RESIDENT & FELLOW SECTION

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Child Neurology: Cognitive delay in a 7-year-old girl

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Organic acidurias are an important group of inherited metabolic disorders that affect the intermediary metabolic pathways of carbohydrate, amino acid, and fatty acid oxidation, leading to the accumulation of organic acids.[1] The 2-hydroxyglutaric acidurias are rare neurometabolic disorders characterized by developmental delay with or without other neurologic dysfunction. Three different subtypes have been described: D-2-hydroxyglutaric aciduria, L-2-hydroxyglutaric aciduria, and combined D,L-2-hydroxyglutaric aciduria. We describe the case of a child presenting with developmental delay who was found to have the classical biochemical, imaging, and genetic features of L-2-hydroxyglutaric aciduria.

Case report. A 7-year-old girl presented to the clinic for evaluation of cognitive delay. The patient, born at 41 weeks gestation, appeared to have met her early milestones on time. Her parents first became concerned about her development at approximately 4 years of age, when she was noted to have difficulty focusing and keeping up with her peers. Teachers described her as easily distracted and forgetful. Over the years, it was noted that she was increasingly lagging behind academically. Developmentally, when she was seen in clinic at age 7, she was able to ride a bike with training wheels, write her name and draw pictures, and dress herself. Her speech was difficult to understand.

She had a history of 3 convulsive febrile seizures at a younger age. Otherwise, she had not been noted to have any cognitive or neurologic decompensations with intercurrent illnesses. There was no family history of seizures or developmental delay. Her parents are originally from a small village in Eritrea and they denied any consanguinity.

On examination, her head circumference was 53.7 cm, at the 98th percentile. Weight and height were at the 50th percentile. She was able to state her name but was unable to recall the day of the week or month. She was able to follow a 2-step command, repeat 3 digits forward, and print her name legibly, but she had difficulty with right/left differentiation, subtracting, and reading. Her speech was suggestive of a lingual dysarthria, with about 25%–50% of her speech understandable to the examiner. She had mildly decreased tone throughout and had difficulty hopping or standing on each foot. Though her gait was normal, she was unable to tandem gait. The rest of her neurologic examination was normal for age.

What would her developmental age be based on the description given above? Would you consider brain imaging as part of the workup for developmental delay in a child?

Her developmental skills were approximately in the 4- to 5-year-old range. As part of the American Academy of Neurology (AAN)-recommended workup for children with developmental delay, an MRI of the brain was done (Level B; Class III evidence).[2] This showed extensive relatively symmetrical white matter (WM) hyperintensity involving mostly the subcortical WM (figure). There was relative sparing of the periventricular and perirolandic WM. Both the caudate and lentiform nuclei showed abnormal signal with sparing of the thalamus. The dentate nuclei showed similar increased signal intensity. There was sparing of the corpus callosum and brainstem.

What conditions can produce this MRI pattern of WM involvement or abnormal signal in the basal ganglia? What would be the next step in your workup?

The differential diagnosis for the imaging findings discussed above would include Canavan disease, Kearns-Sayre syndrome, 3-hydroxy-3-methylglutaryl-coenzyme A lyase deficiency, and succinic semialdehyde dehydrogenase deficiency.[3]

Bloodwork performed included a normal thyroid-stimulating hormone level, plasma pyruvate, lactic acid, amino acid screen, total/free carnitine levels, and acylcarnitine profile. Urine was sent for analysis of organic acids and the results showed "massive excretion of 2-hydroxyglutaric acid" (>1,000 mmol/mol creatinine). At this point genetic testing was performed, showing a homozygous mutation in the L-2-hydroxyglutarate dehydrogenase gene. The mutation consisted of a T>G transversion (c. 903T>G) in exon 7, resulting in the substitution of tyrosine by a stop codon at position 301 (p.Tyr301X). Based on these

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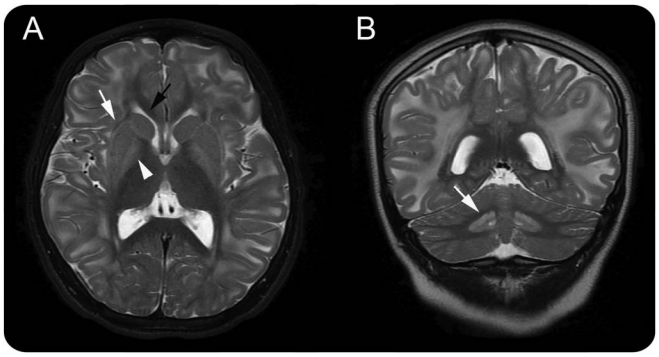
Figure **T2 MRI sequences show characteristic pattern of white matter involvement**



(A) Significant relatively symmetrical white matter disease with sparing of the splenium of the corpus callosum and the thalami. An outer rim of higher signal intensity is seen around the head of the caudate (black arrow) and putamen (white arrow). The entire globus pallidus shows high signal intensity (arrowhead). (B) Coronal sequence shows hyperintensity of the dentate nucleus (arrow).

results and clinical presentation, a diagnosis of L-2-hydroxyglutaric aciduria was made.

DISCUSSION The algorithm to evaluate children presenting with global developmental delay varies case by case. In our case, an MRI of the brain was performed as the initial investigation after confirming that the newborn metabolic screen was negative. This was based on the AAN guidelines for the evaluation of children with global developmental delay, which state that the diagnostic yield of neuroimaging increases in the presence of physical findings (in our case macrocephaly, dysarthria, decreased tone, and ataxia) (Level C; Class III evidence).[2] After obtaining the MRI of the brain, urine organic acid levels were sent. It was only at this point that genetic testing was performed to confirm the diagnosis of L-2-hydroxyglutaric aciduria.

L-2-Hydroxyglutaric acid is generated from an NADPH-dependent conversion of 2-ketoglutaric acid in a reaction catalyzed by L-malate dehydrogenase, a mitochondrial enzyme in the tricarboxylic acid (TCA) cycle. L-2-Hydroxyglutaric acid has no known function in humans and this reaction is thought to be an unwanted side reaction of L-malate dehydrogenase. L-2 Hydroxyglutarate dehydrogenase is the enzyme that prevents the loss of these carbon moieties from the TCA cycle and also protects from toxic accumulation of L-2-hydroxyglutaric acid by irreversibly converting it back to 2-ketoglutaric acid with flavin-adenine dinucleotide as a coenzyme, acting as a "housecleaning" enzyme for this unwanted side reaction.[4] The biochemical hallmark of L-2-hydroxyglutaric aciduria is the accumulation up to 300 times control values of urinary L-2-hydroxyglutaric acid. L-2-Hydroxyglutaric acid levels are also elevated in the plasma and CSF.[5]

Pathogenic mutations of L-2-hydroxyglutarate dehydrogenase causing L-2-hydroxyglutaric aciduria were first identified in 2004, with the majority of the variants being missense mutations that alter invariably conserved amino acids.[6] The L-2-hydroxyglutarate dehydrogenase gene has been mapped to chromosome 14q22.1. L-2-Hydroxyglutaric aciduria is inherited in an autosomal recessive fashion with 88 unique DNA variants being reported as of March 2012 in the Leiden Open Source Variation Database (http://www.LOVD.nl/L2HGDH). However, not all of these 88 DNA variants have been proven to be pathologic. In our case, genetic testing confirmed that the clinical syndrome was secondary to a mutation in exon 7 of the L-2-hydroxyglutarate dehydrogenase gene. Though missense mutations are more commonly described, nonsense mutations, as in our case, have also been found to cause L-2-hydroxyglutaric aciduria. No evident clinical phenotypical differences among patients with different pathologic mutations were found when 106 patients with elevated concentrations of 2-hydroxyglutarate in the urine were evaluated.[7] Because it is an autosomal recessive disorder, our patient's parents were counseled regarding the 25% chance that future children will manifest the disorder and the 50% chance that other children will be carriers of the mutation. However, they were not planning to have more children.

L-2-Hydroxyglutaric aciduria has a highly characteristic pattern of MRI abnormalities. These include the following:

1. Symmetrical WM abnormalities with preferential involvement of the subcortical WM with sparing of the internal capsule, corpus callosum, cerebellar WM, and brainstem
2. Involvement of the dentate nucleus, putamen, caudate, and globus pallidus
3. Atrophy of the cerebellar vermis and hemispheres may be present

The basal ganglia and dentate nucleus are affected early during the disease with abnormalities of the putamen and caudate nucleus starting at the outer rim and moving inwards.[3] These MRI findings can help the clinician differentiate from other cerebral organic acidurias. For example, patients with glutaric aciduria type I will have temporal lobe hypoplasia, dilated sylvian fissures and external CSF spaces, and T2 hyperintensities.[8]

Organic acidurias can be divided into classical and cerebral groups based on their clinical features.[1] Patients with classical organic acidurias usually present with acute metabolic decompensation after a short symptom-free period at birth. In contrast, cerebral organic acidurias such as L-2-hydroxyglutaric aciduria typically present with neurologic symptoms in the absence of severe metabolic derangements. The pattern of presentation of the neurologic symptoms can

also help distinguish between the different cerebral organic acidurias. For example, in glutaric aciduria type I the symptoms occur acutely, while in L-2-hydroxyglutaric aciduria there is more of an insidious onset with slow progression. However, the neurologic symptoms themselves usually overlap between different conditions and alone would be poor predictors of a specific cerebral organic aciduria. Clinically, most patients with L-2-hydroxyglutaric aciduria present in childhood with developmental delay usually consisting of mild to moderate psychomotor retardation. Cerebellar ataxia and epilepsy occur in about two-thirds of patients while macrocephaly and extrapyramidal symptoms are present in half. Hypotonia is usually prevalent in the early stages of the disease with spasticity appearing later. Our patient demonstrates many of these characteristic features, including macrocephaly, dysarthria, ataxia, mild hypotonia, and cognitive delay. No epidemiologic studies are yet available to determine incidence, life expectancy, or whether incidence differs by ethnicity. However, disease progression is usually slow, with most patients reaching adulthood.[5]

Only 2 case reports in the literature document specific therapies producing improvement of neurologic function with decrease in the urinary excretion of L-2-hydroxyglutaric acid.[9,10] Further studies are needed to identify therapeutic strategies that decrease cerebral formation of L-2-hydroxyglutaric acid. The improvement in neurologic function following biochemical alteration is encouraging for the future outlook of this rare disease.

AUTHOR CONTRIBUTIONS

Dr. Cachia was responsible for drafting and revising the manuscript for content, including medical writing for content, study concept and design, acquisition and analysis of data, concept, and analysis of data. Dr. Stine was responsible for drafting and revising the manuscript for content, including medical writing for content, analysis and interpretation of data, and study supervision.

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