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A hypothesis about the role of fetal hemoglobin in COVID-19

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ABSTRACT

COVID-19 infection is less common in children (with higher fetal hemoglobin levels). In our preliminary study, we also observed a low prevalence and fatality of COVID-19 in countries with high rate of hemoglobinopathy carries. Given these two facts, the hemoglobin structure can play a role in the physiopathology of COVID-19 disease. Several drugs are known to increase fetal hemoglobin in adults. Adding these drugs to COVID-19 clinical trials may improve the patients' outcomes.

Introduction

The first case of COVID-19 infection was diagnosed in the city of Wuhan, China. The World Health Organization (WHO) declared the outbreak and status of public health emergency with an international concern on January 31st, 2020. However, COVID-19 became a pandemic in less than three months. The underlying pathogen was soon discovered as a novel member of the coronavirus family. On February 11th, 2020 International committee on taxonomy of viruses called this enveloped, positive-strand RNA beta Genus coronavirus as the "severe acute respiratory syndrome-related coronavirus 2" or SARS-Co-V 2 [1]. The main presentation of infection includes fever, cough, shortness of breath, myalgia, hemoptysis, abdominal pain, nausea, vomiting, and diarrhea. It presents with severe forms of infection in about 15–25% of patients with mortality of about 4–5% [2]. The COVID-19 pandemic is one of the worst challenges modern medicine has ever encountered. There is no standard treatment for this infection, and there are many ongoing clinical trials to find a possible treatment regimen.

The low incidence and prevalence of the COVID-19 in children is unusual behavior in this infection. The commonly accepted explanation of the low prevalence of COVID-19 disease in children is the lower presentation of angiotensin-converting enzyme 2 (ACE2) protein in children. It is believed that the entry of the SARS-CoV-2 into the cells depends on the attachment to the ACE2 protein. This protein is less mature in young children [3]. The other hypothesis for the low incidence of the COVID-19 infection in pediatric is the presence of fetal hemoglobin (HbF). It has been shown that SARS-Co-V2 proteins can attack the heme on the 1-B chain of hemoglobin, causing separation of the iron from the porphyrin [4]. It appears that these phenomena mainly happen in normal hemoglobin. Up to 80% of newborn hemoglobin is consistent with fetal hemoglobin containing alpha and gamma chains, which is likely less susceptible to the virus than adult hemoglobin. Another strange behavior of this infection is the fact that the highest mortality rates of the COVID-19 have been reported in the developed countries with robust healthcare systems. Tropical countries have witnessed less fatal cases [5].

Hypothesis

If the HbF of children has the prophylactic behavior against the SARS-Co-V, the same thing may be true for other variants of hemoglobin (carriers of the hemoglobinopathies). To evaluate the possible relationship between the mortality and morbidity of the COVID-19 and the hemoglobin structures, we conducted a pilot study. The number of deaths as well as case fatality of each country was collected using the John Hopkins University data set [5] dated May 2nd, 2020. Also, the prevalence of major hemoglobinopathies in each country was recorded [6]. The prevalence of the hemoglobinopathy was considered the sum of the prevalence of beta-thalassemia carriers, sickle cell carriers, alpha thalassemia carriers, Hb E, and C carriers [6]. We evaluated the fatality of COVID-19 with regards to the prevalence of hemoglobinopathies in each country. Fig. 1 A shows the plot regarding the prevalence of hemoglobinopathies and the number of deaths by COVID-19. Fig. 1 B shows the case fatality of COVID-19 and the prevalence of hemoglobinopathies. It appears that the more the prevalence of hemoglobinopathies the less the mortality and case fatality. Presence of this relation does not prove the hemoglobin structure as the deterministic factor for COVID-19 mortality and morbidity; this relationship can be because of

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other confounding variables or simply inefficient patient detection and mortality report in tropical countries. However, the role of hemoglobin structure in COVID-19 pathophysiology needs further evaluation.

Hypothetically, the less fatality of this virus in the countries with higher hemoglobinopathies (and a high prevalence of malaria) may be related to hemoglobin structure. Given the natural selection, the structure of hemoglobin in these regions is slightly different than the rest of the world (e.g., high prevalence of the hemoglobin S). It is possible that altered hemoglobin not only helps these people to survive malaria but the COVID-19 virus as well.

If hemoglobin structure can affect the pathogenesis of the COVID-19, it would be a suitable target for treatment. It is not possible to change the adult hemoglobin structure in patients with COVID-19, but there are already several medications capable of increasing the HbF level temporarily. Adding such drugs may improve the results of the COVID-19 clinical trials.

Hemoglobin F (HbF; $\alpha 2\gamma 2$)

Fetal hemoglobin (hemoglobin F, HbF) is the main hemoglobin before birth and constitutes 60–80% of total hemoglobin in the full-term newborns. HbF level decreases 6–12 months after birth and represents less than 1% of hemoglobin in healthy adults and has no significant role in adult physiology, in which the dominant hemoglobin is HbA ($\alpha 2\beta 2$). However, the HbF level becomes important in many hemoglobinopathies, such as sickle cell anemia and beta-thalassemia. Increased HbF in these patients improves their symptoms. In adults, HbF genes are normally integrated within in hematopoietic stem cells and can be reactivated. Effect of different medications on the increase in the Hg F level has been studied extensively [7–10]. HbF inducer agents can increase the HbF level by multiple mechanisms, including Janus kinase/signal transducers and activators of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways. Erythropoietin (EPO) is the main HbF inducer cytokine capable of using all of the abovementioned mechanisms [7]. Also, they are many different medications capable of targeting these mechanisms. The most well-known drugs are thalidomide, pomalidomide, hydroxyurea (HU), and decitabine [7]. The HbF inducer medication, which can be considered to be used in COVID-19 infection, have been summarized in Table 1.

Conclusion

In our preliminary study about the prevalence of hemoglobinopathies in different countries and the mortality rate of COVID-19, it appears that the mortality is lower in countries with a higher prevalence of hemoglobinopathies. This finding does not prove the direct association, and the observed finding can be because of other confounding variables or poor patient detection in tropical countries. However, it may be worth evaluating the role of hemoglobin in the pathophysiology of COVID-19. We suggest adding HbF inducer medications to the current COVID-19 clinical trials. Among the HbF inducer medications, thalidomide because of its concurrent immunomodulatory effects and erythropoietin because of targeting multiple mechanisms and low side effects appear more promising.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

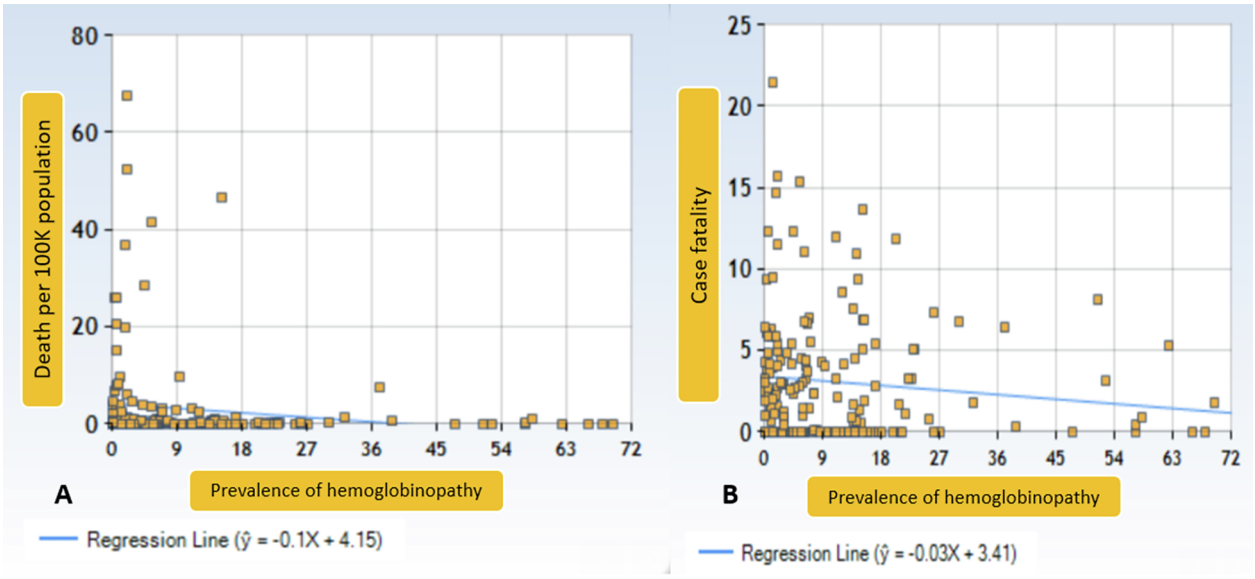

Fig. 1. A: Plot of the number of COVID-19 death per 100 K population per country (Y-axis) and the prevalence of hemoglobinopathy (X-axis). B: Plot of case fatality of COVID-19 per country (Y-axis) and the prevalence of hemoglobinopathy (X-axis).

Table 1
Potential HbF inducer canditates to treat the COVID-19.

Medication	Category	Mechanism of action	Side effects	Comments
Hydroxyurea [10]	Chemotherapy agents	Multifactorial effects on HbF. A ribonucleotide reductase inhibitor. Transient cytostasis. Releasing the nitric oxide (NO). Induction of miR-26b, a microRNA that inhibits MYB and indirectly stimulates HbF production.	Neutropenia, bone marrow suppression and anemia.	The first medication approved for sickle cell disease. The therapeutic effects and side effects are well known. High rate of side effects is challenging in critical COVID-19 patients.
Pomalidomide [8–10]	Immunomodulatory drugs	Histone acetylation at gamma-globin gene promoter. Acetylation of H3K9 and H3K14 at LCR region of the γ-globin gene and reversing the hemoglobin silencing caused by down-regulation of BCL11A, SOX6, LSD1, GATA1, and KLF1.	Asthenia, neutropenia, anemia, upper respiratory tract infection, nausea, and diarrhea	The 3rd generation of immunomodulatory drugs. High rate of side effects is challenging in critical COVID-19 patients
5-Azacytidine, decitabine and citarabine [10]	Chemotherapeutic agents (DNA methyltransferase inhibitors)	DNA methyltransferase Inhibitors. Inhibitor of the DNA methylation	Thrombocytopenia, anemia, body temperature increased, neutropenia, myelosuppression	High rate of side effect is challenging in critical COVID-19 patients.
Panobinostat [8]	HDAC inhibitors	Pan-histone deacetylase (HDAC) inhibitor.	Thrombocytopenia	Increase HbF by 2-fold
Mithramycin and cisplatin [10]	DNA binding agents	DNA-binding activity	Thrombocytopenia	Thrombocytopenia is challenging in critical COVID-19 patients.
RN-1 [8]	LSD1 inhibitor	Lysine-specific demethylase 1 (LSD1) inhibitor.	40% reduction in platelets. Dose-dependent neutropenia	Thrombocytopenia and neutropenia are challenging in critical COVID-19 patients.
Decitabine and Tetrahydrouridine [8]	Decitabine: nucleoside analog	Decitabine: Inhibitor of DNA methylation. Decitabine incorporates into DNA, causing depletion in DNA methyltransferase 1 without cytotoxicity. Decitabine is rapidly metabolized by cytidine deaminase (CDA). Tetrahydrouridine is a CDA inhibitor that prevents decitabine degradation and increases the effect of Decitabine up to 10 fold.	Decitabine: Dose-related neutropenia and thrombocytopenia. No information available on the adverse effects of the drug combination.	Thrombocytopenia and neutropenia are challenging in critical COVID-19 patients.
Rapamycin [10]	mTOR inhibitors	FRAP-mTOR inhibition. FRAP-mTOR is a control protein that regulates the initiation and elongation of translation, ribosome biosynthesis, and amino acid transport.	Peripheral edema, hypertension, hyperlipidemia	Limited information about its effect on HbF
Thalidomide [7,10,11]	Immunomodulatory drugs	Histone acetylation at γ-globin gene promoter. Activation of the P38MAPK signaling pathway. Suppression of NF-KB induction by inflammatory cytokines such as tumor necrosis factor (TNF- α), vascular endothelial growth factor (VEGF), and prostaglandin E2 synthesis (PG-E2).	Teratogens, somnolence, constipation, gynaecomastia, deep venous thrombosis (DVT).	It is approved for multiple myeloma. High inductive effect in increasing the HbF level. Reducing inflammation and inhibiting angiogenesis. Has been used to treat dysregulated pulmonary inflammation in acute lung injury, idiopathic pulmonary fibrosis, sarcoidosis, chronic obstructive pulmonary disease (COPD), infections, and asthma. Thalidomide reduces the level of TNFα which ends in decrease in production of IL-6. Thalidomide may have dual effects in COVID-19; Increasing the HbF and reducing the pulmonary inflammation by decreasing TNF- α, VEGF and IL-6.
Erythropoietin (EPO), stem cell factor and tumor growth factor-β [7,10]	Cytokines	Increase in the frequency of erythroid progenitors programmed to hemoglobin F.	EPO: Nausea, elevated body temperature, vomiting, increased iron absorption, and extramedullary hematopoiesis	EPO can activate many mechanisms to induce HbF production. Its side effects are less severe and can be considered in COVID-19 patients.
Nicotinic acid [7]	Antilipemic agents; vitamins	Stimulate erythroid differentiation in K562 cell line.	Diarrhea	Limited information about its effect on HbF

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.109994.

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