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LETTER TO THE EDITOR

Do congenital bleeding disorders have a protective effect against COVID-19? A prospective study

Dear Editor,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is the most common medical challenge around the world at this time, having infected about 30 million people, and caused hundreds of thousands of deaths.[1] The infection has various effects on the patient's life; those with underlying diseases are more prone to the severe form of the disorder.[2,3] Coagulopathy, most commonly hypercoagulability, is a prominent feature of coronavirus disease 2019 (COVID-19).[3] Although less common, hemorrhage is another serious complication. About one-third of deaths have been attributed to thrombotic events,[4] and thrombotic complications frequently have been observed among patients hospitalized with COVID-19, even in those under anticoagulation.[3,4] Congenital bleeding disorders (CBDs) are accompanied by various underlying disorders, including cardiovascular diseases, potentially making them more susceptible to the severe form of COVID-19.[5] The effect of a disease with a *hypercoagulable* state on patients with inherited *hypocoagulability* is illuminating. Only a few case reports and small case series are available in this context.[6,7] Our primary observation revealed a more favorable outcome of COVID-19 on patients with CBDs.[6] We found a protective effect on patients with CBDs against COVID-19 hypercoagulability and therefore a lower rate of morbidity and mortality. In the present study, we prospectively assessed the patients with CBDs infected by SARS-CoV-2 infection.

This prospective study was conducted on patients with CBDs from June 2020 to September 2020. The study was approved by the ethical committee of Shahid Beheshti University of Medical Sciences, and written consent was obtained from all participants. All patients with CBDs who were referred to the Iranian Comprehensive Hemophilia Care Center (ICHCC) for their routine check-up, prophylaxis, or on-demand therapy were included in the study. All patients were checked for body temperature, and oxygen saturation (SpO2) using pulse oximetry and were interviewed about signs and symptoms of COVID-19. All patients were checked by complete blood count (CBC) (Sysmex kx_21 haematology analyser), C-reactive protein (CRP) (Mindray Chemistry Analyzer; BS-200), and SARS-COV-2 immunoglobulin (Ig) G, and IgM. All suspected patients, based on results of the tests and clinical presentations, were assessed by reverse transcriptase–polymerase chain reaction (RT-PCR) for SARS-CoV-2 infection. Those with positive RT-PCR, and/or SARS-CoV-2 antibody, were considered positive for COVID-19. Those with positive RT-PCR were followed until symptoms resolved and a negative RT-PCR was obtained. In addition, during the study period, data of other patients affected by CBDs and a positive RT-PCR throughout the country were collected.

During the study period, we followed 61 patients: 46 with positive RT-PCR, 15 with positive SARS-CoV-2 IgG (of whom 6 also were positive for SARS-CoV-2 IgM). Forty-nine (~80%) patients were male, and 12 were female. Mean age of the patients was 35.3 years (ranging from 2 months to 66 years). These included 33 patients with hemophilia A (HA) (55%), 9 hemophilia B (HB) (15%), 9 von Willebrand disease (VWD) (15%), 4 factor (F) X deficiency (6.6%), 2 FV deficiency (3.3%), 2 FVII deficiency (1.7%), 1 platelet function disorder (1.7%), 1 vitamin K-dependent coagulation factor (VKCF) deficiency (1.7%). Most patients (n: 27, ~82%) had severe (FVIII:C < 1%) HA, while 6 had mild (FVIII:C > 5%) HA. The majority of HB (n: 7, ~78%) had the severe form of the disorder. Six patients (~66%) had type 3 VWD, while the remaining (~33%) had type 1 VWD. Three of 4 patients with FX deficiency had severe (FX:C < 1%) deficiency, while both patients with FV deficiency had mild factor deficiency (FV:C > 30%) (Table 1).

Two patients, one type 3 VWD and one severe HA, had a high-titer inhibitor (>5 Bethesda units). The majority of patients had a mild course of SARS-CoV-2 infection (14 asymptomatic, 38 mild symptoms), while 9 required hospitalization, including 3 in intensive care units. No death was observed during the study period, nor any thrombotic event reported. Within the study population, 2 patients had cardiovascular disease, one diabetes, one diabetes and hepatitis B, one hypothyroidism, and one thyroidectomy. The symptomatic patients experienced fever (~53%), sore throat (~28%), and myalgia (~28%). Shortness of breath (15.6%), loss of smell and taste (15.6%), headache (12.5%), fatigue (12.5%), coughing (12.5%), diarrhea (12.5%), vomiting (9.4%), and abdominal pain (6.2%) were other symptoms. Eleven patients (18.35%) received prophylaxis, while the rest received on-demand therapy. Of the five patients with hemarthrosis, all but one had severe HA. Menorrhagia occurred in one female carrier of HA. Two patients with VWD, type 1 and 3, experienced epistaxis.

This prospective study identified 61 patients with COVID-19:46 with positive RT-PCR and 15 with a positive IgG. No patient experienced a thrombotic event over the course of the study. Hemorrhagic events did take place, but only in patients receiving on-demand replacement therapy. Moreover, all bleeds but one occurred in patients with severe CBDs, among whom this rate of bleeding can be considered normal. The overall mortality rate of COVID-19 in the general population is ~3%.[8] Not one death has occurred among the ~12 000

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TABLE 1 Characteristics of patients with congenital bleeding disorders and SARS-CoV-2 infection

Disorder	Number	Mean age (Year)	Male/female	Clinical presentations during COVID-19	Bleeding episodes
HA	Severe: 27 Mild: 6	~35	30/3	Asymptomatic: 37% Fever: ~59%[a] Myalgia: ~35% Sore throat: ~18% Shortness of breath: ~18% Vomiting: ~18% Diarrhea: ~18% Fatigue: ~12% Cough: ~12% Headache: ~6% Abdominal pain: ~6%	Hemarthrosis: ~15%[b] Menorrhagia: ~3%
HB	Severe: 7 Mild: 2	44.8	8/1	Asymptomatic: ~11% Sore throat: ~33% Fever: ~33% Headache: ~11% Myalgia: ~11% Diarrhea: ~11% Fatigue: ~11% Cough: ~11%	Hemarthrosis: ~11%[b]
VWD	Type 1:4 Type 3:6	36.1	6/3	Asymptomatic: ~67% Sore throat: ~67% Fever: ~67% Myalgia: ~33% Diarrhea: ~33% Fatigue: ~33%	Epistaxis: ~22% Hemarthrosis: ~11%
FXD	Severe: 3 Mild: 1	15.3	2/2	Asymptomatic: 25% Cough: 50% Shortness of breath: 25% Fever: 25% Diarrhea: 25%	—
FVD	Mild: 2	42.4	1/1	—	Epistaxis: 50%
FVIID	Severe: 2	31.5	2/0	Headache: 50% Myalgia: 50% Fatigue: 50% Nausea: 50%	—
VKCFD	Mild	37	Female	Shortness of breath Myalgia Fever	—
IPFD	NA	45	Female	NA	NA

Abbreviations: FVD, Factor V deficiency; FVIID, Factor VII deficiency; HA, Hemophilia A; HB, Hemophilia B; IPFD, Inherited platelet function disorder; NA, Not available; VKCFD, Vitamin K dependent deficiency; VWD, von Willebrand disease.

[a]Symptomatic patients.

[b]All patients.

Iranian patients with CBDs since the pandemic's onset, appearing to show a potential protective effect against COVID-19 on patients with CBDs.[6] In an earlier study, we reported a patient with type 1 VWD and a thrombotic event [6]; this did not occur in the study at hand. Since thrombotic events are among the leading causes of death in patients with COVID-19, absence of thrombosis significantly decreases the rate of mortality, as observed in this study. The majority of patients have had a mild COVID-19 related phenotype, as has been reported elsewhere.[9] Our hypothesis was that CBD patients with moderate-to-severe deficiency are protected against COVID-19-related hypercoagulability. This study showed that the rate of COVID-19 is not low among patients with CBDs, who probably are enjoying a favorable outcome. A considerable number of patients with CBDs and COVID-19 are asymptomatic, as in the general population.

The international society of thrombosis and hemostasis (ISTH) recommended anticoagulation for all hospitalized patients to forestall thrombotic morbidity or mortality.[10] Our data demonstrated that hypocoagulability plays a major role in decreasing the rate of morbidity and mortality in patients with COVID-19, emphasizing the role of anticoagulation therapy, despite controversial reports on the effectiveness of anticoagulation.[11,12]

Although some types of CBDs have a propensity to thrombotic events, most present a state of general hypocoagulability, making patients less prone to thrombotic events, even in COVID-19, which has a tendency to a state of hypercoagulability.[6] In patients with VWD, particularly type III, pulmonary thrombosis—proposed as the main pulmonary complication in COVID-19—really is less probable. Moreover, a venous thromboembolism (VTE), particularly deep vein thrombosis (DVT), as a common complication of COVID-19, is less likely in patients whose severe factor deficiency interrupts the coagulation cascade.[4]

Our other study also revealed that even COVID-19 can increase acute phase reactants, including coagulation factors, lessening the severity of the bleeding tendency, a phenomenon that could be named a "reciprocal effect."

During the study period, the seven patients who were under regular prophylaxis did not experience a more serious course of COVID-19. It appears that replacement therapy does not eliminate the CBD-related protective effect. A replacement therapy that raises the deficient factor level to normal range might eliminate this protective effect. A more flexible replacement therapy could be considered. Although data of the present study are valuable, further studies on a large number of patients are require to answer all questions about the effects of COVID-19 on the life of patients with CBDs.

KEYWORDS

congenital bleeding disorders, COVID-19, hypercoagulability, hypocoagulability, SARS-CoV-2

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CONFLICT OF INTEREST

The authors have no competing interests.

AUTHOR CONTRIBUTIONS

A. Dorgalaleh designed the work and wrote the manuscript. Sh. Tabibian, M. Bahraini, A. Namwar, A. Anvar, M. Shams, A. Noroozi-Aghideh, and F. Rad performed laboratory analysis. A. Dabbagh, and M. Baghaipour performed clinical studies. All the authors approved the submission.

DATA AVAILABILITY STATEMENT

Data are available upon request.

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