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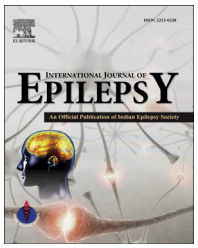

Case Report

Batwing appearance – A neuroradiologic clue to glutaric aciduria-type 1

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ARTICLE INFO

Article history:
Received 6 October 2014
Accepted 11 February 2015
Available online 26 May 2015

Keywords:
Inborn errors of metabolism
Neurodegenerative disorders
Basal ganglia diseases

ABSTRACT

Glutaric aciduria type 1 (GA-1) is a rare inherited neurometabolic disorder due to enzymatic block in the common degradation pathway for lysine and tryptophan. We report a 16 month girl child who presented with an initial acute encephalopathic crisis followed by static encephalopathy with characteristic neuroimaging findings. Diagnosis was confirmed by demonstrating elevated urinary glutaric acid and 3-hydroxyglutaric acid levels. Early diagnosis and adequate dietetic therapy can prevent most of the neurological symptoms.

1. Introduction

Glutaric aciduria type 1 is a rare inherited autosomal recessive inborn error of metabolism due to a deficiency of the mitochondrial enzyme glutaryl coenzyme A (CoA) dehydrogenase which is involved in the catabolism of L-lysine, L-hydroxylysine and L-tryptophan. It has an estimated prevalence of 1 in 100,000 newborn babies. Elevated levels of glutaric acid and its metabolites in the body tissues are responsible for the protean manifestations like acute encephalopathic crises, dystonia, dyskinesia, macrocephaly and mental retardation. Characteristic neuroimaging findings and specific metabolic investigations help in making an early diagnosis. Treatment is by restriction of glutarigenic amino acids, lysine, tryptophan and hydroxyl lysine, and supplementation with carnitine and riboflavin. This article aims to describe our patient with this progressive neurodegenerative condition.

2. Case report

A 16 month old female child was born by second degree consanguineous parentage to a second gravida mother with an uneventful antenatal period at full term by normal vaginal delivery. Her birth weight was adequate and she had an uneventful neonatal period. She achieved social smile and cooing at 3 months, grasping objects at 4 months, neck holding and hand regard by 5 months and sitting with support by 6 months. She remained asymptomatic till 7 months of age when, in association with a transient viral illness, she developed acute encephalopathic features, recurrent tonic seizures and loss of previously acquired milestones. She was started on oral lorazepam and phenobarbitone. Since then she has not achieved any further milestones and continues to have frequent dystonic spasms of neck and limbs. The neurological examination revealed microcephaly (head circumference-

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http://dx.doi.org/10.1016/j.ijep.2015.02.001

41.5 cm), failure to thrive (weight and height less than 5th percentile), bilateral palmar fisting with cortical thumb and intermittent tongue thrusting and dystonic movements of neck in addition to generalized hypertonia. The acute encephalopathic presentation and subsequent neuroregression following a trivial illness during the infancy period as well as the presence of marked extrapyramidal features made us consider the possibility of an underlying neurometabolic disorder like mitochondrial cytopathy or inborn errors of metabolism like glutaric aciduria type 1, biotin responsive basal ganglia disease, organic acidemias and urea cycle defects.

EEG showed paroxysms of slow waves seen synchronously on both sides. Routine hematological and biochemical investigations including thyroid function tests were within normal limits except for mild anemia. CSF analysis was normal and showed normal levels of CSF lactate and pyruvate. Plasma lactate was normal. Computerized Tomography (CT) of the brain showed widening of the sylvian fissures and temporal lobe atrophy with "bat wing sign" as well as bilateral symmetrical basal ganglia hypodensities. Magnetic Resonance Imaging (MRI) of the brain (Fig. 1) confirmed the CT findings with bilateral symmetric T2 weighted hyperintense signals visualized in basal ganglia (Fig. 2) and minimal diffusion restriction (Figs. 3 and 4) in the basal ganglia bilaterally. Tandem mass spectroscopy showed elevated levels of plasma glutarylcarnitine and elevated C5DC/C8 ratio suggestive of glutaric aciduria type 1 which was further confirmed by demonstrating elevated urinary glutaric acid and 3-hydroxyglutaric acid levels. Therapeutic intervention by a low protein diet with restriction of lysine and tryptophan was initiated. High doses of riboflavin and L-carnitine were also supplemented. Antiepileptics were continued for seizure control.

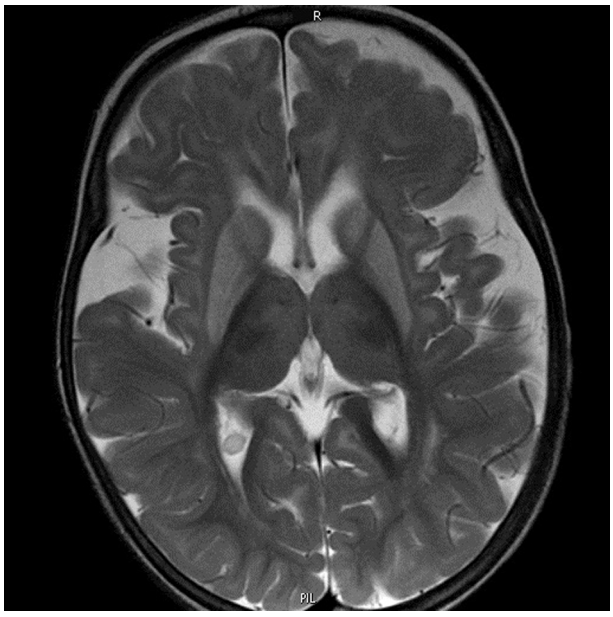

Fig. 2 – T2 axial view of MRI of brain showing bilateral symmetric hyperintense signals in the basal ganglia.

3. Discussion

Glutaric aciduria type 1 was first reported in 1975 by Goodman et al.[1] It is a rare disorder of lysine and tryptophan metabolism

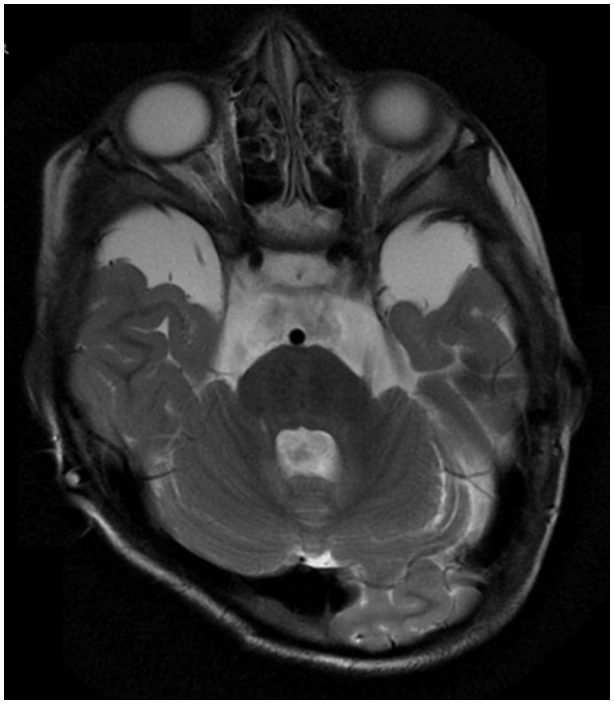

Fig. 1 – T2 axial view of MRI of the brain showing enlarged pretemporal subarachnoid spaces.

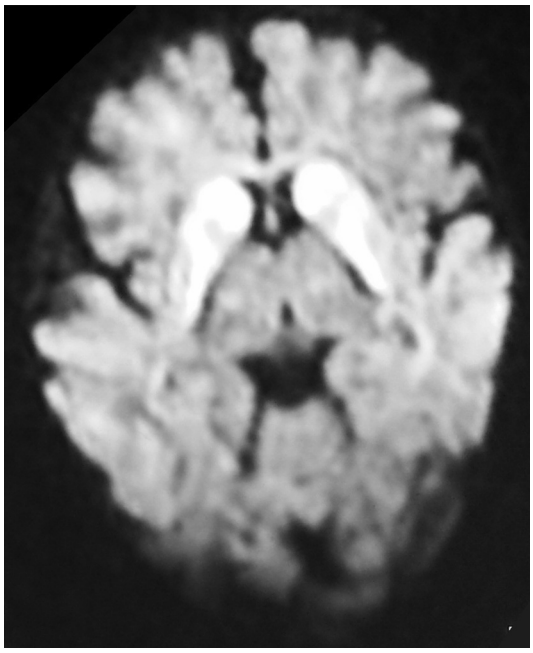

Fig. 3 – Diffusion weighed MR imaging showing bilateral symmetric bright signals in the regions of caudate and putamen.

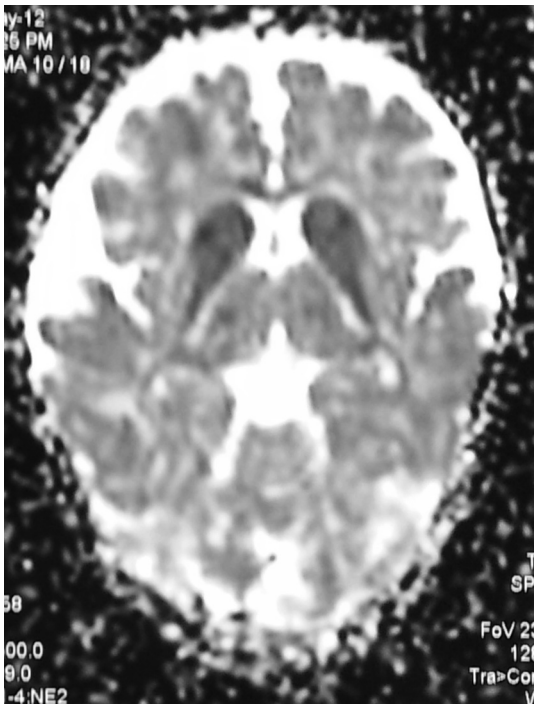

Fig. 4 – Apparent diffusion coefficient MR imaging showing bilateral symmetric dark signals in the corresponding basal ganglia regions.

resulting in accumulation of toxic metabolites which lead to nerve cell damage with resultant brain atrophy and macrocephaly as well as dystonia secondary to striatal degeneration. The enzyme implicated is glutaryl-CoA dehydrogenase (GCDH) located in the mitochondria and encoded by a nuclear gene on chromosome locus 19p13.2.[2] It is important for the intermediary step in the metabolism of L-lysine, hydroxy-L-lysine, and L-tryptophan which involves the oxidative decarboxylation of glutaryl-CoA to crotonyl-CoA.

A deficiency of GCDH leads to the accumulation of glutaric acid and its metabolites, glutaconic acid, and 3-hydroxyglutaric acid in the body. These excess metabolites are excreted in the urine in elevated quantities which can be detected by urine organic acids analysis by gas chromatography–mass spectroscopy (GC–MS) or by urine acylcarnitine profile. Urinary detection of elevated glutaric acid, 3-hydroxyglutaric acid and glutaconic acid is diagnostic for GA-I. Excess glutaryl-CoA reacts with carnitine to form glutarylcarnitine which can be detected by tandem mass spectrometry in dried blood-spots (DBS), an important component of newborn screening.

Genetic heterogeneity and phenotypic variability characterize this disease. Acute neurological symptoms generally occur between 6 and 18 months and are usually triggered by an intercurrent childhood infection, fever or dehydration. Some infants are born with macrocephaly which may be the earliest sign. In an Indian cohort of 11 patients with GA-1 reported by Kamate et al,[3] 72.7% were noted to have macrocephaly. Muranjan et al[4] reported four cases of glutaric aciduria type 1, of which two were noted to have microcephaly. Our patient also had microcephaly which is a less common association. GA I usually presents as an acute encephalopathic metabolic crisis with feeding difficulties, irritability, vomiting, lethargy, and hypotonia during infancy, subsequently leading to a severe dystonic movement disorder. The characteristic clinical features that may aid in suspecting specific neurometabolic disorder with extrapyramidal involvement has been enumerated in Table 1. The pathologic correlate of the acute neurologic deterioration is acute striatal necrosis which is primarily due to toxic effects of 3-hydroxyglutarate on the striatum, mostly affecting GABAergic medium-spiny neurons.[5] Seizures may be part of the symptomatology at the onset of glutaric aciduria type I, but most paroxysmal movements appear to be dystonic episodes.[6] Metabolic crises are triggered by infection, fever, or fasting and become less frequent as the child ages. Bahr et al[7] reported an adolescent GA-1 patient with leukoencephalopathy who presented at a later age with recurrent headaches and oculomotor symptoms responding to carnitine supplements. Kalita et al[8] reported a case of GA-1 that presented with recurrent febrile encephalopathy. Rare complications like rhabdomyolysis, even progressing to status dystonicus, and acute pancreatitis have been reported. Characteristic radiological findings can help clinch the diagnosis. Widening of the sylvian fissures, mesencephalic cistern, and enlarged pretemporal subarachnoid spaces[9] with "batwing" or "box-like" fissures[10] are cardinal MRI features in glutaric aciduria type 1. Other causes of batwing appearance in MRI are enlisted in Table 2. The pathogenesis of subdural effusions is considered to be due to the disproportional temporal lobe hypoplasia with tearing of the arachnoidal membrane.[11] Other findings are subdural effusions, white matter changes, ventriculomegaly, and basal ganglia lesions. Caudate and putaminal necrosis has also been characteristically noted in biotin responsive basal ganglia disease. In the CT and MR findings of the previously reported glutaric aciduria type 1 patients reviewed by Brismar et al,[12] white matter changes was found in 51%, brain atrophy/hypoplasia in 61%, open opercula with wide cerebrospinal fluid spaces anterior to the temporal lobes were seen in 93% and volume loss with high T2 signals of basal ganglia were seen in 44% of the patients. Early prenatal diagnosis made by MRI as early as 22 weeks gestation has also been reported.[13] Diffusion-weighted MR imaging demonstrates more extensive disease than that apparent on conventional MR images, with bilateral involvement of the basal ganglia, consistent with acute necrosis.[14]

Table 1 – Characteristic features to identify etiology of progressive encephalopathy with marked extrapyramidal signs in infancy.

Characteristic finding	Causes
Acute onset	Gluatric aciduria type 1 Biotin responsive basal ganglia disease
Parkinsonian features	Tyrosine hydroxylase deficiency Biopterin metabolism defects
Laryngeal stridor	Pelizeus–Merzbacher disease
Self mutilation	Lesch–Nyhan syndrome
Kernicterus	Crigler–Najjar syndrome

Table 2 – Causes of batwing appearance in MRI.

Batwing 'sylvian fissures'
Glutaric aciduria type 1
Idiopathic external hydrocephalus
Severe developmental delay
Nonaccidental injury

Subdural effusions or hemorrhages with/without retinal hemorrhage are also observed in nonaccidental head injury or shaken baby syndrome with child abuse. Menkes disease can present with subdural collections/hematomas, additionally exhibiting excessively tortuous intra-cranial and extra-cranial arteries. Other disorders with basal ganglia involvement include methylmalonic acidemia, propionic aciduria, Cockayne disease, hypomyelination with atrophy of the basal ganglia and cerebellum, GM2 gangliosidosis and Leigh disease.

Early diagnosis, prevention of acute metabolic crises and emergency care during intercurrent illnesses constitute the crux of the management of GA-1. Basic principles of emergency management is the prevention or reversal of a catabolic state by administration of a high energy intake (plus insulin to control for hyperglycemia), transient restriction of natural protein, prevention of secondary carnitine and maintenance of normal fluid, electrolytes, and pH status. Dietary treatment consists of a low lysine, low tryptophan diet with adequate calorie supplementation and administration of riboflavin and L-carnitine.[15] Few other neurological syndromes that also show characteristic response to riboflavin supplementation have been enumerated in Table 3.

Early institution of therapy can deter the progression of the neurological disability in most patients. Pre-symptomatic diagnosis and treatment initiation is known to prevent the onset of symptoms and may lead to normal development. Lee et al[16] reported that 6 patients with GA-I diagnosed by newborn screening had promising outcomes, though the risks of disease progression prior to 1 year of age remain significant. Genetic counseling and prenatal diagnosis which is done by demonstrating increased concentration of glutaric acid in amniotic fluid are important aspects of management.

4. Conclusion

This case report highlights the various aspects of diagnosis and management of this rare but potentially treatable disease.

Table 3 – Riboflavin responsive neurological syndromes.

Neurological syndromes showing response to riboflavin therapy	Predominant involvement
Brown-Vialetto-van Laere syndrome & Fazio –Londe syndrome	Bulbar
Ethyl malonic adipic aciduria	Hepatomuscular
Riboflavin-responsive oxidative phosphorylation complex I deficiency	Multiple
Riboflavin responsive multiple Acyl-CoA dehydrogenase deficiency	Muscle
Glutaric aciduria type 1	Extrapyramidal
Glutaric acidemia type 2	Brain, Liver, Heart
Riboflavin-responsive lipid-storage myopathy	Muscle

Prompt identification of the clinical scenario with high index of suspicion aided by neuroimaging can ensure early diagnosis in glutaric aciduria type 1. Urinary analysis for organic acids is diagnostic. Effective emergency management of acute metabolic crises can help prevent further neurological deterioration. Low lysine, low tryptophan diet with supplements of L-carnitine and riboflavin form the mainstay of lifelong dietary therapy.

Conflicts of interest

All authors have none to declare.

Contribution of each author

Anusha Doraiswamy – data collection and compilation, drafting of manuscript.

Bhanu Kesavamurthy – concept of manuscript, final synopsis.

Lakshminarasimhan Ranganathan – critical review of literature.

Key messages

1. Clinical presentation can be as acute encephalopathy or chronic extrapyramidal syndrome.
2. Characteristic neuroimaging findings serve to clinch the diagnosis and strong index of suspicion to be kept in the presence of subdural collections.
3. Early diagnosis can minimize the neurological damage and ensure better outcome.

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