Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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OPINION

Glucose-6-Phosphate Dehydrogenase Deficiency: An Actionable Risk Factor for Patients with COVID-19?

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common X-linked mutation that is more prevalent in African, Asian, Latin American and Mediterranean populations. Although most individuals are asymptomatic, exposure to certain food, drugs, or infections can trigger acute hemolytic anemia. Given the potential for coronavirus to trigger oxidative stress, unrecognized G6PD deficiency in the presence of the COVID-19 viral infection may cause hemolytic crisis and worse outcome in affected individuals. Further, since certain drugs that may be used to treat COVID-19 infection may cause hemolytic crisis in individuals with G6PD deficiency, it may be warranted to recommend adding G6PD deficiency to the list of screening elements in a COVID-19 workup for those patients where there is a high suspicion for this genetic mutation. © 2020 IMSS. Published by Elsevier Inc.

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COVID-19 presents as mild to moderate disease in the majority of patients, but as severe acute respiratory syndrome in hospitalized patients who progress to a severe form. Risk factors identified for susceptibility to worse outcomes for COVID-19 include comorbidities such as hypertension, diabetes, cardiovascular disease, chronic lung disease, and older age (1).

Several factors are associated with more severe disease and fatal outcomes in COVID-19 patients. In a cross sectional analysis examining laboratory parameters of COVID-19 cases associated with mortality, a significant elevation of d-dimer, a biomarker of fibrin formation and degradation, was present in those patients who did not survive. Other biomarkers that are present in those with more severe disease are an increase in inflammatory biomarkers of IL6, increase in liver transaminases, lower platelets and increase ferritin (2). Venous thromboembolism has been reported in those who die from the disease (1). This presentation has overlapping features of individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency who experience hemolytic crisis after being exposed to oxidative agents or viral infections and therefore raises the specter that G6PD deficiency is a predisposing factor that could lead to a more severe COVID-19 illness.

Glucose-6-Phosphate Dehydrogenase Deficiency Genetic Features and Prevalence

G6PD deficiency is a common X-linked disorder affecting approximately 350–400 million people worldwide (3). G6PD is found in all cells of the body and catalyzes the initial step in the pentose phosphate pathway (4,5). This pathway functions to protect red blood cells against oxidative stress through the production of nicotinamide adenine dinucleotide phosphate which is generated by G6PD to supply glutathione.4 G6PD deficiency is categorized as class I–IV corresponding to G6PD enzyme activity. The majority of persons are defined class II–III (associated with 10–60% enzyme activity) with fewer persons having a

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more severe class I form (associated with less than 10% G6PD activity) (5). Classical events which trigger red cell hemolysis are the ingestion of fava beans, certain drugs and infection (4). Hydroxychloroquine, a drug that is under investigation to treat COVID-19, has been reported to trigger hemolytic crisis in patients with G6PD deficiency (6,7). Therefore, when an unexpected drop in hemoglobin occurs in a patient with COVID-19, it may also alert the clinician to the need to further evaluate for the possibility of G6PD deficiency.

G6PD deficiency has a higher prevalence across African, Asian, Latin America, and Mediterranean populations (3). The prevalence of G6PD deficiency commonly maps to populations where historically malaria was prevalent and is likely to have been a protective adaptation since cells deficient in G6PD inhibit the growth of specific types of malaria (4). In the United States, estimated prevalence of G6PD deficiency based on estimates from the military population is 12% in African American males, 4% in African American females, 4% in Asian males, 2% in Hispanic males and 0.3% in nonhispanic Caucasian males (8).

Glucose-6-Phosphate Dehydrogenase Deficiency Risks in COVID-19

G6PD deficiency may also result in vulnerability to coronavirus infection. A study examining G6PD deficient cells incubated with human coronavirus 229E found that these cells exhibited significantly higher coronavirus viral gene expression and viral particle production (9). Further, older individuals with G6PD deficiency are more at risk of a pre-existing state of having red blood cells with lower amounts of G6PD, lower glutathione and a higher red blood cell turnover (10). This may predispose older aged patients with G6PD deficiency to have a lower threshold for hemolytic crisis following exposure to certain triggering event such as coronavirus.

Conclusion

Taken together, there are multiple pathways where unrecognized G6PD deficiency could be associated with severe COVID-19 infection and worse outcomes:

a) Unrecognized G6PD deficiency in the presence of the viral infection itself may cause hemolytic crisis and worse outcome.
b) Unrecognized G6PD deficiency is a risk factor for complications -not associated with hemolytic crisis but associated with venous thrombosis and cascade of CV complications.
c) Administration of hydroxycholorquine for treatment of COVID-19 in patients with unrecognized G6PD deficiency could lead to worse outcomes associated with hemolytic crisis.

Based on this evidence, it may be warranted to recommend adding G6PD deficiency to the list of screening elements in a COVID-19 workup for those patients where there is a high suspicion for this genetic mutation.

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