Case Report

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A Case Report on a Patient with Glutathione Synthetase Deficiency and Her Outcomes

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ABSTRACT

Background: Glutathione synthetase deficiency (GSSD) is a rare autosomal recessive disorder linked to glutathione metabolism. In severe cases, it is characterized by significant metabolic acidosis, hemolytic anemia, and various neurological complications. Biochemical analyses typically reveal considerable urinary excretion of 5-oxoproline.

Case Presentation: Here, we present a case involving a three-day-old infant with a birth weight of 3.3 kg, who was admitted due to cyanosis and grunting. The infant's parents were consanguineous. The family had a history of a previous child who succumbed at the age of 2 months with similar symptoms and high anion gap metabolic acidosis. Laboratory tests indicated severe metabolic acidosis along with a marked increase in 5-oxoproline among the organic acids in the urine. The infant received treatment with vitamins C and E. On follow-up at 7 years and 6 months of age, the child demonstrated expected normal developmental progress but was prescribed anti-epileptic medications due to recurrent seizures, occurring four times.

Conclusion: We recommend that GSSD be considered in cases of metabolic acidosis and hemolytic anemia in neonates. Early diagnosis and timely therapeutic interventions may lead to improved clinical outcomes.

Introduction

Glutathione synthetase deficiency (GSD) is a rare autosomal recessive disorder that represents an inborn error in glutathione metabolism. The clinical manifestations of this condition can vary widely among patients, encompassing hemolytic anemia, metabolic acidosis, and neurological issues. Common symptoms include hyperbilirubinemia, recurrent bacterial infections, and sepsis.[1] Diagnosis is typically achieved through urine analysis, which reveals elevated levels of 5-oxoproline, coupled with genetic testing that identifies mutations in the glutathione synthetase gene.[2] Management strategies primarily focus on correcting metabolic imbalances and providing supportive care, which may incorporate vitamin supplements. Regular follow-ups are crucial to monitor the development of potential neurological impairments, as affected individuals often experience neurodevelopmental delays despite early interventions.[2] GSD can manifest in various forms: mild, moderate, and severe. The mild form mainly affects erythrocytes and typically results in mild to moderate hemolytic anemia without significant complications. Conversely, the severe form also referred to as 5-oxoprolinuria or pyroglutamic aciduria, involves systemic effects that impact multiple cell types throughout the body. Symptoms of severe GSD may surface in newborns within the first few days of life, including jaundice, acute metabolic acidosis, and differing degrees of hemolytic anemia. Chronic metabolic acidosis can persist even after initial recovery, with severe episodes often triggered by infections like gastroenteritis or following surgical interventions. [2,3]

As GSD progresses, affected individuals may experience progressive neurological decline, which can manifest as intellectual disability, spastic tetraparesis, ataxia, tremors, dysarthria, and seizures. Additionally, there is an increased susceptibility to infections, potentially due to granulocyte dysfunction.[4] The moderate form of GSD generally presents with milder metabolic acidosis and lower levels of 5-oxoprolinuria compared to the severe form, and it typically does not involve significant neurological complications. Acute management during GSD episodes involves hydration and correction of acidosis, usually through sodium bicarbonate infusion, and targeted interventions to manage anemia and hyperbilirubinemia.[2,4,5] Chronic management may necessitate long-term alkali therapy and supplementing vitamins C and E and selenium.[4–7] It is vital to limit exposure to drugs and oxidative agents that may provoke hemolysis or exacerbate catabolic stress. Supplementing with vitamin E may help mitigate granulocyte dysfunction, reducing the risk of recurrent infections.[1,3,5] The genetic inheritance of GSD is autosomal recessive, located on chromosome 20q11.23.[1,3] Laboratory evaluations typically identify metabolic acidosis, mild to moderate hemolytic anemia, and increased levels of 5-oxoprolinuria.[1,5] High concentrations of 5-oxoproline can also be detected in the bloodstream, with substantially reduced glutathione levels observed in erythrocytes.4 Diagnosis may be confirmed via DNA analysis or enzyme activity assessment in erythrocytes or skin fibroblasts, with prenatal diagnosis possible through the measurement of 5-oxoproline in amniotic fluid or direct DNA analysis of amniocytes or chorionic villus samples.[4,8]

Case Presentation

A three-day-old infant, born via normal vaginal delivery with a birth weight of 3,300 grams, was hospitalized due to symptoms of cyanosis and grunting. The parents of the infant were related, raising concerns about potential genetic conditions. Notably, there was a history of a previous child in the family who died at two months of age under similar circumstances, characterized by cyanosis, grunting, and high anion gap metabolic acidosis. Upon metabolic examination, the infant exhibited a significant elevation in 5-oxoproline levels in urine. Her

laboratory findings are presented in Table 1. Given the findings, the infant was diagnosed with glutathione synthetase deficiency and treated with intravenous bicarbonate aimed at correcting the metabolic acidosis. Subsequently, the patient was prescribed vitamin E at 10 mg/kg/day and vitamin C at 500 mg/day. During follow-up, the infant was hospitalized again at six months of age due to episodes of vomiting, respiratory distress, and convulsions, for which she received treatment with phenobarbital. Additionally, she experienced further complications, including high fever, respiratory distress, and a confirmed blood culture positive for Streptococcus pneumonia. A 7 years and 6 months of age, she demonstrated expected normal developmental progress but was prescribed anti-epileptic medications due to recurrent seizures, occurring four times.

Table 1. Laboratory Findings

CBC	
WBC/mm3	12600
Hb (g/dL)	12.8
MCV	108
PLT/mm3	405000
VBG	
pH	7.14
HCO3− (mmol/L)	4

Discussion

This case report highlights a rare yet critical instance of GSD in a neonate, marked by cyanosis and grunting at three days of age. The history of similar symptoms leading to the demise of a sibling emphasizes the need for thorough genetic history-taking in pediatric assessments, particularly within consanguineous families. GSD, an autosomal recessive disorder, presents a range of symptoms, including hemolytic anemia, metabolic acidosis, and neurological impairment. A documented case of a male Japanese infant illustrated the severity of GSD, with the child experiencing significant hemolytic anemia and metabolic acidosis at birth, followed by progressive neurological symptoms.[2] Another case noted a newborn boy diagnosed with the most severe phenotype, characterized by distinct clinical features and elevated urinary 5-oxoproline levels.[9] Furthermore, a case study reported a male newborn suffering from GSD who presented with severe metabolic acidosis, hemolytic anemia, and hyperbilirubinemia but unfortunately succumbed to the disease despite interventions.[10] Collectively, these cases underline the critical need for early diagnosis, comprehensive long-term follow-up, and effective management strategies to address the complex clinical manifestations associated with this rare disorder.[1,4,5]

The discussion surrounding GSD in neonates highlights the critical need for heightened awareness and early intervention in pediatric populations, particularly in individuals with familial or consanguineous backgrounds. The clinical presentation of GSD can be severe, often manifesting within the first days of life, as seen in various case reports that demonstrate a range of symptoms, including hemolytic anemia, metabolic acidosis, and neurological impairment.[2] The tragic cases noted, where infants exhibited life-threatening conditions shortly after birth, accentuate both the urgency and complexity of diagnosing this rare disorder. Moreover, the hereditary nature of GSD, an autosomal recessive condition, calls for meticulous genetic history evaluation to inform diagnosis and prevention strategies, especially in families with a history of similar neonatal symptoms. Early recognition and comprehensive management protocols are essential to mitigate the potentially devastating outcomes associated with GSD, emphasizing the importance of multidisciplinary care approaches that address medical and supportive needs over the long term.[4] As the literature indicates, fostering a deeper understanding of this rare condition among healthcare providers can improve patient outcomes through timely diagnosis and intervention.

GSSD is part of a spectrum of metabolic disorders linked to dysfunction in glutathione synthesis.[1,4] The elevated levels of 5-oxoproline in this infant, identified through urine organic

acid analysis, are characteristic of this condition and provide a diagnostic biomarker that can guide early treatment interventions.[8] The reported history of high anion gap metabolic acidosis and hemolytic anemia further supports the diagnosis, marking the importance of differential diagnosis in newborns presenting with similar symptoms. The timely initiation of vitamin E and vitamin C to combat the oxidative stress resulting from decreased glutathione levels is notably significant in this case.[5] The evidence provided by Njålsson Nyalsson et al. emphasizes the critical nature of early intervention. By administering these vitamins, the treatment aims to mitigate cellular damage and potentially stave off the progression from a moderate to severe phenotype of GSSD.[11] This approach aligns with the growing understanding that metabolic disorders often have a better prognosis with early detection and treatment, which is particularly crucial in hereditary conditions where outcomes are often dictated by the promptness of the intervention.

The subsequent complications at six months, notably the episodes of vomiting, respiratory distress, convulsions, and the severe infection with Streptococcus pneumoniae, highlight the vulnerability of infants with metabolic disorders to infections and systemic stressors.[4,12] The added challenge of managing these complications underlines the need for vigilant follow-up care in such patients. The use of phenobarbital for convulsions indicates an acute response to neurological symptoms, which may be exacerbated by metabolic instability or underlying neurometabolic processes related to GSSD.[4,7] This case also emphasizes the critical role of long-term monitoring and multidisciplinary care in infants diagnosed with metabolic disorders. Lifelong management strategies, including supplementation and monitoring for complications, are paramount in enhancing the quality of life and extending the survival of affected individuals. Moreover, this case reiterates the importance of further research into the long-term outcomes and treatment efficacy for patients with GSSD, potentially prompting the exploration of more targeted interventions and anticipatory guidance for parents.

Guidelines for Pediatric Metabolic Specialists on GSSD in Neonates:

Pediatric metabolic specialists play a crucial role in the early diagnosis, management, and long-term care of conditions like GSD. Based on the case reports and discussions surrounding GSD in neonates, several implications and recommendations can be made for specialists in this field:

1. Enhanced Genetic Counseling: Genetic specialists should prioritize comprehensive assessments of genetic history, particularly in families with consanguinity or a history of metabolic disorders. This proactive strategy is essential for the early identification of infants at risk and can provide valuable insights for family planning.

2. Early Screening Protocols: The implementation of newborn screening initiatives that encompass tests for metabolic disorders, such as Glycogen Storage Disease (GSD), is vital for facilitating timely diagnoses and interventions. Given the rapid onset of symptoms in affected infants, early detection is critical.

3. Interdisciplinary Collaboration: Establishing a multidisciplinary care team that comprises geneticists, dietitians, neurologists, and other relevant specialists is crucial for holistic management. A coordinated approach ensures that the diverse needs of patients are addressed, thereby enhancing overall treatment outcomes.

4. Education and Training: Promoting awareness and knowledge of GSD among healthcare professionals, including pediatricians and emergency department staff, is imperative. Ongoing training programs and updates on metabolic disorders can improve the identification and prompt management of these conditions in clinical environments.

5. Tailored Treatment Plans: It is essential to develop individualized treatment protocols that reflect the distinctive clinical

presentations of each patient. Such plans may involve vitamin supplementation, dietary modifications, and various supportive interventions to manage oxidative stress and metabolic discrepancies.

6. Long-term Monitoring: Protocols for long-term follow-up care must be established to ensure continuous monitoring of complications, developmental milestones, and nutritional status. This vigilance is key to addressing the chronic elements of GSD and enhancing the quality of life for individuals affected by the disorder.

7. Research and Data Collection: Encouraging research into the long-term outcomes and treatment effectiveness for patients with GSD will deepen the understanding of this condition. Systematic data collection regarding patient experiences and responses to treatment can inform future clinical practices and guidelines.

8. Support for Families: Providing comprehensive resources and support for families affected by GSD is essential. This includes access to support groups, educational materials, and counseling services to assist them in managing the difficulties associated with the disorder.

9. Emergency Preparedness: The development of emergency care protocols specifically tailored for infants with metabolic disorders is critical to ensuring the prompt and effective management of acute complications, such as seizures or infections, which are particularly common in this vulnerable population.

10. Advocacy for Policy Changes: Advocating for policies that promote research funding and improve access to care for metabolic disorders is vital for augmenting resources available for diagnosis, treatment, and support for affected families.

Conclusion

This report offers important insights into the complexities of GSSD, emphasizing the vital role of early diagnosis and the strong link between timely interventions and positive clinical outcomes. A comprehensive management strategy is essential for addressing the unique challenges of metabolic disorders in neonates, particularly GSSD. Early recognition of symptoms and timely interventions can significantly improve both immediate health and long-term developmental outcomes for affected infants. Healthcare professionals need to be equipped with the necessary knowledge and resources for prompt identification and treatment. The report emphasizes the importance of collaboration among medical professionals, researchers, and patient advocacy groups to enhance understanding and management of GSSD through research and standardized care practices. Ultimately, advancing knowledge in this area will lead to better clinical practices and improved quality of life for those impacted by rare metabolic disorders.

Conflict of Interest

The authors declare that there is no conflict of interest.

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Ethical Considerations

This study received approval from the Ethics Committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.REC.1403.119).

Author's Contribution

Conducting patient examinations, N.M. and H.E.; writing and editing the manuscript, S.M. All authors have reviewed and approved the final version of the manuscript.

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