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Case Report

Pathology Section

A Case of Glutaric Aciduria Type I: An Unusual Cause of Macrocephaly and Developmental Delay

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ABSTRACT

Glutaric Aciduria Type I (GA-I) is a rare autosomal recessive neurometabolic disorder caused by deficiency of glutaryl-CoA dehydrogenase, leading to accumulation of glutaric acid and 3-hydroxyglutaric acid with subsequent neurotoxicity. A seven-month-old male infant presented with developmental regression, macrocephaly, and recurrent seizures since five months of age. Seizures were characterised by tonic posturing of all four limbs with upward deviation of eyes, followed by postictal drowsiness. Neuroimaging revealed widened Sylvian fissures with a characteristic "bat-wing" appearance, hypoplastic temporal lobes, basal ganglia involvement, and a left-sided subdural haematoma. Tandem mass spectrometry showed elevated glutaryl carnitine (C5-DC: 0.47 µmol/L), and genetic analysis identified a homozygous missense variant in the GCDH gene (c.769C>T; p.Arg257Trp), confirming the diagnosis. The child was managed with a lysine-restricted diet, L-carnitine, riboflavin, and antiepileptic therapy. The subdural haematoma was managed conservatively following neurosurgical consultation. This case highlights the importance of early recognition of GA-I in infants presenting with macrocephaly, developmental delay, and characteristic neuroimaging findings, as prompt diagnosis and metabolic therapy can prevent irreversible neurological injury and improve long-term outcomes.

Keywords: Carnitine, Organic acidemia, Seizure, Subdural haematoma, Tandem mass spectrometry

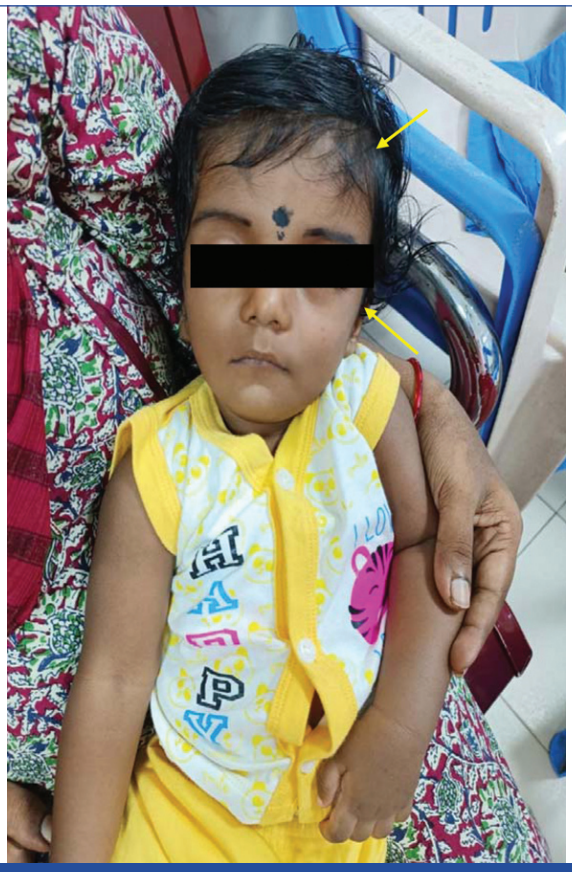
CASE REPORT

A seven-month-old male infant, second born to third-degree consanguineous parents, presented with global developmental delay, regression of milestones, and recurrent seizures since five months of age. The child was apparently well until five months of age, following which he developed multiple seizure episodes. The seizures were characterised by tonic posturing of all four limbs with upward deviation of eyes, lasting less than one minute, followed by postictal drowsiness. He had 3-4 similar episodes during initial hospitalisation and was started on clonazepam. Following the onset of seizures, regression of previously attained milestones was noted. Prior to illness, the child had achieved neck control at three months, rolling over and bimanual grasp at five months, social smile at two months, and recognition of parents at three months. Antenatal and perinatal history was uneventful. The child was born at term by Lower Segment Caesarean Section (LSCS) with a birth weight of 2.5 kg and cried immediately after birth.

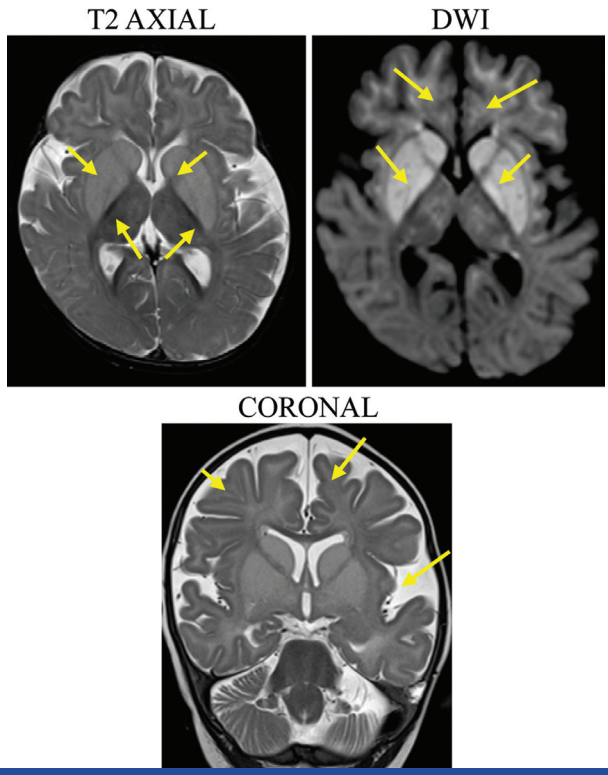
Developmental assessment revealed severe global developmental delay with a developmental quotient of approximately 25%. Family history revealed third-degree consanguinity, one healthy sibling, and a history suggestive of sudden infant death in a paternal relative. There was also a history of progressive gait abnormalities in the father and paternal aunt, though no formal evaluation was performed. Genetic evaluation of affected family members could not be performed due to resource limitations. Anthropometry showed weight 7 kg (0 to –2 SD), length 70 cm (+1 to +2 SD), and head circumference 48 cm (+2 to +3 SD), suggestive of macrocephaly.

On examination, the child had dysmorphic facies including depressed nasal bridge and low-set ears [Table/Fig-1]. Neurological examination revealed generalised hypotonia with evolving appendicular hypertonia, brisk deep tendon reflexes, and extensor plantar response appropriate for age. Systemic examination revealed that cardiovascular, respiratory, and abdominal examinations were within normal limits.

The Magnetic Resonance Imaging (MRI) brain showed widened Sylvian fissures with characteristic "bat-wing" appearance, hypoplastic temporal lobes, symmetrical signal changes in bilateral basal ganglia, and prominent extra-axial spaces [Table/Fig-2]. Computed Tomography (CT) brain revealed a large left convexity subdural haematoma (~16 mm) with midline shift and mass effect [Table/Fig-3]. There was no history of trauma or non accidental



[Table/Fig-1]: Facial dysmorphism showing macrocephaly (arrow) depressed nasal bridge and low-set ears.



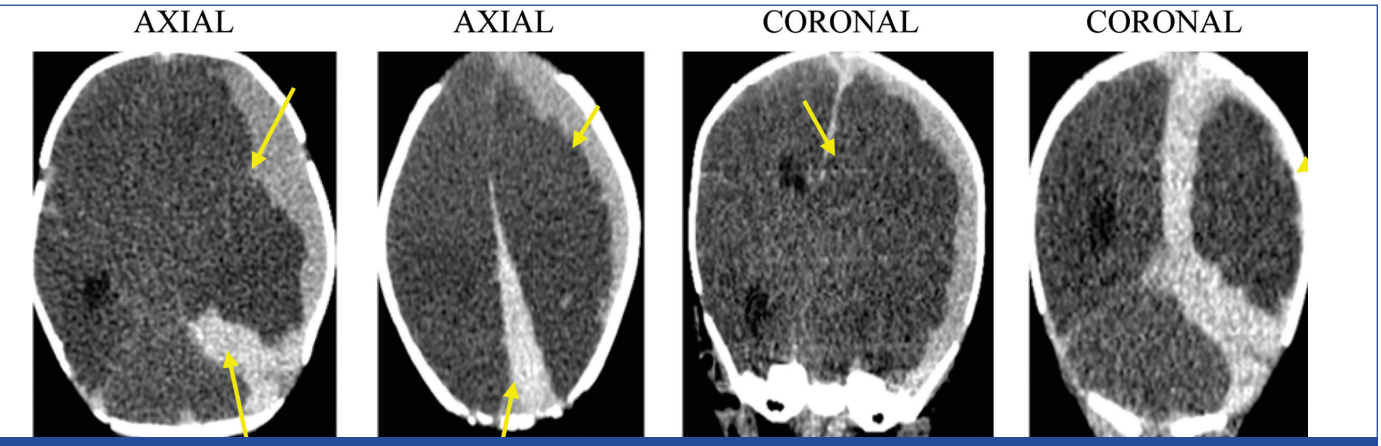
[Table/Fig-2]: MRI brain showing widened Sylvian fissures "bat-wing appearance", basal ganglia involvement, and prominent extra-axial spaces.

The child was started on Trihexyphenidyl 0.25 mg twice daily, Clonazepam 0.5 mg twice daily, L-carnitine 2.5 mL twice daily, and Riboflavin 100 mg once daily as adjunctive metabolic therapy, along with supportive care. A lysine-restricted diet was advised and continued during follow-up, with avoidance of high-lysine foods such as meat, dairy products, and pulses. After two weeks of hospitalisation, the child was discharged on the same medications. At three-month follow-up, partial seizure control and mild neurological improvement were observed.

At 3-month follow-up, the child continued on the same medications with partial control of seizures. Mild neurological improvement was noted in the form of reduced irritability, improved neck holding, better interaction with caregivers, and decreased frequency of abnormal movements; however, developmental delay persisted.

DISCUSSION

The GA-I is a rare autosomal recessive neurometabolic disorder caused by deficiency of glutaryl-CoA dehydrogenase, resulting in accumulation of glutaric acid and 3-hydroxyglutaric acid. These metabolites exert neurotoxic effects, particularly involving the basal ganglia [2]. Clinically, GA-I commonly presents with macrocephaly, developmental delay, and regression of milestones. Early manifestations may precede acute encephalopathic crises, emphasising the importance of early recognition [3,4]. Several studies have reported cases of GA-I presenting with subdural haematoma, which can mimic non accidental injury. Kölker S et al., described the phenotypic variability of GA-I, including subdural collections



[Table/Fig-3]: CT brain showing left convexity subdural haematoma with midline shift.

injury, and no external signs of injury. Coagulation profile was normal. Despite the presence of a left convexity subdural haematoma (~16 mm) with mild midline shift, the child remained haemodynamically stable without signs of raised intracranial pressure, focal neurological deficits, or rapid neurological deterioration. Following neurosurgical consultation, conservative management with close clinical and radiological monitoring was advised, considering the underlying diagnosis of GAI and the absence of indications for immediate surgical intervention.

Tandem mass spectrometry showed elevated glutaryl carnitine (C5-DC: 0.47 µmol/L) [Table/Fig-4]. Genetic analysis identified a homozygous missense variant c.769C>T (p.Arg257Trp) in exon 8 of the GCDH gene, which was classified as likely pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines proposed by Richards S et al., [1]. Metabolic evaluation revealed normal plasma amino acid levels with low free carnitine and elevated glutaryl carnitine levels [Table/Fig-4,5].

Differential diagnoses considered included hypoxic-ischaemic encephalopathy, non accidental injury, mitochondrial disorders, and other organic acidemias, which were excluded based on clinical history, imaging findings, and metabolic evaluation. Hence, a final diagnosis of GA-I with subdural haematoma presenting as developmental regression and seizures was made.

Carnitine	Observed values (µmol/L)	Reference range (µmol/L)
Free carnitine, C0	6.17 ↓	9.00 - 69.00
Acetylcarnitine, C2	4.15	2.00 - 63.00
Propionylcarnitine, C3	0.42	0.08 - 5.65
Butyrylcarnitine, C4	0.04	0.00 - 1.30
3-OH-butyrylcarnitine, C4-OH	0.01	0.00 - 0.50
Isovaleryl/2-methylbutyrylcarnitine, C5	0.07	0.00 - 0.70
3-OH-isovalerylcarnitine, C5-OH	0.07	0.00 - 0.80
Glutarylcarnitine, C5-DC	0.47 ↑	0.00 - 0.38
Tiglylcarnitine, C5:1	0.01	0.00 - 0.25
Hexanoylcarnitine, C6	0.02	0.00 - 0.40
Adipylcarnitine, C6DC	0.02	0.00 - 0.60
Octanoylcarnitine, C8	0.01	0.00 - 0.48

[Table/Fig-4]: Acylcarnitine profile showing low free carnitine and elevated glutarylcarnitine suggestive of Glutaric Aciduria Type I (GA-I).

Amino acid	Observed values (µmol/L)	Reference range (µmol/L)
Alanine	231.00	74.00 - 613.00
Arginine	19.64	0.00 - 72.00

Argininosuccinic acid	0.06	0.00 - 2.02
Citrulline	9.93	0.00 - 45.00
Glycine	195.95	2.00 - 745.00
Leucine/Isoleucine/Hydroxyproline	63.00	26.00 - 300.00
Methionine	10.73	1.00 - 44.00
Ornithine	77.28	0.00 - 239.00
Phenylalanine	34.69	21.00 - 136.00
Proline	101.80	38.00 - 385.00
Tyrosine	59.90	17.00 - 250.00
Valine	83.21	41.0 - 285.00

[Table/Fig-5]: Plasma amino acid profile showing amino acid levels within normal reference range.

in affected children [5]. Boy N et al., further highlighted that early clinical features such as macrocephaly and delayed milestones may be present before neurological deterioration [6]. Previous reports by Kölker S et al., Boy N et al., and Harting I et al., have demonstrated that infants with GA-I may present with macrocephaly and subdural haematoma in the absence of trauma, often leading to diagnostic confusion with non accidental injury [5-7].

The pathogenesis of subdural haematoma in GA-I is attributed to stretching of bridging veins due to cerebral atrophy [7]. In such scenarios, absence of trauma, normal coagulation profile, and characteristic neuroimaging findings help differentiate metabolic causes from traumatic aetiologies [8]. Neuroimaging plays a pivotal role in diagnosis. Classical MRI findings include widened Sylvian fissures ("bat-wing" appearance), frontotemporal atrophy, and basal ganglia involvement. These features help distinguish GA-I from hypoxic-ischaemic encephalopathy, mitochondrial disorders, and other organic acidemias [9]. Early diagnosis is crucial, as prompt initiation of therapy can prevent irreversible neurological damage. Management includes a low-lysine diet, L-carnitine supplementation, and riboflavin in selected cases [10,11]. During intercurrent illnesses, emergency protocols with adequate caloric intake and avoidance of catabolism are essential [12]. Studies have shown that early-treated patients have significantly improved neurological outcomes compared to those diagnosed after symptom onset. Regular follow-up with biochemical monitoring is important to ensure treatment adherence and to reduce long-term neurological disability [13,14]. This case underscores the importance of considering metabolic disorders such as GA-I in infants presenting with macrocephaly and subdural haematoma, to avoid misdiagnosis and ensure timely intervention.

CONCLUSION(S)

The GA-1 is a rare but important neurometabolic disorder that should be suspected in infants presenting with macrocephaly, developmental regression, seizures, and subdural haematoma without a history of trauma. Characteristic neuroimaging findings, supported by tandem mass spectrometry and genetic analysis, are essential for establishing an early diagnosis. Timely initiation of metabolic therapy, including lysine-restricted diet, L-carnitine, and riboflavin supplementation, may significantly reduce neurological deterioration and improve long-term outcomes. This case emphasises the need for increased clinical awareness to prevent delayed diagnosis and misinterpretation as non accidental injury. Early recognition and multidisciplinary management are crucial in minimising irreversible neurological damage and improving quality of life.

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