CASE REPORT

Rare presentation of a treatable disorder: glutaric aciduria type 1

Monica S Badve, Sandeep Bhuta, Jim McGill

Abstract

A 32-year-old female patient presented with migraine and a bipolar disorder with frontal lobe dysfunction and bilateral pyramidal tract signs on examination. MRI brain revealed confluent bilateral symmetric white matter signal abnormality on T2 and FLAIR images with mild cerebral atrophy. Classic widening of Sylvian fissures and CSF space anterior to temporal lobes was seen. In view of the clinical and radiologic findings suggestive of a leukodystrophy, she was investigated for the same. Her investigations revealed an high level of urinary glutaric acid 857 mmol/mol creatinine (normal <4 mmol/mol creatinine) and 3-hydroxyglutaric acid 44 mmol/mol creatinine (normal <1 mmol/mol creatinine) and plasma glutaryl carnitine 1.2 micromol/L; (normal <0.34 micromol/L). This was diagnostic of glutaric aciduria type 1. She was started on L-carnitin with which she showed clinical improvement.

Testing for urinary organic acids is important when looking for treatable metabolic disorders (such as glutaric aciduria type I) in patients with leukodystrophy.

Glutaric aciduria type I (GAI) is a rare autosomal recessive disorder caused by the deficiency of mitochondrial enzyme glutaryl-CoA dehydrogenase (GCDH). This results in the accumulation of glutaric acid, 3-hydroxyglutaric acid and glutaryl carnitine. Usually this disorder presents in infancy with striatal necrosis resulting in dystonia and spasticity.

We report a rare late-onset presentation of glutaric aciduria type 1 in adulthood.

Case report

A 32-year-old, right-handed married female patient presented with worsening migraine headaches that had developed at the age of 17 years. She also suffered from bipolar disorder. Neurologic examination revealed broken pursuit movements with normal saccades and fusion. Tone, power and deep tendon reflexes were normal with bilateral extensor plantars. There was no family history of neurologic illness.

The MRI brain showed a confluent bilateral symmetric white matter signal abnormality on T2 and FLAIR images with mild cerebral atrophy. These lesions demonstrated no restricted diffusion or enhancement on post contrast images. MRI brain also revealed wide opercula giving rise to dilatation of Sylvian fissures secondary to fronto-temporal atrophy (Figure 1).

Neuropsychologic testing revealed reduced verbal fluency and motor sequencing suggestive of frontal lobe dysfunction. In view of the clinical history, frontal lobe dysfunction, bilateral pyramidal tract signs and MRI appearance of white matter disease, she was investigated for a leukodystrophy. Her plasma lysosomal enzyme studies, plasma amino acids, blood lactate and blood very long chain fatty acids were normal. However, on urinary organic acid testing, there was an abnormally high level of urinary glutaric acid 857 mmol/mol creatinine (normal <4 mmol/mol) and 3-hydroxyglutaric acid 44 mmol/mol creatinine (normal <1 mmol/mol). Plasma glutaryl carnitine was 1.2 micromol/L (normal <0.34 micromol/L).
Genetic testing revealed that she was compound heterozygous for p.Asn215fs, c.636-10_642dup mutation in exon 8* and the p.Glu365Lys, c.1093G>A mutation in exon 11* of the GCDH gene. The p.Asn215fs, c.636-10_642dup mutation in exon 8* has not been previously described. She was started on L-carnitine at 100 mg 4 times a day with monitoring of plasma carnitine levels.

On follow-up, 3 months later, she was found to have improved mood with reduced mood swings and reduced migraine episodes. Her migraine also improved with propranolol 10 mg BD.

Figure 1. MRI brain. FLAIR axial images (A&B) demonstrate bilateral widened opercula (arrows) with prominent Sylvian cisterns. Confluent diffuse subcortical white matter signal abnormality in frontoparietal and occipital lobes. Note normal appearance of basal ganglia. No restricted diffusion seen on ADC maps (C). No enhancement seen post contrast (D)
Discussion

GAI usually presents in infancy with acute encephalitis-like metabolic crisis leading to a severe dystonic movement disorder.\(^2,3\) With age, muscle tone tends to increase, and dystonia may be accompanied by akinetic-rigid parkinsonism.\(^4\) The usual neuroradiologic findings in children are macrocephaly, frontotemporal atrophy, and after the encephalopathic crisis, atrophy of the caudate nucleus and putamen.\(^5,6\) Rarely have white matter abnormalities been observed, without the involvement of the basal ganglia, as in our patient. These white matter abnormalities suggestive of leucoencephalopathy are usually seen in adult-onset presentations.\(^7,8\)

There is tremendous clinical and neuroradiologic variability in this disease.\(^5,7\) The white matter changes on MRI brain possibly represent underlying mitochondrial dysfunction.\(^1\) Our patient reported a migraine which is similar to headaches described in adult patients previously reported.\(^7,8\) This is possibly related to the underlying GAI.

Patients with an adult or late-onset presentation usually do not develop dystonia or parkinsonism unlike the early-onset presentation. Our patient showed clinical improvement with L-carnitine supplementation.\(^8,9\) Patients with GAI can develop secondary carnitine depletion. Carnitine supplementation can result in conjugation of glutaryl-CoA resulting in physiological detoxification and replenishes the intracellular coenzyme A pool.\(^10\)

GAI should be included in the differential diagnosis of diffuse white matter disease in adults with appropriate clinical history and investigated accordingly. Testing for urinary organic acids should be done in adult patients with leukodystrophy since GAI is potentially treatable.

L-carnitine supplementation may halt disease progression and reduce disability in affected patients.

Competing interests: Nil.

Author information: Monica S Badve, Staff Neurologist, Department of Neurology, Gold Coast University Hospital, Gold Coast, Australia—and Senior Lecturer, School of Medicine, Griffith University, Gold Coast, Australia; Sandeep Bhuta, Senior Staff Radiologist, Department of Medical Imaging, Gold Coast University Hospital, Gold Coast, Australia—and Associate Professor, School of Medicine, Griffith University, Gold Coast, Australia; Jim McGill, Consultant, Department of Chemical Pathology, Pathology Queensland, Royal Brisbane Hospital, Brisbane, Australia

Correspondence: Dr Monica S Badve, Gold Coast University Hospital, Level 5, A-Block, 1 Hospital Boulevard, Southport, QLD 4215, Australia. monicabadve@gmail.com

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