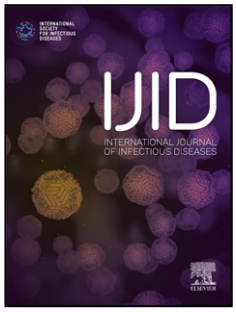
Journal Pre-proof



COVID-19 and Sickle Cell Disease in Bahrain

Abdulkarim AbdulRahman, Salman AlAli, Omar Yaghi, Mohammed Shabaan, Sameer Otoom, Stephen L. Atkin, Manaf AlQahtani

PII: S1201-9712(20)32149-4

DOI: https://doi.org/10.1016/j.ijid.2020.09.1433

Reference: IJID 4667

To appear in: *International Journal of Infectious Diseases*

Received Date: 23 May 2020

Revised Date: 22 September 2020

Accepted Date: 22 September 2020

Please cite this article as: AbdulRahman A, AlAli S, Yaghi O, Shabaan M, Otoom S, Atkin SL, AlQahtani M, COVID-19 and Sickle Cell Disease in Bahrain, *International Journal of Infectious Diseases* (2020), doi: https://doi.org/10.1016/j.ijid.2020.09.1433

COVID-19 and Sickle Cell Disease in Bahrain

Abdulkarim AbdulRahman, Salman AlAli, Omar Yaghi, Mohammed Shabaan, Sameer Otoom, Stephen L Atkin, Manaf AlQahtani

Abdulkarim AbdulRahman, Bahrain National Taskforce to Combat COVID-19, Mohammed bin Khalifa Cardiac Centre, Bahrain. abdulkarim.md@live.com

Salman AlAli, Bahrain National Taskforce to Combat COVID-19, Bahrain Defense Force Hospital, Bahrain. salmanyalali@gmail.com

Omar Yaghi, Bahrain National Taskforce to Combat COVID-19, Bahrain Defense Force Hospital, Bahrain. omar.s.yaghi@gmail.com

Mohammed Shabaan, Supreme Council of Health, Bahrain. MSH@sch.org.bh

Sameer Otoom, Royal College of Surgeons in Ireland-Bahrain. sotoom@rcsi-mub.com

Stephen L Atkin, Royal College of Surgeons in Ireland-Bahrain. satkin@rcsi.com

Manaf AlQahtani. Bahrain National Taskforce to Combat COVID-19, Bahrain Defense Force Hospital, Bahrain. mqahtani@rcsi-mub.com

*Corresponding author: Stephen Atkin, Royal College of Surgeons in Ireland-Bahrain, PO Box 15503, Bahrain

Highlights

- Sickle cell disease results from a mutation in the hemoglobin beta chain
- SARS-CoV-2 may decreased heme oxygen-carrying capacity
- Reduced oxygen carrying capacity may lead to sickle cell crisis
- No increased disease severity was seen in covid-19 infected sickle cell patients
- No patient underwent a sickle cell crisis with concurrent SARS-Cov-2 infection
- SARS-Cov-2 clearance rate did not differ between those with and without sickle cell disease

Abstract

Introduction. Coronavirus disease 2019 (COVID-19) is caused by the newly identified strain of the coronavirus family that has been shown to affect the hemoglobin beta chain, the same chain that has the sickle cell disease mutation. This study was undertaken to see if COVID-19 infection increased disease severity in patients with sickle cell disease (SCD)

Methods. Mass screening of the Bahraini population was undertaken between February and April 2020.

Results 38,092 Bahraini people were tested during this period for COVID-19, of whom 378 (1%) were SCD patients. Six patients with SCD had COVID-19 (1.6%); three remained asymptomatic, two had mild symptoms and only one required oxygen therapy. The SCD patients had a similar average length of stay when compared to non-sickle cell disease COVID-19 patients (10.7 days).

Conclusion. The infection rate, clinical course and viral clearance seen for the SCD patients with COVID19 was not different than those without SCD.

Key words: COVID-19; SARS-CoV-2; Sickle cell disease;

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the newly identified strain of the coronavirus family, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (1). Virus isolation and nucleic acid sequencing have shown that the novel coronavirus is a positive-stranded RNA8 (2). It has been suggested that the virus acts through ACE2, CD147 and CD26 receptors on the erythrocytes resulting in a hemoglobinopathy interaction with the hemoglobin molecule; viral ORF8 surface glycoproteins combine with porphyrin to form a complex with 1-beta chain of hemoglobin with or without hemolysis forming a dysfunctional hemoglobin resulting in decreased heme oxygen-carrying capacity (2-4).

Sickle cell disease (SCD) is an inherited hemoglobinopathy due to a mutation in the hemoglobin-Beta gene found on chromosome 11. SCD affects 1% of the Bahrani population (5) and causes the RBC to sickle, causing sickle cell crisis that may result in hypoxic injury to organs. The prevalence of SCD in Bahrain has decreased from the 1980s when the prevalence was 2% due to education and a premarital testing program that tests for both sickle cell and thalassemia (5). Couples with risk of passing on hemoglobinopathies are referred for genetic counselling. In addition, a screening program for sickle cell disease has been introduced where all newborn babies are screened for the disease (6). Sickle cell disease diagnosis is established by hemoglobin electrophoresis and confirmed by a positive sickling test result.

Patients with sickle cell disease are all in a regular follow-up program and are managed with disease modifying agents such as hydroxyurea. Patients are referred for hematopoietic stem cell transplantation when possible.

Infections may induce sickle cell crisis requiring hospital admission (7), and with several anecdotal reports suggesting worse COVID-19 complications in SCD (8-11). A review of the literature on COVID-19 and 19 SCD cases highlighted that SARS-CoV-2 infection should be considered to be an important triggering factor of sickle-cell crisis and that there are many unanswered questions including the potential increased risk of SARS-CoV-2 infection in SCD and is there a role for preventative red blood cell exchange (12). This study was undertaken to determine if patients with SCD are a high-risk group, as has been suggested (13).

Methods

In Bahrain, mass population screening for COVID-19, including mobile clinics, was established. In this cross-sectional study, all COVID-19 testing data on the Bahraini population was reviewed from the start of the screening in February until April 25, 2020.

SCD status of subjects was acquired from hospital medical records and the E-government authority of open data portals. Further details on the length of stay and time to viral clearance were collected from the medical records of all patients with COVID-19. The diagnostic test used for SARS-CoV-2 was real time RT-PCR: all were tested for E gene and positive samples were confirmed after being tested for N Gene and RdRp gene (from Tib Molbiol) (14). Viral clearance was defined as 2 RT-PCR negative tests 24 hours apart. Ethical permission was granted by the National Research Committee of COVID-19.

Statistical analysis

Statistical analysis was performed using the STATA statistical computer package (StataCorp. 2013. Stata Statistical Software). Differences between the patients with and without SCD were compared by a two-way T-Test.

Result

Table 1 shows the demographics between those with and those without SCD.

The Bahraini population is 689,714, and a total of 6933 (1%) Bahraini people are affected by SCD. 38,092 Bahraini people were tested during this period for COVID-19, of whom 378 (1%) were SCD patients.

Of the 38,092 individuals tested for COVID-19, 696 (1.83%) were infected.

387 (1% of those tested) also had SCD, of whom 6 patients (1.6%) had COVID-19 (p=0.55).

Of the 6 SCD with COVID-19 (Table 2), three remained asymptomatic and one developed mild symptoms of an upper respiratory tract infection. Two patients developed moderate symptoms, and only one of them required oxygen therapy. These two patients did not require ventilator support or ICU care. The maximum length of stay was 12 days. All 6 patients were discharged, their average length of stay was 9.8 days. The SCD patients had a similar average length of stay when compared to non-sickle cell disease COVID-19 patients (10.7

days), which is the time to viral clearance (2 RT-PCR negative tests 24 hours apart) (p=0.11, not significant)

Discussion

Whilst there were only 6 patients with SCD who developed COVID-19 disease, it can be seen that there was no indication of more severe COVID-19 disease compared to those without SCD. The time to viral clearance was not different between those with and without SCD, with a similar hospital stay; further, in the course of the infection, only one patient required oxygen therapy, and none required ventilator support. In addition, no SCD patient suffered a sickle cell crisis as we had hypothesized given that the SARS-CoV-2 virus may affect the hemoglobin beta chain (2) and that infection may precipitate a crisis (7). Others have hypothesized that in Beta-thalassemia, where there is a fault in hemoglobin beta-chain synthesis, this may result in immunity to SARS-CoV-2 infection (15) and may therefore be protective, but that was not seen in the SCD patients studied.

At the time of writing the paper, the prevalence of COVID19 disease in Bahrain is approximately 0.1% with only 2464 cases documented. 114,110 tests have been conducted, reaching to about 71 tests per 1000 people. Of the 2464 cases, 8 deaths were recorded, 1189 cases recovered, and 1447 cases were admitted. All COVID19 cases were admitted to either isolated COVID19 ICU, hospital or an isolation facility depending on the patients' medical requirement.

The percentage of the tested SCD people (1%) reflected the overall population with SCD within the Bahraini community. 1.8% of all COVID-19 tested individuals were positive, including those with and without SCD, suggesting that there is no increased infection rate in those with SCD. However, the main limitation of this observational study is the low number of SCD who had COVID-19 and the possibility of a type 2 statistical error due to low power.

In conclusion, the infection rate, clinical course and viral clearance seen for the SCD patients with COVID19 was not different than those without SCD. It is therefore encouraging that

they are not at increased risk during the course of COVID-19 infection, nor at risk for a sickle cell crisis.

DECLARATIONS

Ethics approval and consent to participate: The study was approved by the National Covid-19 Ethics Committee.

Consent for publication: All authors gave their consent for publication.

Availability of data and materials: All the data for this study will be made available upon reasonable request to the corresponding author.

Funding: No funding was received to perform this study.

Author contributions

AA and SA analyzed the data and wrote the manuscript. OY MS, and SA contributed to study design, collected, analysed, and interpreted data and edited the manuscript. MA supervised data collection, data analysis and edited the manuscript. SLA, SO data interpretation and the writing of the manuscript. All authors reviewed and approved the final version of the manuscript.

Manaf Alqahtani is the guarantor of this work.

Conflict of interest statement

Conflict of interest. The authors have declared that no conflict of interest exists.

References

1. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nature microbiology. 2020;5(4):536-44.
2. Wenzhong L, Hualan L. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. ChemRxiv 2020. Preprint https://doi org/1026434/chemrxiv.11938173:v6.
3. Liu W, Li H. COVID-19 Disease: ORF8 and surface glycoprotein inhibit heme metabolism by binding to porphyrin. ChemRxiv; 2020.
4. Wenzhong L, Hualan L. COVID-19 Disease: ORF8 and surface glycoprotein inhibit heme metabolism by binding to porphyrin. ChemRxiv 2020. Preprint https://doi org/1026434/chemrxiv.11938173:v3.
5. Al Arrayed SS, Haites N. Features of sickle-cell disease in Bahrain. 1995.
6. Shaikha Al Arrayed M, Amani Al Hajeri M, CABFM I. Clients' satisfaction of the premarital counseling service in Bahrain. Bahrain Medical Bulletin. 2009;31(3).
7. Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: a review. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2010;14(1):e2-e12.
8. McCloskey KA, Meenan J, Hall R, Tsitsikas DA. COVID-19 Infection and Sickle Cell Disease: A UK Centre Experience. British journal of haematology. 2020.
9. Hussain FA, Njoku FU, Saraf SL, Molokie RE, Gordeuk VR, Han J. COVID-19 infection in patients with sickle cell disease. British journal of haematology. 2020.
10. Beerkens F, John M, Puliafito B, Corbett V, Edwards C, Tremblay D. COVID-19 pneumonia as a cause of acute chest syndrome in an adult sickle cell patient. American journal of hematology. 2020.
11. De Luna G, Habibi A, Deux JF, Colard M, Pham Hung d'Alexandry d'Orengiani AL, Schlemmer F, et al. Rapid and severe Covid-19 pneumonia with severe acute chest syndrome in a sickle cell patient successfully treated with tocilizumab. American journal of hematology. 2020.
12. Sahu KK, Siddiqui AD, Cerny J. Managing Sickle Cell Patients With COVID- 19 Infection: The Need to Pool Our Collective Experience. Br J Haematol. 2020.
13. Roy NBA, Telfer P, Eleftheriou P, de la Fuente J, Drasar E, Shah F, et al. Protecting vulnerable patients with inherited anaemias from unnecessary death during the COVID-19 pandemic. British journal of haematology. 2020;189(4):635-9.
14. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3).
15. Lansiaux E, Pébaÿ PP, Picard J-L, Son-Forget J. COVID-19: beta-thalassemia subjects immunised? Medical Hypotheses. 2020:109827.

Table 1: Characteristics of Non Sickle cell and Sickle cell disease patients who were tested for SARS-CoV-2 infection

Factor	Level	Non Sickle Cell Disease	Sickle Cell disease
N		37705	387
Age in Year, median (IQR)		33 (24, 46)	30 (23, 40)
Gender	**Female**	14305 (37.9%)	165 (42.6%)
	Male	23400 (62.1%)	222 (57.4%)

Table 2. Characteristics of the six patients with sickle cell disease and SARS-CoV-2 infection

Age (years)	Gender	SCD genotype	Chief complaints	SARS-Cov2 PCR	Chest Xray	Hb (g/dl)	WBC (x10^9/L)	CRP (mg/L)	Maximum oxygenation support	Management	Discharge day
23	Male	HbSS	Asymptomatic: tested positive on returning from travel	Positive	Normal	17.1	3.28	N/A	None	Observation alone	10
40	Male	HbSS	Fever, myalgia, cough and diarrhea	Positive	Infiltrates	7.4	13.73	137	Nasal Cannula 2LO_2	Blood transfusion, Antibiotics	10
52	Male	HbSS	Asymptomatic: tested positive on returning from travel	Positive	Normal	10.2	6.77	7.3	None	Observation alone	12
25	Male	HbSS	Asymptomatic: tested positive on contact tracing	Positive	Normal	12.8	3.71	4.5	None	Observation alone	8
21	Female	HbSS	Fever, loss of smell and taste	Positive	Normal	13.8	4.61	4.22	None	Supportive and IVF	8
24	Female	HbSS	Fever and myalgia	Positive	Normal	8.5	11.63	1.48	None	Antibiotics, Supportive care	9