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D-Glyceric Aciduria in a Six-Month-Old Boy Presenting with West Syndrome and Autistic Behaviour

Abstract

D-Glyceric aciduria is a disease with a very heterogenous group of symptoms, with D-glyceric acid excretion as the chief common characteristic. Findings described in previous patients include progressive neurological impairment, hypotonia, seizures, failure to thrive and metabolic acidosis. However, there are also asymptomatic patients with mild neurological impairment. A six-month-old boy was admitted to our clinic with the complaints of dullness to his environment, seizures and autistic behaviour. EEG revealed multifocal generalized epileptic activity in a hypsarrhythmia pattern. Organic acid analysis (GC-MS) in urine revealed increased glyceric acid excretion. Analysis of the optical form of glyceric acid by a polarimetric method supported the diagnosis of D-glyceric aciduria. MRI showed white matter lesions with cerebral atrophy, particularly in the frontotemporal regions, and reversible abnormalities in the mesencephalon, thalami and globus pallidium resolving after fructose restriction in the diet. To our knowledge, this is the first case report of a patient with D-glyceric aciduria who presented with West syndrome and autistic behaviour in whom serial MRI findings are also defined.

Key words

D-Glyceric Aciduria \cdot West Syndrome \cdot Autistic Behaviour \cdot MRI Findings

Introduction

D-Glyceric acid is an intermediate metabolite of serine and fructose metabolism. Its increase as a biochemical symptom was first reported by Brandt et al in 1976 [2] in a 5-month-old boy having characteristic features of nonketotic hyperglycinemia with severe neurological impairment, myoclonic jerks and increased plasma glycine levels. Since then only a few patients have been reported [1].

Clinical symptoms observed in D-glyceric aciduria are severe metabolic acidosis from birth and failure to thrive, intermittent vomiting and abdominal distension, progressive neurologic disease (hypotonia, opistotonus, myoclonic jerks), delayed motor development, axial hypotonia and spastic paraparesis although there are also asymptomatic patients with only D-glyceric acid excretion in urine [1]. Besides this clinical diversity, there are three enzyme defects; D-glycerate dehydrogenase, triokinase and D-glycerate kinase, defined as the underlying metabolic defect in some of these patients [4,7,11].

In this report, in addition to serial MRI findings, we describe clinical and biochemical findings in a patient with D-glyceric acidemia who presented with infantile spasms and autistic behaviour.

Case Report

A 6-month-old boy was admitted with complaints of being unresponsive to his environment and experiencing sudden, sharp, jerky movements and irrelevant crying many times during sleep.

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He was the 3rd child of first degree consanguineous healthy parents and was born following an uneventful pregnancy and delivery at term with a birth weight of 3700 g. He had two healthy sisters aged 9 and 5, respectively. He did not exhibit any neurodevelopmental milestones except head control, which was first noted at 5 months of age.

On admission, he had poor eye contact and was unresponsive to his mother. His head circumference was 44 cm (<2 SD). He had autistic behaviour; no visual contact or glancing at face, striking rhythmic head rocking movements. He had visual fixation to bright objects and follow up to midline, and was responding only to sharp voices. He was hypotonic, had head control but was unable to sit without support. Deep tendon reflexes were hyperactive with bilateral flexor plantar response.

Laboratory investigations revealed a reduced hemoglobin level consistent with iron deficiency anemia. Blood chemistry, including renal and liver function tests, blood cholesterol and triglyceride levels were normal. Blood pH and bicarbonate level, blood lactate, pyruvate and ammonia levels and CSF lactate and pyruvate levels were found to be normal. Serum and urine amino acid screening as well as lysosomal enzyme analysis of leukocytes were normal. Brain stem auditory response (BAER) and visual evoked potentials (VEP), electroretinography (ERG) were normal, but an electroencephalogram (EEG) revealed multifocal generalized epileptic activity in a hypsarrhythmia pattern. He was put on vigabatrin therapy and his attacks decreased to once or twice per night. On follow-up examination at 11 months of age, he still had epileptic fits once or twice at night and autistic behaviour as observed at previous examinations, but was very charming and cheerful with tactile stimuli. EEG findings were still compatible with hypsarrhytmia pattern. He was given adrenocorticotropic hormone (ACTH) therapy for six weeks and his seizures decreased. Urinary organic acid analysis (GC-MS) revealed increased glyceric acid excretion (76.6 mmol/mol creatinine; normal: <9), whereas urinary oxalate excretion and renal ultrasound were normal. Analysis of the optical form of the glyceric acid by a polarimetric method supported the diagnosis of D-glyceric aciduria [5]. EEG revealed bilateral hemispheric epileptiform activity posteriorly especially dominant at the left side and a hypsarrhythmia pattern. ERG and BAER were found to be normal but VEP showed P1 latency delay. MRI at the age of 16 months showed focal hyperintense areas in the periventricular and subcortical white matter (Fig. 1A). There was increased T₂ signal intensity in the mesencephalon (Fig. 1B, D), pontine tegmentum (Fig. 1C), bilateral dentate nuclei, globus pallidium and thalami (Fig. 1A, D) in a symmetric fashion. White matter myelination was not complete and slightly retarded for his age. The ventricles and cortical sulci, particularly in the frontotemporal region, were enlarged. A fructose free diet was initiated. At the age of 28 months, he had seizures with an average of twice a week, autistic behaviour and severe motor and mental retardation, had no visual contact, but started to sit with support and turn from one side to the other. After initiation of the fructose free diet, D-glyceric acid excretion in urine was within normal limits and VEP was detected to be normal, but BAER showed a bilateral sensorineural type of hearing loss. Follow-up MRI obtained at three years of age revealed further myelination of the white matter. The areas of abnormal signal intensity in the periventricular and subcortical white matter remained unchanged (Fig. 2A). However, the T_2 hyperintensity in the mesencephalon, thalami (Fig. **2B**) and globus pallidi resolved. The signal abnormality in the dentate nuclei persisted. The degree of cerebral atrophy did not show any interval change. Besides fructose restriction in the diet, the patient was also on vigabatrin and diazepam therapy and besides autistic features, VEP and BAER also improved.

Further urine analysis of both parents for D-glyceric acid excretion was found to be within normal limits.

Discussion

Infantile spasms or West syndrome are an age dependent, multietiological epileptic encephalopathy characterised by the following triad: epileptic spasms, arrest of psychomotor development and hypsarrhythmia [12]. It is considered as the unspecific response of an immature brain to a variety of brain insults. Etiological groups are usually categorised into prenatal, perinatal and postnatal depending on the time of cerebral insult [10,12]. West syndrome can be associated with metabolic diseases such as phenylketonuria, nonketotic hyperglycinemia, urea cycle and respiratory chain enzyme deficiencies and biotinidase deficiency [6,12]. In our patient, the clinical and electrophysiological features enabled us easily to diagnose infantile spasms or West syndrome. However, the presence of first degree consanguinity, associated with autistic behaviour, severe mental and motor delay and relative response to antiepileptic treatment suggested an underlying metabolic disorder. It is well known that autistic behaviour may accompany metabolic disorders during the clinical course of the disease and therefore, these findings urged us to perform the urinary organic acid analysis demonstrating the increased excretion of glyceric acid. The L-stereoisomer of this compound, L-glyceric acid is increased in the urine in primary hyperoxaluria type 2 [7]. This is a condition characterised by recurrent nephrolithiasis and an associated excretion of oxalic acid in the urine, without any sign of central nervous system involvement [7]. Normal urinary oxalate excretion within 24 hours and renal ultrasound excluded this entity in our patient. Furthermore, we analysed the optical form of the glyceric acid by a polarimetric method indicating the diagnosis of D-glyceric aciduria [5].

In general, three types of D-glyceric aciduria are recognized, i.e. acidotic presentation, neurological presentation and absence of clinical symptoms. Clinical features have a wide spectrum including severe metabolic acidosis from birth, failure to thrive, delayed motor development, severe encephalopathy with hyperglycinaemia, mental retardation, speech delay, microcephaly, hypotonia, opistotonus, myoclonic jerks or recurrent seizures [1,2,7]. In a previous report by Bonham et al [1], four children who were excreting massive amounts of D-glyceric acid in their urines and other family members were studied extensively. Only two children were symptomatic and were exhibiting only mild neurological features limited to microcephaly and speech delay. Fructose and serine loading tests resulted in a deficiency of Dglycerate kinase, indicating the potentially benign nature of the disease. Largillière et al [9] described a 3 year-old Turkish girl with profound encephalopathy, spastic tetraplegia and hypotrophy in whom a therapeutic trial with sodium benzoate decreased plasma D-glycerate without any clinical improvement and concluded that D-glyceric aciduria can only be a biochemical finding

Short Communication

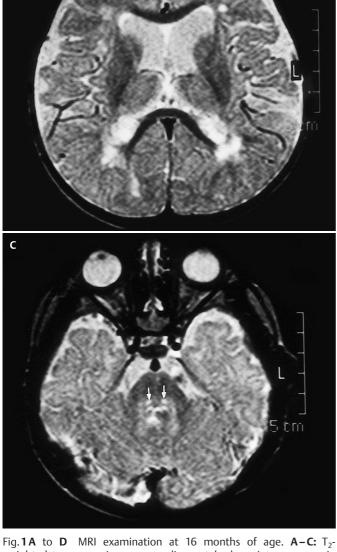
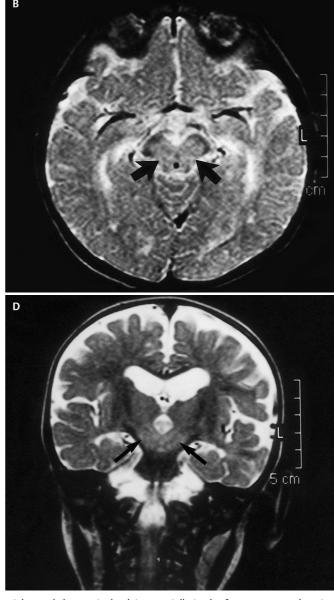


Fig. **1A** to **D** MRI examination at 16 months of age. **A**–**C**: T_2 -weighted transverse images revealing patchy hyperintense areas in the white matter, mostly involving the periventricular region (**A**) and involvement of the mesencephalon (black arrows) (**B**), pontine tegmentum (small white arrows) (**C**) and thalami (**A**) bilaterally. The ven



tricles and the cortical sulci, especially in the fronto-temporal region, are enlarged. Note the myelination is not complete yet. **D** T_2 -weighted coronal image showing increased signal intensity in the bilateral thalami and mesencephalon (black arrows).

without any causal relationship with the various pathological symptoms associated with it.

Despite the large amounts of D-glyceric acid excretion in the urine, our patient did not develop ketotic episodes. He had a marked neurodevelopmental delay and failure to thrive, and clinical findings in the form of marked hypotonia, infantile spasms and autistic behaviour became prominent at the age of 6 months after the introduction of fructose in the diet.

There are three enzyme defects defined in patients with D-glyceric aciduria: D-glycerate dehydrogenase, triokinase and D-glycerate kinase [4,7,11]. In our patient, a fibroblast culture was obtained; however, a loading test was not performed in order not to provoke further deterioration and D-glycerate kinase is the affected enzyme in fructose-related patients. MRI findings in our patient revealed abnormal patchy areas in the periventricular and subcortical white matter associated with cerebral atrophy with frontotemporal prominence that remained unchanged in the follow-up. However, noteworthy was the resolving of the abnormal signal intensity in the mesencephalon, thalami and globus pallidum. The involvement was symmetric on the initial examination at the age of 16 months, but disappeared on the follow-up at three years of age. The dentate nuclei showed persistent symmetric involvement.

MRI findings on the initial examination suggested a metabolicdegenerative disease, though not specific for any known disorder. In a patient with West syndrome patchy white matter lesions may be associated with a variety of causes [12]. However, the possibility of hypoxic-ischemic injury, cerebral dysplasia, infection, hemorrhage and trauma was confidently eliminated in Downloaded by: Collections and Technical Services Department. Copyrighted material

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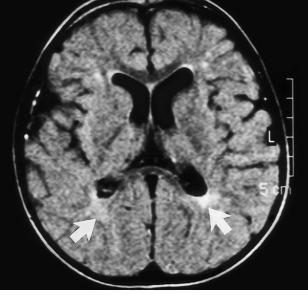
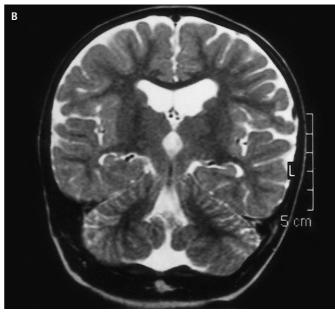


Fig. **2A** and **B** MRI examination at three years of age. **A** Transverse FLAIR image corresponding to Figure **1 A** showing hyperintense white matter lesions (white arrows) with no significant interval change. The degree of cerebral atrophy remains unchanged. **B** T_2 -weighted coro-



nal image corresponding to Figure **1 D**, except for slight difference in angulation showing resolution of the abnormal signal intensity in the mesencephalon and thalami.

this patient based on MRI findings. Periventricular leukomalacia could easily be ruled out in the presence of bilateral thalamic, pallidal and mesencephalic involvement. Konishi et al [8] reported non-specific periventricular hyperintensity in their group of patients with West syndrome; however, the involvement in our patient was not confined to periventricular white matter but additional lesions also existed.

To our knowledge, cerebral MRI findings in D-glyceric aciduria have not been reported in the literature before [3]. Besides, the control MR examination disclosed resolution of the abnormal signal intensity in the brain stem (mainly in the mesencephalon) and deep gray matter (thalami and globus pallidum) following a fructose free diet by elimination of fruits and fruit containing products from the diet, though not necessarily accompanied by full clinical recovery. However, there was some improvement including the patient starting to sit with support, decrease in the severity of autistic behaviour as well as resolution of VEP abnormality. We also found D-glyceric acid excretion within normal limits, which indicates effective fructose restriction in the diet. This observation in the MRI findings may suggest the presence of reversible morphological abnormalities, such as edema, at least in the initial period, which may benefit from fructose restriction.

In conclusion, we believe that D-glyceric aciduria should be considered in patients with West syndrome and autistic behaviour. MRI is not only useful in demonstrating brain involvement but may also show resolution of the abnormalities in the follow-up.

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