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REVIEW ARTICLE

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Sickle cell trait and the potential risk of severe coronavirus disease 2019—A mini-review

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Abstract

Coronavirus Disease 2019 (COVID-19) pandemic is a rapidly evolving public health problem. The severity of COVID-19 cases reported hitherto has varied greatly from asymptomatic to severe pneumonia and thromboembolism with subsequent mortality. An improved understanding of risk factors for adverse clinical outcomes may shed some light on novel personalized approaches to optimize clinical care in vulnerable populations. Emerging trends in the United States suggest possibly higher mortality rates of COVID-19 among African Americans, although detailed epidemiological study data is pending. Sickle cell disease (SCD) disproportionately affects Black/African Americans in the United States as well as forebearers from sub-Saharan Africa, the Western Hemisphere (South America, the Caribbean, and Central America), and some Mediterranean countries. The carrier frequency for SCD is high among African Americans. This article underscores the putative risks that may be associated with COVID-19 pneumonia in sickle cell trait as well as potential opportunities for individualized medical care in the burgeoning era of personalized medicine.

KEYWORDS

acute chest syndrome, coronavirus disease 2019, sickle cell disease, sickle cell trait, Thromboembolism, Vaso-Occlusive Crisis (VOC)

1 | INTRODUCTION

Following the emergence of Coronavirus Disease 2019 (COVID-19) in Wuhan (China) around December 2019,[1] the infection has become a pandemic, decimating over three hundred thousand globally.[2] The severity of COVID-19 cases reported hitherto has varied greatly from asymptomatic to severe pneumonia and thromboembolism, accompanied by overt respiratory failure with subsequent mortality.[3-5] As the COVID-19 pandemic continues to evolve, potential risk factors that may predispose individuals to fatal outcomes are increasingly becoming topical. There are ongoing epidemiological investigations and discussions of potentially at-risk populations and ethnicities.[6,7] An improved understanding of the risk factors as well as clinical course for severe COVID-19 may shed some light on novel personalized approaches to optimize clinical care and outcomes.

Emerging trends in the United States suggest possibly higher mortality rates of COVID-19 among African Americans,[8,9] although epidemiological study data with adequate denominator[10] across board is pending. There is no doubt that socio-economic determinants of health play crucial roles in health inequities and disease trajectory.[11] Nevertheless, interplay of genetic and environmental factors contributes to overall clinical outcomes in a substantial burden of human diseases.[12-17] Sickle cell disease (SCD) disproportionately affects Black/African Americans in the United States as well as forebearers from sub-Saharan Africa, the Western Hemisphere (South America, the Caribbean, and Central America), and some Mediterranean countries.[18-20] Increasing evidence suggests that COVID-19 pneumonia can cause acute chest syndrome (ACS), a potentially life-threatening complication in SCD.[21-23] These observations raise questions on the potential contributions of SCD-related complications, for instance

thromboembolism to the severity of COVID-19. Increasing evidence suggests a higher risk of venous thromboembolism in COVID-19,[3-5] prompting ongoing considerations and potential applications of prophylactic anticoagulation[24] and therapeutic thrombolysis.[25]

Being the carrier state for an autosomal recessive genetic disorder, sickle cell trait is frequently perceived to be a relatively benign condition; however, this remains controversial.[26-30] Conditions of increased oxygen demands may trigger sickle-related complications in heterozygotes.[31-44] COVID-19 causes severe pneumonia in at-risk individuals resulting in an increased oxygen demand. Yet, the notion that COVID-19 associated pneumonia may result in poor clinical outcomes in sickle cell trait if unrecognized is less discussed. This mini-review highlights the putative risks of severe COVID-19 in SCD and sickle cell trait, with a focus on the risks associated with the heterozygous state.

2 | EPIDEMIOLOGY AND MOLECULAR PATHOGENESIS OF SICKLE CELL TRAIT

Sickle cell trait affects approximately 300 million people globally.[45] Owing to its protective effects against severe malaria, sickle cell trait confers an evolutionary survival advantage.[46] The highest prevalence of sickle cell trait is in Africa and among people of African descent across the world.[18,47] In the United States, national estimates of the sickle cell trait prevalence from Newborn Screening data suggest about 1.5% with about 8% prevalence among African Americans, almost 3 million individuals.[48] About 1%-3% of the European population carries a gene mutation for hemoglobinopathy, particularly sickle cell trait.[49-52] Approximately 5% of the world carry a significant hemoglobin gene variant.[52] A recent global meta-estimate of birth prevalence of SCD was approximately 112 per 100 000 live births with about 10 folds higher birth prevalence in Africa, 1125 per 100 000.[18,47]

Being the heterozygous state, red blood cells in sickle cell trait have one copy of normal adult hemoglobin (Hb) denoted as HbA and one copy of mutant Hb (HbS) resulting in Hb genotype of HbAS.[53] HbS results from a missense mutation causing amino acid substitution whereby valine replaces glutamic acid in the 6th codon of the β chain.[54,55] The presence of HbA attenuates HbS phenotype, reducing the probability of polymer formation; hence, normal hematological parameters are observed in the majority of individuals with sickle cell trait.[54] Nevertheless, cumulative evidence suggests that hypoxia may trigger sickle-related complications such as splenic infarction, thromboembolism, papillary necrosis, exertional rhabdomyolysis, and death in sickle cell trait.[26,31-40,43,44]

3 | COVID-19 PNEUMONIA IN SCD: POTENTIAL RELEVANCE TO SICKLE CELL TRAIT

As of May 16, 2020, 15 SCD patients with COVID-19 have been reported in the clinical scientific literature indexed in PubMed.[56] These studies are summarized in Table 1. Beerkens et al[57] described the first documented case of SCD patient who developed ACS in the setting of COVID-19. The index case was on maintenance hydroxyurea therapy for SCD. He was initially started on hydroxychloroquine for severe COVID-19 pneumonia. He later developed ACS, requiring urgent exchange red blood cell transfusion. Nur et al[58] observed ACS in two SCD patients who presented with VOC. Subsequently, a case series by Hussain and colleagues demonstrated a milder COVID-19 course in four SCD patients, who seemed to have benefited from early risk stratification and initiation of treatment.[59] A larger case series of 10 SCD patients described 6 confirmed cases of COVID-19, one of which was fatal.[23] There are two independent case reports of patients with severe COVID-19 who responded well to tocilizumab.[21,22] The dataset on COVID-19 in SCD patients continues to evolve.

Although ACS has been reported in a few patients with sickle cell trait,[60,61] it appears to be exceedingly rare. An increased risk of thromboembolism in sickle cell carriers seems to be a better recognized sickling complication in heterozygotes.[62-66] The risk of hypercoagulability in sickle cell carriers is a subject of active investigations and discussions.[66-68] A prospective study of African Americans demonstrated a 2-fold increase in the risk of pulmonary embolism in carriers of sickle cell trait.[63] A recent study demonstrated an increased risk of ischemic stroke in individuals who carry sickle cell trait and have concomitant chronic kidney disease.[69] Likewise, sickle cell trait has been associated with an increased risk of coronary artery diseases in African American men who have chronic kidney diseases.[70] The potential contributions of thrombosis related complications of sickle cell trait to the severity of COVID-19 necessitate further studies particularly due to the higher risk of thromboembolism in COVID-19.[3-5]

Although the risk of COVID-19 induced complications in SCD is increasingly becoming topical, the potential risk in sickle cell trait warrants consideration given the greater prevalence of the heterozygous state. Healthcare providers are likely to be on the lookout for complications in SCD patients with COVID-19 pneumonia, whereas individuals with sickle cell trait may be at an increased risk of unrecognized COVID-19 induced sickle-related complications. Publicizing these potential complications in carriers may help healthcare providers to include sickling complications in their differential diagnosis when assessing individuals who are from ethnicities with a high prevalence of sickle cell trait. This may facilitate prompt recognition of at-risk individuals and the provision of individualized care for instance: anticoagulation,[3,4] oxygen therapy,[59] blood transfusion,[57,58] red blood cell exchange transfusion,[57,71] or extracorporeal membrane oxygenation[72-74] when necessary. Individuals who have sickle cell trait and are aware of their HbS genotype could be encouraged to self-identify when presenting to healthcare providers for COVID-19 assessment. Increasing the public awareness of sickle-related complications may also embolden individuals who are aware of their carrier status to seek medical assessment early for COVID-19. Recent prenatal research data suggest that many sickle cell carriers may not view SCD as a severe disorder[75]; therefore, it is possible that

TABLE 1 Summary of Published Cases of COVID-19 in SCD

Reference	Age (years)/Gender (M/F) if Known	Complications of SCD during COVID-19	Main treatment	Reported outcome
Beerkens et al[57]	21/M	VOC, ACS	Red blood cell (RBC) exchange transfusion	Favorable
Nur et al[58]	24/M	VOC, ACS	Oxygen and opioid therapy	Favorable
Nur et al[58]	20/F	VOC	Opioid therapy	Favorable
De Luna et al[21]	45/M	ACS	IV tocilizumab, RBC exchange transfusion	Favorable
Hussain et al[59]	32/M	VOC,? ACS	RBC exchange transfusion, intubation, ICU	Favorable
Hussain et al[59]	37/F	VOC	IV fluids and opioid	Favorable
Hussain et al[59]	22/F	Suspected ACS	Ceftriaxone, IV opioid	Favorable
Hussain et al[59]	41/M	VOC	IV fluids and opioid	Favorable
Odièvre et al[22]	16/F	ACS and PE	Non-invasive ventilation, RBC exchange transfusion, ICU	Favorable
[a]McCloskey et al[23]	57/unknown	Extremely Unwell	Palliation	Fatal
[a]McCloskey et al (5 additional cases)[23]	Unknown range	VOC	Oxygen and analgesic therapy	Favorable

Abbreviations: ACS, Acute Chest Syndrome; F, Female; ICU, Intensive Care Unit; IV, Intravenous; M, Male; PE, Pulmonary Embolism; VOC, Vaso-Occlusive Crisis.

[a]Limited information available, article is in press.

individuals who have sickle cell trait may benefit from an improved awareness of sickle-related complications, particularly during the COVID-19 pandemic.

4 | CONCLUSIONS

As highlighted by the medical literature, sickle cell trait potentially increases the risk(s) of hypercoagulability.[30,63-66] During intercurrent COVID-19, this may lead to poor clinical outcomes. There is no reported case of COVID-19 in sickle cell trait in the clinical scientific literature as of May 16, 2020.[56] This mini-review is describing the putative risks to patients with COVID-19 who may have happened to be sickle cell carriers. It is pertinent to acknowledge that there is no evidence of cause-effect relationship(s) for the hypothesized association between sickle cell trait and COVID-19 thus far. Although there is always the limitation of generalizability of risk, an improved awareness of the potential risk of sickle-related complications in carriers may translate into reduced morbidity and perhaps mortality among vulnerable communities in the evolving COVID-19 pandemic.

The high prevalence of sickle cell trait among African Americans raises fundamental clinical scientific questions on the potential roles of hemoglobin genotype in COVID-19 severity considering the mortality trends. Genetic factors predisposing individuals to an increased risk of COVID-19 mortality continue to be subjects of active investigations. In addition to genes and pathways that are directly targeted by COVID-19, hemoglobin genotype may be a less evident marker of risk for COVID-19 severity. Further molecular epidemiological analysis of COVID-19 disease course and hemoglobin genotype in African Americans are recommended to delineate the potential risks. Given the prevalence among African Americans, strategies to improve awareness of possible risks during COVID-19 pneumonia in sickle cell trait are suggested to individualize medical care in the burgeoning era of personalized medicine.

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