CASE REPORT

L-2 Hydroxyglutaric aciduria presenting with status epilepticus

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SUMMARY

L-2 Hydroxyglutaric aciduria is a rare, progressive, autosomal recessively inherited metabolic disorder of organic acid metabolism. It is characterised by macrocephaly, progressive neurological syndrome with cerebellar features, mental deterioration, typical brain MRI findings and the presence of L-2 hydroxyglutaric acid in urine samples. We report on an 11-year-old patient who presented to the emergency department with a generalised status epilepticus, which was subsequently diagnosed as L-2 hydroxyglutaric aciduria owing to rare and different clinical presentation. Brain MRI showed peripheral white matter abnormalities in cerebral hemispheres, basal ganglia and dentate nuclei. In conclusion, L-2 hydroxyglutaric aciduria should be considered in cases of epileptic seizures such as status epilepticus, cerebellar signs and progressive neurological course.

BACKGROUND

L-2 Hydroxyglutaric aciduria (L2HGA) is a rare organic aciduria. It is characterised by increased urinary excretion of L-2 hydroxyglutaric acid and a slowly progressive course of central nervous system involvement. Seizures are present in more than half of patients, usually occurring late in the course of the disease.^{1 2}

We report the case of an 11-year-old girl who presented at the emergency department with a generalised status epilepticus and was subsequently diagnosed with L2HGA.

CASE PRESENTATION

An 11-year-old girl was admitted to the paediatric intensive care unit owing to recurrent seizures. The patient's family described recurrent convulsions during the previous 24 h, which started from the right side of the body and then became generalised. There was no history of fever, febrile or afebrile convulsion, drug intake or head trauma. The parents were healthy and non-consanguineous, and the patient was born at term via normal delivery after an uneventful pregnancy. The current patient is the family's second child; the first child was followed by our clinic for hydroxyglutaric aciduria diagnosis. The parents described normal development in the patient's motor, social and language skills since infancy.

On admission, the patient was afebrile. She was disorientated, incoherent and gave incomprehensible answers to questions. Deep tendon reflexes were hyperactive. There were neither lateralising neurological signs nor nuchal rigidity. The remainder of the physical examination was normal.

The recurrent seizures were controlled with midazolam and phenytoin. An EEG performed 12 h after the termination of the status epilepticus demonstrated slowing in the left hemisphere with frequent sharp waves. Levetiracetam was started for recurrent seizures.

INVESTIGATIONS

On admission, all routine chemical and haematological investigations and serum ammonia gave normal results. A CT of the brain was normal. Lumbar puncture was performed to rule out central nervous system infection. There were no cells in the cerebrospinal fluid examination, and protein and glucose values were normal (40 mg/dL (15–60 mg/dL) and 72 mg/dL (blood glucose was 112 mg/dL), respectively). Cerebrospinal fluid pressure was normal.

After 2 days postictal, a neurological examination revealed mild cerebellar dysfunctions (gait ataxia, dysmetria, dysdiadochokinesia and dysarthria), mild macrocephaly (just above the 97th percentile) and mild mental retardation. During the interview, the child's speech was found to be dysarthric. Vital findings were normal.

On the second day of antiepileptic treatment, laboratory tests were all within normal ranges (complete blood count, blood chemistry, blood and urine amino acids, lysosomal enzyme screen, lactic and pyruvic acid levels in serum and cerebrospinal fluid, copper levels in serum and urine, and ceruloplasmin level). Tandem mass spectrometry and lysosomal enzyme screening for metabolic disorders were normal. Urinary L-2 hydroxyglutaric acid excretion was 2120 mg/g creatine (normal value <10 mg/g creatine). Genetic analysis was not performed. MRI revealed mild bilateral hyperintense lesions, predominantly in the right-frontal subcortical cerebral white matter, globus pallidus and dentate nuclei (figure 1). The periventricular white matter, thalami and brainstem were spared.

DIFFERENTIAL DIAGNOSIS

Other metabolic diseases and leukodystrophies should be considered in the differential diagnosis of macrocephaly, neurological deterioration and deep white matter lesions. Macrocephaly is a finding that must alert the clinicians to the possibility of a cerebral organic aciduria, although it is shared by several other metabolic diseases such as glutaric aciduria type I.

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Figure 1 Axial T2-fluid attenuated inversion recovery (A) and T2-weighted sequences (B) hyperintense lesions, predominantly in the right-frontal subcortical cerebral white matter, globus pallidus (A), and dentate nuclei (B).

TREATMENT

Considering the laboratory and radiological findings, the patient was diagnosed with L2HGA. She was put on a protein-restricted diet, oral riboflavin (200 mg/day) and carnitine (1 g/day) supplement therapy.

OUTCOME AND FOLLOW-UP

The patient was discharged from the department of paediatric neurology on oral levetiracetam and phenytoin therapy. After 6 months following initial presentation, the patient remains free of seizures on the above regime, with no evidence of further deterioration in her psychomotor development.

DISCUSSION

L2HGA is an autosomal recessive metabolic disorder. The disease is characterised by psychomotor delay and cerebellar signs, often associated with macrocephaly. Age range varies widely, from neonatal period up to mid-fifties. It shows indications at young ages, with retardation in motor development steps, seizure and macrocephaly. At older ages, walking disorder owing to ataxia and mental retardation may draw attention.¹

Although rare, epileptic seizures or even status epilepticus can occur early in the course of L2HGA, most probably because of early subcortical white matter alterations with subsequent development of epilepsy. Febrile convulsions, partial and grandmal seizures have been reported, and are generally difficult to control,¹⁻⁴ similar to our patient, who required polytherapy. Recurrent generalised tonic-clonic convulsions may be related to severe subcortical involvement, as in the case of our patient, who presented with status epilepticus, which subsequently led to the demonstration of specific clinical and radiological findings and finally to the diagnosis of L2HGA. Macrocephaly is present in nearly 50% of affected patients with L2HGA, including our patient, and can sometimes be the first manifestation of the disease.¹ Contrary to the parental reports of 'normal' development, it is most likely that mild ataxic symptoms as well as mild mental retardation were present, but went unnoticed prior to admission to the clinic.

Characteristic cranial MRI findings of L2HGA consist of predominantly subcortical leukoencephalopathy, centripetal extension of white matter involvement and bilateral nucleus dentatus lesions with variable basal ganglia involvement. The periventricular white matter, thalamus, brain stem and spinal cord are spared. Neuroradiological features of subcortical leukoencephalopathy with dentate nuclei and basal ganglia involvement are rather specific and should lead to further biochemical investigations. Definitive diagnosis depends on the detection of L-2 hydroxyglutaric acid in urine, blood and cerebrospinal fluid.¹⁻⁵ Increased urinary excretion of L-2 hydroxyglutaric acid and typical MRI findings in this patient established the diagnosis of L2HGA.

Normally being the two isoforms of 2-hydroxyglutaric acid, L and D configurations are found in the urine in equal amounts. Two different clinical conditions have been identified with regard to the increase in L-D configurations. While D-2-hydroxyglutaric aciduria is a grave neurological syndrome, arising in the neonatal period, L-2-hydroxyglutaric aciduria is a neurological encephalopathy form that progresses more slowly.¹⁻⁵⁻⁶ In our case, despite the lack of L, D is a form separation, the patient was diagnosed with L-2-hydroxyglutaric aciduria in light of clinical and imaging findings.

Despite the significant developments regarding the clinical features and diagnosis of L-2-hydroxyglutaric aciduria neither the metabolic defects nor pathogenetic mechanisms causing leukoencephalopathy have been established, and no specific treatment has yet been developed.

In contrast to other organic acidurias, the lack of acute metabolic decompensation attacks in L2HGA may lead to misdiagnosis. Until recently, L2HGA has been considered among the diseases for which underlying metabolic defects cannot be identified.⁶ Moroni *et al*⁵ suggested that L2HGA exerts an excitotoxic effect on neurons, similar to that encountered for other organic acids and amino acids. Rzem *et al*⁷ demonstrated that L-2 hydroxyglutarate is normally metabolised to α -ketoglutarate (a compound amply provided by other sources) and concluded that the pathological findings in this metabolic disorder are a toxic effect of L-2 hydroxyglutarate on the central nervous system. Topcu *et al*⁸ used homozygosity to map L2HGA to chromosome 14q22.1. They found nine mutations in the L-2 hydroxyglutarate dehydrogenase gene. The gene encodes a putative mitochondrial protein, which the authors dubbed as 'duranin', with homology to FAD-dependent oxidoreductases.⁸

Treatment approaches, physical treatment and rehabilitation comprise L-carnitine (50–100 mg/kg/day) and riboflavin (200 mg/day) supports and supportive treatments such as

control of epileptic seizures with drugs. The relationship between riboflavin treatment and urinary hydroxyglutaric acid excretion has not yet been established.^{6–9} We therefore prescribed L-carnitine and riboflavin treatments in oral form, as stated in the literature. During follow-up, we observed clinical recovery final findings.

Learning points

- ▶ During L-2 hydroxyglutaric aciduria, there are no acute metabolic symptoms, clinical symptoms are minor and showing slow progression, and the disease can be seen across quite a wide age range, so that diagnosis can be difficult.
- ▶ In patients with refractory convulsions such as status epilepticus with cerebellar findings and macrocephaly, as in the case of our patient, metabolic disorders should be considered and treatment should be established immediately in order to prevent many potential complications.
- ▶ Neuroradiologic features of a subcortical leukoencephalopathy with dentate nuclei and basal ganglia involvement are rather specific and should lead to further biochemical investigations.
- ▶ Definitive diagnosis depends on detection of L-2-hydroxyglutaric acid in urine, blood, and CSF by means of gas chromatography-mass spectrometry.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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