

L-2-Hydroxyglutaric Aciduria – a Rare Type of Organic Aciduria Presenting as Seizures and Developmental Delay in a Filipino Child

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ABSTRACT

L-2-hydroxyglutaric aciduria (L-2-HGA) is a rare, autosomal recessive organic aciduria with increased levels of L-2-hydroxyglutaric acid in the urine and other body fluids. Clinical presentation includes developmental delay, epilepsy, and typical neuroimaging findings.

This is a report of the clinical, neuroimaging, and biochemical findings of the first diagnosed case of L-2-hydroxyglutaric aciduria in the Philippines. This paper likewise reaffirms the importance of locally available biochemical tests in diagnosing inborn error of metabolism.

Key Words: L-2-hydroxyglutaric aciduria, organic aciduria, developmental delay, seizures, developmental regression

Introduction

L-2-hydroxyglutaric aciduria (L-2-HGA) is a rare neurodegenerative metabolic disorder that follows an autosomal recessive mode of inheritance. It is characterized by elevated levels of L-2-hydroxyglutaric aciduria in urine, plasma, and cerebrospinal fluid (CSF).^{1,2} Clinical manifestations of the condition include speech and mental developmental delay, pyramidal and extrapyramidal signs, demyelination of white matter, cerebellar dysfunctions, epilepsy, macrocephaly, and other neurologic symptoms.^{2,3,4} In some patients, brain tumor formation was also reported.^{5,6} Typically the disorder presents in infancy but there are reported adult cases with a milder phenotype.^{7,8} The diagnosis of L-2-HGA is established by urine organic acid screening of 2-hydroxyglutaric acid and following chiral differentiation. The estimated prevalence and incidence of L-2-HGA are unknown but it has been reported to affect 140 cases worldwide.⁹

In this report, we present the clinical, biochemical, and neuroimaging findings of the first case of L-2-hydroxyglutaric aciduria in the Philippines.

Case Report

This female patient was 5 years of age at the time of evaluation. On review of history, she is the first child of healthy, non-consanguineous Filipino parents. The maternal and neonatal histories were unremarkable. Her development was normal during the first year of life. At around 1 year of age, she had generalized tonic clonic seizures accompanied by loss of consciousness that lasted for a few seconds. She was admitted at a local hospital and remained well with no recurrence of seizures. She was not maintained on any anti-epileptic medication. However, she was noted to have a weak grip of the right hand described as frequently dropping her milk bottle. Her developmental progress continued to be at par with age.

At 3 years of age, during a bout of fever, the generalized tonic clonic seizures recurred and lasted longer. She was brought to a nearby hospital where status epilepticus was considered. She was prescribed with unrecalled antibiotics and Valproic acid. Cranial CT scan showed a hypodense lesion on the subcortical frontal lobe. She was diagnosed with meningitis and treated with antibiotics.

From 3-5 years of age, the seizures were controlled; however, there was progressive weakening of the grip on both hands and dragging of the left foot on ambulation was noted. She started to have delay in language and personal/social skills. She exhibited hyperactivity and violent behavior described as biting or throwing things at people when she felt frustrated. Cranial magnetic resonance imaging of the brain revealed extensive symmetrical signal abnormalities predominantly involving the subcortical white matter of the cerebral hemispheres bilaterally with accompanying symmetric involvement of the basal ganglia bilaterally, as well as the medial cerebellar hemispheres (Figure 1).

On physical examination at 5 years of age, head circumference was at 85th-95th percentiles for age. She was not particularly dysmorphic. Neurologic examination showed normal muscle tone, strength and reflexes. There were no tremors. Her gait was noted to be unsteady.

Urinary organic acid was semi-quantitatively analyzed using gas chromatography-mass spectrometry. Internal standards used in the analysis were phenylbutyric acid and tricarballic acid. Organic acids were extracted by acidification, saturation with salt, and adding ethyl acetate.

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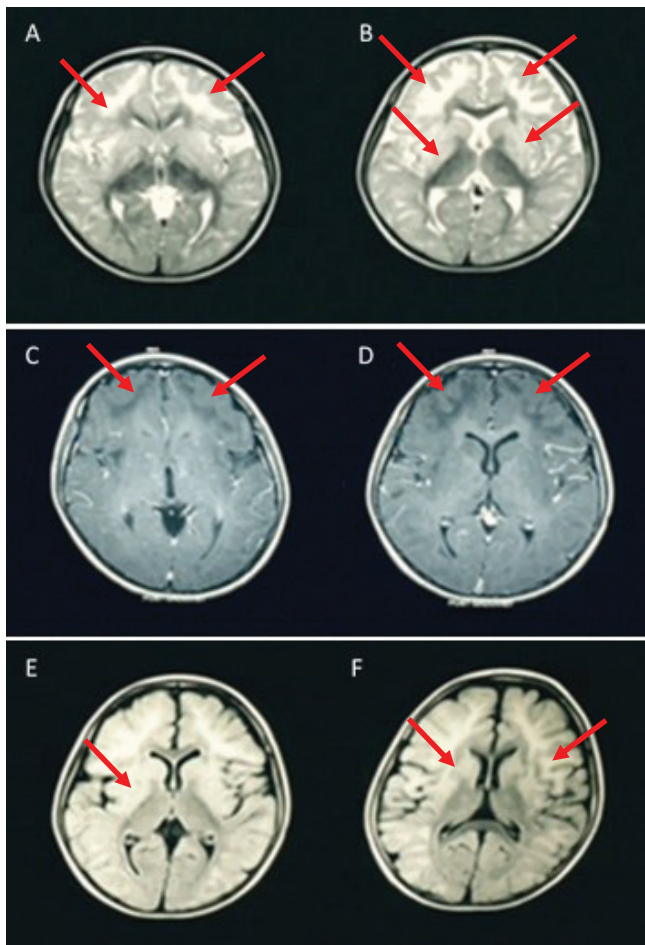


Figure 1. Cranial MRI of the patient. (A, B, C, D) Extensive symmetrical signal abnormalities predominantly involving the subcortical white matter of the cerebral hemispheres bilaterally (E, F) with accompanying symmetric involvement of the basal ganglia bilaterally.

After separation, sample was dried and derivatized with BSTFA + 1% trimethylchlorosilane and injected for analysis. Result showed moderately increased level of 2-hydroxyglutaric acid (Figure 2).

The enantiomeric determination of L-2-Hydroxyglutaric acid was done at Murdoch Research Institute in Australia using liquid chromatography–tandem mass spectrometry, which revealed gross excretion of L-2-hydroxyglutaric acid at 1470 $\mu\text{mol}/\text{mmol}$ of creatinine (normal range 1–19 $\mu\text{mol}/\text{mmol}$ creatinine).

Discussion

L-2-HGA is a rare organic aciduria that is inherited in an autosomal recessive pattern. The conversion of L-2-hydroxyglutaric acid to α -ketoglutarate is catalyzed by the enzyme L-2-hydroxyglutarate dehydrogenase (L2HGD) with FAD as cofactor.¹⁰ Molecular studies has showed that mutations in the *L2HGDH* gene results to impaired enzyme

activity of L-2-hydroxyglutarate dehydrogenase leading to accumulation of L-2-hydroxyglutaric acid.¹¹ The increased levels of L-2-hydroxyglutaric acid may have a toxic effect to the central nervous system.¹⁰ Progress in the understanding of the pathophysiology of L-2 hydroxyglutaric aciduria showed spongiosis and vacuolar lesions in mouse models leading to a consideration that it could be a disorder of metabolite repair.¹²

The disorder has a slow progression without specific clinical signs. Thus, there are delays in the diagnosis of some L-2-HGA patients with a mild phenotype.¹³ Our patient's clinical manifestations were compatible with L-2-HGA. Clinical history showed that symptoms started at the age of 1 with seizures followed by motor weakness, developmental delay and ataxia. There are few accounts of L-2-HGA in the literature and among those reported include a 15-year-old boy examined due to epilepsy, whose history revealed that the seizures started at the age of 18 months and eventually showed language regression, progressive intellectual deterioration, and worsening gait.³ An adult patient on the other hand was reported to show moderate to severe mental retardation, ataxia, distal tremor in the upper limbs with dystonic movement of the right hand, tetrahyperreflexia, and focal motor deficiencies.¹⁴

The patient's cranial MRI revealed the typical abnormalities seen in L-2-HGA cases. Magnetic resonance imaging studies of L-2-HGA patients showed highly characteristic abnormalities in the subcortical cerebral white matter, signal changes in the putamina and dentate nuclei, and cerebellar atrophy.^{4,14}

2-hydroxyglutaric acid is normally found in urine with equal levels of both L and D configuration. Two other biochemical variants of 2-hydroxyglutaric aciduria (2HGA) have been identified with regard to elevated levels of the L, D configurations.^{13,15}

D-2-hydroxyglutaric aciduria (D-2-HGA) is biochemically characterized by increased D-2-hydroxyglutaric acid in urine, plasma, and CSF. D-2-HGA results from mutations in the *D2HGDH* gene and *IDH2* gene. Clinical findings include developmental delay, epilepsy, and hypotonia with cardiomyopathy found to be exclusive to one phenotype.¹³ In the combined D,L-2-hydroxyglutaric aciduria (D,L-2-HGA), both the D and L configuration are moderately increased in urine and plasma. D,L-2-HGA clinically presents with severe neonatal epileptic encephalopathy, seizures, and hypotonia and is caused by *SLC25A1* gene mutations.^{16,17} Clinical evaluation and brain MRI findings are relevant in the diagnosis of 2HGA. However, enantiomeric differentiation is required for an accurate differential diagnosis of the disorder.¹³

In our patient, diagnosis was confirmed through organic acid analysis, which showed significant elevation of 2-hydroxyglutaric acid, and enantiomeric identification of L-2-hydroxyglutaric acid. Without the availability of enzyme

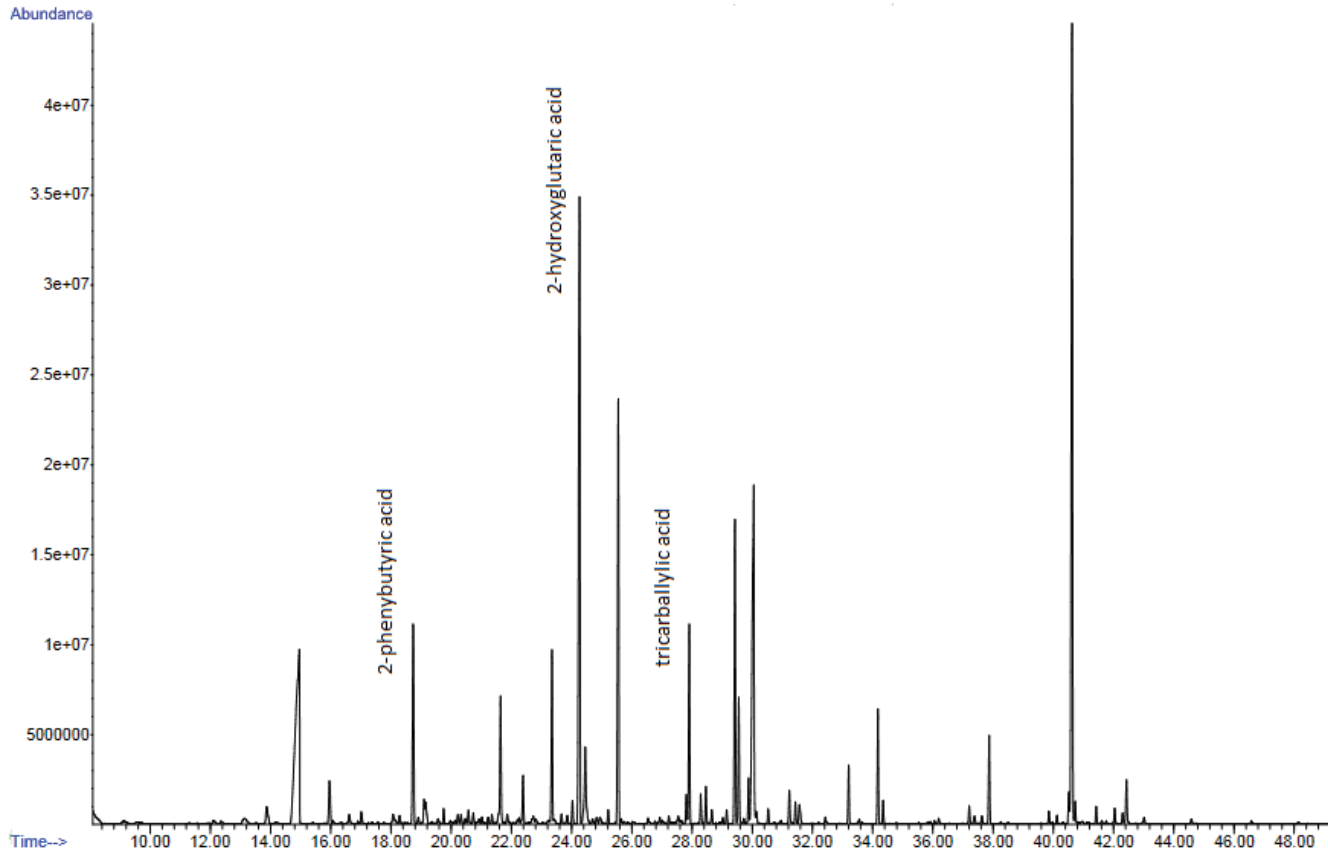


Figure 2. Total ion chromatogram of urinary organic acid metabolites showing increased 2-hydroxyglutaric acid compared to internal standards 2-phenylbutyric and tricarballic acids.

assays and mutational analysis, the importance of biochemical test for the diagnosis of organic acidurias is reinstated in this report.

Specific therapeutic approaches for L-2-HGA has not yet been established but with L2HGD being FAD-dependent, supplementation with FAD and riboflavin (precursor of FAD) were investigated for its possible therapeutic role. A patient from Japan was given 30 mg/day of FAD, which reduced tremor and dystonia gradually and decreased urinary 2-hydroxyglutaric acid.¹⁸ Treatment with riboflavin (100mg/day) of a 16-year-old patient showed partial improvement in cognitive and motor performances but increasing the dosage showed no further improvement.¹⁹ In contrast, a report also showed that riboflavin treatment to a 9-year-old patient was unsuccessful without significant reduction in L-2-hydroxyglutaric acid, neurological assessment and MRI readings remain unchanged.²⁰ These trials show that riboflavin and FAD treatment may only be effective in cases of mild missense mutations in *L2HGDH*.¹³ Our patient did not receive any medical therapy for L2HGA but continued to receive supportive management for the control of her seizures.

Conclusion

In summary, the clinical description and biochemical findings in this paper are consistent with L-2-hydroxyglutaric aciduria. Baseline urine amino acid and organic screening are helpful tools in diagnosing children with nonspecific neurologic symptoms such as developmental delay, seizures or intellectual impairment.

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Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

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