Rev Nefrol Dial Traspl. 2025;45(1):43-48

A Rare Cause of Acute Kidney Injury: G6PD Deficiency and Rhabdomyolysis

Una Causa Rara de Lesión Renal Aguda: Deficiencia de G6PD y Rabdomiólisis

Neriman Sıla Koç[1]

RESUMEN

La deficiencia de G6PD, un trastorno genético ligado al cromosoma X, típicamente induce episodios hemolíticos bajo estrés oxidativo causado por factores como infecciones o ciertos alimentos. Nuestro informe describe a un hombre sirio de 31 años que desarrolló lesión renal aguda debido a rabdomiólisis severa, hemólisis intravascular y metahemoglobinemia severa tres días después de su primera ingesta de habas. Diagnosticado con deficiencia de G6PD, requirió hemodiálisis temporal debido a una lesión renal aguda anúrica severa. Las pruebas genéticas y la actividad enzimática reducida confirmaron una mutación hemicigota c.563 C>T p.ser188phe, asociada con la variante mediterránea de la deficiencia de G6PD. Este caso subraya el riesgo raro pero significativo de complicaciones, como la rabdomiólisis y la lesión renal aguda, en la deficiencia de G6PD, especialmente tras el consumo de habas. Nuestros hallazgos destacan la importancia del reconocimiento temprano y el manejo integral de estas complicaciones severas en poblaciones predispuestas a la deficiencia de G6PD. Este caso contribuye a la limitada literatura sobre la tríada asociada con la deficiencia de G6PD, que incluye metahemoglobinemia severa, rabdomiólisis y crisis hemolítica aguda provocada por favismo.

Palabras clave: Rabdomiólisis; Metahemoglobinemia; Hemólisis; Deficiencia de Glucosa-6-Fosfato Deshidrogenasa; Lesión renal aguda

ABSTRACT

G6PD deficiency, an X-linked genetic disorder, typically induces hemolytic episodes under oxidative stress from factors like infections or certain foods. Our report involves a 31-year-old Syrian male who developed acute kidney injury due to severe rhabdomyolysis, intravascular hemolysis, and severe methemoglobinemia three days after his first consumption of fava beans. Diagnosed with G6PD deficiency, he needed hemodialysis for a while due to severe anuric acute kidney injury. Genetic testing and decreased enzymatic activity confirmed a hemizygous c.563 C>T p.ser188phe mutation associated with the Mediterranean variant of G6PD deficiency. This case underscores the rare but significant risk of complications that have rhabdomyolysis and acute kidney injury in G6PD deficiency, especially following fava bean consumption. Our findings highlight the importance of early

Correspondencia:
Neriman Sıla Koç
ORCID:
0000-0002-4654-9002
silacank@gmail.com

Financiamiento:
Ninguno

Conflicto de intereses:
Ninguno que declarar

Recibido: 26-11-2024
corregida: 20-01-2025
Aceptación: 29-01-2025

1) Harran University Medical Faculty, Department of Internal Medicine, Division of Nephrology, Sanliurfa

recognition and comprehensive management of these severe complications in populations predisposed to G6PD deficiency. This case adds to the limited literature on the triad associated with G6PD deficiency, which includes severe methemoglobinemia, rhabdomyolysis, and acute hemolytic crisis caused by favism.

Keywords: Rhabdomyolysis; Methemoglobinemia; Hemolysis; Glucose-6-phosphat dehydrogenase deficiency; Acute kidney injury

INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, a common X-linked genetic disorder, causes hemolytic episodes under oxidative stress from drugs, infections, or fava beans (favism) [(1)]. Symptoms include hemoglobinuria, anemia, jaundice, fever, back pain, headache, and nausea [(2)]. While hemolytic crises are linked to high methemoglobin (metHb) levels, symptomatic methemoglobinemia is rarely noted but is crucial for diagnosis and treatment [(1)]. G6PD deficiency often results in acute intravascular hemolysis and acute kidney injury (AKI). Limited literature exists on myoglobinuria and rhabdomyolysis in G6PD-deficient individuals [(3)]. We report a 31-year-old male with G6PD deficiency who developed AKI, severe hemolysis, rhabdomyolysis, and methemoglobinemia after consuming fava beans, the first in the literature.

CASE REPORT

Our patient, a previously healthy 31-year-old Syrian male farmer, presented with back pain, jaundice, and oliguria. Initial tests showed impaired renal function and severe anemia. He had no history of chronic disease, drug use, or exposure to organophosphates, narcotics, or herbals.

Upon admission, his vitals were as follows: heart rate 70/min, blood pressure 115/60 mmHg, respiratory rate 22 / min, fever 37.4°C, and oxygen saturation 85%. He had mild scleral icterus, cyanotic lips, normal breath sounds, bilateral costovertebral and abdominal tenderness, and dark urine with anuria. Laboratory results at admission are shown in **Table 1**.

Table 1: Laboratory results at admission

Parameter	Results
Hemoglobin	6.6g/dL
Hematocrit	17%
White Blood Cell	21,800/ µL
Neutrophils	16,300/ µL
Platelets	219,000/ µL
Glucose	140 mg/dL
Blood urea nitrogen	143 mg/dL
Creatinine	4.4 mg/dL
Uric acid	7.0 mg/dL
Aspartate aminotransferase	185 U/L
Alanine aminotransferase	30 U/L
Total bilirubin	5.6 mg/dL
Direct bilirubin	2.68 mg/dL
Albumin	4.8 g/dL
Sodium	134 mmol/L
Potassium	4.4 mmol/L
Calcium	8.6 mg/dL
Phosphate	4.2 mg/dL
Creatine kinase	3290 U/L
Lactate dehydrogenase	3388 U/L
C-reactive protein	11 mg/dL
pH	7.36
HCO3	23.6
PCO2	43.3
Lactate	0.8
Methemoglobin	29.60%

***G/dL**: Grams per deciliter, **HCO3**: Bicarbonate, **Mg/dL**: Miligrams per deciliter, **Mg/L**: Miligrams per liter, **Mmol/L**: Milimoles per liter, **PCO2**: Partial pressure of carbon dioxide, **U/L**: Units per liter, **µl**: Microliter*

Due to his low oxygen saturation and cyanosis, he was admitted to the intensive care unit. Physical examination and imaging (chest radiography and thorax computed tomography) were normal, suggesting methemoglobinemia as the cause of low saturation. Methylene blue was unavailable, so he received 500 mg of vitamin C for three days.

Abdominal ultrasonography showed normal kidney dimensions and increased parenchymal echogenicity. A urine examination revealed hemoglobinuria without red blood cells. The patient had rhabdomyolysis, elevated CK levels and myoglobinuria, and hemolysis with

 ISSN 0326-3428

high LDH levels. Methemoglobinemia added complexity to the case. A corrected reticulocyte count was 2.66%. A blood smear showed numerous schistocytes and microspherocytes. The Coombs tests were negative, and autoimmune antibody screening revealed no positive results. Hemoglobin electrophoresis ruled out hemoglobinopathy, and no monoclonal gammopathy was detected.

Iron studies showed iron 195 µg/dL, an iron-binding capacity <20000 µg/dL, B12 209 pg/mL, folic acid 4.39 ng/mL, and ferritin 7541.9 ng/mL. Intramuscular B12 treatment was initiated for possible profound deficiency. He received nasal oxygen, intravenous hydration, RBC transfusions, empirical piperacillin-tazobactam, and serial metHb monitoring. Cultures showed no bacterial growth.

All these findings suggested G6PD deficiency. When questioned about favism, it was discovered that he had consumed a large quantity of fava beans three days before hospitalization, marking his first intake. Only a genetic test was sent during the acute-hemolytic crisis to avoid false negative results. Three weeks post-hemolytic crisis confirmed G6PD deficiency with G6PD levels were 2.6 IU/g Hb (normal: 6.97-20.5 IU/g Hb). Genetic tests also revealed a hemizygous c.563 C>T p.ser188phe mutation, indicating likely pathogenicity.

By the second day, CK, LDH, and bilirubin levels decreased, and hemoglobin decline slowed. The pain subsided, and he received four RBC transfusions. He became anuric on the first day and required 23 days of hemodialysis. Urine output increased on the 11th day, but hemodialysis continued for hyperkalemia. Methemoglobinemia normalized by the third day. Laboratory parameters are shown in **Figure 1** and **Figure 2.**

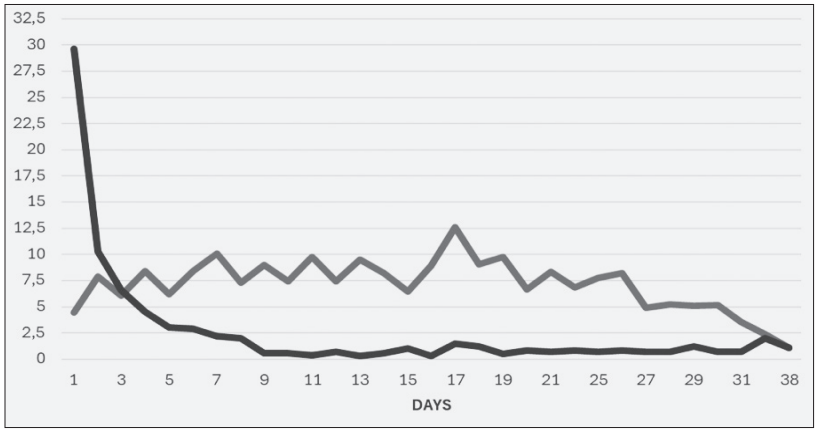

Figure 1: Changes in creatinine and methemoglobin levels

***Cre**: Creatinine, **METHB**: Methemoglobin*

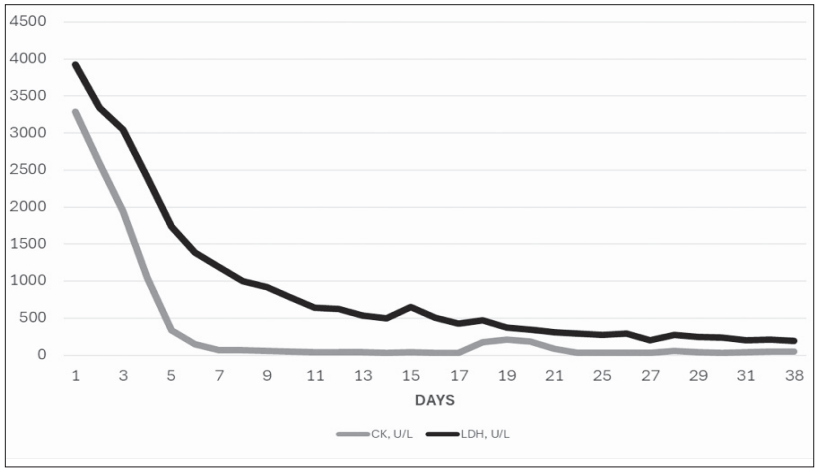

Figure 2: Changes in creatine kinase and lactate dehydrogenase levels

***CK**: Creatine kinase, **LDH**: Lactate dehydrogenase*

He was discharged for outpatient follow-up as creatinine decreased to 3.5 mg/dL, returning to normal later. With a confirmed G6PD deficiency diagnosis, he was given medication and dietary guidance.

DISCUSSION

The present case is a very rare case of severe intravascular hemolysis and rhabdomyolysis related to AKI and methemoglobinemia in an adult with G6PD deficiency.

Although methemoglobinemia is a significant finding in G6PD deficiency, it is rarely mentioned in the literature. A study in 1987 reported methemoglobin levels above 5% in 7 patients with G6PD deficiency [4]. These patients have been documented to experience moderate methemoglobinemia during hemolytic crises, with both adult and pediatric cases described [2,5]. Acute hemolysis and methemoglobinemia are rarely seen together in favism. However, a case series from 2020 and a case report 2021 documented varying degrees of methemoglobinemia (3.5%-35%) in 9 patients after ingesting fava beans [6,7].

In an adult case report by Hassan et al., a previously healthy 70-year-old Omani patient, like ours, was diagnosed with G6PD deficiency following intravascular hemolysis with methemoglobinemia [8].

When the MetHb concentration exceeds 35%, the oxygen saturation plateaus at 85% on pulse oximetry, as in our patient [9]. Treatment is recommended when MetHb levels are above 30% or if the patient is symptomatic. Typically, a 1% methylene blue solution and 100% oxygen are used to treat MetHb. NADPH met-Hb reductase uses methylene blue as an electron acceptor, with the pentose phosphate pathway producing NADPH. However, methylene blue should not be used in G6PD deficiency, as it relies on NADPH produced by G6PD to reduce met-Hb. Due to its oxidant potential, methylene blue can cause hemolysis in G6PD-deficient individuals, making it ineffective and potentially harmful [10].

Rhabdomyolysis, characterized by the disintegration of skeletal muscle tissue and the release of myoglobin into thecirculation, is an uncommon consequence of G6PD deficiency. In 1989, Bresolin et al. first described four patients with G6PD deficiency and rhabdomyolysis, termed "muscle G6PD deficiency" [11]. G6PD enzyme is expressed in all tissues, and its activity in muscle cells correlates strongly with that in erythrocytes. Ninfali et al. found a significant relationship between G6PD activity in quadriceps muscle biopsies and erythrocytes in patients with G6PD deficiency [12]. This relationship suggests that G6PD deficiency could cause rhabdomyolysis and symptoms like myalgia, weakness, and muscle fatigability due to oxidative stress damaging myocytes. Subsequently, several cases of rhabdomyolysis in both adults and children with G6PD deficiency have been reported, some following exercise and one after exposure to mothballs [3,13-17]. As in our patient, the coexistence of favism and rhabdomyolysis has not been reported.

Only two of the reported cases in the literature required renal replacement therapy due to oliguric AKI, similar to our case. One involved an 11-year-old Indian girl whose cause of hemolysis was unknown, but she followed medication for a viral upper respiratory tract infection a week prior [3]. The other case was a 19-year-old African American male hospitalized for COVID-19, where hemolysis worsened, and methemoglobinemia occurred after rasburicase treatment [17]. Our case is the first G6PD deficiency case with severe rhabdomyolysis and AKI due to favism.

Enzymatic activity forms the basis for diagnosing G6PD deficiency. Reticulocytosis, hemolysis, or blood transfusions may artificially increase activity [1]. Although insufficient time had passed for the transfused RBCs to be completely replaced by native RBCs, we examined the patient's enzymatic activity 3 weeks after the hemolysis resolved and confirmed the diagnosis of G6PD deficiency.

G6PD deficiency is classified into five categories based on the clinical spectrum and G6PD levels [1]. In our patient, the G6PD gene sequencing revealed a hemizygous c.563 mutation, causing the Mediterranean variant (class II), known for its severity. This variant results from a single C-T transition at nucleotide position 563, leading to a serine-phenylalanine substitution at amino acid position 188 [18]. Many communities in the Mediterranean region share the c.563T mutation, which also seems to be dominant in populations in North Africa and

Southern Europe, including Sephardic Jews, people living in southern Italy, Sicily, and Sardinia, as well as those in Türkiye, Iran, and other Middle Eastern Arab countries. Due to poor enzyme stability, the Mediterranean c.563T mutation causes a severe loss of enzymatic activity, classified as a WHO class II deficiency [19].

Until age 31, our patient had no history of hemolytic episodes. The hemolysis improved significantly within 3 days, but AKI healing took about a month. Interestingly, individuals with G6PD deficiency don't always experience favism when consuming fava beans, with the reasons remaining unclear. Some authors suggest that the type and amount of beans consumed may influence hemolytic events [20]. In our case, consuming beans for three consecutive meals likely exacerbated the severity of hemolysis, rhabdomyolysis, and methemoglobinemia.

Tests conducted upon admission, including G6PD enzyme activity and genetic testing, confirmed G6PD deficiency as the underlying cause of the hemolytic crisis and its subsequent impact on renal and muscular tissues. This case highlights the necessity of considering rare enzymatic deficiencies in diagnosing AKI, especially when symptoms indicate multi-organ involvement.

CONCLUSION

This case study aims to raise awareness about the potential complications of G6PD deficiency, including its interaction with rhabdomyolysis, AKI, hemolysis, and methemoglobinemia. By clarifying the underlying pathophysiological mechanisms, we seek to enhance early recognition and proper management of these intricate disorders, particularly in populations with a higher prevalence of G6PD deficiency.

Ethics Statement: Not applicable.

Inform Consent: The patient gave consent for publication.

BIBLIOGRAPHY

1) Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. Lancet. 2008;371(9606):64-74.
2) Schuurman M, van Waardenburg D, Da Costa J, Niemarkt H, Leroy P. Severe hemolysis and methemoglobinemia following fava beans ingestion in glucose-6-phosphatase dehydrogenase deficiency: case report and literature review. Eur J Pediatr. 2009;168(7):779-782.
3) Talwar M, Krishnamurthy S, Parameswaran N, Delhikumar CG, Haridasan S, Srinivas BH. Severe acute kidney injury owing to rhabdomyolysis and intravascular haemolysis in an 11-year-old child with G6PD deficiency. Pediatric Int Child Health. 2019;39(2):150-153.
4) De Flora A, Benatti U, Guida L, Forteleoni G, Meloni T. Favism: disordered erythrocyte calcium homeostasis. Blood. 1985;66(2):294-297.
5) Foltz LM, Dalal BI, Wadsworth LD, Broady R, Chi K, Eisenhauer E, et al. Recognition and management of methemoglobinemia and hemolysis in a G6PD-deficient patient on experimental anticancer drug Triapine. Am J Hematol. 2006;81(3):210-1. Doi: 10.1002/ajh.20547.
6) Ata F, Muthanna B, Javed S, Uddin M, Yassin MA. Favism Induced Methemoglobinemia in G6DP Deficient Patients: Case Series and Review of Literature. Blood. 2020;136 (Supplement 1):11-12.
7) Al-Dubai H, Al-Mashdali A, Hailan Y. Acute hemolysis and methemoglobinemia secondary to fava beans ingestion in a patient with G6PD deficiency: A case report of a rare co-occurrence. Medicine (Baltimore). 2021;100(47):e27904. Doi: 10.1097/MD.0000000000027904.
8) Hassan KS, Al-Riyami AZ, Al-Huneini M, Al-Farsi K, Al-Khabori M. Methemoglobinemia in an elderly patient with glucose-6-phosphate dehydrogenase deficiency: a case report. Oman Med J. 2014;29(2):135-137. Doi: 10.5001/omj.2014.33.
9) Haymond S, Cariappa R, Eby CS, Scott MG. Laboratory assessment of oxygenation in methemoglobinemia. Clin Chem. 2005;51(2):434-44. Doi: 10.1373/clinchem.2004.035154.
10) Mullick P, Kumar A, Dayal M, Babbar S, Kumar A. Aniline-induced methaemoglobinaemia in a glucose-6-phosphate dehydrogenase enzyme deficient patient. Anaesthesia Intensive Care. 2007;35(2):286-288.
11) Bresolin N, Bet L, Moggio M, Meola G, Fortunato F, Comi G, et al. Muscle glucose-6-phosphate dehydrogenase deficiency. J Neurol. 1989;236(4):193-198.
12) Ninfali P, Baronciani L, Bardoni A, Bresolin N. Muscle expression of glucose-6-phosphate

dehydrogenase deficiency in different variants. Clin Genet. 1995;48(5):232-237.
13) Ninfali P, Bresolin N, Baronciani L, Fortunato F, Comi G, Magnani M, et al. Glucose-6-phosphate dehydrogenase Lodi844C: a study on its expression in blood cells and muscle. Enzyme. 1991;45(4):180-187.
14) Mangat C, Inoue S, Saah E, Sharman M. Acute haemolytic anaemia and myolysis due to G6PD deficiency. BMJ Case Rep. 2014;2014:bcr2014203631. Doi: 10.1136/bcr-2014-203631.
15) Eziokwu AS, Angelini D. New Diagnosis of G6PD Deficiency Presenting as Severe Rhabdomyolysis. Cureus. 2018;10(3):e2387. Doi: 10.7759/cureus.2387.
16) Kimmick G, Owen J. Rhabdomyolysis and hemolysis associated with sickle cell trait and glucose-6-phosphate dehydrogenase deficiency. South Med J. 1996;89(11):1097-1098.
17) Yu R, Chen CR, Evans D, Qing X, Gotesman M, Chandramohan G, et al. Glucose-6-phosphate dehydrogenase deficiency presenting with rhabdomyolysis in a patient with coronavirus disease 2019 pneumonia: a case report. J Med Case Rep. 2022;16(1):106. https://doi.org/10.1186/s13256-022-03322-w
18) Awab GR, Aaram F, Jamornthanyawat N, Suwannasin K, Pagornrat W, Watson JA, et al. Protective effect of Mediterranean-type glucose-6-phosphate dehydrogenase deficiency against Plasmodium vivax malaria. Elife. 2021;10:e62448. Doi: 10.7554/eLife.62448.
19) Sirdah M, Reading NS, Perkins SL, Shubair M, Aboud L, Prchal JT. Hemolysis and Mediterranean G6PD mutation (c.563 C>T) and c.1311 C>T polymorphism among Palestinians in the Gaza Strip. Blood Cells Mol Dis. 2012;48(4):203-208.
20) Diegues A, Simões P, Ceriz T, Lopes AR, Tomé E. Favism: A Case Report. Cureus. 2022;14(3): e23269. Doi: 10.7759/cureus.23269.