G6PD deficiency and severity of COVID19 pneumonia and acute respiratory distress syndrome: tip of the iceberg?

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Short Report

Keywords: COVID19, G6PD, African American, X-linked

Abstract

The severe pneumonia caused by human coronavirus (hCoV)-SARS-CoV-2 has inflicted heavy causalities, especially among the elderly and those with comorbid illnesses irrespective of age. The high mortality in African Americans and males, in general, raises concern for a possible X-linked mediated process that could affect viral pathogenesis and the immune system. We hypothesized that G6PD, the most common X-linked enzyme deficiency associated with redox status, may have a role in the severity of pneumonia. A retrospective chart review was performed in hospitalized patients with COVID19 pneumonia needing supplemental oxygen. A total of 17 patients were evaluated: six with G6PD deficiency and 11 with normal levels. The two groups (normal and G6PD def) were comparable in terms of age, sex and comorbidities and laboratory parameters LDH, IL-6, CRP, and ferritin. Thirteen patients needed ventilatory support, with 6 in the G6PD group (83% vs. 72%). The main differences indicating increasing severity in the G6PD def group included G6PD levels (12.2 vs. 5.6, *P=0.0002*), PaO2/FiO2 ratio (159 vs. 108, *P=0.05*), days before intubation (2.5 vs. 4.8 *P= 0.03*), days on mechanical ventilation (10.25 vs. 21 days P=0.04), hemoglobin level (10 vs. 8.1 P=0.03) and hematocrit (32 vs. 26 P=0.015). Only one patient with G6PD deficiency died; 16 were discharged home. Our clinical series ascribes a possible biological role for G6PD deficiency in SARS-CoV2 viral proliferation. It is imperative that further studies be performed to understand the interplay between the viral and host factors in G6PD deficiency that may lead to disparity in outcomes.

Key Points

- COVID19 Studies show higher mortality in men due to severe pneumonia and ARDS, indicating possible X-linked mediated differences
- G6PD, the most common X-linked enzymopathy, is highly prevalent in African Americans and Italians and maintains redox homeostasis.
- Preclinical studies using G6PD deficient (G6PD def) cells infected with human coronavirus (hCoV) show impaired cellular responses, viral proliferation and worsening oxidative damage.
- A retrospective chart review of hospitalized patients with COVID19 pneumonia needing supplemental oxygen showed differences between the two groups (normal and G6PD def) in hematological indices; the G6PD def group demonstrated a prolonged PaO2/FiO2 ratio, days before intubation and longer days on mechanical ventilation, indicating the severity of the pneumonia.

Introduction

The novel coronavirus SARS-CoV2 that causes coronavirus disease 2019 (COVID19) has approximately afflicted over 10 million people worldwide [1-4], including approximately 2.3 million in the United States. Among the 1,482 patients hospitalized reported by the COVID-19−Associated Hospitalization Surveillance

Network (COVID-NET), 74.5% were aged ≥50 years, and 54.4% were male[2,5,6]. The male predominance hints at X linked related differences in the predilection to the severity of illness. One such possibility is X-linked glucose-6-phosphate dehydrogenase (G6PD) deficiency, the most common enzymopathy, commonly manifesting as hemolysis due to oxidative stress[7-9]. With over 200 mutations identified in G6PD, mainly in the coding regions, causing various degrees of deficiency, it is found at a high frequency among African Americans, Mediterraneans, and Asians[8]. We report here the clinical scenarios of six COVID19-positive patients with no previous respiratory issues with G6PD deficiency who required longer ventilatory support and ICU care compared to 11 matched controls. Given the role of G6PD in altering redox homeostasis[10], we hypothesize that the deficiency further enhances oxidative stress by uncontrolled production of reactive oxygen species (ROS) during this rapidly evolving inflammation caused by the SARS-CoV-2 virus and host immune system, leading to abnormal pulmonary vascular performance and respiratory decline. This case series warrants a systematic investigation of the role played by G6PD in unrelenting COVID19-induced pneumonitis.

Methods

We reviewed the charts of 17 patients for whom G6PD levels were available. G6PD deficient patients (3 severe and 3 mild) and compared them to 11 age- and comorbidity-matched controls from Houston area hospitals who were admitted to the hospital and ICU with confirmed COVID19 infection. Clinical data were obtained through an Institutional Review Board (IRB)-approved protocol PRO00025607 that allowed review of medical records. The data reported here are those available through June 20, 2020. Each patient had at least 21 days of follow-up.

Statistical Analysis:

Descriptive statistics were used to summarize the data; results are reported as the means and medians, as appropriate. The unpaired t-test was performed using GraphPad Prism 8 for macOS version 8.4.2 (464), April 7, 2020, GraphPad Software, San Diego California USA, www.graphpad.com. All comparisons were one-tailed; a p-value of less than 0.05 was considered significant.

Results

The qualitative polymerase chain reaction (PCR) test for SARS-CoV2 was positive in 17 patients: 6 with G6PD deficiency and 11 with normal G6PD levels at the time of hospitalization. We used the two groups (Normal and G6PD def) for comparison as they were matched by age-median of 53.3 vs. 53.5 years (p-value of 0.49), gender (50% men), and similar comorbidities such as diabetes, hypertension, and obesity with body mass index (BMI) of 35.5 vs. 31.2 (p-value 0.39), respectively. The G6PD cohort had a higher number of African-Americans (66% vs 45%) than the normal cohort (Table 1). All patients presented with cough and shortness of breath. Chest computed tomography (CT) at admission showed variations in bilateral peripheral patchy ground-glass opacities but was highly suggestive of COVID19 pneumonia. All patients received standard of care treatment as approved by the hospital COVID19 task force, and this

included supportive care, hydroxychloroquine, and in some instances compassionate use remdesivir, convalescent plasma, and anticoagulation if clinically not contraindicated. No patient tested positive for other respiratory viruses or had any other documented bacterial infections. Thirteen of 17 patients needed ventilatory support, with 8 in the normal G6PD group and 5 in the G6PD deficient group. Laboratory data (Table 2) were significant for elevated lactate dehydrogenase (LDH), C-reactive protein (CRP), interleukin-6 (IL-6), and ferritin, with no significant differences between the two groups. A significant difference between the normal G6PD and G6PD deficient patients (Figure 1 A-G) was noticed for G6PD levels (12.2 vs. 5.6, *P=0.0002*), partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio (159 vs. 108, *P=0.05*), days before intubation (2.5 vs. 4.8 *P*= 0.03), days on mechanical ventilation (10.25 vs. 21 days *P*=0.04), hemoglobin level (10 vs. 8.1 *P*=0.03) and hematocrit (32 vs. 26 *P*=0.01). Three patients required blood transfusion (1 in the normal group and 2 in the G6PD group). Only one patient with G6PD deficiency died as the family decided to withdraw care. Of the 16 surviving patients, five were discharged to rehabilitation units, and 11 were discharged from the ICU to the general wards and eventually home (Figure 1G).

Discussion

Emerging data from COVID19 show that the case fatality rate (CFR) is higher in males, indicating possible X-linked mediated differences in the crosstalk between SARS-CoV-2 and immune effectors[2,5,6]. We illustrate the potential role of G6PD deficiency in patients hospitalized for COVID19 pneumonia affecting the severity of the disease and clinical management. The gene encoding G6PD is located near the telomeric region of the distal arm of the X chromosome (band Xq28), a well-documented hot spot of a group of genes that includes fragile X, color vision, hemophilia A, and congenital dyskeratosis[8]. There are more than 200 point mutations identified in the G6PD gene resulting in many biochemical variants and deficiency of the gene product G6PD, which is the rate-limiting enzyme in the pentose-phosphate pathway[8,9]. The variants are grouped into four classes: a) Class I variants- comprise the most severe form of G6PD deficiency and lead to chronic non-spherocytic haemolytic anaemia and typically occur with enzyme activity <10% of normal; b) Class II variants typically have <10% residual enzyme activity but no haemolytic anaemia; c) Class III and IV variants (10–60% and 60–150% activity, respectively) have milder phenotypes, and haemolysis occurs only after extreme oxidative stress[11]. Very severe G6PD deficiencies are sporadic and rare, whereas less severe deficiencies are polymorphic and more common in tropical areas, postulated to evolve as protection against malaria[7,8]. Males are more commonly affected when hemizygous and can be either phenotypically normal or deficient[11]. Homozygous females are as deficient as hemizygous males, whereas heterozygous females are mosaics with intermediate levels of deficiency as a result of random X-chromosome inactivation (lyonization)[12]. Thus far, there are no reports of an association between G6PD deficiency and COVID19, likely because G6PD deficiency was either rare or of mild variety or not reported in the respective populations[2-4]. Nevertheless, given the high prevalence of this mutation in African Americans (1 in 10) and Italians,[5,7] it is important to elucidate the biological differences in the outcomes of COVID19 infection. In our study, a total of 17 patients were

enrolled where the G6PD levels were known. Six were identified with G6PD deficiency; we used the 11 patients with normal levels as the comparator group. In the deficiency group, two males (both African Americans) had levels less than 4.5, and the other four patients, two males and three females (likely hemizygous), had levels just below the lower limit of the established reference (9.9 to 16.6 U/g Hb)[13].

G6PD converts glucose-6-phosphate into 6-phosphogluconolactone and catalyzes the generation of reduced nicotinamide adenine dinucleotide phosphate (NADPH). Furthermore, NADPH is the critical cofactor for the enzyme glutathione reductase, which reduces glutathione disulfide (GSSG) into reduced glutathione (GSH). GSH eliminates ROS by scavenging hydroxyl radicals, singlet oxygen, and electrophiles. The deficiency is most pronounced on erythrocytes, which depend solely on the cytosolic pentose phosphate pathway and generation of GSH for oxidative protection. Generally, the outcomes for G6PD-deficient patients are favorable if they can avoid oxidative triggers commonly encountered due to drugs (including some antimalarial drugs, sulfonamides, and rasburicase)[7,9]. Fatigue is the most common symptom, followed by dyspnea, dizziness, headache, pallor, chest pain, and jaundice if hemolysis is severe. A quantitative analysis of G6PD activity[13] can provide a definitive diagnosis of G6PD deficiency so that individuals can be advised to avoid drugs, foods, or other oxidizing agents that may precipitate a hemolytic crisis. The severity of hemolysis is variable and depends on the G6PD allelic mutation and factors such as the dose of the inciting drug. The usual management is supportive care and blood transfusion if hemolysis is severe.

The reasons for testing G6PD in our patients was proactive baseline measurement in preparation for hydroxychloroquine use. As expected, in our study, there were significant differences in the G6PD levels that also correlated with the differences in haemoglobin and haematocrit (Table 1). More importantly, there is an increase in the severity of the pulmonary process, as demonstrated by the higher requirements of oxygen and longer time on mechanical ventilation. The differences seen as a measure of the lowest PaO2/FiO2 are also shown by the similarity of the Rothman index between admission and the time of mechanical ventilation with subsequent deterioration in the deficiency group (Table 2 and Figure 1 A-G). The limitation of this study is the retrospective review, the sample size and the lack of power to detect the differences due to intervention. Nevertheless, given the high prevalence of this mutation in African Americans (1 in 10) and Italians,[3,5] it is important to elucidate the biological differences in the outcomes of COVID19 infection.

Two questions that are of utmost clinical importance that need answers are: 1) Does the deficiency increase the susceptibility and/or the severity to COVID19? 2) How do we judiciously use the pharmacologic array of medications that can potentially worsen the deficiency? One of the severe manifestations of COVID19 is ARDS characterized by the acute onset of hypoxemia, reduced lung compliance, diffuse lung inflammation and bilateral opacities on chest imaging attributable to noncardiogenic pulmonary edema[14]. As details of the pathobiology are still emerging, our understanding of similar viral-mediated lung injury from the previous human coronavirus (hCoV) epidemics of severe acute respiratory syndrome (SARS) and middle eastern respiratory syndrome (MERS) points to the central

oxidative stress on the pulmonary vasculature by ROS production causing further alveolar damage limiting gas exchange and setting up right to left shunting of venous blood[15-17]. The pathophysiologic process of pulmonary vascular endothelial diathesis is caused by increased oxidant stress and reduced bioavailable nitric acid[15-17]. This has also been reported in influenza infection, which provokes a pro-oxidant condition by increasing ROS production in the host cell to facilitate viral proliferation[18,19]. ROS further inactivate nitric oxide, resulting in nitric oxide insufficiency[20]. The primary determinant of protection against oxidative stress is the ability to maintain GSH stores through the synthesis of NADPH. Since NADPH concentrations are primarily maintained by G6PD encoded by its gene located on Xq28, it follows that its deficiency could result in an inability to eliminate ROS, as seen in our patients.

There is now accumulating evidence that G6PD deficiency affects cells other than erythrocytes [10,21-24]. The replication and spread of respiratory viruses normally involves activation of the antiviral innate immune responses and culminates in the production of type I interferons (IFNs) and proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), which in turn upregulate antiviral proteins[24]. In an *in vitro* study, when G6PD-deficient human fibroblasts and human lung epithelial carcinoma A549 cells were treated with G6PD-RNA interference (RNAi), they showed reduced viability and a 3-fold increase in viral replication[21]. In another study, the authors reported a marked reduction in antiviral genes, such as TNF-α, in G6PD-deficient A549 cells after infection with HCoV-229E compared to the parental cell lines[23]. Their observations also include decreased nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) activation in virus-infected host cells, pointing to a reduced ability to activate timely antiviral responses. Furthermore, a few studies indicate that oxidative stress increases the susceptibility of non-erythroid G6PD-deficient cells to viral infection, which could be ameliorated by antioxidant agents, such as lipoic acid[21].

In another study, G6PD-deficient peripheral blood mononuclear cells (PBMCs) from patients and human monocytic (THP-1) cells showed impaired inflammasome activation. In particular, G6PD knockdown reduced the expression of mature interleukin (IL)-1β but not the expression of caspase-1 or the components of the inflammasome (NLRP3, ASC, and pro-Caspase-1) pathway[10]. Additionally, there was a differential expression of cytokines between the G6PD-deficient cells and the normal cells. Furthermore, as reported in severe influenza pneumonia[17,19], this pro-oxidant condition can induce secretion of inflammatory cytokines, including interleukin (IL)-1β, IL-6, IFN, and TNF-α, from the microenvironment. This uncontrolled pro-inflammatory response, referred to as the cytokine storm, is abetted by the action of monocytes/macrophages and neutrophils on infected lung epithelial cells[22]. Taken together, these results indicate that G6PD deficiency can allow viral proliferation even as it impairs the cellular immune response through abnormal redox homeostasis. It is imperative that further studies be performed to have an enhanced understanding of the interplay between the viral and host factors in G6PD deficiency that may lead to disparity in outcomes. This will have significant clinical implications in the management of patients with COVID19 infection.

Declarations

Author Contributions:

Conception and design: JGY, FZ, SS, and SPI

Manuscript writing: JGY, FZ, GY, MY, SP, JE, SP, YZ, SS and SPI

Data Collection and analysis: JGY, FZ, GY, MY, SP, JE, YZ, SS and SPI

Final approval of manuscript: JGY, FZ, GY, MY, SP, JE, SP, YZ, SS and SPI

Accountable for all aspects of the work: JGY, FZ, MY, SP, JE, SP, YZ, SS and SPI

Statement of Consent: Clinical data were obtained through an Institutional Review Board (IRB)-approved protocol PRO00025607 that allowed review of medical records.

Acknowledgements: To Marianne Younes, MA, for editorial support and to Collaborative Action for SARS-CoV-2 Eradication (CARE) Inc- a 501(c) Not for profit group.

Compliance with Ethical Standards:

Funding: No funding for this study.

Conflict of Interest: None for all others except for SS and SPI not pertaining to this work-

SS: Consultant and advisor for United Therapeutics, Actelion and Bayer pharmaceuticals. Also served as speaker for Liquidia technologies. SI: Research Grant and Consultant - Seattle Genetics, Rhizen, Daiichi Sankyo, Trillium; Research Grant- Merck, Affimed, Spectrum

Statement of Consent: Clinical data were obtained through an Institutional Review Board (IRB)-approved protocol PRO00025607 that allowed review of medical records.

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Tables

Table 1: Patient characteristics			
Characteristics	Normal G6PD (n=11)	Deficient G6PD (n=6)	t test-one tailed (p-value)
Age (median)	53.3	53.5	0.49
Sex:			
Female	5	3	0.63
Male	6	3	
Race/Ethnicity:			
African American	5	4	0.38
Caucasian	5	0	
Hispanic	0	1	
Asian	0	1	
Prefer not to say	1	0	
BMI (median)	35.5	31.2	0.39
Co-morbidities			
Hypertension	2	1	
Diabetes Mellitus	4	1	
BMI>36	3	2	
Previous malignancy	1	0	
G6PD mean	12.2 (9.6-15.3)	5.6 (1.8-9.3)	**0.0002**
Symptoms	Cough, Shortness of breath, chest discomfort		
Lowest PaO2/FiO2	159	108	0.05
Rothman Index (mean)	58.63	68.8	0.12
Length of stay (mean)	18 (7-32)	23.5 (7-51)	0.18
Wait and watch days before intubation	2.5 (1-6)	4.8 (3-7)	**0.03**
Length of mechanical ventilation	10.25 (4-16)	21 (5-46)	**0.04**
Discharge status:			
Home	10	2	-

Rehabilitation/Long term facility	3	2

Table 2: Laboratory characteristics			
Characteristics	Normal G6PD (n=11)	Deficient G6PD (n=6)	t test- One tailed (p-value)
Lowest WBC	5.2 (2.1-6.9)	5.1 (3.0-8.3)	0.16
Lowest Neutrophils %	60 (35-74)	62 (47-82)	0.37
Lowest ALC	618 (191-1917)	393 (111-738)	0.16
Lowest Hemoglobin	10 (6.5-13)	8.1 (6.6-11)	**0.02**
Lowest Hematocrit	32 (20-40)	26 (22-34)	**0.015**
Platelets	425 (337-626)	405 (179-571)	0.38
Peak Lactate	2.1 (1.2-3.5)	5.0 (1.3-16)	0.05
Peak IL-6	577 (5-2957)	278 (57-669)	0.24
Peak CRP	21 (0.87-41)	28 (15-51)	0.11
Peak Ferritin	1371 (476-3648)	7095 (916-32659)	0.07
Peak LDH	518 (208-862)	663 (378-996)	0.11
Peak D-dimer	5.7 (0.41-20)	13 (0.6-20)	0.05
Peak AST	134 (32-350)	176 (18-302)	0.20
Peak ALT	148 (22-527)	216 ((35-503)	0.22
Peak Alkaline phosphatase	167 (65-449)	131 (58-279)	0.26
Peak Total bilirubin	1.6 (0.5-3.8)	2.0 (0.5-2.3)	0.22
Highest creatinine	3.3 (0.7-17)	2.0 (0.86-6.4)	0.27
Highest glucose	209 (91-310)	242 (133-378)	0.23
Highest Triglyceride	193 (85-543)	218 (65-416)	0.35
Peak Troponin-I	0.85 (0.006-6.8)	0.28 (0.006-0.5)	0.26
Highest QTc on EKG	476 (437-551)	486 (446-528)	0.32

Figures
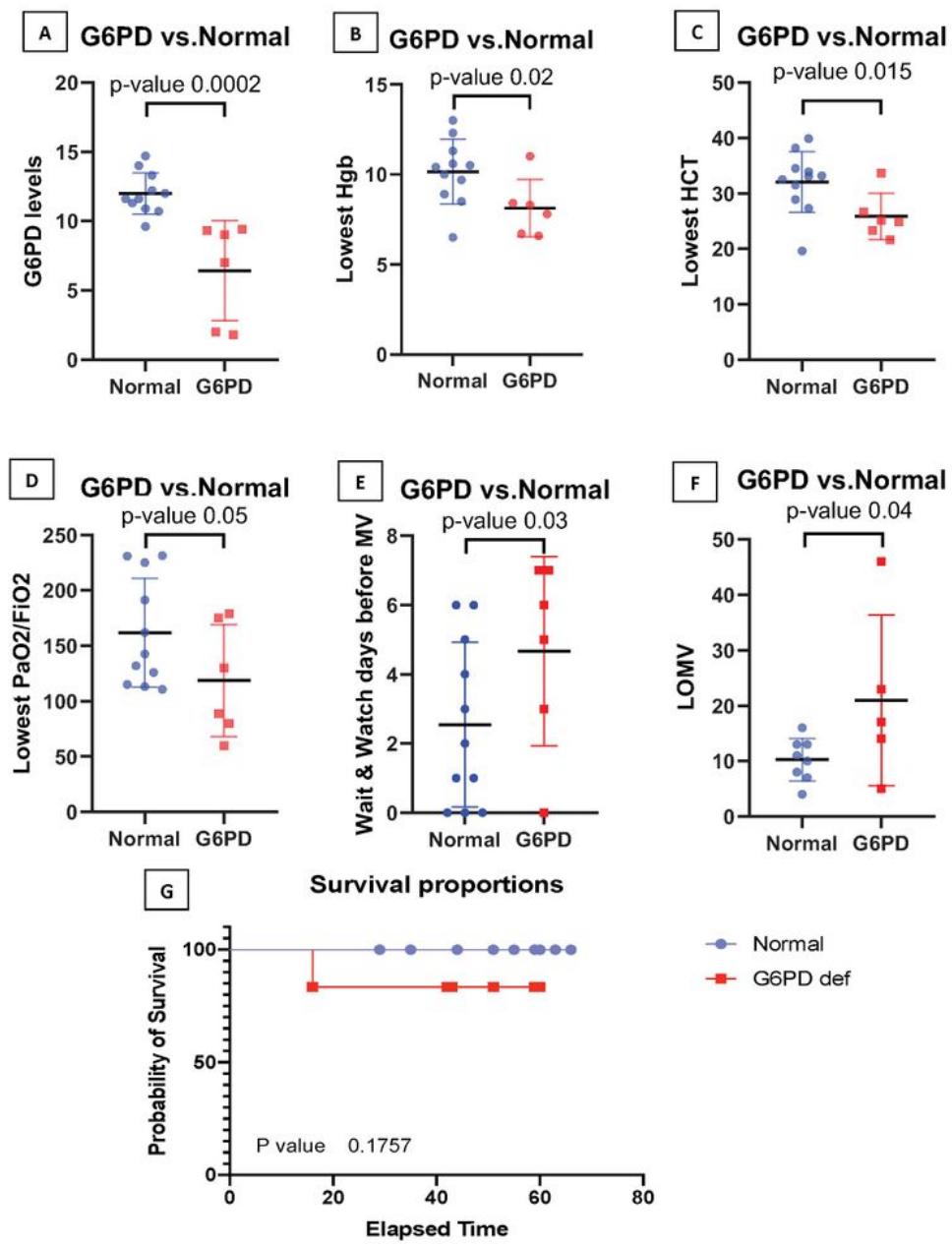
Figure 1 A-G A. Differences in G6PD mean, B. Lowest Hemoglobin, C. Lowest Hematocrit, D. Lowest PaO2/FiO2, E. Wait and watch days before intubation, F. Length of mechanical ventilation (LOMV) and G. Kaplan-Meier Survival Curve. A p-value of less than 0.05 was considered significant.

Figure 1

A-G A. Differences in G6PD mean, B. Lowest hemoglobin, C. Lowest hematocrit, D. Lowest PaO2/FiO2, E. Wait and watch days before intubation, F. Length of mechanical ventilation (LOMV) and G. Kaplan-Meier survival curve. A p-value of less than 0.05 was considered significant.