Annals of Clinical Case Reports

Case Report
Published: 03 Apr, 2023

Glutathione Synthetase Deficiency with Hypokalemia as the First Manifestation

*Xing Y, Zhao W, Pi Y, Zhang Y, Li Y and Zhang H**

Department of Pediatrics, The Second Hospital of Hebei Medical University, China

Abstract

In July 2022, a 10-year-old boy presented to a hospital pediatric department with intermittent limb weakness for 10 days, aggravated during the preceding 12 h. After treatment with potassium supplementation for "hypokalemia and hypernatremia," he was discharged with a nominal blood potassium level. Three days later, he presented to our emergency department with numbness in both lower limbs, generalized weakness, presence of severe hypokalemia, and metabolic acidosis. A blood and urine metabolic screen reported elevated 5-oxoproline. High-throughput genetic sequencing revealed the presence of the c.491G>A (p.R164Q) and c.809A>G (p.Y270C) missense mutations in exons 5 and 9 respectively of the glutathione synthetase gene. A diagnosis of glutathione synthetase deficiency was made, and the boy was treated symptomatically and followed for more than three months. The acidosis was difficult to correct, but the hypokalemia did not recur. Glutathione synthetase deficiency is rare in clinical practice, and severe hypokalemia from damage to the renal tubules caused by organic acid accumulation as the presenting symptom - such as in the case described here - has not previously been reported either nationally or internationally.

Keywords: Glutathione Synthetase Deficiency; Hypokalemia; Metabolic acidosis; 5-Oxoprolinuria

Introduction

Glutathione Synthetase Deficiency (GSD) is a rare disorder of glutathione metabolism with a heterogeneous clinical presentation. More than 80 cases have been reported worldwide [1]; nine have been reported in China, all with onset in the neonatal period or infancy, and with first presentations involving shortness of breath, dyspnea with varying degrees of respiratory involvement, poor milk intake, poor mental development, and other symptoms associated with metabolic acidosis and anemia [2-6]. In this clinically rare disease, the onset of severe hypokalemia because of injury to the renal tubules caused by the accumulation of organic acids has not so far been reported in China or abroad as a presenting symptom. Here, we report exactly such a case in a 10-year-old boy.

Case Presentation

In July 2022, a 10-year-old boy presented to a hospital pediatric department with intermittent limb weakness for 10 days, aggravated during the preceding 12 h. Upon a diagnosis of "hypokalemia and hypernatremia," he was treated with potassium supplementation and discharged with a blood potassium measurement of 3.7 mmol/L. Ten days after that diagnosis and three days after his discharge, the boy again developed generalized weakness with shortness of breath and was seen in our emergency department.

Electrocardiography demonstrated sinus tachycardia with low flat inversions of leads II, III, and aVF. Blood tests revealed elevated leukocytes, neutrophils, and ultrasensitive C-reactive protein, and liver function tests found elevated transaminases. The child was in poor spirits, but was not experiencing vomiting, diarrhea, or dizziness. He was admitted to the hospital on an emergent basis for hypokalemia, cause to be investigated.

The boy had been delivered at full term. Any history of intrauterine distress or postnatal asphyxia was denied. The boy's speech and intelligence were within the norms for his age. He had a history of hypokalemia (blood potassium 2.2 mmol/L) with hypernatremia six months in the past, which improved after treatment with potassium supplementation.

On physical examination, temperature was 36.5°C; respiration, 35/min; blood pressure, 153/84 mmHg; and heart rate, 158 bpm with rhythmical, strong heart sounds, and no murmur in the valve

OPEN ACCESS

Correspondence:
Huifeng Zhang, Department of Pediatrics, The Second Hospital of Hebei Medical University, Shijiazhuang, China, Tel: +86 13333015983; E-mail: 13333015983@163.com

Received Date: *15 Mar 2023*
Accepted Date: *29 Mar 2023*
Published Date: *03 Apr 2023*

Citation:
Xing Y, Zhao W, Pi Y, Zhang Y, Li Y, Zhang H. Glutathione Synthetase Deficiency with Hypokalemia as the First Manifestation. Ann Clin Case Rep. 2023; 8: 2400.

ISSN: 2474-1655.

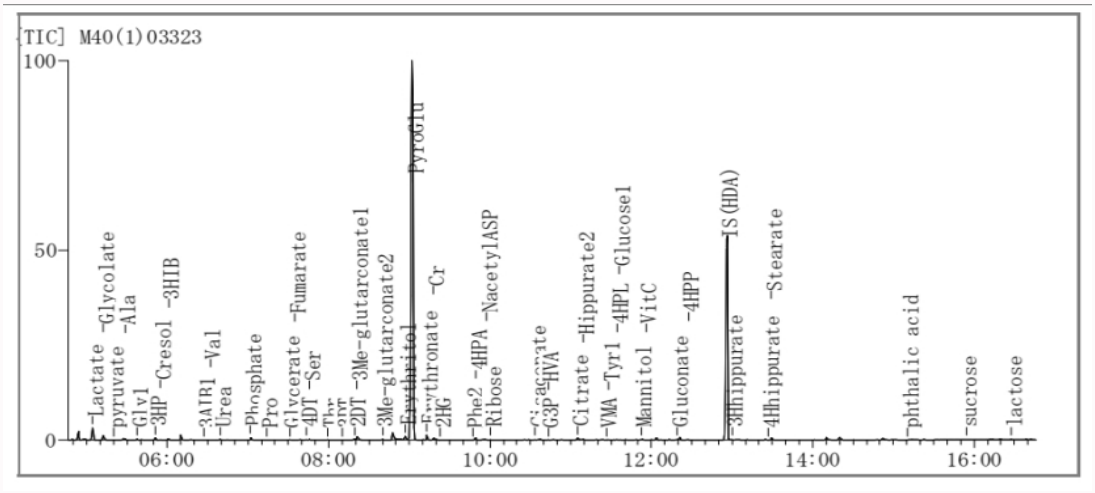

Figure 1: Results of urine organic acid analysis in this boy.

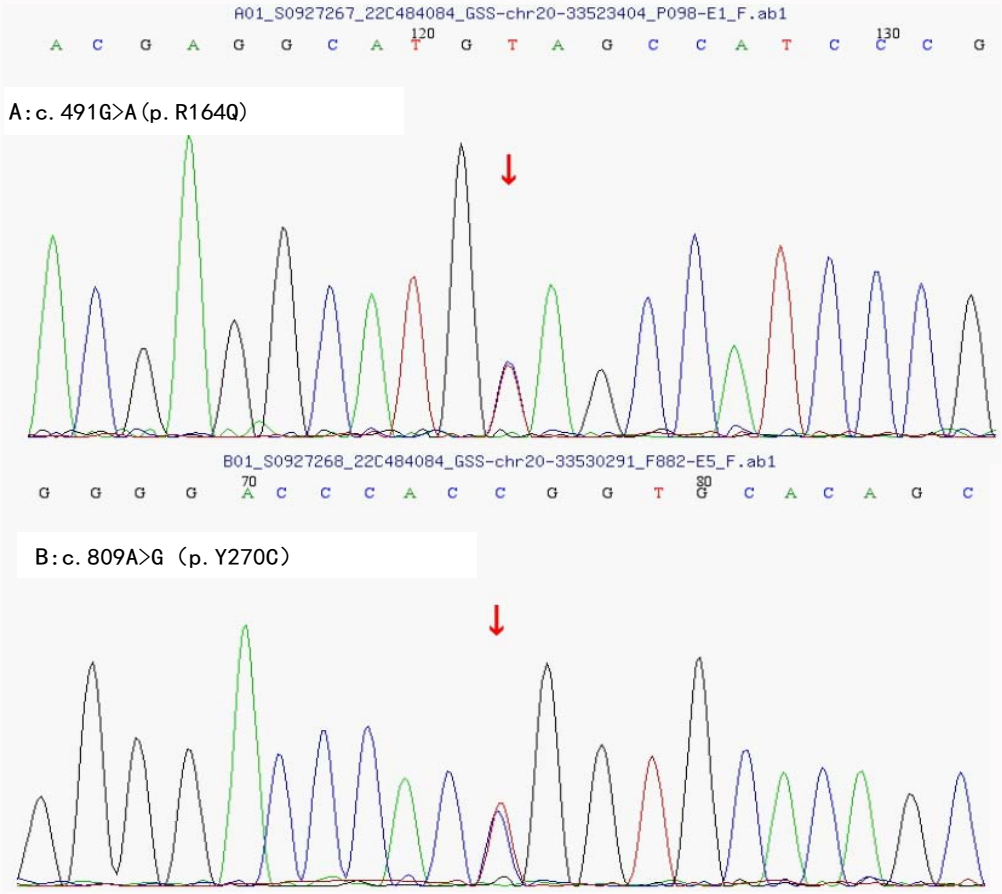

Figure 2: Results of high-throughput sequencing in this boy with Glutathione Synthase (GSS) deficiency.
A) Missense mutation of c.491G>A in exon 5 of GSS gene; B) C.809A>G missense mutation in exon 9; The arrow shows the mutation site.

auscultation area. The boy's nutritional status was good, and he had no facial deformities. His height was 150 cm; weight, 60 kg; and body mass index, 26.67. His consciousness was clear, but his mental health was poor. No yellowing of the skin, rash, bleeding or petechiae, congested pharynx, enlarged tonsils, or shortness of breath was evident. His abdomen was flat, with no pain or muscle tension. Liver and spleen were not palpable under the ribs. No swelling in the lower limbs was observed. The muscle strength of both upper limbs was assessed as grade III, and the muscle strength of both lower limbs, as grade I-II. Muscle tone was low, and bilaterally, the biceps and triceps reflexes and Achilles tendon reflexes could not be elicited. Bilaterally, the Bartholomew and Gram signs were negative.

Ancillary testing revealed ketones, 0.7 mmol/L; procalcitonin, 0.11 ng/dL; pH, 7.088; $PaCO_2$, 12.7 mmHg; potassium, 2.17 mmol/L; sodium, 151.6 mmol/L; bicarbonate, 3.7 mmol/L; BE, -23.9; glutamate,

10.0 mmol/L; lactate, 1.34 mmol/L; and total body hemoglobin, 13.9 g/dL. Results from complete thyroid function tests revealed third-generation thyroid-stimulating hormone, 0.032 mIU/L (reference: 0.55-4.78 mIU/L); total triiodothyronine, 3.01 nmol/L (0.92-2.79 nmol/L); free triiodothyronine, 6.95 pmol/L (3.50-6.50 pmol/L); total thyroxine, 90.30 nmol/L (58.1-140.6 nmol/L); and free thyroxine, 12.80 pmol/L (11.50-22.70 pmol/L). Urine tests revealed protein, 2+; occult blood, 1+; specific gravity, 1.022; and 24-h protein, 1.36 g (0.00-0.15 g). Morning pro-adrenocorticotropic hormone and serum cortisol were 260.00 pg/mL (10.00-63.00 pg/mL) and 54.69 μg/dL (5.27-22.45 μg/dL) respectively. Measurement of renin-angiotensin-aldosterone (recumbent) revealed no significant abnormality, with renin 3.52 pg/mL (4-24 pg/mL); angiotensin II 67.33 pg/mL (25-129 pg/mL); aldosterone 201.61 pg/mL (10-160 pg/mL); plasma renin activity 0.36 ng/mL/h (0.41-2.44 ng/mL/h); and aldosterone/renin 57.28 (0-37). Autoantibodies, complement tests, troponin, B-type natriuretic peptide precursors, routine disseminated intravascular coagulation, tumor tetralogy, and 17α-hydroxyprogesterone were not significantly abnormal. Cranial computed tomography suggested a slightly enlarged occipital pool. Chest computed tomography suggested scattered exudative lesions in the upper lobe of the right lung and both lower lobes of the lung, with possible inflammation. Magnetic resonance imaging of the pituitary and bilateral adrenal glands (plain and enhanced) did not demonstrate any significant abnormalities.

The boy was initially diagnosed with hypokalemia, hepatic impairment, metabolic acidosis, hypernatremia, upper respiratory tract infection, and obesity. He was urgently treated with high-concentration potassium pump and sodium bicarbonate to correct acidity. Extended-release nifedipine was administered to lower blood pressure. The boy's condition stabilized. Blood and urine metabolic screening returned results of glutamate 412.52 mmol/L (45.00-280.00 mmol/L) and urinary 5-oxoproline 445.2 mmol/L (0.0-10.0 mmol/L). A retest to clarify the cause demonstrated that 5-oxoproline was still elevated, suggesting 5-oxoprolinuria. A urinary organic acids analysis revealed a slight increase in lactate, 3-hydroxypropionic acid, 4-hydroxyphenyllactate, and 4-hydroxyphenylpyruvate, and a significant increase in 5-oxoproline, but no other abnormal metabolites (Figure 1), raising suspicion of pyroglutamaturia. A clinical diagnosis of GSD was made, and high doses of oral vitamins C and E were administered; intravenous alkaline supplementation was gradually reduced and then stopped, being replaced with oral sodium bicarbonate; potassium supplementation was stopped; and oxidizing drugs such as phenobarbital, aspirin, and sulfonamides were avoided.

Genetic Testing

With the consent of the boy and his family, whole-exome sequencing of peripheral blood was performed, and high-throughput sequencing detected the c.491G>A (p.R164Q) variant in exon 5 of the glutathione synthetase gene, which resulted in a change from tyrosine to cysteine at position 270 (p.Y270C). This variant was assessed as pathogenic based on the interpretation guidelines published by the American College of Medical Genetics and Genomics. Furthermore, the variant c.809A>G (p.Y270C) was detected in exon 9, which resulted in a change from arginine to glutamine at position 164 (p.R164Q). This variant was classified as a suspected pathogenic variant based on the American College of Medical Genetics and Genomics guidelines.

Sanger validation of the two detected missense mutations is shown in Figure 2. The origin of the mutation could not be verified because the boy's family consisted of adoptive parents, and parental samples could not be obtained.

Discussion

Patients with GSD can present with 5-oxoprolinuria, isolated hemolytic anemia, and/or high anion gap metabolic acidosis and central nervous system damage. Urinary stones, mental retardation, neonatal hypoglycemia, unilateral femoral hypoplasia, and microcephaly have also been reported [7-9]. The diagnosis is made based on clinical presentation and detection of elevated urinary 5-oxoproline and of reduced glutathione synthetase activity in red blood cells or cultured skin fibroblasts. It can be confirmed by genetic testing. Treatment includes correction of acidosis, blood transfusions, and antioxidant supplementation. The most important determinants of prognosis and survival in patients with GSD are early diagnosis and treatment.

The impaired glutathione synthesis that underlies GSD is catalyzed by glutathione synthetase through the addition of glycine to dipeptides, with the final step being catalysis through the c-glutamyl cycle. The lack of glutathione synthetase impairs that cycle, leading to an accumulation of c-glutamylcysteine, which is converted to 5-oxoproline via the c-glutamyl cyclotransferase pathway [10], producing the elevated urinary 5-oxoproline observed in patients.

Glutathione is one of the most important antioxidants in eukaryotes; it is involved in a variety of essential physiologic processes such as maintenance of cell membrane integrity, defense against oxidative stress, and coenzyme functions [11]. Lack of glutathione can lead to oxidative damage in various tissues, neuronal cell death, and neurologic diseases [12]. Simultaneously, the accumulation of 5-oxoproline induces oxidative stress, which impairs energy metabolism in neuronal cells.

As a metabolic disorder, GSD is the result of a variety of genetic variants, such as missense/nonsense, splice, and deletion/insertion mutations. The disease is autosomal recessive, and patients with the disorder can be divided into three groups based on their clinical phenotype. Patients with mild GSD have mutations that affect enzyme stability and lead to compensatory hemolytic anemia; patients with moderate GSD also have metabolic acidosis; and patients with severe GSD also develop neurologic defects and show increased susceptibility to bacterial infections. Early supplementation with vitamins C and E can improve long-term patient outcomes.

Metabolic acidosis is the characteristic pathophysiologic process of GSD. Oxidative respiratory chain complex I causes abnormal mitochondrial respiratory capacity [13], which in turn leads to metabolic acidosis as a result of reduced renal tubular resorption of bicarbonate, impaired hydrogen ion secretion, reduced ability to acidify urine, reduced ammonia secretion, and reduced production and excretion of urinary titratable acid and ammonia.

Most (90%) of the potassium ions filtered into the glomerular capsule are absorbed by the proximal tubule and the ascending crude segment of the medullary collaterals. The accumulation of organic acids triggers a decrease in tubule function, which in turn affects potassium resorption in the proximal tubule, leading to hypokalemia. This vicious cycle continues until the clinical signs of severe hypokalemia, such as limb weakness, are noticed by parents, who subsequently seek medical attention. Acidosis also increases aldosterone secretion, which explains why aldosterone was elevated

at the beginning of our patient's illness and then normalized on its own.

Conclusion

In this case, with the accumulation of organic acids, renal tubular function decreased. With the decline of renal tubular function, more acid will accumulate, leading to more serious renal injury. This vicious cycle made the renal tubular function of the child worse, and then the clinical manifestations of severe hypokalemia, such as limb weakness, were found by the parents and then went to hospital. Intravenous bicarbonate normalizes blood pH to a physiologic range and improves tubule function, thus explaining the normalization and stabilization of potassium in our patient after the metabolic acidosis was corrected. Early correction of metabolic acidosis can effectively restore the function of the renal tubules and prevent the recurrence of severe hypokalemia.

References

1. Xia H, Ye J, Wang L. A case of severe glutathione synthetase deficiency with novel GSS mutations. Braz J Med Biol Res. 2018;51(3):e6853.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
3. Yang QP. Glutathione synthetase deficiency and literature review. Zhonghua Fuyoulinchuang Yixue Za Zhi. 2021;17(04):425-30.
4. Liu C, Wang YH. Gene analysis and literature review of glutathione synthetase deficiency in. Zhongguo Fuyou Jiankang Research. 2017;28(11):1435-8.
5. Wang H J, Lu T T, Li D X. A case of glutathione synthetase deficiency caused by GSS gene mutations. Zhonghua Er Ke Za Zhi. 2017;55(8).
6. Li X, Ding Y, Liu Y, Ma Y, Song J, Wang Q, et al. Five Chinese patients with 5-oxoprolinuria due to glutathione synthetase and 5-oxoprolinase deficiencies. Brain Dev. 2015;37(10):952-9.
7. Calpena E, Casado M, Martínez-Rubio D, Nascimento A, Colomer J, Gargallo E, et al. 5-Oxoprolinuria in Heterozygous Patients for 5-Oxoprolinase (OPLAH) Missense Changes. JIMD Rep. 2013;7:123-8.
8. Guney Varal I, Dogan P, Gorukmez O, Dorum S, Akdag A. Glutathione synthetase deficiency: A novel mutation with femur agenesis. Fetal Pediatr Pathol. 2020;39(1):38-44.
9. Kaur P, Chaudhry C, Panigrahi I, Srivastava P, Kaur A. Gas chromatography mass spectrometry aided diagnosis of glutathione synthetase deficiency. Lab Med. 2022;53(3):e59-59e61.
10. Pederzolli CD, Mescka CP, Zandoná BR, de Moura Coelho D, Sgaravatti AM, Sgarbi MB, et al. Acute administration of 5-oxoproline induces oxidative damage to lipids and proteins and impairs antioxidant defenses in cerebral cortex and cerebellum of young rats. Metab Brain Dis. 2010;25(2):145-54.
11. Njålsson R. Glutathione synthetase deficiency. Cell Mol Life Sci. 2005;62(17):1938-45.
12. Ristoff E, Mayatepek E, Larsson A. Long-term clinical outcome in patients with glutathione synthetase deficiency. J Pediatr. 2001;139(1):79-84.
13. Bugarski M, Ghazi S, Polesel M, Martins JR, Hall AM. Changes in NAD and lipid metabolism drive acidosis-induced acute kidney injury. J Am Soc Nephrol. 2021;32(2):342-56.