CASE REPORT

Contribution of brain MRI in a patient diagnosed with 2-hydroxyglutaric aciduria

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SUMMARY

L-2-Hydroxyglutaric aciduria is a rare autosomal recessively inherited metabolic disorder of organic acid metabolism. Clinical findings are characterised by progressive neurological syndrome with cerebellar signs, mental deterioration and macrocephaly. Diagnosis is via increased levels of L-2 hydroxyglutaric acid in urine, plasma and cerebrospinal fluid. Brain magnetic resonance imaging (MRI) shows peripheral white matter abnormalities in cerebral hemispheres, basal ganglia and dentate nuclei. In this report, we present an rare 8-year-old patient with a rare mental retardation, cerebellar findings, macrocephaly and typical brain MRI findings, who was subsequently diagnosed with L-2-hydroxyglutaric aciduria. In conclusion, in patients with progressive mental retardation, macrocephaly and cerebral findings, L-2-hydroxyglutaric aciduria should be considered in case of deep white matter and dentate nuclei involvement in MRI.

BACKGROUND

L-2-hydroxyglutaric aciduria is a rare autosomal recessive genetic disease, which is known as multiple acyl CoA dehydrogenase deficiency. Clinically, it shows progressive psychomotor developmental delay and cerebral symptoms. However, the onset of symptoms ranges from neonatal period to late adulthood. Unlike other organic aciduria, no acute metabolic seizure is observed. Brain magnetic resonance imaging (MRI) can assist in diagnosing subcortical white matter, basal ganglion and dentate nuclei involvement despite deep white matter protection. Diagnosis is via elevated L-2-hydroxyglutaric acid in blood, urine and cerebro-spinal fluid (CSF) gas chromatography.¹⁻³

An 8-year-old boy diagnosed with L-2-hydroxyglutaric aciduria is presented as a rare case. Furthermore, the case report draws attention to the diagnostic importance of typical MRI findings.

CASE PRESENTATION

An 8-year-old boy was presented to our polyclinic owing to hand trembling, learning difficulty, forgetfulness, speech disorder and frequent falls while walking. The patient history indicated that the family had become aware of these problems over the last 3–4 years; hand trembling and speech disorder gradually increased, and the patient had experienced learning difficulties since starting school (1 year). In addition, the family reported that he did not articulate some words while speaking, could not pronounce them correctly and had difficulty in expressing himself. Neither patient nor

family histories showed any diseases. The family described retardation in the patient's psychosocial motor development during infancy. The patient began to hold his head up at 4–5 months; began to sit with support at 12–14 months; began to sit unsupported at 16–18 months and began to walk after 2.5 years. He began to say single words when he was 12-months old and simple sentences when he was 2–2.5 years old.

On physical examination, he had a height of 127.5 cm (50th percentile), a body weight of 27 kg (50–75th percentile) and head circumference of 54.3 cm (90–97th percentile). Vital findings were normal. Cerebellar test showed intentional tremor in hands, ataxia, dysmetria, dysdiadochokinesia and dysarthria. Plantar reflexes were bilateral flexor. Other examination findings were normal. Fundus oculi examination was normal in both eyes. IQ test indicated slight mental retardation.

INVESTIGATIONS

In laboratory tests, full blood count, blood glucose urea, creatine, liver enzymes, arterial blood gases, ammoniac and lactate values were found to be normal. Levels of urine copper levels and ceruloplasmin were within normal limits. Tandem mass scan test, urine and blood amino acids were normal. Urine organic acid analysis identified elevated excretion of 2-hydroxyglutaric acid (1230 mg/g creatine, normal value <10 mg/g creatine) and 3-hydroxyglutaric acid (35 mg/g creatine, normal value <5 mg/g creatine). No genetic analysis was performed. Brain MRI showed centrifugal involvement in subcortical white matter with more significant levels in bilateral dentate nuclei, basal ganglia and frontals (figure 1).

DIFFERENTIAL DIAGNOSIS

Canavan's disease, other methabolic diseases and leucodystrophies 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 and Canavan's disease.

Brain stem involvement and centripetal extension of white matter abnormalities differentiate Canavan's disease from L-2-hydroxyglutaric aciduria.

TREATMENT

The patient was diagnosed with L-2-hydroxyglutaric aciduria, based on clinical, laboratory and imaging

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Figure 1 Image of hypointense areas in T1-weighted sagittal (A) section and particularly in subcortical areas in frontal and dentate nuclei. Image of hyperintense lesions in T2-weighted axial (B–F) sections, subcortical deep white matter particularly more significant in frontals (B–E), basal ganglia (B–C) and dentate nuclei (F).

findings. The patient was started on riboflavin (200 mg/day) and L-carnitine (1 g/day) treatment and followed-up.

OUTCOME AND FOLLOW-UP

Follow-up showed no progress in clinical status after approximately 1 year.

DISCUSSION

L-2-Hydroxyglutaric aciduria is a rare, slowly progressing neurodegenerative metabolic disease. Symptoms include delayed motor development, seizure and macrocephaly. Walking disorder owing to ataxia and mental retardation appear as age increases.¹ Macrocephaly, which was identified in our patient, is observed in 50% of patients and might sometimes be the first finding. Diagnosis is confirmed by elevated L-2-hydroxyglutaric acid in body fluids. MRI can indicate the involvement of

subcortical white matter—which is characteristic for the disease—cerebellar atrophy and symmetric basal ganglia involvement in dentate nuclei. Outward involvement of white matter is distinctive from other leucodystrophies.^{2–3} Neurometabolic disease was considered in the patient, who was presented with progressive mental retardation and cerebellar findings. He was diagnosed with L-2-hydroxyglutaric aciduria owing to typical MRI findings and elevated L-2-hydroxyglutaric acid in urine. The cause of lesions observed in MRI images in L-2-hydroxyglutaric aciduria could not be explained. However, it is thought these may be owing to excitatory and neurotoxic effect of L-2 hydroxyglutaric acid.^{1–3} In addition, distinctive diagnosis should be made for Van der Knaap disease, Canavan disease and Alexander disease, which show similar MRI findings.^{2–4} Treatment consists of physical therapy and rehabilitation, and supportive therapies such as L-carnitine (50–100 mg/kg/day) and riboflavin (200 mg/day).^{4–5}

In conclusion, metabolic diseases should be considered in patients with progressing mental retardation, macrocephaly and cerebellar findings. Furthermore, distinctive diagnosis should be made for L-2-hydroxyglutaric aciduria in patients with deep white matter and dentate nuclei involvement in brain MRI.

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.
- ▶ Neuroradiological features of a subcortical leucoencephalopathy 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 cerebrospinal fluid 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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