QJM: An International Journal of Medicine, 2022, 1–2

https://doi.org/10.1093/qjmed/hcac184
Advance Access Publication Date: 29 July 2022
Case report

CASE REPORT

COVID-19 infection unmasking glucose-6-phosphate dehydrogenase deficiency

S.P. Devarashetty[1], P.K. Ponna[2], V. Devarakonda[2] and Poornima Ramadas[1]

[1]Department of Hematology-Oncology, Louisiana State University Health Shreveport, 1501 Kings Highway, Shreveport, LA, 71103, USA and [2]Department of Internal Medicine, Louisiana State University Health Shreveport, 1501 Kings Highway, Shreveport, LA, 71103, USA

Address correspondence to S.P. Devarashetty, Department of Hematology-Oncology, Louisiana State University Health Shreveport, Shreveport, LA, USA. email: sindhu.priya1509@gmail.com

Learning points for clinicians

Glucose-6-phosphate dehydrogenase (G6PD) enzyme plays a vital role in hexose monophosphate shunt pathway, essential for energy metabolism of red blood cells (RBCs). G6PD deficiency predisposes the destruction of RBCs from oxidative stress involving illnesses, drugs and chemicals. Coronavirus disease 2019 posed new challenges in diagnosing G6PD deficiency, given its association with hemolysis.

Case presentation

A 39-year-old African American male was admitted for coronavirus disease 2019 (COVID-19) infection and diabetic ketoacidosis. His vital signs were stable, except for hypoxia requiring 4–5 l on nasal cannula. He was started on insulin drip and transitioned to subcutaneous insulin. Remdesivir was started for COVID-19 infection. Hemoglobin was 13.6 g/dl on admission, but started dropping, with a nadir hemoglobin of 6.4 g/dl in 7 days. Haptoglobin <8 mg/dl, Lactate Dehydrogenase (LDH) >2000 U/l and reticulocytosis, suggestive of hemolytic anemia. No other cytopenias were seen. A direct antiglobulin test was negative and there was no prior history of blood transfusion or hematological disorders. Peripheral smear showed blister and bite cells (Figure 1) concerning for glucose-6-phosphate dehydrogenase (G6PD) deficiency. His G6PD level was found to be low at 3.9 U/g Hb (39% of mean normal). He received one unit of red blood cell (RBC) transfusion and was started on oral folic acid daily. Hemoglobin improved with COVID-19 infection recovery. The patient was discharged with stable hemoglobin. Repeat G6PD levels done in 4 weeks showed low activity at 2.3 U/g Hb (23% of mean normal). Gene sequencing showed hemizygosity for Variant A-(202), Ferrara I, confirming WHO class III variant of G6PD deficiency. The patient was counseled extensively on drugs to avoid and the possibility of hemolysis from stressful situations and infections.

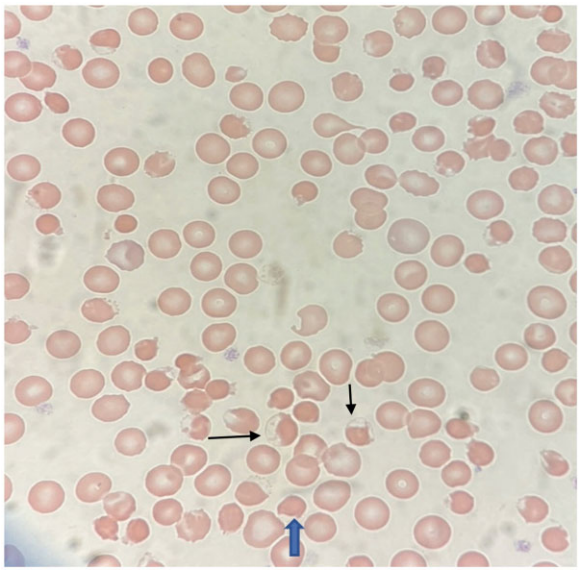

Figure 1. Blister cells (arrows) and bite cells (arrow).

Submitted: 21 June 2022; **Revised (in revised form):** 28 June 2022

Table 1. Classification of G6PD deficiencies following WHO recommendations

G6PD variant[a]	Enzymatic activity	Clinical symptoms
Class I	<1% or not detectable	Severe hemolytic anemia
Class II	<10% (severe enzyme deficiency)	Intermittent hemolysis with infection, drugs or chemicals
Class III	10–60% (moderate enzyme deficiency)	Intermittent hemolysis with infection, drugs or chemicals
Class IV	60–90% of normal activity	No hemolysis
Class V	>110%, increased enzymatic activity	No hemolysis

[a]Other variants that are identified are G6PD A, variant similar to class III and G6PD Mediterranean variant, similar to class II deficiency.

Discussion

G6PD deficiency is an X-linked recessive disorder and its gene is located on the X chromosome (band Xq28)[1]; the deficiency primarily affects African American males.[2] Heterozygous female carriers can experience symptoms based on the degree of lyonization.[3] The G6PD enzyme protects RBCs from oxidative stress (acute microbial illnesses), drugs (primaquine, hydroxychloroquine), chemicals (amyl nitrite, mothballs) and foods (fava beans) in Hexose Monophosphate Shunt Pathway and its deficiency leads to hemolysis. Clinical presentation varies from asymptomatic state to episodic anemia to chronic hemolysis.[3]

G6PD deficiency has been classified into variants based on the magnitude of the enzyme deficiency and the severity of the hemolysis (see Table 1).

G6PD status is important in regulating reactive oxygen species (ROS) by maintaining redox homeostasis and keeping ROS at normal levels, as ROS at higher levels are cytotoxic.[4] G6PD is required for the maintenance of the innate immune response, inflammasome activation and pathogen clearance through redox homeostasis; its deficiency may enhance viral infections.[5]

COVID-19 is also influenced by genetic variants of G6PD deficiency, which, in turn, are related to an impaired immune response. Multiple factors (age, comorbidities, ethnicity) influence the morbidity and mortality of COVID-19 infections. Age-associated accumulation of oxidative stress from COVID-19 and impaired redox reactions from G6PD can worsen the severity of viral infections.[5] It is unclear if hydroxychloroquine causes hemolysis in G6PD-deficient people with COVID-19; its use should be avoided if in doubt. The use of antioxidants and some anti-aging drugs, along with COVID-19 vaccinations, is promising for COVID-19 infection.

In our patient with this class III G6PD variant, hemolysis resolved and Hb normalized with supportive care and recovery from the infection, and no other triggers were identified.

Conclusion

G6PD is essential for an adequate immune response. It is important to check G6PD status in COVID-19-infected patients with hemolytic anemia. This is particularly important with ethnic groups predisposed to having deficiency, as it causes impaired cellular responses, viral proliferation and worsening oxidative damage.

Conflict of interest: None declared.

References

1. Glader B. Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency. 2022. https://www.uptodate.com (25 April 2022, date last accessed).
2. Beutler E. The molecular biology of enzymes of erythrocyte metabolism. In: Stamatoyannopoulos G, Nienhuis AW, Majerus PW, eds. *The Molecular Basis of Blood Disease*. Philadelphia, PA: WB Saunders, 1993, 29.
3. Yang HC, Ma TH, Tjong WY, Stern A, Chiu DT. G6PD deficiency, redox homeostasis, and viral infections: implications for SARS-CoV-2 (COVID-19). *Free Radic Res* 2021; **55**:364–74.
4. Elhabyan A, Elyaacoub S, Sanad E, Abukhadra A, Elhabyan A, Dinu V. The role of host genetics in susceptibility to severe viral infections in humans and insights into host genetics of severe COVID-19: a systematic review. *Virus Res* 2020; **289**: 198163.
5. Delgado-Roche L, Mesta F. Oxidative stress as key player in severe acute respiratory syndrome coronavirus (SARS-CoV) infection. *Arch Med Res* 2020; **51**:384–7.