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Letters to the Editor / Cartas al Editor

COVID-19 - G6PD DEFICIENCY AND HYDROXYCHLOROQUINE

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Dear Editor:

G6PD deficiency increased in interest during the Covid-19 pandemic, due to the hydroxychloroquine (HCQ) utilization for early treatment[1-8]. Mutations in the g6pdx gene of the X chromosome are sex-linked and hemizygous males can have the condition, and females are rarely symptomatic carriers, or heterozygous G6PD deficient 1. G6PD acts in processing of antioxidants and glutathione reduction, and its deficiency increase oxidative damage to red blood cells (RBCs).

Manifestations follow trigger mechanisms: fava beans, quinine derivatives, and infections[1]. Deficiency degrees are variable, the diagnosis is confirmed by enzymatic activity and molecular analysis, and the best management is avoiding exposure to oxidative stressors[1].

Afra *et al*. evaluated the linking of HCQ to hemolysis in COVID-19, focusing on inconsistency, lack of clarity, and controversies detected in reviewed reports[2]. They commented that HCQ has been utilized for more than 50 years and hemolysis due to this drug in people with G6PD deficiency has not been conclusively proven in any of the reported large trials. Hemolysis did not occur in 11 deficient patients in more than 700 months of exposure. Besides, there is evidence of a complement-mediated procoagulant state, a prerequisite for atypical hemolytic-uremic syndrome in patients with COVID-19. They concluded that lacks evidence to establishing HCQ as the sole cause of hemolysis[2].

Aguilar *et al*. reported potential risks of HCQ for COVID-19 outweighing their benefits[3]. A 51-year-old man with comorbidities had COVID-19 and community pneumonia treated

with levofloxacin, and required hemodialysis before admission. He underwent HCQ (400 mg twice daily on day 1, and 400 mg once daily on days 2-4). The G6PD deficiency was confirmed one day after completion of HCQ therapy. There was low hemoglobin 8.4 g/dL, reticulocytosis, and elevated lactic dehydrogenase on admission. The hemolytic anemia improved with RBCs transfusion[3]. They stressed the lack of HCQ-induced hemolysis in the literature and the high dose of 800 mg in the COVID-19 pneumonia protocol twice the normal dose of HCQ in Rheumatology. The hemolysis was before the HCQ use, the patient had kidney failure; and COVID-19 can trigger hemolysis in G6PD deficient[3]

Mastroianni *et al*. reviewed hemolytic anemia and the use of HCQ in G6PD-deficient patients[4]. A 32-year-old male had COVID-19 and bilateral interstitial pneumonia. He used HCQ (400 mg twice daily on day 1, and 200 mg twice daily from day 2 to day 5). He had low hemoglobin 7.7 g/dl on day 2 and hemolysis without schistocytes or reticulocytosis, and G6PD deficiency, and improved with transfusion of RBCs. The authors commented on a study of 18 G6PD-deficient patients using HCQ without hemolysis, reinforcing the lack of evidence that this drug causes hemolytic anemia. Viral infections can promote oxidative stress, and hemolysis was reported in G6PD-deficient patients with COVID-19, but who did not undergo the HCQ[4].

Onori *et al*. reviewed the G6PD-deficiency and HCQ in COVID-19, and commented the well tolerated antiviral effect against SARS, Zika, rabies, Ebola, poliovirus, HIV, influenza A and B, hepatitis A and C, Chikungunya, and Dengue[5]. In a case with moderate deficiency, a single dose of HCQ was taken on day 6, but he had hemolysis on day 5. In a case with severe deficiency, HCQ started on admission and the hemoglobin dropped (13.3 to 11.8 g/dl) on day 2 and the drug seemed to be the "culprit". In other case of deficiency HCQ started on admission, the drop in hemoglobin occurred 48 h after, and HCQ was considered the "culprit". In a fourth case with severe deficiency, HCQ administration started on admission and was stopped after 3 doses. Hemoglobin dropped from 12.2 to 9.1 g/dl over 10 days, but the patient had hemoglobin D disease. In another case with moderate deficiency, HCQ started 48 h after admission. Hemoglobin dropped from 12.4 to 6.6 g/dl on day 8, and HCQ seemed to be the "culprit". Finally, in a case of severe deficiency, HCQ started on admission, hemoglobin dropped from 10 to 7.7 g/dl on day 2, and the drug seemed to be the "culprit". They concluded that the deficiency affects redox homeostasis and immune responses, enhancing viral infection and hemolysis can occur in COVID-19. The use usually effective, safe, and well-tolerated of HCQ in G6PD-deficient people can be argued in COVID-19. HCQ acts as a trigger in earlier modified scenery, not as an "innocent" bystander[5].

Ramirez *et al*. evaluated the prevalence of variants in G6PD gene in African descents, and suggested that these variations can play a role in adverse effects of HCQ treatment for COVID-19[6]. They commented that G6PD enzyme acts in the production of nicotinamide adenine dinucleotide phosphate (NADPH) required in the glutathione mediated detoxification of reactive oxygen species; and low NADPH may not be sufficient to neutralize the reactive oxygen species induced by HCQ[6]. Although yet not known about SARS-Cov-2 virus, they commented that G6PD-deficient cells are more vulnerable to alphacoronavirus 229E infection in vitro, related to high oxidant production[6].

Sgherza *et al*. reported a 61-year-old Caucasian man with G6PD deficiency and COVID-19 treated by HCQ (200 mg, thrice daily), darunavir (800 mg, once a day), and

azithromycin (500 mg, once a day) for 7 days, without hemolysis. There was a decrease in the hemoglobin without hemolysis. They commented on the use of HCQ in G6PD deficiency, and the variables influencing hemolysis risk that should be investigated to discriminate patients who may have benefits of this drug[7].

Youssef *et al*. reviewed the severity of pneumonia in 17 patients with COVID-19 needing supplemental oxygen, six (35%) with G6PD deficiency, and 11 (65%) normal controls 8. The main differences of severity were the G6PD levels (12.2 *vs*. 5.6), PaO2/FiO2 ratio (159 vs. 108), days on mechanical ventilation (10.25 vs. 21), hemoglobin level (10 *vs*. 8.1), and hematocrit (32 vs. 26). Only one G6PD-deficient died. They emphasized the role of deficiency in viral proliferation[8].

Although HCQ utilized in COVID-19 might trigger hemolysis in some G6PD-deficient patients, it can also represent an "innocent bystander" and one must compare risks with benefits.

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