in lentiform nucleus, caudate and dentate nucleus are also described [4]. Besides the MRI findings, elevation of L-2-hydroxyglutaric acid in urine, plasma and cerebrospinal fluid, and mutational analysis of the *L2HGDH* gene confirm the diagnosis [1-3]. No specific treatment exists for this condition and supportive measures include treatment of seizures, cognitive and physical rehabilitation. Some case reports have described improvement with riboflavin and L-carnitine supplementation [1, 5]. Here we report the first case of L2HGA in a 17-year-old Mexican-Mayan female presenting with cerebellar syndrome, seizures and cognitive impairment. She was diagnosed with L2HGA based on MRI findings, high levels of L-2-hydroxyglutaric acid in urine, and mutation of *L2HGDH* gene. Also, we documented improvement of movement disorders with use of L-carnitine and vitamins/minerals supplementation.

CASE REPORT

A 17-year-old, right-handed female patient was referred to a movement disorders specialist to evaluate upper extremities tremor. Her parents were healthy, apparently non-consanguineous, originated from southeast Mexico in the Mayan area of Yucatan Peninsula. She was born after an uneventful pregnancy and normal childbirth. At 13 months, she started with recurrent non-febrile generalized tonic-clonic seizures. Since then, she experienced psychomotor developmental delay, exhibiting the ability to walk at the age of 4 years and incomplete language development at 5 years. Schooling was delayed and received assistance from special schools and ongoing physical and cognitive therapy. At that time, she had a non-specific diagnosis of

generalized epilepsy and global development delay. During next ten years she experienced gradually neuropsychiatric symptoms including anxiety, aggressive behaviors to family members, self-injury, and irregular sleep pattern. At the age of 15, she developed upper extremity tremor and gait instability, and she was referred to a movement disorders specialist. She was on chronic treatment with levetiracetam 2 g/day and risperidone 2 mg/day.

Her general examination was normal including head circumference. The neurological examination revealed cognitive impairment, slurred speech, hypometric horizontal saccades spasticity in lower extremities, strength grade 4 of 5 in the Medical Research Council scale in the major muscles of four extremities; hyperreflexia was present in all extremities, with bilateral extensor plantar response; rest and action tremor, dysdiadochokinesia, and dysmetria on the finger-nose maneuver were present in both upper extremities; her walking was unstable, slow, with slight dragging of the legs, and inability for tandem gait (Video 1). Complete blood count, biochemistry profiles, lactate, thyroid function, and blood ceruloplasmin tests were normal. Brain MRI revealed in T2W, T2-FLAIR and DWI bilateral hyperintensities in the subcortical white matter in fronto-parieto-temporal lobes, and symmetrical hyperintensities in the dentate nuclei and basal ganglia without involvement of thalamus and brainstem (Figure 1). Because of the high suspicion of L2HGA, a urine screening examination was performed using the total ion chromatogram method of urinary metabolites by gas chromatography/mass spectrometry (GC/MS), which revealed elevated excretion of 2-hydroxyglutarate. Genetic test was conducted on peripheral blood using isolated genomic DNA. Sanger sequencing of the *L2HGDH* gene (OMIM 609582, 14q21.3) revealed a homozygous variant c.569C>T in exon 5 of *L2HGDH* gene. A final diagnosis of L2HGA was made and we started supplementation



Video 1 L Hydroxyglutaric aciduria segment. Patient manifesting rest, postural and intentional tremor in both upper extremities, dysarthria, dysdiadochokinesia, and unstable gait with dragging of the legs.

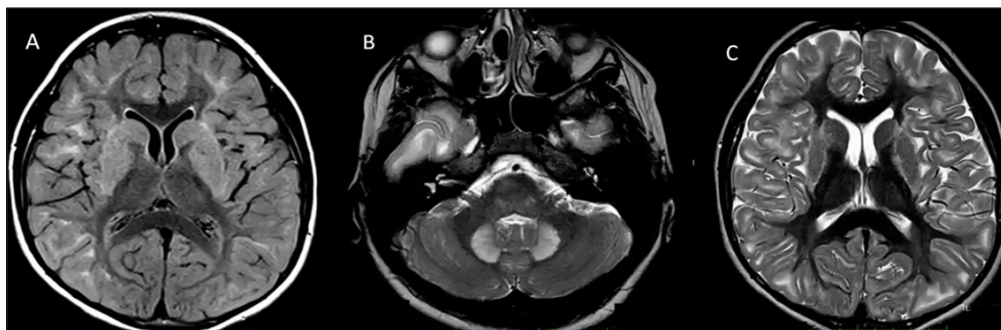


Figure 1 Axial brain MRI sequences. **(A)** FLAIR sequence shows bilateral subcortical white matter hyperintensities in frontal – parietal and temporal lobes. **(B)** T2WI with bilateral hyperintensities of dentate nuclei, and **(C)** T2WI showing bilateral hyperintensities in basal ganglia. Note in **(A)** and **(C)** the sparing of both thalami.

with multivitamins and levocarnitine 3 g/day showing improvement in upper extremities tremor and gait (Video 2). She lost follow up almost two years because of SARS-CoV2 pandemic and stopped the treatment, showing a worsening of motor symptoms. After reinitiation of levocarnitine and multivitamins, she improved again.



Video 2 L2 hydroxyglutaric aciduria segment 2. Improvement of upper extremities tremor and gait with the use of levocarnitine and vitamin supplements.

DISCUSSION

Initially described in 1980 by Duran et al in a 5-year-old Moroccan boy with psychomotor delay, dystrophy and large amounts of 2- hydroxyglutaric acid in the urine [6], L2HGA is classified as an organic cerebral aciduria caused by L-2-hydroxyglutarate dehydrogenase enzyme deficiency which is involved in the oxidation of L-2-hydroxyglutarate (L-2-HG) to alpha 2- ketoglutarate. The accumulation of L-2-HG has toxic effects to the brain due to free radical formation and increases of glutamate uptake in synaptosomes and synaptic vesicles, leading to a progressive leukoencephalopathy [2]. Clinical course is usually chronic and gradually progressive with ataxia, spasticity, dystonia, seizures, macrocephaly, and

intellectual disability [1–5]. Our case represents a new report of L2HGA in a Mexican patient from the Mayan area of Yucatan. To our knowledge, this is the first report of a Mexican patient and one of the few reports of L2HGA in Latin America. This supports that L2HGA is a rare but pan-ethnic disease, although most of cases have been reported in Turkey. Our patient showed classical MRI findings which was a clue to conduct the next diagnostic studies. Typically, abnormalities of predominantly subcortical cerebral white matter in combination with abnormalities of the dentate nucleus, globus pallidus, putamen, and caudate nucleus has been described in L2HGA [1–5, 7]. In a large series of 56 patients, the appearance of the MRI abnormalities was characterized by more global and confluent abnormalities of the cerebral white matter, caudate nucleus, and putamen, and by atrophy of the cerebral white matter and cerebellar hemispheres [8]. The differential diagnosis of L2HGA includes D-2 hydroxyglutaric aciduria (D2HGA) and combined L2HGA and D2HG (D, L-2-HGA). The clinical phenotype of D2HGA includes epilepsy, psychomotor delay, cardiomyopathy, facial dysmorphism, dystonia and chorea-athetosis [9]; brain MRI shows enlargement of the lateral ventricles, subdural effusions, subependymal pseudocysts, delayed myelination, and callosal agenesis [1, 9]. These radiological signs were not found in our case. D, L-2-HGA is characterized by elevated levels of both D-2-HG and L-2-HG in body fluids; the clinical manifestations include severe neonatal epileptic encephalopathy, absence of developmental progress, and often early death [10]. Impaired function of the mitochondrial citrate carrier due to pathogenic mutations within the SLC25A1 gene has been identified as the underlying molecular cause of the disease [11]. The clinical course described in D, L-2-HGA was not compatible with our patient.

Patients with L2HGA have a predisposition to cerebral neoplasms. This may be related to the pathologic accumulation of L2HGA because high amounts of 2-HG have been found in brain neoplasms like astrocytoma,

medulloblastoma, ependymoma, oligodendroglioma, and others [12]. Our patient was negative for tumors.

L2HGA gene (14q22.1) encodes a putative mitochondrial protein with homology to flavin adenine dinucleotide (FAD) dependent oxidoreductases. So far, the human gene mutation database has reported 52 missense or nonsense mutations implicated in the reduced action of the L2HGDH enzyme [13–15]. The genetic variant detected in our patient is a missense mutation leading to a substitution of a threonine by a isoleucine in position 190 of the encoded protein (p.Thr190Ile) lying in the highly conserved FAD-binding domain, disturbing the enzymatic function. Pathogenicity of this genetic variant was predicted to be deleterious, damaging or disease causing by five bioinformatic prediction tools such as *PROVEAN*, *MutationAssessor*, *FATHMM-MKL*, *SIFT*, *PolyPhen-2*. Clinical variant classification confers it a variant with uncertain significance (VUS). This variant c.569C>T has been only once reported in an Iranian patient showing intellectual disability and epilepsy [16]. Previous studies with extensive families from different populations and ethnicities have not recorded our mutation [7, 17]. According to <http://www.LOVD.nl/L2HGDH> missense mutations are the most frequent changes, in about 32%. The severity of damage to L2HGDH varies with the type of mutation. The type of the amino acid replacement as well as the sum of the bonds and it forces affect the binding and dissociation of the L-2 hydroxyglutaric acid molecule with the L2HGDH enzyme to alter its action [15].

Treatment of L2HGA is symptomatic for seizures, motor, cognitive and behavioral symptoms. Supplementation with FAD and its precursor riboflavin has been reported successful for symptomatic treatment, improving functionality in some cases [2, 18, 19]. The rationale for its use is the theoretical increase of residual activity of L2HGDH by FAD and riboflavin [20]. Based on these experience, we decided to treat the patient with a daily dose of vitamin supplements (riboflavin content of 3.400 mg) and levocarnitine (3 g) for a period of a year, showing improvement in gait and hands tremor.

This new case of L2HGA in a different ethnic group adds information about a rare condition, being important of having a high index of suspicion in patients with non-defined diagnostic of seizures, cerebellar ataxia, cognitive delay, and typical MRI findings. For symptomatic treatment, the use of riboflavin and levocarnitine should be offered to patients.

ETHICS AND CONSENT

The authors confirm that the approval of an institutional review board was not required for this work. Written consent for publication was obtained from patient.

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

- 1) Research project: A. Conception, B. Organization, C. Execution
- 2) Analysis: A. Design, B. Execution, C. Review and Critique
- 3) Manuscript: A. Writing of the first draft, B. Review and Critique

RLO: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

LEPM: 1B, 1C, 2B, 2C, 3A, 3B

LJGH: 1A, 2C, 3C

AUTHOR AFFILIATIONS

Roberto Leal-Ortega, MD  orcid.org/0000-0001-5582-8962

Department of Neurology, Hospital Regional de Alta Especialidad de la Península de Yucatán. Mérida, Mexico

Luis Enrique Parra-Medina, MD  orcid.org/0000-0003-1600-5706

Department of Neurology, Instituto Nacional de Neurología y Neurocirugía “Manuel Velasco Suárez”. Mexico City, Mexico

Lizbeth Josefina González-Herrera, PhD  orcid.org/0000-0002-8620-3954

DIMYGEN Laboratorio S.C.P, Mérida, Yucatán, México; Laboratory of Genetics. Centro de Investigaciones Regionales “Dr. Hideyo Noguchi”, Universidad Autónoma de Yucatán. Mérida, Mexico

REFERENCES

1. **Ahmed S, Siddiqui A, DeBerardinis RJ, Ni M, Lai W, Cai F**, et al. L-2-hydroxyglutaric aciduria –review of the literature and case series. *Annals of Medicine and surgery*. 2023; 85: 712–717. DOI: <https://doi.org/10.1097/MS9.0000000000000326>
2. **Shah H, Chandarana M, Sheth J, Shah S**. A case report of chronic progressive pancerebellar syndrome with leukoencephalopathy: L-2 hydroxyglutaric aciduria. *Movement Disorders Clinical Practice*. 2020; 7(5): 560–563. DOI: <https://doi.org/10.1002/mdc3.12967>
3. **Kranendijk M, Struys E, Salomons G**, et al. Progress in understanding 2-hydroxyglutaric acidurias. *J Inherit Metab Dis*. 2012; 35: 571–87. DOI: <https://doi.org/10.1007/s10545-012-9462-5>
4. **Muthusamy K, Sudhakar S, Christudass C**, et al. Clinoradiological spectrum of L-2-hydroxy glutaric aciduria: typical and atypical findings in an Indian Cohort. *J Clin Imaging Sci*. 2019; 9: 3. DOI: <https://doi.org/10.25259/JCIS-9-3>

5. **Topçu M, Aydin OF, Yalçinkaya C, Haliloğlu G, Aysun S, Anlar B**, et al. L-2-hydroxyglutaric aciduria: a report of 29 patients. *Turk J Pediatr.* 2005; 47: 1–7.
6. **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): 109–12. DOI: <https://doi.org/10.1007/BF02312543>
7. **Bozaci AE, Er E, Ünal AT, Tas I, Ayaz E, Ozbek MN**, et al. Glutaric aciduria and L-2-hydroxyglutaric aciduria: Clinical and molecular findings of 35 patients from Turkey. *Molecular Genetics and Metabolism Reports.* 36(2023). DOI: <https://doi.org/10.1016/j.ymgmr.2023.100979>
8. **Steenweg ME, Samomons GS, Yapici Z, Uziel G, Scalais E, Zafeiriou DI**, et al. L-2 hydroxyglutaric aciduria: pattern of MR imaging abnormalities in 56 patients. *Radiology: Volume 251: Number 3—June 2009.* DOI: <https://doi.org/10.1148/radiol.2513080647>
9. **Mahfoud A, Domínguez CL, Rashed M, Duran M, Rodríguez T, Rodríguez D**, et al. Aciduria D-2 hidroxiglutarica. Reporte de dos casos. *Invest Clin.* 50(3): 369–375, 2009.
10. **Muntau AC, Roschinger W, Merckenschlager A, van der Knaap M, Jakobs C, Duran M**, et al. Combined D-2- and L-2-hydroxyglutaric aciduria with neonatal onset encephalopathy: a third biochemical variant of 2-hydroxyglutaric aciduria? *Neuropediatrics.* 2000; 31: 137–140. DOI: <https://doi.org/10.1055/s-2000-7497>
11. **Nota B, Struys EA, Pop A, Jansen EE, Fernandez-Ojeda MR, Kanhai WA**, et al. Deficiency in SLC25A1, Encoding the Mitochondrial Citrate Carrier, Causes Combined D-2- and L-2-Hydroxyglutaric Aciduria. *The American Journal of Human Genetics.* 92: 627–631, April 4, 2013. DOI: <https://doi.org/10.1016/j.ajhg.2013.03.009>
12. **Patay Z, Mills JC, Löbel U, Lambert A, Sablauer A, Ellison DW.** Cerebral Neoplasms in L-2 Hydroxyglutaric Aciduria: 3 New Cases and Meta-Analysis of Literature Data. *AJNR Am J Neuroradiol.* 33: 940–43 May 2012. DOI: <https://doi.org/10.3174/ajnr.A2869>
13. **Topcu M, Jobard F, Halliez S, Coskun T, Yalcinkaya C, Gerceker FO**, et al. L-2-hydroxyglutaric aciduria: identification of a mutant gene C14orf160, localized on chromosome 14q22.1. *Hum Mol Genet.* 2004; 13(22): 2803–11. DOI: <https://doi.org/10.1093/hmg/ddh300>
14. **Jović NJ, Kosać A, Koprivšek K.** L-2-Hydroxyglutaric Aciduria: A Case Report. *Srp Arh Celok Lek.* 2014 May–Jun; 142(5–6): 337–341. DOI: <https://doi.org/10.2298/SARH1406337J>
15. **Muzammal M, Di Cerbo A, Almusalami EM, Farid A, Khan MA, Ghazanfar S**, et al. In Silico Analysis of the L-2-Hydroxyglutarate Dehydrogenase Gene Mutations and Their Biological Impact on Disease Etiology. *Genes.* 2022; 13: 698. DOI: <https://doi.org/10.3390/genes13040698>
16. **Hu H, Kahrizi K, Musante L, Fattahi Z, Herwig R, Hosseini M**, et al. Genetics of intellectual disability in consanguineous families. *Mol Psychiatry.* 2019 Jul; 24(7): 1027–1039. Epub 2018 Jan 4. PMID: 29302074. DOI: <https://doi.org/10.1038/s41380-017-0012-2>
17. **Steenweg M, Jakobs C, Errami A, van Dooren S, Adeva Bartolomé MT, Aerssens P**, et al. An Overview of L-2-Hydroxyglutarate Dehydrogenase Gene (*L2HGDH*) Variants: A Genotype–Phenotype Study. *Human Mutation.* 31(4): 380–390, 2010. DOI: <https://doi.org/10.1002/humu.21197>
18. **Yılmaz K.** Riboflavin treatment in a case with l-2-hydroxyglutaric aciduria. *Eur J Paediatr Neurol.* 2009; 13: 57–60. DOI: <https://doi.org/10.1016/j.ejpn.2008.01.003>
19. **Samuraki M, Komai K, Hasegawa Y, Kimura M, Yamaguchi S, Terada N**, et al. A successfully treated adult patient with L-2-hydroxyglutaric aciduria. *Neurology.* 2008; 70: 1051–2. DOI: <https://doi.org/10.1212/01.wnl.0000287141.90944.95>
20. **Weimar C, Schlamann M, Krägeloh-Mann I, Schöls L.** L-2 hydroxyglutaric aciduria as a rare cause of leukencephalopathy in adults. *Clin Neurol Neurosurg.* 2013; 115: 765–6. DOI: <https://doi.org/10.1016/j.clineuro.2012.06.040>

TO CITE THIS ARTICLE:

Leal-Ortega R, Parra-Medina LE, González-Herrera LJ. L-2 hydroxyglutaric aciduria: report of a Mexican-Mayan patient with the mutation c.569C>T and response to vitamin supplements and levocarnitine. *Tremor and Other Hyperkinetic Movements*. 2024; 14(1): 12 pp. 1–6. DOI: <https://doi.org/10.5334/tohm.854>

Submitted: 21 December 2023 **Accepted:** 23 February 2024 **Published:** 07 March 2024

COPYRIGHT:

© 2024 The Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. See <http://creativecommons.org/licenses/by/4.0/>.

Tremor and Other Hyperkinetic Movements is a peer-reviewed open access journal published by Ubiquity Press.

