MR imaging findings of glutaric aciduria type II

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ABSTRACT

Glutaric aciduria type II, also known as multiple acyl coenzyme A dehydrogenase deficiency, is an autosomal recessive, mitochondrial organic acid disorder that impairs electron transfer flavoprotein (ETF) or ETF-ubiquinone oxidoreductase, and causes a defect in flavin metabolism or transport. It has a heterogeneous clinical presentation, with at least three different phenotypic appearances. Magnetic resonance (MR) imaging of the brain in this disorder shows a T2-weighted prolongation in the corpus striatum, putamen, caudate nucleus, middle cerebral peduncles and splenium of the corpus callosum. We report a seven-month-old male Caucasian child who presented at the paediatrics emergency department with a sweetish breath. He was clinically diagnosed with diabetic ketoacidosis. However, on MR imaging, brain evaluation and laboratory analysis, he was found to have glutaric aciduria type II.

Keywords: magnetic resonance imaging, multiple acyl coenzyme A dehydrogenase deficiency

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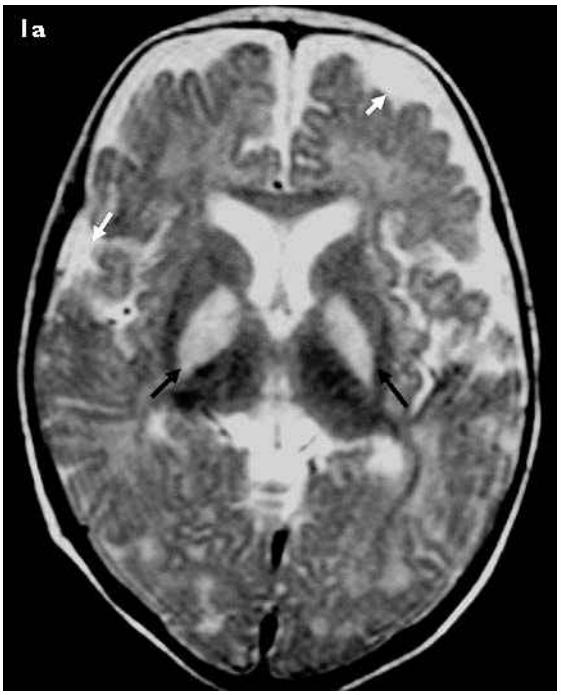
INTRODUCTION

Glutaric aciduria type II, also known as multiple acyl coenzyme A dehydrogenase deficiency is a metabolic disease that is inherited in an autosomal recessive manner, and results in an inborn metabolic error of the fatty and amino acids. Variability in the clinical expression and severity of the disease is often seen. Magnetic resonance (MR) imaging of the brain typically shows a T2-weighted hyperintensity of the basal ganglia, along with a bat-wing appearance of widened sylvian fissures.

CASE REPORT

A seven-month-old male Caucasian child presented to the paediatric emergency department with a history of a peculiar sweat sock breath odour for four days, fever for two days and an altered sensorium for the past one day. On examination, acidic breathing and hypotonia were found. Laboratory investigations revealed a high anion gap and hypoglycaemia. The clinical possibilities of diabetic ketoacidosis or renal causes for electrolyte



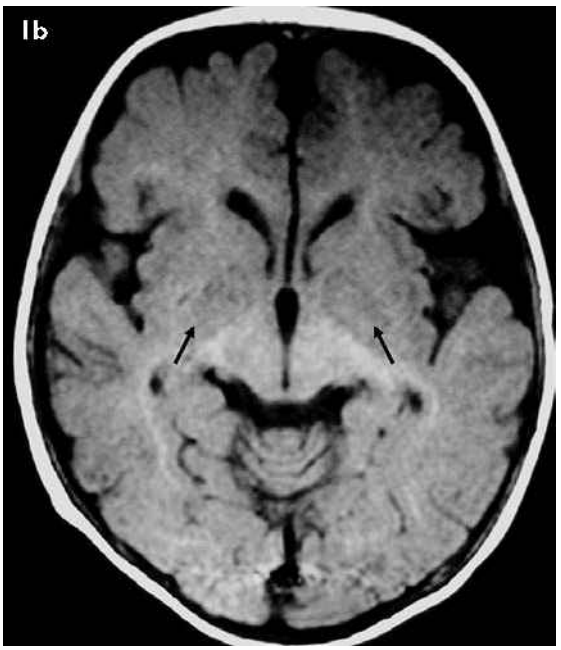


Fig. 1 (a) Axial T2WI MR image shows bilateral symmetrical hyperintensities in both globus pallidi (black arrows) and increased perisylvian and fronto-temporal extra axial cerebrospinal fluid spaces (white arrows). (b) Axial T1WI MR image shows mild hypointensity (arrows) noted in the globus pallidus on both sides.

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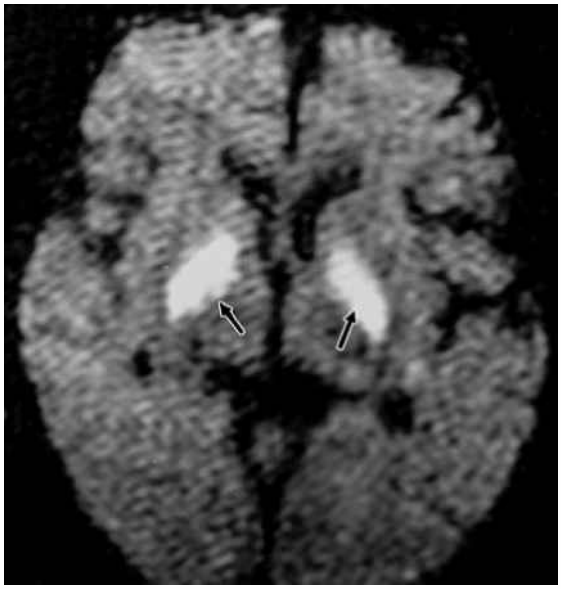

Fig. 2 Diffusion-weighted MR image shows restricted diffusion in the bilateral globus pallidi (arrows).

imbalance were considered. Due to the persistent altered sensorium, MR imaging of the brain was planned.

MR imaging of the brain was performed on a 1.5T MR unit. Axial and sagittal T1-weighted (T1WI) (TR = 102/TE = 14) and T2-weighted (T2WI) (TR = 2735/TE = 102) image sequences were performed with a slice thickness of 5 mm, without any inter-slice gap. In addition, coronal fluid attenuated inversion recovery (FLAIR) and diffusion-weighted imaging were performed. The results revealed bilaterally symmetrical T2WI hyperintensities in the globus pallidus (Fig.1a), which were mildly hypointense on T1WI images (Fig.1b).

On diffusion-weighted imaging, diffusion restriction was observed in the globus pallidus (Fig. 2). The putamen, caudate nuclei and thalami on both sides were normal. Nearly symmetrical enlargement of the perisylvian cerebrospinal fluid (CSF) spaces and fronto-parietal subdural spaces was present (Fig.1a). White matter signal intensity was normal. Magnetic resonance spectroscopy (MRS) was attempted but could not be performed satisfactorily, as the child was moving during the MRS examination and could not be sedated for a long time.

Urine biochemistry revealed an excretion of glutaric, propionic and methyl malanoic acids. Based on the presentation, image results and laboratory findings, a diagnosis of glutaric aciduria type II was made.

DISCUSSION

Glutaric aciduria type II is an organic acid disorder, first described by Przyrembel et al in 1976.[1] It is an autosomal recessive mitochondrial disorder that impairs either the electron transfer flavoprotein (ETF), the ETF-ubiquinone oxidoreductase (ETF-QO), or causes a defect in the flavin metabolism or transport. This will result in the intramitochondrial accumulation of those metabolites that require transfer electrons to flavoprotein.[2,3]

This inherited disorder has varied and heterogeneous clinical presentations, with at least three different phenotypic appearances. The first type is a neonatal onset disease associated with congenital anomalies that present during the first two days of life. The second is a neonatal onset disorder that is not associated with congenital anomalies and presents within the first week of life. Both the first and second clinical types present with hypotonia, hypoglycaemia, and metabolic acidosis. The third type has a variable course and age of presentation. The patients may be adults and often have intermittent episodes of vomiting and proximal myopathy, along with hypoglycaemia.[2]

The associated anomalies are facial dysmorphism, bilateral polycystic and dysplastic kidneys, fatty degeneration of the liver and heart, focal cerebral microgyria, hypoplasic lungs, thymic lymphoid atrophy and genitalia abnormalities. The characteristic sweetish or sweat sock odour of patients with glutaric aciduria type II is due to the accumulation of isovaleric acid and its metabolites, and is also found in patients with isovaleric aciduria.[4]

This reported case had no history of an acute hypoxic event or trauma. There was also no previous history of meningitis or encephalitis, or any family history of a similar disease. On clinical examination, the patient was found to have facial dysmorphism. The MR imaging of the brain showed T2-WI prolongation in the corpus striatum, putamen, caudate, middle cerebral peduncles and splenium of the corpus callosum. Neuronal loss in the basal ganglia with gliosis was described for these MR images.[5,6] Lesions in the bilateral globi pallidi are attributed to focal neuronal loss, hypomyelination or glial scarring. These are seen in inborn errors of metabolism such as canavans disease, metchromatic leucodystrophy, maple syrup urine disease, methylmalonic acidaemia and lactic acidaemia.[7] The other causes of globus pallidus T2-WI hyperintensities in infants and children are kernicterus,[8] chronic carbon monoxide intoxication,[9] neurofibromatosis type-1,[10] methanol poisoning and Kearns-Sayre syndrome.[11,12]

While the presence of bilateral globus pallidus hyperintensities is not pathognomic of any of the abovementioned entities, careful evaluation of the history can rule out most of the acute causes such as carbon monoxide poisoning, methanol poisoning and

acute hypoxia. The remaining conditions are mostly more insidious in presentation. Out of these, Leigh's disease mainly involves the putamen, along with the globus pallidus, caudate, thalamus, brainstem and white matter. Mitochondrial cytopathies affect the basal ganglia and the cerebral cortex in the form of infarction. In leucodystrophies such as Canavan's disease, the involvement of cerebral white matter is a predominant finding, with or without basal ganglia involvement. In other conditions, such as maple syrup urine disease, metachromatic leucodystrophy, methylmalonic acidaemia and other lactic acidaemias, correlation of the MR imaging should be done as well as a biochemical profile and a muscle biopsy, if necessary. The presence of a sweet breath odour on clinical examination in a young child is also an important clue for the diagnosis of glutaric aciduria type II.

Knowledge of the patients' history, MR findings and their differential diagnoses can help in differentiating the acute causes of bilateral globus pallidus hyperintensities from chronic causes, followed by treatment or prognostication of the latter group of diseases.

Defective neuronal proliferation and migration *in utero*, especially in the temporal lobes, results in hypoplasia. Symmetrically enlarged CSF spaces in the anterior temporal fossae and fronto parietal extra axial (subdural) spaces are also observed. There is a concomitant hypomyelination of the corpus callosum and focal cortical dysplasia with heterotopias. MRS of this encephalomyopathy may show elevated lactate levels and an abnormally high choline-creatine ratio, indicating dysmyelination in the brain. Low phosphorous levels presented in the muscle point to a low energy state with mitochondrial dysfunction.[3]

Biochemical assessments have shown profound nonketotic hypoglycaemia, metabolic acidosis and organic (dicarboxylic) aciduria with inconsistent combinations of organic acids, including short chain volatile acids (isovaleric, isobutyric, 2-methylbutyric), glutaric, ethylmalonic, 3-hydroxyisovaleric, 2-hydroxyglutaric, 5-hydroxyhexanoic, adipic, suberic, sebacic and dodecanedioic acids.[3] Liver biopsies can reveal fatty metamorphosis, while muscle biopsies may show vacuolar myopathy with lipid accumulations. A high-calorie diet that is low in fat and protein, along with oral supplements of L-carnitine (100 mg/kg per day) and riboflavin (100 mg/day) has resulted in significant improvement in this lipid myopathy.

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