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Neonatal-Onset Glutaric Aciduria Type II: A Case Report and Literature Review

Yamen Elmoghany

yamen.elmoghany@medcarehospital.com

Medcare Hospital Sharjah

Mohammed Abozaid

Medcare Hospital Sharjah

Mona Hassan

Medcare Hospital Sharjah

Aijas Moidu

Medcare Hospital Sharjah

Priya Rani

Medcare Hospital Sharjah

Maria Sarwar

Medcare Hospital Sharjah

Aniya Ahammed

Medcare Hospital Sharjah

Case Report

Keywords: Glutaric aciduria type II, multiple acyl-CoA dehydrogenase deficiency, MADD, neonatal metabolic crisis, consanguinity, inborn errors of metabolism

Posted Date: June 30th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9638079/v1

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Additional Declarations: No competing interests reported.

Abstract

Glutaric aciduria type II (GA2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is a rare autosomal recessive disorder of fatty acid and amino acid metabolism with fewer than 100 neonatal-onset cases reported worldwide.[1] We report a term male neonate born to consanguineous parents (second-degree relatives) via in vitro fertilization who presented with sudden cardiorespiratory arrest at 36 hours of life after an initially normal postnatal course. Clinical features included severe metabolic acidosis, lactic acidosis, profound hypoglycemia (10 mg/dL), and seizures. Despite aggressive resuscitation, the infant died at 72 hours of life. Plasma acylcarnitine profile revealed elevated short, medium, and long-chain acylcarnitines, and whole genome sequencing confirmed homozygous mutations consistent with GA2.[2] This case adds to the limited literature on neonatal-onset GA2 and highlights the importance of documenting rare metabolic disorders to improve understanding of disease patterns, inform newborn screening strategies, and guide genetic counseling in populations with high consanguinity rates.

Introduction

Glutaric aciduria type II (GA2), also known as multiple acyl-CoA dehydrogenase deficiency (MADD), is a rare autosomal recessive disorder affecting mitochondrial fatty acid, amino acid, and choline metabolism caused by mutations in ETFA, ETFB, or ETFDH genes.[3][4] The precise incidence remains unknown, and fewer than 100 neonatal-onset cases have been documented in the medical literature since the condition was first described in 1976.[1] Three clinical phenotypes exist: neonatal-onset with congenital anomalies (Type I), neonatal-onset without anomalies (Type II), and late-onset disease (Type III).[1] The neonatal-onset forms carry a universally poor prognosis, with most affected individuals not surviving the initial metabolic crisis.[1]

Given the rarity of this condition, each documented case contributes valuable information to the collective understanding of disease presentation, geographic distribution, genetic variants, and outcomes. This report presents a case of fatal neonatal-onset GA2 in a male infant born to consanguineous parents and integrates findings from published cases to identify common features and highlight unique aspects of this presentation.

Case Presentation

A male neonate was born at term (40 weeks) to consanguineous parents (second-degree relatives). The pregnancy was achieved via IVF for gender selection after three healthy female siblings. The mother was 23 years old, G4P3, with no history of abortions or fetal demise. Infectious screening was negative and prenatal imaging was normal.

The infant was delivered with Apgar scores of 8 and 9. Birth weight was 3.62 kg, length 52 cm, and head circumference 36 cm. Cord gas showed mild respiratory acidosis that normalized within one hour. The infant was initiated on exclusive breastfeeding and appeared well at the 24-hour examination.

At 36 hours, the infant became lethargic with poor feeding, then suddenly became apneic and cyanotic. Cardiopulmonary resuscitation was initiated and the infant was transferred to the NICU. After intubation and three doses of epinephrine over 15 minutes, the infant stabilized. Initial blood gas revealed severe metabolic acidosis and lactic acidosis with profound hypoglycemia of 10 mg/dL. Treatment included normal saline boluses, 10% dextrose infusion, and sodium bicarbonate. Empiric antibiotics were started. Hemoglobin was 8 mg/dL requiring transfusion. Brain ultrasound showed mild supratentorial bleeding without structural anomalies. Echocardiogram and abdominal ultrasound were normal.

On day two, the infant improved and was extubated to NCPAP with feeds resumed. However, seizures developed requiring phenobarbital loading. At 72 hours, sudden cardiorespiratory arrest occurred and the infant expired despite full resuscitation. Blood samples were obtained during resuscitation for genetic testing. Plasma acylcarnitine profile (2 weeks post-mortem) revealed elevated short, medium, and long-chain acylcarnitines with elevated non-esterified fatty acids.[2] Whole genome sequencing (3 weeks post-mortem) confirmed homozygous mutations consistent with GA2.

Literature Review

The first detailed description of neonatal GA2 was published by Sweetman et al. in 1980, reporting two infants who presented with overwhelming illness very early in life and died in the neonatal period, demonstrating neonatal acidosis, hypoglycemia, hyperammonemia, massive lactic aciduria, and glutaric aciduria.[5] An acrid odor resembling sweaty feet was noted as a diagnostic clue in those cases, a feature not documented in our patient, possibly due to the acute nature of the presentation and focus on resuscitation.[5]

The clinical course in our case closely mirrors the Saudi Arabian series reported by al-Essa et al. (2000), which included seven patients with five having neonatal-onset disease.[2] Similar to our case, all parents in that series were consanguineous with first- or second-degree relationships, and the neonatal-onset form presented as overwhelming illness with severe hypoglycemia and metabolic acidosis leading to rapid death.[2] Neuroimaging in that series showed brain atrophy, white matter disease, and fluid-filled cavities in the periventricular area, whereas our patient's brain ultrasound showed only mild supratentorial bleeding, possibly reflecting the earlier timing of imaging before full disease manifestation.[2]

Freneaux et al. (1992) studied eight patients with ETF deficiency, including six with severe neonatal-onset GA2, and demonstrated that beta-oxidation pathway flux correlated well with clinical phenotypes, with neonatal-onset patients showing palmitate oxidation ranging from 2% to 22% of control values.[6] Seven different ETFA mutations were identified, with the most common being a methionine for threonine substitution at codon 266.[6] The specific mutation in our patient awaits detailed characterization from the genetic laboratory.

Shevell et al. (1995) reported detailed neuroimaging findings in a patient with typical neonatal-onset GA2, demonstrating hypoplastic temporal lobes with marked widening of sylvian fissures creating a

characteristic "bat-wing" appearance, delayed myelination, and corpus callosum hypoplasia.[7] Our patient was scheduled for brain MRI but expired before the study could be completed, representing a limitation in comparing neuroimaging features.

Angle and Burton (2008) reported three infants who, despite diagnosis and treatment in the neonatal period through expanded newborn screening, experienced either unexpected sudden death or acute life-threatening events during the first year of life.[8] This finding is particularly relevant to our case, as the metabolic crisis occurred at 36 hours of life, typically before newborn screening results would be available, highlighting that even with screening programs, the most severe cases may decompensate before intervention is possible.[8]

Recent case reports from Asia have expanded the geographic and genetic diversity of documented cases. Ou et al. (2020) reported a Chinese female infant who developed hypoglycemia and hypotonicity on the first postnatal day with compound heterozygous ETFDH mutations, complicated by purulent meningitis and septicemia.[9] Ding et al. (2020) reported another neonatal-onset case with compound heterozygous ETFDH mutations who presented with severe hypoglycemia at 25 days of age and died at 4 months despite treatment.[10] Our patient's presentation at 36 hours falls between these reported onset times, consistent with the variable timing of metabolic decompensation in neonatal-onset GA2.

Ali et al. (2021) identified 13 patients with GA2 through the UAE newborn screening program, with the ETFDH:p.Gln269His variant observed in homozygous state in nine patients.[11] This regional data is particularly relevant given our patient's birth in Dubai, suggesting that specific founder mutations may be prevalent in Gulf populations and supporting the value of expanded newborn screening in this region.[11]

Parvini et al. (2025) reported the first case of neonatal-onset GA2 caused by an ETFA variant in the Iranian population, identified through pre-pregnancy counseling in a couple with a history of two neonatal deaths suspected of metabolic disorder.[12] This case demonstrates the value of genetic diagnosis for reproductive planning, directly applicable to our patient's family who may benefit from preimplantation genetic diagnosis for future IVF cycles.[12]

Bisschoff et al. (2024) reported 14 affected individuals from South Africa, with the most severe and fatal presentations associated with specific genotypes causing MADD types I and I/II.[13] Van Rijt et al. (2019) developed a MADD disease severity scoring system demonstrating that fatty acid oxidation flux and specific acylcarnitine markers discriminated neonatal from later-onset patients.[14] Van Rijt et al. (2020) reported that D,L-3-hydroxybutyrate treatment showed clinical improvement in 70% of patients for cardiomyopathy, leukodystrophy, and other symptoms, though this therapy was not available for our patient given the post-mortem diagnosis.[15]

Common features across published cases and our patient include consanguinity as a major risk factor, presentation with severe metabolic acidosis and hypoglycemia in the first days of life, rapid clinical deterioration despite aggressive supportive care, and universally poor prognosis for severe neonatal-onset forms. Features present in other cases but not documented in our patient include the

characteristic sweaty feet odor, congenital anomalies (our patient had Type II without anomalies), and detailed neuroimaging findings (MRI not completed). Features unique to our case include conception via IVF for gender selection in a consanguineous couple, raising important considerations about genetic screening in assisted reproduction, and the foresight to obtain samples during terminal resuscitation enabling post-mortem genetic confirmation.

Discussion

This case adds to the limited literature on neonatal-onset GA2, with fewer than 100 cases reported worldwide.[1] The rationale for publishing this case extends beyond documenting another fatal outcome. First, each case contributes to understanding geographic and ethnic distribution of GA2, particularly in Gulf populations where consanguinity rates are high and specific founder mutations may exist.[11] Second, the use of IVF for gender selection in a consanguineous couple highlights an important opportunity for genetic counseling and preimplantation genetic diagnosis that was missed, providing a teaching point for reproductive medicine practitioners.[12] Third, the post-mortem genetic confirmation demonstrates the value of obtaining samples during acute crises, enabling genetic counseling for the family despite the fatal outcome. Fourth, documentation of rare metabolic disorders informs newborn screening program development and resource allocation in regions where such programs are being expanded.[11][8]

The parents face 25% recurrence risk with each future pregnancy. Given that this pregnancy was achieved through IVF, preimplantation genetic diagnosis represents a viable option for future pregnancies, as demonstrated in the Iranian case where prenatal diagnosis enabled informed reproductive decisions.[12] Carrier testing should be offered to the three healthy female siblings and extended family members.

Conclusion

This case demonstrates the classic presentation and tragic outcome of severe neonatal-onset GA2, consistent with published case series from multiple populations. Despite advances in diagnosis through newborn screening and understanding of the molecular basis, treatment options for severe neonatal disease remain limited. This case adds to the growing literature on GA2 in consanguineous populations and underscores the importance of genetic counseling for at-risk families, the value of obtaining diagnostic samples during acute crises, and the need for expanded newborn screening programs in regions with high consanguinity rates.

Abbreviations

GA2
Glutaric aciduria type II
MADD

multiple acyl-CoA dehydrogenase deficiency

Declarations

Ethics approval and consent to participate

Written informed consent was taken by parents to proceed with the case report

Consent for publication

Written informed consent for publication of clinical details and/or clinical images was obtained from the parents of the patient.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the NGDC repository, PRJCA064692

Competing Interests

There are no conflict of interests for any authors and no authors received any funding for this project

Authors' contributions

Y.S and M.H wrote the manuscript, M.A and A.M edited and reviewed the manuscript, put data into repository, P.R, A.A, and M.S accessed the data and wrote parts of the manuscript. All authors reviewed and approved the manuscript

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