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Acute Flaccid Paralysis in Infancy: A Rare Presentation of Glutaric Aciduria Type I

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Abstract

Glutaric aciduria type I (GA1) is a rare autosomal recessive disorder caused by deficiency of glutaryl-CoA dehydrogenase, disturbing lysine, hydroxylysine, and tryptophan metabolism [1]. Although typical presentations include dystonia and developmental delay, acute flaccid paralysis (AFP) is a seldom recognized manifestation [2]. We describe a 10-month-old girl, evaluated at Wadia Children's Hospital, Mumbai in June 2023, presenting with AFP and neuroregression post-febrile illness. MRI revealed striatal injury and subdural collections. Diagnosis was confirmed by elevated glutarylcarnitine (C5DC) and pathogenic GCDH mutation. Early lysine-restricted diet and carnitine supplementation stabilized her course. This report emphasizes the need to consider GA1 in AFP, especially with macrocephaly and suggestive neuroimaging, and highlights that prompt management is crucial for improved outcomes [3].

Keywords: Glutaric aciduria type I, acute flaccid paralysis, macrocephaly, basal ganglia injury, metabolic disorder

Introduction

GA1 is a rare metabolic disorder resulting from bi-allelic mutations in the GCDH gene, leading to accumulation of neurotoxic glutaric acid and related metabolites [4]. The basal ganglia are particularly vulnerable, and clinical onsets may be triggered by stress (infection, fever), often after a symptom-free period [5]. Macrocephaly, dystonia, and developmental delay are typical, but AFP remains an unusual presentation and may be mistaken for Guillain–Barré syndrome or

Vol.9, No. 04; 2025

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spinal muscular atrophy [6]. Neuroimaging—especially widened Sylvian fissures and striatal lesions—can aid in early detection and prompt metabolic testing [7]. This report highlights a rare case of GA1 manifesting predominantly with AFP, underscoring diagnostic and management considerations [8].

Materials and Methods

The case was evaluated and managed at Wadia Children's Hospital, Mumbai in June 2023. A detailed clinical evaluation and investigations were performed, including neurological examination, magnetic resonance imaging (MRI) and MR spectroscopy, tandem mass spectrometry (TMS) for acylcarnitine profile, urine organic acid analysis, and molecular genetic testing confirming a pathogenic GCDH mutation. Written informed consent was obtained from the parents, and institutional ethical clearance was secured prior to diagnosis and therapy [9]. Standard metabolic emergency protocols and dietary management were followed as per established recommendations [10].

Case Presentation

A 10-month-old girl presented after five days of fever and loose stools, followed by regression of motor milestones without seizures or prior neurologic illness. On examination:

- *Large head circumference (49 cm)*
- *Frontal bossing*
- *Generalized hypotonia*
- *Full Glasgow Coma Score (15/15)*
- *Preserved reflexes*

Investigations

- **MRI Brain:** Bilateral subdural hematomas, symmetrical putamen/thalamic changes, widened Sylvian fissures ("bat-wing" appearance).
- **MR Spectroscopy:** Reduced N-acetylaspartate (NAA), normal choline/creatine peaks.
- **TMS Screening:** Elevated C5DC (glutarylcarnitine).
- **Genetic Testing:** Homozygous pathogenic GCDH mutation confirmed.

Anthropometric Profile

Parameter	Measured	Expected	Interpretation
Weight	8 kg	8.5 kg	Mild undernutrition
Length	72 cm	72 cm	Normal
Head Circumference	49 cm	45 cm	Macrocephaly

Vol.9, No. 04; 2025

ISSN: 2581-3366

Management

- Lysine- and tryptophan-restricted diet using specialised metabolic formulas.
- Oral carnitine supplementation to aid excretion of toxic metabolites and prevent secondary carnitine deficiency.
- Close monitoring and parental education regarding metabolic crises and emergency management during intercurrent illnesses [11].

Discussion

Glutaric aciduria type I (GA1) is a potentially treatable cause of severe neurological impairment when detected early [12]. It results from deficiency of glutaryl-CoA dehydrogenase in the lysine, hydroxylysine, and tryptophan catabolic pathway, leading to accumulation of glutaric acid and 3-hydroxyglutaric acid in body fluids and tissues; these metabolites exert neurotoxic effects, particularly on the basal ganglia, resulting in characteristic movement disorders and, in some cases, acute encephalopathic crises [13]. While dystonia, developmental delay, and movement disorders are commonly described presentations [14], AFP is a rare and underrecognized manifestation [1,2]. In regions where AFP commonly prompts evaluation for polio, Guillain–Barré syndrome, transverse myelitis, or spinal muscular atrophy, GA1 can be overlooked [3]. In our case the index presentation was symmetric limb weakness and hypotonia with preserved reflexes and consciousness, a clinical picture that may mimic peripheral causes of AFP. Pathophysiologically, selective vulnerability and necrosis of striatal GABAergic neurons from accumulation of neurotoxic metabolites can disrupt tone-regulatory circuits, producing a flaccid presentation early in the disease course rather than the typical hyperkinetic syndromes [4,5].

Neuroimaging as a Diagnostic Clue

MRI commonly demonstrates widened Sylvian fissures with frontotemporal atrophy (the "batwing" sign), symmetric basal ganglia lesions—particularly striatal (putamen) signal changes—and sometimes subdural collections [6,7]. In this patient, bilateral subdural hematomas accompanied striatal changes. Subdural collections in GA1 are commonly attributed to stretching and vulnerability of bridging veins secondary to macrocephaly and frontotemporal atrophy rather than to non-accidental trauma; misinterpretation can therefore provoke unnecessary child protection investigations if the metabolic context is not considered [8,9].

Triggering Factors and Metabolic Crisis

Clinical deterioration in GA1 is frequently precipitated by catabolic stressors such as fever, infection, prolonged fasting, or surgical stress that amplify lysine catabolism and provoke accumulation of toxic metabolites [10,11]. Our patient's deterioration after a febrile gastroenteritis-like illness is consistent with this well-described pattern [12].

Vol.9, No. 04; 2025

ISSN: 2581-3366

Diagnostic Challenges and the Importance of Early Detection

Several factors impede timely diagnosis, especially in low- and middle-income settings: rarity and limited clinician familiarity with atypical phenotypes; overlap with more common causes of AFP; limited availability of TMS-based newborn screening; and imaging interpretation pitfalls where subdural hematomas divert attention from a metabolic etiology [7,13]. Published data strongly support that early detection—ideally by newborn screening using tandem mass spectrometry—before the first metabolic crisis reduces the incidence of severe striatal injury and improves neurodevelopmental outcomes [16,17].

Therapy, Crisis Management, and Prognosis

Management aims to limit precursor availability and accelerate clearance of toxic metabolites. Core strategies include dietary restriction of lysine and tryptophan (using specialised formulas), carnitine supplementation to promote excretion of acylcarnitines, and aggressive management of intercurrent illnesses with catabolic avoidance and prompt caloric support [14,15]. During acute crises, intensified metabolic support and careful monitoring are imperative. Outcomes vary; children diagnosed and managed before their first encephalopathic crisis may achieve near-normal development, while those with established striatal necrosis often have permanent motor deficits, dystonia, or developmental impairment [16,18].

This case underscores the value of incorporating GA1 into newborn screening programs, particularly in populations with higher consanguinity, as screening with TMS enables pre-symptomatic identification and initiation of preventive measures that markedly reduce morbidity [16,17]. Clinicians should maintain a high index of suspicion for GA1 in infants with AFP when macrocephaly and symmetric basal ganglia lesions are present, recognize that subdural collections can be part of GA1's imaging phenotype and are not always traumatic, and expedite metabolic testing (TMS, urine organic acids) and genetic confirmation (GCDH) when imaging or clinical context suggests GA1. Early dietary therapy and carnitine supplementation, combined with vigilant crisis management, offer the best chance to prevent further neurological deterioration [12–15]. In conclusion, GA1 should be included in the differential diagnosis of AFP in infants, especially if macrocephaly and classical neuroimaging features are identified, with rapid metabolic and genetic workup and timely treatment being essential to prevent progression and improve long-term outcomes [17,18].

Conclusion

Glutaric aciduria type I must be considered in infants presenting with acute flaccid paralysis, particularly when macrocephaly and symmetric basal ganglia lesions are evident on MRI. Newborn screening and early dietary and supportive management are crucial to reducing the risk of irreversible neurological disability.

Vol.9, No. 04; 2025

ISSN: 2581-3366

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Conflict of Interest

No conflicts declared.

Abbreviations

- GA1 – Glutaric Aciduria Type I
- AFP – Acute Flaccid Paralysis
- C5DC – Glutarylcarnitine
- GCDH – Glutaryl-CoA Dehydrogenase
- MRI – Magnetic Resonance Imaging
- NAA – N-acetylaspartate
- TMS – Tandem Mass Spectrometry

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Vol.9, No. 04; 2025

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