

Pediatric Glutaric Aciduria Type 1: 14 Cases, Diagnosis and Management

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Abstract

Introduction: Glutaric aciduria type I is an autosomal recessive disorder of lysine metabolism due to the defect of the enzyme glutaryl-CoA dehydrogenase. The regression of milestones following an intercurrent infection with disabling dystonia is the common presentation. We report the clinical features, diagnosis, and management of 14 south Indian children with glutaric aciduria type I. **Results:** Males predominated the study (57.1%). The mean age of onset of the symptoms was 8.57 ± 3.57 months. The mean age at the time of diagnosis was 35.21 ± 48.31 months. The history of consanguinity was noted in 57.1%. Development was normal prior to the onset of acute crises in nearly three fourths. Acute crises triggered by infection followed by the regression of milestones was the major presenting feature in 10 children (71.4%). Macrocephaly was another prominent feature in an equal number. Bat's wing appearance (fronto temporal atrophy) was present in all children. Nearly 80% had moderate to severe disability in the form of dystonic movement disorder and spastic quadriparesis. **Conclusion:** Glutaric aciduria type I has to be identified and managed early to have a better outcome.

Keywords: Bat's wing appearance, dystonia, glutaric aciduria type I

INTRODUCTION

Glutaric aciduria type I (GAI) is an autosomal recessive disorder caused by the deficiency of glutaryl CoA dehydrogenase, a mitochondrial matrix enzyme involved in the degradation of lysine, hydroxy lysine, and tryptophan.^[1] This results in the accumulation of glutaric acid, 3 hydroxy glutaric acid, and glutaconic acid in the body fluids mainly affecting the central nervous system. The estimated prevalence of GA- I is approximately 1 in 100,000 live births.^[2] Acute encephalopathic crises typically between 6 and 18 months of age, precipitated by an intercurrent infection, immunization, or surgery leads to a severe dystonic-dyskinetic disorder.^[3] Most patients have macrocephaly at birth or develop later. There are a few case reports and isolated case series of this disorder in Indian literature. We report here the clinical features, diagnosis, and management of 14 south Indian children with glutaric aciduria type I.

MATERIALS AND METHODS

Retrospective chart review of patients with a diagnosis of inborn error of metabolism was performed at the Pediatric Neurology outpatient department attached to a Tertiary Care Hospital over a period of 4 years from 2016 to 2019. Diagnosis of GA- I was suspected on historical, clinical, and characteristic neuroimaging findings and confirmed by blood tandem mass spectrometry (TMS) and/or urine gas chromatography and mass spectrometry (GC/MS). The clinical, laboratory, and neuroimaging findings were extracted and entered in a proforma and the data was analyzed after obtaining approval from the institutional review board. The outcome was assessed

from the follow-up notes in the chart. Patients who did not come for follow-up visits were contacted over the mobile phone and enquired about the present status of the child and the details were recorded.

RESULTS

There were 45 cases of inborn errors of metabolism identified during this period of which 14 cases were found to be glutaric aciduria type I (31%). Males predominated the study (57.1%). The mean age of onset of the symptoms was 8.57 ± 3.57 months. The mean age at the time of diagnosis was 35.21 ± 48.31 months. History of consanguinity was noticed in 57.1%. Developmental milestones were normal in the majority (78.6%).

Acute encephalopathic crises triggered by infection followed by the regression of milestones was the major presenting feature noticed in 10 children (71.4%). Macrocephaly was another

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prominent feature noted in 10 (71.4%) children. Seizures were the presenting symptom in 2 cases, 1 had macrocephaly,

Another otherwise asymptomatic. Insidious onset chronic encephalopathy with developmental delay was documented in 2 children (14.3%). 12 out of 14 children (87.7%) had movement disorder predominantly dystonia.

Neuroimaging revealed fronto temporal atrophy with Bat's wing appearance in all (100%) children. Nearly 90% had involvement of corpus striatum [Figure 1a-1c]. Bilateral subdural collections were seen in 2 children (14.3%) [Figure 1d] and deep white matter changes mimicking leucodystrophy in 3 children (21.4%) [Figure 1e, 1f].

On laboratory evaluation, all children had normal blood sugar, serum electrolytes, ammonia, and lactate. Urine ketone bodies were negative. All patients showed elevated glutaryl carnitine levels (C5-DC) with a mean of $0.59 \mu\text{mol/L}$ ($0.56-0.62 \mu\text{mol/L}$) against the normal value ($0.00-0.40 \mu\text{mol/L}$). Eight patients for whom urine organic acids was sent showed increased urinary excretion of glutaric acid and 3OH glutaric acid on GC/MS. Genetic sequencing could not be carried out due to financial constraints.

All our patients were started on protein restricted diet especially low lysine diet and carnitine supplementation— 100mg/kg/day in addition to multi disciplinary care including physiotherapy, occupational therapy, and speech therapy. They were advised to limit the intake of foods containing high protein such as meat, fish, poultry, eggs, milk, cheese and other dairy products, soy and soy products, potatoes, and nuts. Dystonia was managed with anticholinergics, benzodiazepines, and baclofen and seizures with anticonvulsants. Parents were educated about the symptoms of a metabolic crisis such as vomiting, irritability, poor feeding and provided with a written treatment plan

to be followed during emergencies according to the recent guidelines. Growth parameters were monitored in addition to hemoglobin, calcium, liver enzymes, vitamin B12 levels, and serum protein levels during follow up visits.

The mean duration of follow up was 16.07 ± 9.47 months. Only 2 children who did not have acute crises prior to diagnosis (patient 5, 11) are gaining milestones normally, they do not have focal neurological deficits as well. Eight (57.1%) have achieved independent sitting, yet to stand or walk with mild to moderate dystonia. Remaining four (21.4%) are bedridden with severe movement disorder. The clinical and neuroimaging features are depicted in Table 1.

DISCUSSION

Glutaric aciduria type I is an important but rare organic aciduria with an estimated prevalence of approximately 1 in 100,000 births. It is caused by mutations in the *GCDH* gene, located to 19p13.2.^[4] Biochemically, GA- I is characterized by an accumulation of glutaric acid (GA), 3-hydroxyglutaric acid (3-OH-GA), glutaconic acid, and glutaryl carnitine (C5DC). These can be detected in body fluids (urine, plasma, CSF) and tissues by gas chromatography/mass spectrometry (GC/MS) or tandem mass spectrometry (TMS/MS).^[5] Diagnosis can be confirmed by significantly reduced enzyme activity and or detection of disease-causing mutations on both *GCDH* alleles.^[6] Over 200 *GCDH* mutations have been reported worldwide. Exons 11 and 8 of the *GCDH* gene seem to be the mutational hot spot regions and c. 1204C> T (p.Arg402Trp) is probably the most common mutant allele in Indian patients with GAI.^[7]

The usual age of presentation for GA- I is 6 months to 2 years of life. Acute neuroregression or dystonia following

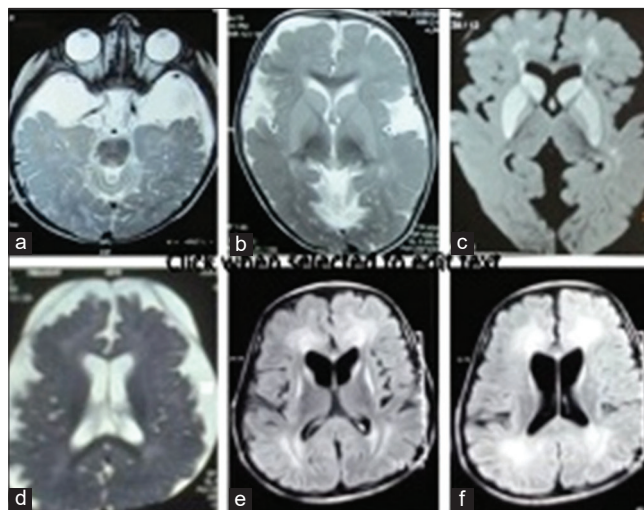


Figure 1: Patient 3(a-c).Magnetic resonance imaging T2 axial images of the brain (a,b) showing bilateral fronto temporal atrophy, wide open sylvian fissures - Bats wing appearance and involvement of caudate and putamen. Diffusion weighted image (c) showing diffusion restriction in caudate, putamen during acute encephalopathic crisis. Patient 4(d). Axial T2 MR image showing bilateral chronic sub dural hematomas in frontal regions. Patient 14(e,f). Axial Fluid attenuated inversion recovery (FLAIR) sequences showing periventricular and deep white matter involvement with caudate and putamen atrophy

Table 1: Clinical and neuroimaging features of children with Glutaric aciduria type 1

| Patient | Age of onset & Sex | Age at diagnosis | Cons Anguinity | Acute meta bolic crisis | Large Head | DD | Seiz ures | Movement Disorder | MRI/CT - Fronto temporalatrophy | BG changes | SDH | WM Changes | Period of follow up |
|---------|--------------------|------------------|----------------|-------------------------|------------|----|-----------|--|---------------------------------|--------------------------|-----|------------|---------------------|
| 1. | 6m Male | 18m | -- | + | + | + | -- | Dystonia | + | + | -- | -- | 24m |
| 2. | 8m Male | 11m | + | + | + | -- | -- | Dystonia Generalised | + | + | + | -- | 36m |
| 3. | 16m Female | 18m | + | + | -- | -- | -- | Dystonia UL Spastic quadripareisis | + | + | -- | -- | 30m |
| 4. | 6m Male | 7m | + | + | + | -- | + | Dystonia Spastic quadripareisis | + | GP | + | -- | 6m |
| 5. | 5m Male | 7m | -- | -- | + | -- | + | -- | + | -- | -- | -- | 12m |
| 6. | 6m Male | 7m | + | + | + | -- | + | Dystonia UL | + | + | -- | -- | 12m |
| 7. | 4m Female | 8m | -- | + | -- | -- | -- | Dystonia UL | + | + | -- | -- | 18m |
| 8. | 6m Female | 12m | + | + | -- | -- | -- | Dystonia UL | + | + | -- | -- | 10m |
| 9. | 11m Female | 15m | + | -- | + | + | -- | Dystonia L UL | + | + | -- | -- | 18m |
| 10. | 10m Female | 12m | + | + | + | -- | -- | Oro facial dystonia Choreoathetosis | + | + | -- | -- | 12m |
| 11. | 6m Male | 6m | + | -- | -- | -- | + | -- | + | -- | -- | -- | 3m |
| 12. | 12m Male | 11y | -- | -- | + | + | -- | Generalised dystonia,Chorea upper limbs, bipyramidal signs | + | + | -- | + | 12m |
| 13. | 12m Male | 10y | -- | + | + | -- | + | Dystonia UL Orofacial dyskinesia Spastic quadripareisis | + | + | -- | + | 24m |
| 14. | 12m Female | 10y | -- | + | + | -- | + | Dystonia UL Spastic quadripareisis Dysarthria | + | Caudate putamen atrophy+ | -- | + | 8m |

an initial phase of normal or almost normal development is a common mode of presentation, at times preceded by seizures.^[8] The other frequent presentation of GA- I is a chronic encephalopathy associated with choreoathetosis or dystonia^[9] often misdiagnosed as athetoid cerebral palsy. Acute encephalopathic crises triggered by infection followed by the regression of milestones was noticed in 10 (71%) of the patients in our cohort. The characteristic neurologic sequelae of these crises are acute bilateral striatal injury followed by axial hypotonia, generalized dystonia and other dyskinetic/hyperkinetic movement disorders, spasticity, developmental regression, seizures, and ultimately dystonic tetraparesis.^[6,8] Dystonia was the predominant type of movement disorder noticed in our cohort to an extent of 88%. Two children (14.3%) (Patients 9,12) had an insidious onset chronic encephalopathy pattern with developmental delay, involuntary movements and were diagnosed as extrapyramidal cerebral palsy prior to referral to our centre. Zayed *et al.* have demonstrated acute onset of neuro regression in 71.9% and

insidious onset of symptoms in 19% of children in their cohort of 89 patients with GAI.^[10]

The interval between the onset and diagnosis varied between 1 to 4 months in the majority. However, diagnosis was delayed up to 10–11 years in 3 children (Patients 12,13,14). Though 2 of them had an encephalopathic crises at 1 year of age, glutaric aciduria was not suspected. One was labeled as leucodystrophy (Patient 13) and the other was diagnosed as post encephalitic sequelae (Patient 14) elsewhere. Patient number 12 had an insidious onset with developmental delay and movement disorder, hence misdiagnosed as extrapyramidal cerebral palsy. The clinical finding of macrocephaly along with characteristic imaging findings helped us to suspect GAI in these children.

Macrocephaly may be the first manifestation of GA- I.^[11] Mahfoud *et al.* have reported the finding of in utero macrocephaly as a sign to early diagnosis of GAI.^[12] Macrocephaly was observed in 71% of our children, which

is in agreement with studies by Sahedal *et al.* and Kamate *et al.*^[13,14] Frequency of epilepsy is increased in patients with GA- I , and seizures might even be the initial clinical presentation.^[15] Two of our children had seizures as their initial presentation. Glutaric aciduria type I so far had been considered a pure “cerebral organic aciduria.” As a first extracerebral manifestation, a recent study reported an increased frequency of chronic kidney disease in affected adults.^[16]

The characteristic imaging findings of GA - I include fronto temporal atrophy, incomplete opercularization of the insular cortex, widening of the Sylvian fissures and enlarged anterior temporal CSF spaces described as typical BAT’S WING appearance.^[17] Fronto temporal atrophy was noted in all our patients (100%) and is in accordance with the study by Kamate *et al.* Structural changes of basal ganglia occur during acute decompensation. 79% of our patients showed bilateral corpus striatal involvement, which is in agreement with the study by Singh *et al.*^[18] Deep white matter and diffuse periventricular white matter involvement can occur in early or late onset subtypes of GA I and they seem to be correlated with duration of the disease.^[19] As the disease progresses, generalized cerebral atrophy, ventricular dilatation, and basal ganglia atrophy become more conspicuous. Three children of our cohort, who were diagnosed as GA I at 10 –11 years of age showed periventricular and deep white matter changes in addition to the other characteristic imaging findings. Subdural hygromas and subdural hemorrhages may accompany cerebral atrophy in children with GAI . Cerebral atrophy and tearing of bridging veins represent the most likely mechanism for the development of these collections. Since affected individuals may remain asymptomatic, subdural hematomas in GA- I may be mistaken as abusive head trauma.^[20] Two of our cases had bilateral subdural haemorrhages (SDH). One of them had a history of fall from cot, diagnosed as traumatic subdural haemorrhage and underwent subdural tapping. One should always look for additional imaging findings in such cases. SDH is usually found in combination with other imaging abnormalities characteristic for GA- I (i.e. fronto temporal atrophy, wide open opercula, and involvement of basal ganglia).

Metabolic derangement, which is the hallmark of organic aciduria, is minimal or absent in GA I even during acute episodes. None of our children showed metabolic derangement.

Ideally GA I should be diagnosed in the newborn period with newborn screening, since with early management children can be asymptomatic. Patients diagnosed by neonatal screening had a much better speech and fine and gross motor development and a significantly lower incidence of macrocephaly or muscular tone abnormalities than patients who were diagnosed by referral and were delayed in their diagnosis.^[10] The overall morbidity score of patients who were diagnosed at the neonatal screening was significantly more favorable compared to that of patients who were diagnosed later in life^[8] that underlies the importance of newborn screening to diagnose treatable

neurometabolic disorders such as GA I at the earliest. In the absence of universal newborn screening, GA I should be suspected in children who present with unexplained macrocephaly, acute encephalopathy, loss of milestones following infections, movement disorders, especially dystonia following infections with typical neuroimaging findings.

Differential diagnosis includes encephalitis, Reye’s syndrome, familial infantile bilateral striatal necrosis during the acute crisis and postencephalitic sequelae, dystonic cerebral palsy, battered child syndrome with chronic subdural effusions in the chronic phase.

Treatment consists of protein restricted diet, especially low lysine diet, carnitine supplementation in the dose of 100 mg/kg/day, and intensified emergency treatment during catabolism. 80–90% of individuals remain asymptomatic if treatment is started in the newborn period before symptom onset. Treatment after symptom onset, however, is less effective. Management of acute metabolic crisis includes the prevention or reversal of a catabolic state by administration of a high-energy intake (plus insulin to control for hyperglycemia if required), reduction of GA and 3-OH-GA production by transient reduction or omission of natural protein for 24-48 hours, amplification of physiological detoxification mechanisms and prevention of secondary carnitine depletion by L-carnitine supplementation (doubling the maintenance dose of 100 mg/kg day) and maintenance of normal fluid, electrolytes, and pH status.^[21] In general, treating movement disorder associated with GA- I is challenging, with little evidence regarding the effectiveness of specific drugs. Nearly 80% of our cohort have disabling dystonia, spastic quadriparesis and have not or only regained few milestones and are dependent on the caregiver, which is comparable to the study by Kamate *et al.*

Since GA I is an autosomal recessive disorder and has a recurrence risk of 25% in future pregnancies, prenatal diagnosis should be offered to the family and asymptomatic siblings should be screened for GA I and managed appropriately. Prenatal testing can be performed by genetic and GCDH enzyme analysis of chorionic villi sample or through measuring GA levels in amniotic fluid.

CONCLUSION

Glutaric aciduria type- I is a treatable neurometabolic disorder that should be diagnosed early and appropriately treated to have a better outcome. A high index of suspicion is necessary to identify this disorder in any child presenting with developmental delay, macrocephaly, movement disorder, and neuroimaging revealing fronto temporal atrophy with poor opercularisation of Sylvian fissures.

Points to remember

1. Glutaric aciduria type- I is an autosomal recessive disorder of lysine metabolism.
2. Macrocephaly may be the earliest feature. Hence any

child with unexplained macrocephaly, urine organic acids assessment should be done to rule out glutaric aciduria.

3. In the cases of acute encephalopathic crises associated with acute striatal necrosis triggered by infections, immunizations and surgery is the major prognosticating factor for morbidity.
4. Children with disabling movement disorder may be misdiagnosed as extra pyramidal cerebral palsy.
5. Bilateral subdural collections in children with glutaric aciduria may be mistaken as due to child abuse.
6. Early diagnosis and treatment allows normal growth and development.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent forms in the form the patients have given their consent for their images and other clinical information to be reported in this journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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