Archives of the Balkan Medical Union
vol. 61, no. 2, pp. 320-324
June 2026
Copyright © 2026 Balkan Medical Union

CASE REPORT

GLUTATHIONE SYNTHETASE DEFICIENCY: A CASE OF REFRACTORY METABOLIC ACIDOSIS AND HEMOLYTIC ANEMIA IN A NEWBORN

Evelina KREKO[1]✉, Blerina SARAÇI QIRINXHI[2]

[1] Neonatology Service, University Hospital of Obstetrics and Gynecology "Koço Gliozheni", Tirana, Albania
[2] Radiology Service, Mother Teresa University Hospital Center, Tirana, Albania

Received 16th April 2026, Accepted 07th June 2026
https://doi.org/10.31688/ABMU.2026.61.2.22

Abstract

Introduction. Glutathione synthetase deficiency (GSSD) is a rare autosomal recessive inborn error of metabolism characterized by impaired glutathione synthesis, leading to oxidative stress, hemolytic anemia, and severe metabolic acidosis. Neonatal presentation is often dramatic and associated with high morbidity and mortality.

Case presentation. We report a term neonate who developed early-onset respiratory distress, severe high–anion gap metabolic acidosis, and progressive hemolytic anemia within the first 24 hours of life. Despite intensive supportive therapy, metabolic acidosis remained refractory. Extended metabolic investigations, such as elevated urinary 5-oxoproline, could not be performed in our laboratory. Whole-genome sequencing test results confirmed the diagnosis. Antioxidant therapy and metabolic stabilization resulted in gradual clinical improvement.

Conclusions. This case illustrates the relevance of considering glutathione synthetase deficiency in newborns presenting with unexplained metabolic acidosis and hemolysis. Early metabolic testing and targeted

Résumé

Déficit en glutathion synthétase: un cas d'acidose métabolique réfractaire et d'anémie hémolytique chez un nouveau-né

Introduction. Le déficit en glutathion synthétase (GSSD) est une maladie métabolique héréditaire rare, autosomique récessive, caractérisée par une synthèse altérée du glutathion, entraînant un stress oxydatif, une anémie hémolytique et une acidose métabolique sévère. La présentation néonatale est souvent dramatique et associée à une morbidité et une mortalité élevées.

Rapport du cas. Nous rapportons le cas d'un nouveau-né à terme ayant développé une détresse respiratoire précoce, une acidose métabolique sévère à trou anionique élevé et une anémie hémolytique progressive dans les 24 premières heures de vie. Malgré une prise en charge intensive, l'acidose métabolique est restée réfractaire. Des investigations métaboliques complémentaires, telles que le dosage de la 5-oxoproline urinaire, n'ont pas pu être réalisées dans notre laboratoire. Le diagnostic a été confirmé par séquençage du génome entier. Un traitement antioxydant et une

✉ Address for correspondence: Evelina KREKO
Address: University Hospital of Obstetrics and Gynecology "Koço Gliozheni", Bulevardi Bajram Curri, Tirana, Albania
Email: evelinakreko@yahoo.com; Phone: +355673756184

therapy may be lifesaving and improve neurological outcome.

Keywords: glutathione synthetase deficiency, newborn, metabolic acidosis, hemolytic anemia, inborn errors of metabolism.

List of abbreviations:
GSSD – glutathione synthetase deficiency
WGS – whole genome sequencing
NICU – neonatal intensive care unit

stabilisation métabolique ont permis une amélioration clinique progressive.

Conclusions. Ce cas illustre l'importance de considérer un déficit en glutathion synthétase chez les nouveau-nés présentant une acidose métabolique et une hémolyse inexpliquées. Un dépistage métabolique précoce et une thérapie ciblée peuvent sauver des vies et améliorer le pronostic neurologique.

Mots-clés: déficit en glutathion synthetase, acidose métabolique néonatale, anémie hémolytique, erreurs innées du métabolisme.

Introduction

Glutathione is the most abundant intracellular antioxidant and plays a fundamental role in cellular detoxification, protection against oxidative stress, amino acid transport, and redox homeostasis[1]. During the neonatal period, glutathione is particularly important because newborns are exposed to increased oxidative stress following the transition from intrauterine to extrauterine life. Glutathione synthetase deficiency (GSSD; OMIM #266130) is a rare autosomal recessive disorder caused by pathogenic variants in the GSS gene located on chromosome 20q11.22.[2] The enzyme glutathione synthetase catalyzes the final step in glutathione biosynthesis, converting γ-glutamylcysteine to glutathione. Enzyme deficiency results in depleted glutathione levels and accumulation of 5-oxoproline (pyroglutamic acid), leading to high–anion gap metabolic acidosis[3]

Clinically, GSSD demonstrates a wide phenotypic spectrum ranging from isolated hemolytic anemia to severe neonatal metabolic crisis with neurological impairment[3]. Three clinical forms are described: mild, moderate, and severe. The severe neonatal form is characterized by early metabolic acidosis, hemolytic anemia, seizures, neurological involvement, and high mortality if diagnosis is delayed[4].

Because of its rarity and nonspecific presentation, GSSD is underrecognized in neonatal intensive care units[5,6]. We report a neonate with severe early-onset GSSD to highlight diagnostic challenges and the importance of early metabolic evaluation.

Case presentation

Maternal and Pregnancy History

The infant was born to a 29-year-old mother, gravida 1, para 0, following a pregnancy that was largely uneventful. There was no known parental consanguinity. Antenatal follow-up was regular, and prenatal ultrasonography showed normal fetal growth and anatomy. No evidence of cardiac congenital anomaly was detected during prenatal ultrasonography. There was no history of maternal infection, gestational diabetes, chronic illness, or drug or toxic exposure during pregnancy.

Delivery and Neonatal Adaptation

A male neonate was delivered at 40 weeks by normal vaginal delivery. The birth weight was 2980 g (10th percentile). Apgar scores were 7 at 1 minute and 9 at 5 minutes. No resuscitation was required at birth. The initial adaptation was satisfactory.

Early Clinical Deterioration

At approximately 12–18 hours of life, the newborn developed poor feeding, tachypnea, jaundice, and lethargy, followed by progressive respiratory distress. He was transferred to the neonatal intensive care unit for further management.

Vital signs were as following: temperature 36.5°C, respiratory rate 50 breaths/min, heart rate 130 beats/min, oxygen saturation 95% under supplemental oxygen therapy

At the clinical examination, the newborn had respiratory distress with tachypnea and subcostal retractions, hypotonia and reduced spontaneous movements, mild jaundice, cutis marmorata and dysmorphic features: abnormal earlobe morphology, nail hypoplasia, bilateral single transverse palmar crease, slanting of the palpebral fissure. Also, a systolic murmur at cardiac auscultation and no hepatosplenomegaly.

The initial laboratory tests showed anemia, with hemoglobin 9.6 g/dL, red blood cell count 2,940,000/mm^3, white blood cell count 12,000/mm^3 (52% segmented neutrophils, 31% lymphocytes), platelet count 364,000/mm^3, total serum protein 4.8 g/dL and serum albumin 3.3 g/dL.

Twenty-four hours after the presentation, the patient developed clinical deterioration. Clinically,

Table 1. The initial arterial blood gas analysis

pH	7.12
HCO^{3-}	8 mmol/L
Base excess	–18 mmol/L
Lactate	5.8 mmol/L
Anion gap	32 mmol/L

Table 2. The repeated arterial blood gas analysis.

pH	6.98
HCO_3^-	6.7 mmol/L
Base excess	–27.3 mmol/L
Lactate	8.8 mmol/L
Anion gap	32 mmol/L

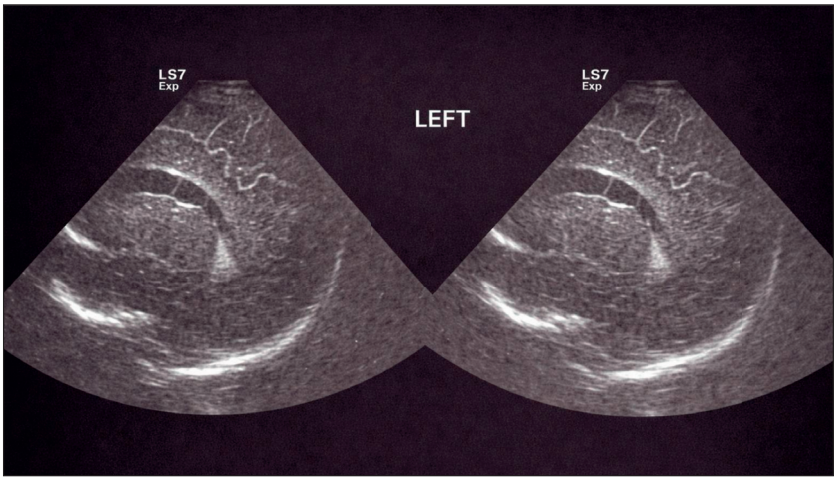


Figure 1. Dilatation of the lateral ventricles to 9 mm, periventricular hyperechogenicity

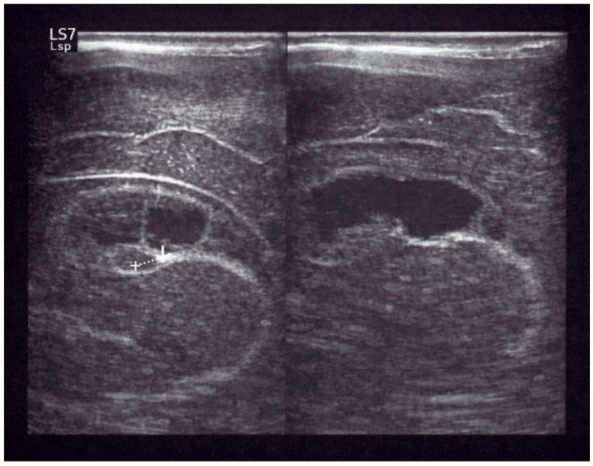


Figure 2. Two subependymal cysts suggest subependymal intrauterine hemorrhage

the patient exhibited pale skin and worsening jaundice. The complete blood count revealed a further decrease in hemoglobin to 8.9 g/dL, with a red blood cell count of 2.72×10^6/µL, and an increased reticulocyte count, consistent with ongoing hemolysis. The patient received red blood cell transfusions, which initially improved hemoglobin levels. However, despite two packed-cell transfusions, hemoglobin fell by more than 1 g/dL per day, indicating the atypical severity of the hemolysis and highlighting the need to consider diagnoses beyond common etiologies.

The repeated laboratory tests showed hemoglobin 8.9 g/dL, red blood cell count 2,720,000/mm³, white blood cell count 8,000/mm³ (36% segmented neutrophils, 49% lymphocytes), platelet count 430,000/mm³, total serum protein 5.0 g/dL, serum albumin 4.0 g/dL.

The patient presented progressive neurological involvement, including hypotonia and focal seizures, managed with phenobarbital, free oxygen through the Hood box, continuous glucose infusion to prevent catabolism (glucose 10% + dopamine), repeated sodium bicarbonate infusions, packed red blood cell transfusion for hemolytic anemia, broad-spectrum antibiotics until infection was excluded (cefotaxime, gentamicin), calcium gluconate 10%.

The initial arterial blood gas analysis showed severe metabolic acidosis (Table 1).

Despite adequate ventilation and bicarbonate therapy, metabolic acidosis remained persistent.

Arterial blood gas analysis performed two days later demonstrated persistent, refractory severe metabolic acidosis (Table 2).

Additional laboratory findings included normal platelet count, normal ammonia levels, negative blood cultures, normal C-reactive protein.

Imaging Studies

The cranial ultrasound revealed dilatation of the lateral ventricles to 9 mm, periventricular hyperechogenicity. Two subependymal cysts suggest subependymal intrauterine hemorrhage (Figures 1,2).

Echocardiography showed "pink" tetralogy of Fallot and abdominal ultrasound normal liver and spleen dimensions.

Diagnostic Assessment

Given the combination of persistent severe high–anion gap metabolic acidosis, hemolytic anemia, and absence of infection or hypoxic injury, an inborn error of metabolism was suspected.

Urinary organic acid analysis to reveal markedly elevated 5-oxoproline, strongly suggestive of GSSD (severe form), could not be performed in our laboratory.

A metabolic screening panel was performed and yielded normal results, as testing for GSSD wasn't included.

Genetic testing for GSS mutations was performed in a private laboratory and the results were not immediately available. Based on biochemical findings and clinical presentation, the genetician requested whole genome sequencing (WGS), and upon its analysis, a genetic diagnosis of autosomal recessive GSSD was established. A heterozygous variant of uncertain significance was identified in the CHD4 gene. The pathogenic variants in this gene are associated with autosomal dominant Sifrim-Hitz-Weiss syndrome, so a correlation with this syndrome is possible.

Treatment and Clinical Course

As the diagnosis was established, the target therapy was initiated, with vitamin C and vitamin E as antioxidants, oral alkali supplementation, strict avoidance of oxidative medications, including paracetamol. Gradual metabolic stabilization was observed over several days, with improvement of acid–base balance and respiratory status. The neonate was bottle-fed after discharge from NICU.

Outcome and Follow-Up

The infant was discharged after 33 days of NICU hospitalization and 18 days of Intermediate Care Unit hospitalization on oral antioxidant therapy and alkali supplementation and did not require supplemental oxygen after discharge from NICU. A multidisciplinary follow-up program involving neurology, cardiology, and general pediatrics was established. Long-term neurodevelopmental surveillance was planned, and neurological manifestations were managed with phenobarbital therapy.

Discussion

GSSD is one of the rarest disorders of glutathione metabolism, with fewer than 100 cases reported worldwide[7]. The neonatal form represents the most severe phenotype and is characterized by early metabolic crisis, hemolytic anemia, and neurological involvement[8].

The pathophysiology is mainly due to glutathione depletion, which leads to increased oxidative stress and accumulation of 5-oxoproline. In neonates, limited metabolic reserve contributes to rapid clinical deterioration.

The diagnosis is often delayed because initial presentation mimics neonatal sepsis or hypoxic–ischemic encephalopathy. Normal ammonia levels and absence of hyperketonemia may further challenge recognition. Persistent high–anion gap metabolic acidosis refractory to standard therapy must prompt evaluation for pyroglutamic aciduria. The condition typically presents in patients who develop an altered level of consciousness and clinical signs of metabolic acidosis during a prolonged hospital stay.

The diagnostic process was particularly challenging in our case because a congenital heart disease had been identified early in life. The initial respiratory distress was therefore reasonably attributed to the underlying cardiac condition. However, the subsequent appearance of additional clinical and biochemical features—including refractory high–anion gap metabolic acidosis and progressive hemolytic anemia—could not be fully explained by the congenital cardiopathy alone, prompting reconsideration of the initial diagnostic assumption and further metabolic investigation.

Early and continuous cardiac monitoring is strongly recommended in patients diagnosed with GSSD, as dilated cardiomyopathy has recently emerged as a potential complication associated with this disorder[9]. Growing evidence suggests that oxidative stress may contribute not only to metabolic instability but also to myocardial involvement, consequently influencing disease progression and clinical severity[10].

Hens et al. have reported the association between increased oxidative stress and congenital heart disease in patients with GSSD. However, current data remain limited and potentially biased, as antioxidant interventions aimed specifically at reducing oxidative stress in this patient population have not yet been systematically evaluated[11].

Recent case reports and reviews emphasize that early diagnosis and intervention significantly improve prognosis and may reduce neurological sequelae[12].

Conclusions

GSSD should be considered in newborns presenting with unexplained high–anion gap metabolic acidosis and hemolytic anemia. Measurement of urinary 5-oxoproline is the key for the diagnosis of the severe form of this disease.

Antioxidant therapy is considered a keystone of management due to the elevated sensitivity of affected neonates to oxidative injury. Screening for GSSD should be considered in neonates presenting with unexplained hemolytic anemia, particularly when accompanied by metabolic acidosis or early neurological manifestations.

Early identification enables the initiation of antioxidant therapy, the prevention of oxidative triggers, and genetic counseling for families. Prognosis depends on severity, timing of diagnosis, and neurological involvement. In our case, long-term multidisciplinary follow-up is required to monitor cardiac function and refine individual risk stratification over time.

Author Contributions:

E.K. was responsible for study design, data collection, manuscript drafting and overall coordination. B.S. was responsible for ultrasound imaging and interpretation. All authors approved the final version of the manuscript.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding the article"

"The authors declare that all the procedures and treatments of this study respect the ethical standarts in the Helsinki Declaration of 1975, as revised in 2008, as well as the national law. Informed consent was obtained from the patient's parents".

"No funding for this study"

Acknowledgements:

None

References

1. Ristoff E, Larsson A. Inborn errors in the metabolism of glutathione. *Orphanet J Rare Dis*. 2007;2:16. doi: 10.1186/1750-1172-2-16
2. Njålsson R, Ristoff E, Carlsson K, Winkler A, Larsson A, Norgren S. Genotype, enzyme activity, glutathione level, and clinical phenotype in patients with glutathione synthetase deficiency. *Hum Genet*. 2005;116(5):384-9. doi: 10.1007/s00439-005-1255-6
3. Mayatepek E. 5-Oxoprolinuria in patients with and without defects in the –glutamyl cycle. *Eur J Pediatr.* 1999; 158:221–225. Doi: 10.1007/s004310051054
4. Green TJ, Bijlsma JJ, Sweet DD. Profound metabolic acidosis from pyroglutamic acidemia: an underappreciated cause of high anion gap metabolic acidosis. *CJEM*. 2010;12(5):449-52. doi: 10.1017/s148180350001263x
5. Kleta R, Stuart CA, Gill F, et al. Disorders of glutathione metabolism. *Molecular Genetics and Metabolism*2004;82(1):56-58. doi: 10.1016/j.ymgme.2004.01.018
6. Bindu BN, Dhamija R, Ferdjallah A. Glutathione synthetase deficiency: 10 years later. *BMJ Case Reports*. 2026; 19(1). doi: 10.1136/bcr-2025-269050
7. Demirsu A, Aliyev F, Yucel E, et al. Glutathione synthetase deficiency: severe hemolysis and metabolic acidosis with symptoms in the intrauterine period. *J Pediatr Endocrinol Metab*. 2025;39(2):188-192. doi: 10.1515/jpem-2025-0459
8. .Ristoff E, Mayatepek E, Larsson A. Long-term clinical outcome in patients with glutathione synthetase deficiency. *J Pediatr*. 2001;139(1):79-84. doi: 10.1067/mpd.2001.114480
9. Leichtweis S, Ji LL. Glutathione deficiency intensifies ischaemia-reperfusion induced cardiac dysfunction and oxidative stress. *Acta Physiologica Scandinavica* 2001;172(1): 1-10. doi: 10.1046/j.1365-201X.2001.00820.x
10. Mårtensson J, Gustafsson J, Larsson A. A therapeutic trial with N-acetylcysteine in subjects with hereditary glutathione synthetase deficiency (5-oxoprolinuria). *J Inherit Metab Dis*. 1989;12(2):120-30. doi: 10.1007/BF01800713
11. Shi Z, Habib GM, Rhead WJ, et al. Mutations in the glutathione synthetase gene cause 5–oxoprolinuria. *Nature Genetics*. 1996; 14(3):361-365. doi: 10.1038/ng1196-361
12. Jury J, Benoist JF, Joubert M, et al. Multiple congenital anomalies in two fetuses with glutathione-synthetase deficit (GSS). *Clinical Genetics*. 2024;106(6):776–781. doi: 10.1111/cge.14613