



# L-2-hydroxyglutaric aciduria – review of literature and case series

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**Background:** L-2-hydroxyglutaric aciduria (L2HGA) is an autosomal recessive, slowly progressive neurodegenerative disease characterized by psychomotor delay and cerebellar dysfunction. The biochemical hallmark is increased concentrations of L2HG in body fluids. Brain MRI exhibits characteristic centripetal extension of the white matter involvement that differentiates it from other leukodystrophies. The authors report two sisters from Pakistan with L2HGA with 4 years of follow-up. The authors have also compared the clinical outcome of our patients with 45 previously reported patients with L2HGA for whom treatment and clinical outcome was reported.

**Case presentation:** The authors report two sisters with L2HGA from Pakistan born to consanguineous parents. The 15- and 17-year-old girls presented with psychomotor delay, seizures, ataxia, intentional tremors, and dysarthria. Both had normal anthropometric measurements for age. Exaggerated tendon reflexes and bilateral sustained ankle clonus were observed in addition to cerebellar signs. Urine organic acids analysis showed marked excretion of 2-hydroxyglutaric acid, chiral differentiation of 2-hydroxyglutaric acid showed it to be L2HGA. Brain MRI of the 15-year-old showed diffuse subcortical white matter changes evident by T2/FLAIR hyperintense signals bilaterally, particularly in the frontal region in the centripetal distribution with some diffusion restriction along involvement of globus pallidus. The characteristic MRI pattern raised the suspicion of L2HGA. Targeted *L2HGDH* sequencing identified a homozygous pathogenic variant, c.829C > T (p.Arg227\*) in *L2HGDH* gene in both girls. Both parents were heterozygous carriers of the familial variant.

**Conclusion:** Neuroradiological features of centripetal subcortical leukoencephalopathy with basal ganglia and dentate nuclei involvement are rather specific to L2HGA and should lead to further biochemical investigations to look for L2HGA and *L2HGDH* gene sequencing.

**Keywords:** case report, L-2-hydroxyglutaric aciduria, neurology, organic acids

## Background

L-2-hydroxyglutaric aciduria (L2HGA) (OMIM # 236792) is an autosomal recessive inherited metabolic disorder, caused by pathogenic variants in the *L2HGDH* gene (14q22.1) encoding mitochondrial 2-hydroxyglutarate dehydrogenase. Duran *et al.*<sup>[1]</sup>

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## HIGHLIGHTS

- First case series of L-2-hydroxyglutaric aciduria, a rare disorder from Pakistan.
- A complete workup enlisting biochemical, molecular, and radiological findings.
- A comprehensive review of literature with treatment options and outcome.

first described the disease in 1980 and since then cases from different regions have been reported world-wide, with an estimated prevalence of less than 1/1 000 000 births<sup>[2]</sup>.

L2HGA usually manifests in the first year of life with a slowly progressive course of cerebellar ataxia, dysarthria, and neurological deterioration. Seizures, macrocephaly, pyramidal and extrapyramidal signs, and growth stunting may also be present<sup>[3]</sup>. Variable age of onset and disease severity is described ranging from a severe neonatal onset with neurological consequences, a moderate to severe form beginning in childhood, and an adult form. No specific treatment exists for L2HGA; management is mainly supportive with specific therapies including flavin adenine dinucleotide sodium (FAD) and levocarnitine chloride<sup>[4,5]</sup>.

The biochemical hallmark of L2HGA is increased concentration of L-2-hydroxyglutaric acid in body fluids, relatively higher in urine, cerebrospinal fluid (CSF) and, to a lesser extent, in plasma. The diagnosis is based on urinary gas chromatography mass spectrometry analysis, revealing increased levels of

2-hydroxy glutaric acid, with 90% of isoforms representing the L-form. As D-2-hydroxyglutaric aciduria (D2HGA) and L2HGA are two distinct organic acidurias, the enantiomeric chiral separation of 2-hydroxyglutaric acid is required for the accurate diagnosis via liquid chromatography mass spectrometry analysis of diacetyl-L-tartrate derivatized 2-HG enantiomers in plasma, followed by molecular analysis of *L2HGDH* gene<sup>[3]</sup>. The evaluation of D and L isomers is further necessary, as few other disorders like combined DL2HGA and lipoyltransferase-1 deficiency also present with elevated 2-HGA. In contrast to L2HGA, combined DL2HGA (OMIM #615182) a rare neuro-metabolic disorder is characterized biochemically with increased excretion of both D- and L2HGA. The disorder is caused by pathogenic mutations within the *SLC25A1* gene. While lipoyl-transferase-1 deficiency (OMIM # 616299) caused by bi-allelic pathogenic variants in the *LIPT1* gene on chromosome 2q11 also shows elevations in lactate, succinate, and 2-HGA on urine organic acid (UOA) analysis.

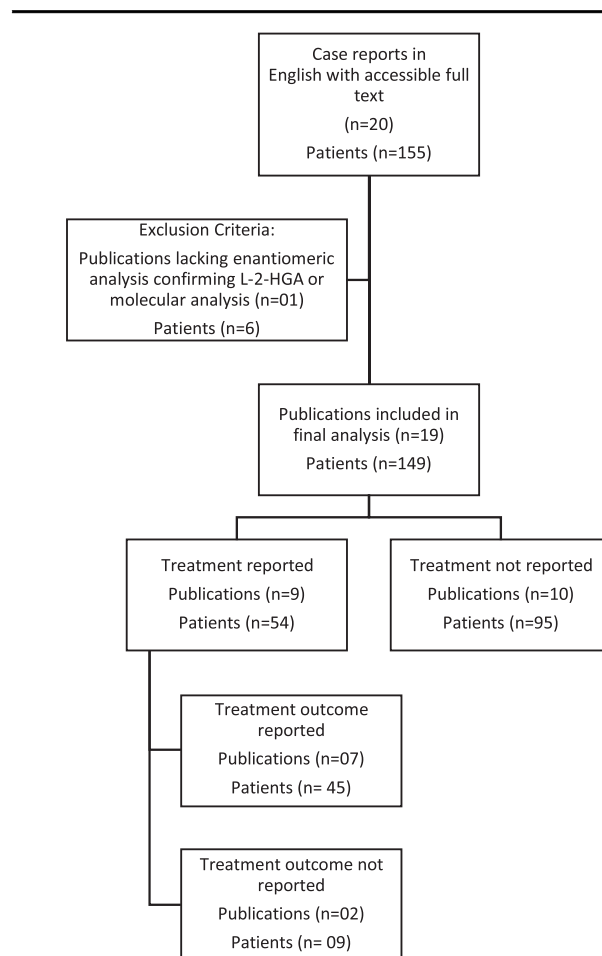
Brain MRI of patients with L2HGA can provide important clues to the diagnosis. T2 hyperintensities pre-dominantly in the anterior subcortical white matter and basal ganglia, classically involving the subcortical U-fibers are seen. The characteristic centripetal extension of the white matter sparing the brainstem and corpus callosum, is the hallmark that differentiates the disorder from other leukodystrophies, particularly Canavan disease<sup>[4]</sup>.

The study was approved by the Institutional Ethics Committee (ERC # 2021-7011-19889) and written informed consent was obtained from the parents of the patient for publication of this case report. We searched the Google Scholar databases for studies with the search terms 'L-2-HGA' and 'L2HGA' or 'L-2-hydroxyglutaric aciduria', without date and language restrictions. The title, abstract and full text of all documents identified according to these search criteria were scrutinized by the authors. Additionally, all references found in the published articles were reviewed for case report ascertainment. The search revealed 20 articles with 155 cases in Figure 1. We excluded cases, which were lacking enantiomeric analysis using chiral configuration to differentiate the L from the D form of 2-HGA, or molecular analysis ( $n=6$ ) as depicted in Table 1 (Supplementary File, Supplemental Digital Content 1, <http://links.lww.com/MS9/A36>).<sup>[6–11]</sup> Here we report two sisters from Pakistani with L2HGA with 4 years of follow-up. We have also compared the clinical outcome of our patient with reported patients with L2HGA for whom treatment and clinical outcome was reported ( $n=45$ ). The work has been reported in line with the PROCESS criteria<sup>[12]</sup>.

## Case presentation

### Case # 1

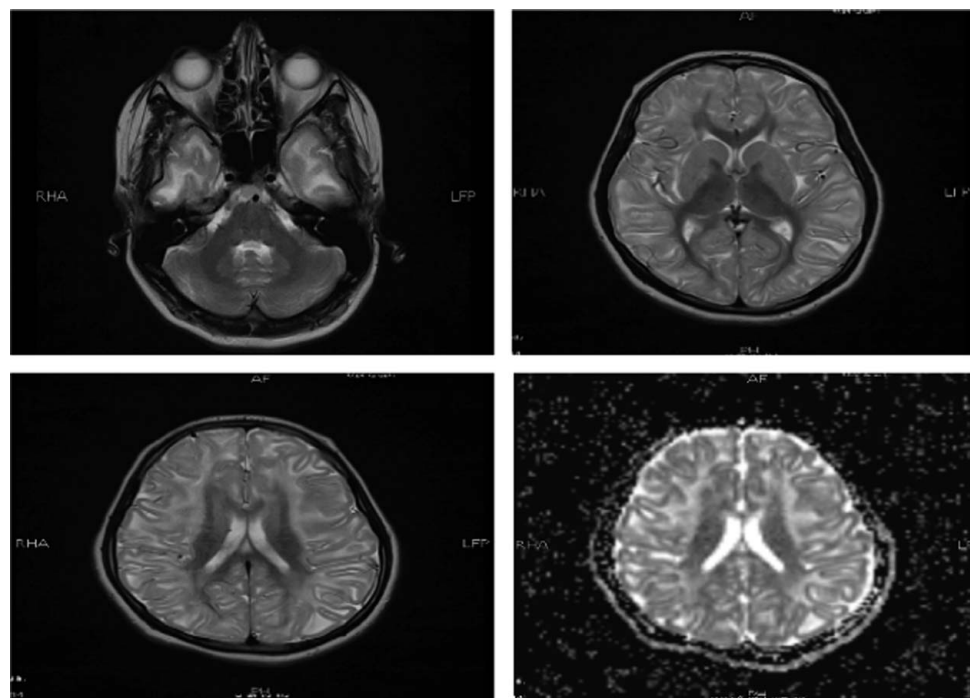
Patient 1, girl was born after an uneventful pregnancy to healthy, consanguineous Pakistani parents. She was delivered via spontaneous vaginal delivery at term. Birth weight was 3.5 kg, other anthropometry at birth and Apgar score at birth were not recalled by parents. Parents did not report major concerns during the neonatal period or infancy. Her early motor milestones in terms of neck control and sitting without support were achieved at around 5 and 8 months of age, respectively. She walked without support after 15 months of age and was noted to be unstable. She spoke her first word after 3 years of age. Schooling was delayed



**Figure 1.** Flowchart of search strategy. L2HGA, L-2-hydroxyglutaric aciduria.

and started at 6 years of age instead of the usual 4 years due to her poor confidence and susceptibility to becoming frightened. She continued schooling only for the next 8 months, during which her teachers reported lack of interest and unclear, slurred speech. Around the same time, she had her first episode of generalized tonic clonic seizures associated with fever and was treated as febrile seizure. She was admitted at 7 years of age with the second episode of generalized tonic clonic seizures. Electroencephalogram at that time was abnormal with generalized epileptiform activity. She was started on oral sodium valproic acid, which she continued for 2 years. She had no seizures during this period, but the anticonvulsant was discontinued after 2 years.

She was first seen at our genetic clinic at the age of 14 years 10 months. Her anthropometric measurements were appropriate for age. The parents reported that she was able to dress and bathe herself but needed assistance in brushing teeth and combing hair due to poor coordination. She used straws to drink water as she was unable to lift the cup due to coarse tremors. During examination she was noted to have scanning speech with slurring of words. She was able to follow commands and perform tasks but had poor hand coordination with dysidiadochokinesia and intentional tremors and past pointing fingers. Her gait was wide-based and ataxic. Deep tendon reflexes were exaggerated, and bilateral sustained ankle clonus was present.

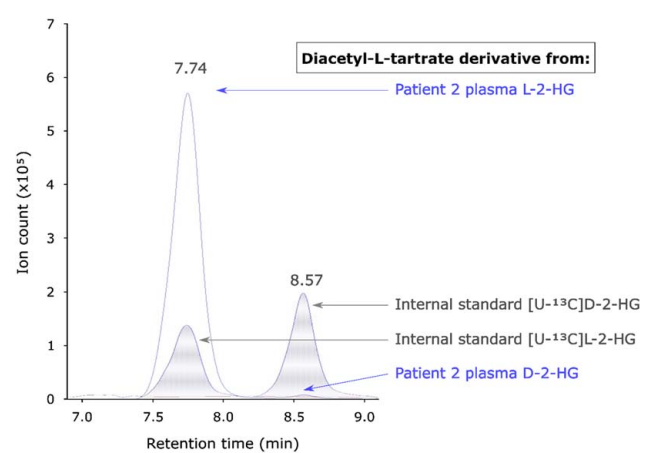


**Figure 2.** Brain MRI features characteristic of L-2-hydroxyglutaric aciduria,

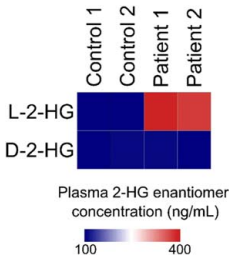
Brain MRI showed diffuse confluent subcortical white matter changes evident as T2/FLAIR hyperintense signals, more in the frontal region with some diffusion restriction, along with involvement of globus pallidus as shown in (Figure 2A–D).

UOA analysis at our laboratory showed marked excretion of 2-hydroxyglutaric acid. Furthermore, for the differentiation for the L2HGA metabolites were extracted from 50 µl of patient plasma samples with 80% methanol–water solution, and the resulting supernatant was dried in a SpeedVac. Dried pellet was mixed with (U13C)-D/L2HG (internal standard for unlabeled samples, Cambridge isotope laboratories, 10 nG in 10 µl acetonitrile). The mixture was dissolved in a diacetyl-L-tartaric

anhydride solution (90 µl, 50 mG/ml in freshly mixed 80% acetonitrile/20% acetic acid, diacetyl-L-tartaric anhydride; Acros Organics). The solution was sonicated, warmed up to 75°C and kept for 30 min, cooled to room temperature, and then centrifuged again to collect the supernatant. The supernatant was again dried with a SpeedVac, and the pellet was reconstituted into 1.5 mmol/l ammonium formate aqueous solution with 10% acetonitrile (100 µl). Liquid chromatography mass spectrometry analysis was performed on an AB Sciex 5500 QTRAP liquid chromatography/mass spectrometer (Applied Biosystems SCIEX) equipped with a triple quadrupole/iontrap mass spectrometer with electrospray ionization interface, and controlled by AB Sciex Analyst 1.6.1 Software. Waters Acquity UPLC HSS T3 column (150×2.1 mmol/l, 1.8 µmol/l) column was used for separation. Solvents for the mobile phase were 1.5 mmol/l ammonium formate aqueous [pH 3.6 adjusted with formic acid (A), and pure acetonitrile (B)]. The gradient elution was: 0–12 min, linear gradient 1–8% B and 12–15 min, 99% B, then the column was washed with 99% B for 5 min before reconditioning it for 3 min



**Figure 3.** Chromatogram showing the liquid chromatography mass spectrometry analysis of diacetyl-L-tartrate derivatized 2-hydroxyglutaric aciduria (2-HG) enantiomers in patient plasma. \*Peaks in grey indicate the spiked L- and D-[U-<sup>13</sup>C]2HG internal standards, respectively).



**Figure 4.** Heatmap showing the quantitation of 2-hydroxyglutaric aciduria (2-HG) enantiomers in patient 1 and 2.

using 1% B. The flow rate was 0.25 ml/min and the column was operated at 35°C. Multiple reaction monitoring was used to check 2-hydroxyglutarate-diacetyl tartrate derivatives: 363/147 ( $M+0$ , CE: -14V); 368/152 ( $M+5$ , CE: -14V). L-2-HG was revealed to be the dominant 2-HG enantiomer in patient plasma as shown in Figure 3. The heat map analysis based on the quantitation of 2-HG enantiomers in plasma sample also revealed elevated L2HGA as shown in Figure 4. Subsequently, targeted *L2HGDH* sequencing was done, which identified a homozygous pathogenic variant, c.829C>T (p.Arg227\*) in *L2HGDH* gene.

After the confirmation of L2HGA, oral riboflavin 100 mg twice daily and oral L-carnitine 1500 mg twice daily were advised. However, these therapies were not initiated, and the patient was lost to follow-up. She returned to clinic at 15 years 8 months, and the parents wished to commence the previously advised treatment. Two months into the treatment, the parents noted improvement in speech in terms of scanning quality, which was by then more understandable. No changes in ataxia, tremors or hand coordination were noted. After 1.5 years of treatment at 17 years 2 months of age, much improvement in speech, tremors, and ataxia was noted. Her speech had very little scanning quality and is more clear. She is now able to lift the cup of water and drink without help, can comb her hair and can manage brushing her teeth. Her gait is much more stable though she still has exaggerated deep tendon reflexes and sustained ankle clonus. She recently experienced a brief episode of seizures. Electroencephalogram showed intermittent independent left dominant bilateral temporal as well as left occipital sharp and slow waves with slow posterior dominant rhythm (on theta range). Oral levetiracetam 750 mg twice daily along with oral pyridoxine 50 mg daily was started.

## Case # 2

This case is a patient # 1's sister. She was born after an uneventful pregnancy via spontaneous vaginal delivery at term. Birth weight was 3 kg, other anthropometry at birth and Apgar score at birth were not remembered by parents. She also had an uneventful early neonatal and infancy period. She achieved neck control and sitting without support at around 4 and 8 months of age respectively. She achieved walking without support after 16 months of age but was noted to be unstable. She spoke her first word after 2 years of age. Schooling was delayed and started at 5 years of age. She faced challenges from bullying at school due to her lack of ability to follow instructions and thus was removed from school by her parents after 2 years. She had a generalized tonic clonic seizure at 8 years of age and was started on oral sodium valproic acid, which she continued for 3 years. She did not experience seizures after the commencement of anticonvulsant.

She was first seen at our genetic clinic at the age of 17 years 4 months. Her anthropometric measurements were appropriate for age. Parents reported that she is better than her younger sister in self-care including bathing, dressing herself, brushing teeth, and combing hair. But she also needs straws to drink water as was unable to lift the cup. During examination she was noted to have scanning speech with slurring of words. She was able to follow commands and perform tasks but had poor hand coordination with dysdiadochokinesia and intentional tremors and past pointing fingers. Her gait was wide based and ataxic. Deep

tendon reflexes were exaggerated, and bilateral sustained ankle clonus was present.

Marked excretion of 2-hydroxyglutaric acid was detected on UOA. Based on her clinical and biochemical features similar to her younger sister, LC-MS analysis of diacetyl-L-tartrate derivatized 2-HG enantiomers in patient plasma revealed L-2-HG as the dominant 2-HG enantiomer as shown in Figures 3 and 4. Additionally, a targeted molecular analysis revealed that, like her sister, she is homozygous for the c.829C>T (p.Arg227\*) in *L2HGDH*. Both parents and a brother were heterozygous for this variant. A brain MRI previously done but films were lost by parents. Digital films were not present for our review.

After the confirmation of the L2HGA oral riboflavin 100 mg twice daily and oral L-carnitine 1500 mg twice daily was advised but she was lost to follow-up. She was brought again at 18 years 2 months and parents wished to commence the previously advised treatment. Two months post-treatment parents noted improvement in scanning quality of speech. No change in ataxia, tremors, or hand coordination was noted. After 1.5 year of continued treatment at 21 years of age her speech, tremors, and ataxia are much improved, she no longer needs straws to drink water. She still has exaggerated deep tendon reflexes and sustained ankle clonus.

## Discussion

Duran *et al.*<sup>[11]</sup> first reported a 5-year-old Moroccan boy with L2HGA based on a solitary, large, and persistent increase of 2-HGA acid in the urine. Eight intellectually challenged patients from five unrelated families with increased L2HGA concentration in the CSF were later reported by Barth *et al.* in 1992<sup>[8]</sup>. In 2004, Topçu *et al.*<sup>[13]</sup> mapped the disorder to chromosome 14q22.1 by homozygosity mapping.

L2HGA is panethnic as cases have been reported from Europe, Turkey, Morocco, Japan, and India<sup>[3–5,14–17]</sup>. For the cases with follow-up details ( $n=45$ ), consanguinity of parents is reported in 21 (47%) patients<sup>[3–5,10,13,15,16]</sup>. The age of diagnosis ranged from 4 months to 43 years. At the time of respective publication one (2.2%) out of 45 cases was reported to be deceased.

The biochemical function or catabolic pathway involving L2HGA followed by preliminary loading and dietary studies have been uninformative to reveal the origin of the compound. In 2004, Rzem *et al.*<sup>[18]</sup> demonstrated that L2HGA is normally metabolized to alpha-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 L2HGA on the central nervous system.

The patients with this rare inherited metabolic disease mainly present with neurological manifestations, including psychomotor retardation, cerebellar ataxia, variable macrocephaly, and epilepsy<sup>[3]</sup>. Literature review as depicted in Table 1 (Supplementary File, Supplemental Digital Content 1, <http://links.lww.com/MS9/A36>), revealed seizures (26%,  $n=39$ ), ataxia (26%,  $n=39$ ), intellectual deficit (22%,  $n=33$ ), dysarthria (11.5%,  $n=17$ ), and delayed walking (11%,  $n=16$ ) as the common presentation. One patient reported by Topçu *et al.*<sup>[19]</sup> had medulloblastoma. Increasing evidence suggests that patients with L2HGA have a predisposition to cerebral neoplasms. This may be related to the pathologic accumulation of L2-HG because

**Table 1**  
**Details of reported cases with therapeutic response (n = 47).**

Study	Ethnicity	Treatment	Post-treatment symptoms
1 <sup>[4]</sup>	NA	Riboflavin, antiepileptic medication	At 14 years – significantly greater seizure activity and reduced motor function. At 15 years – worsening disease activity profile
2 <sup>[5]</sup>	Japan	FAD 30 mg/day and levocarnitine chloride 900 mg/day	Significant improvement in tremor and dystonia
3–4 <sup>[21]</sup>	Netherlands	sodium valproate (VPA). VPA and primidone	Seizure controlled
5–14 <sup>[20]</sup>	India	carnitine (50–100 mg/kg/day) and riboflavin (100–200 mg/day)	Improving/expired/stable/stable/stable/improving/worsening/stable/stable/stable
15 <sup>[17]</sup>	India	Carnitine, riboflavin, and antiepileptic drugs	Some improvement in tremors and gait
16–44 <sup>[19]</sup>	Turkey	L-carnitine supplementation, antiepileptic medication Benserazide hydrochloride and levodopa combination	Cerebellar symptoms, movement disorders and dystonia were responsive to benserazide hydrochloride and levodopa combination
45 <sup>[3]</sup>	Reported from Ireland, patient ethnicity not mentioned	Riboflavin 150 mg twice daily and carnitine 1 g twice daily	clinical status stabilized with no further deterioration occurred
46–47 (Our case)	Pakistani	Riboflavin 100 mg twice daily and L-carnitine 1500 mg twice daily	Speech, tremors and ataxia is improved/speech, tremors and ataxia is improved

FAD, flavin adenine dinucleotide sodium.

high amounts of 2-HG have been found in brain neoplasms that have IDH1 mutations. In our study, similar to the literature, the main symptoms of the patients were psychomotor retardation, cerebellar ataxia, extrapyramidal symptoms, and seizures. Unlike other organic acidurias, L2HGA commonly has a chronic progressive clinical course, which often leads to delayed diagnosis. The literature review revealed variable age of diagnosis ranging from 7 months to 43 years.

Biochemically, the disorder is characterized by increased concentration of L2HGA in body fluids including urine, CSF, and plasma, via urinary gas chromatography mass spectrometry analysis. Chiral confirmation differentiates between the D2 and L2 enantiomers, which is only available at specialized centers<sup>[3]</sup>. The clinical presentation often can suggest either D2HGA or L2HGA. For D2HGA the clinical phenotype encompassed epilepsy, hypotonia, and psychomotor retardation as the primary features. Whereas L2HGA, follows an insidious onset of disease starting in childhood, developmental delay, epilepsy and cerebellar ataxia. The course of the disease is slowly progressive and mild, with patients often remaining undiagnosed until adolescence or even adulthood<sup>[3]</sup>. Brain MRI provides useful clues for the diagnosis of D2HGA including enlargement of the lateral ventricles, subdural effusions, subependymal pseudocysts, signs of delayed cerebral maturation, cerebral white-matter abnormalities, and callosal agenesis differentiating from L2HGA in which the characteristic centripetal extension of the white matter sparing the brainstem and corpus callosum is present<sup>[20]</sup>.

There is no definitive treatment of the disease, and the approach is supportive, seizure control medication, L-carnitine (50–100 mg/kg/day) supplementation, physical therapy and rehabilitation and special training. However, few case reports have shown clinical improvement with riboflavin or with riboflavin and levocarnitine as depicted in Table 1<sup>[17,20,22,23]</sup>. Saidha and colleagues reported a patient who presented late at 31 years of age to the neurological services with childhood diagnosis of undefined mild learning disability. Urinary and CSF enantiomeric analysis showed an L-isomer of 2-HGA. He was started on riboflavin 150 mg twice daily and carnitine 1 g twice daily, following which he stabilized, and no further deterioration occurred. A year later clinical

examination remained unchanged at the time of publication in 2009<sup>[24]</sup>. Likewise, the two sisters presented in this report were also diagnosed late though they had undiagnosed childhood disabilities and clinical improvement was also observed after initiating treatment with Riboflavin and L-carnitine. Riboflavin could raise FAD concentration, and FAD is supposed to rescue the enzymatic activity of L-2-HG dehydrogenase<sup>[25,26]</sup>. Samuraki and colleagues treated their patient at 43 years age, with FAD 30 mg/day and levocarnitine chloride 900 mg/day. They reported that the tremor and dystonia gradually improved in a few weeks. Six months later, the urinary 2-HGA decreased, and the patient retained smooth gait, elaborate hand movements however intelligence remained consistent for 4 years after starting treatment<sup>[5]</sup>. Riboflavin and L-carnitine therapy was also advocated by Muthusamy *et al.*<sup>[20]</sup>, Shah *et al.*<sup>[17]</sup>, and Saidha *et al.*<sup>[24]</sup> with considerable improvement in symptoms and stabilization in 10 cases out of a total of 12, whereas one expired and one case reported deterioration of symptoms.

## Conclusion

Neuroradiological features of centripetal subcortical leukoencephalopathy with basal ganglia and dentate nuclei involvement are rather specific to L2HGA and should lead to further biochemical investigations to look for L2HGA and *L2HGDH* gene sequencing. Early diagnosis and treatment initiation could potentially modify the clinical course.

## Ethics approval

The study was approved by the Institutional Ethics Committee (ERC # 2021-7011-19889).

## Consent for publication

Written informed consent was obtained from the parents of the patient. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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None.

## Author contribution

S.A. performed the literature search, data collection, and write-up of the work in the first draft.

A.S. assisted in data analysis and write up. B.A. conceived the idea, collected the data, and coordinated the writing of the paper and reviewed the final draft. R.D., M.N., W.G., F.C., and H.V. were involved in the laboratory workup and critical revision of the article for the intellectual content. All authors have reviewed the final draft and agreed upon.

## Conflicts of interest disclosure

None.

## Research registration unique identifying number

Not applicable.

## Guarantor

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## Availability of data and materials

Available from corresponding author on reasonable request.

## Provenance and peer review

Not commissioned, externally peer reviewed.

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