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The Effects of Coronavirus Disease 2019 Pandemic on Patients with Hemophilia and Inherited Bleeding Disorders: Results from 2 Centers in Turkey

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What is already known on this topic?

- *Preventive measures to reduce new cases in coronavirus disease 2019 (COVID-19) lockdown caused problems in accessing healthcare in patients with inherited bleeding disorders (IBD). Patients with IBD and COVID-19 infection mostly had a mild/moderate course of the disease and the COVID-19 pandemic did not disrupt the follow-up and treatment of patients.*

What this study adds on this topic?

- *Patients with hemophilia and other IBDs were not at high risk for COVID-19 infection. Coronavirus 2019 infection was mostly a mild/moderate course of the disease in these patients.*
- *In case of severe inflammatory response and thromboembolic complications, anticoagulants can be used.*

ABSTRACT

Objective: Patients with inherited bleeding disorders faced problems in accessing healthcare during coronavirus disease 2019 pandemic. This study aimed to investigate the health problems of patients with inherited bleeding disorders during the coronavirus disease 2019 pandemic.

Material and Methods: Children and adult patients with inherited bleeding disorders who had a coronavirus disease 2019 infection between March 2020 and November 2021 were retrospectively evaluated.

Results: Seven hundred seventy-two patients were reviewed, and 65 patients who had a coronavirus disease 2019 infection (Male/Female: 58/7, mean age 28.2 ±14.1 years) were analyzed. Sixty patients (92%) had hemophilia A or B or von Willebrand's disease and 5 (8%) had rare bleeding disorders. Sixteen (24.6%) patients had a comorbid disease and 6 (9.2%) needed hospitalization due to severe coronavirus disease 2019 infection. Seven patients (10.7%) experienced a bleeding episode and were treated with factor concentrates. Totally, 64 (98.46%) patients recovered from the coronavirus disease 2019 infection and 1 died.

Conclusion: Patients with inherited bleeding disorders and coronavirus disease 2019 infection mostly had a mild/moderate course of the disease.

Keywords: COVID-19, hemophilia, inherited bleeding disorder

INTRODUCTION

At the end of 2019, a respiratory transmitted disease—coronavirus disease 2019 (COVID-19)—caused by severe acute respiratory syndrome-coronavirus-2 has emerged, and a few months later the World Health Organization declared a pandemic.[1,2] Although, most people had mild-to-moderate disease, hemostatic and/or thrombotic complications associated with COVID-19 have been frequently observed. Preventive measures to reduce new cases such as lockdown caused problems in accessing healthcare in patients with chronic diseases like inherited bleeding disorders (IBD).[3] The most prominent forms of IBDs are hemophilia A and B which are caused by deficiencies of coagulation factor VIII or IX. There are 3 forms of hemophilia according to plasma factor levels: mild (5%-40%), moderate (1%-5%), and severe (<1%). Patients with moderate or severe hemophilia are at risk of hemarthrosis, soft-tissue hematomas, intracerebral hemorrhage, and post-surgical bleeding. Patients with severe hemophilia need regular clotting-factor replacement (prophylaxis) or on-demand treatment in case of bleeding at home or healthcare centers.[4] Prophylaxis is the gold standard for the management of patients with severe hemophilia which aims to maintain factor levels above 1 IU/dL to reduce the frequency and severity of bleeds.[5]

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There are 9 hemophilia comprehensive care centers (HCCC) certified by the European Association of Hemophilia and Allied Disorders in Turkey.[6] Therefore, we aimed in this study to investigate the COVID-19 infection-related health problems of the patients with IBD followed up at 2 different HCCCs during the pandemic.

MATERIALS AND METHODS

Patient and Clinical Data

This descriptive study was performed in 2 HCCCs in Ankara and İstanbul, the 2 most populated cities in Turkey. Patients who were followed up regularly for IBD including hemophilia, von Willebrand's disease (vWD), other rare factor deficiencies, or platelet function disorders at these centers between March 2020 and November 2021 were included in the study. Data were collected retrospectively from medical records of the patients including the type of the disease, the regularity of prophylaxis, any bleeding episodes, problems in accessing factor concentrate or health care, having COVID-19 infection, the requirement of hospitalization, and treatment.

Diagnostic Procedures

The nasopharyngeal–oropharyngeal swab samples were obtained from patients with complaints of fever, cough, or other upper/lower respiratory tract symptoms. The COVID-19 disease was confirmed by real-time polymerase chain reaction (PCR) according to the Turkish Ministry of Health COVID-19 Treatment Guidelines.[6,7] Patients older than 50 years or those who had comorbidities, severe pneumonia, hypotension, sepsis, acute renal failure, or arrhythmia were hospitalized. Antiviral treatment (favipiravir) was recommended for confirmed adult cases. This study is approved by the ethics committee of İstanbul Faculty of Medicine (05.04.2022/837020) and it is conducted in accordance with Helsinki Declaration.

Statistical Analysis

All analyses were performed using Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Analysis of data was primarily descriptive for continuous variables using SDs and mean values. Descriptive analysis for categorical variables was presented as frequencies and percentages.

RESULTS

Patients' Characteristics

Seven hundred seventy-two patients who were followed up at these 2 HCCCs were reviewed, and 65 patients had a confirmed COVID-19 infection (Male/Female: 58/7, mean age 28.2 ±14.1 years). There were 16 patients below 18 years of age. The majority of the patients (92%) had hemophilia A or B or vWD. Deficiencies of factors V, X, and XI, and platelet function disorders comprised 8% of the study group. The clinical characteristics of the patients are represented in Table 1. Of the 49 patients with hemophilia, 39 patients (79.5%) had severe, 7 (14%) had moderate, and 3 (6.5%) had mild hemophilia phenotype. Except for 1, all the 42 patients who were on prophylaxis received their therapy regularly at home or in the hospital during the study period. Eight patients (12.3%) who were diagnosed with hemophilia A were on prophylaxis with non-factor replacement therapies (NFRTs) (phase 3 clinical trial), and others were on prophylaxis with recombinant or plasma-derived factor concentrates.

Table 1. Clinical Characteristics of the Patients Recovered from COVID-19 Infection

Characteristics	n (%)
Age (years, mean ± SD)	28.2 ± 14.1
Sex	
Male	58 (89.3)
Female	7 (10.7)
Diagnosis	
Hemophilia A	37 (57)
Hemophilia B	12 (18.5)
vWD	11 (16.5)
Other	5 (8)
Treatment	
Prophylaxis	42 (64.6)
On demand	23 (35.4)
Bleeding episodes	
Yes	7 (10.7)
No	58 (89.3)
Recovery of COVID-19 infection	
Yes	64 (62)
Exitus	1 (0.09)
Hospitalization due to COVID-19 infection	
Yes	6 (9.2)
No	59 (90.8)
Comorbidities	
Yes	16 (24.6)
No	49 (75.4)

vWD, von Willebrand's disease.

Coronavirus Disease 2019 Infection-Related Health Problems

Fifty-eight patients (89.2%) were admitted to the hospital with fever or COVID-19-related respiratory symptoms such as cough or shortness of breath. Seven (10.8%) patients had a history of contact with COVID-19-positive people. Six patients (9.2%) were hospitalized due to severe infection and 1 of them was a child. The clinical characteristics of the hospitalized patients in detail are presented in Table 2. The hospitalized patients did not receive anticoagulants and used their coagulation factor prophylaxis regularly in close contact with their hematologist. All patients on prophylaxis with NFRTs had a mild infection and received in-home treatment. Pediatric patients with COVID-19 infection had fever and respiratory symptoms. All of them continued their routine prophylaxis and no additional treatment was given for COVID-19 infection. Sixteen (24.6%) patients had a comorbid disease including diabetes,[4] hypertension,[2] obesity,[1] chronic obstructive pulmonary disease,[2] valvular heart disease,[1] or other chronic autoimmune diseases.[5] Two patients with comorbidities were hospitalized due to severe COVID-19 disease and 1 of them with leukemia died. Antiviral treatment (favipiravir) was given in 32 adult patients (49%). There was no thrombotic complication in the patients who had been involved in COVID-19 disease.

Seven patients (10.7%) experienced a bleeding episode during the COVID-19 infection. Joint was the most common site of

Table 2. The Clinical Characteristics of the Hospitalized Patients

Patient No.	1	2	3	4	5	6
Age	70	34	38	35	38	9
Disease/type	Hemophilia B/ severe	Hemophilia A/ mild	Hemophilia A/ severe	Factor X deficiency	Hemophilia A/ severe	Hemophilia A/ severe
Routine treatment	NFRT	No	Prophylaxis	No	Prophylaxis	Prophylaxis
Comorbidities	No	No	No	No	Epilepsy	Leukemia
Bleeding	No	Lung	GIS	No	No	CNS
Fever	No	No	No	Yes	No	Yes
Cough	Yes	Yes	Yes	No	Yes	Yes
Dyspnea	No	Yes	No	No	No	
Thorax CT	Normal	Patch-like shadows	Normal	Normal	Normal	Ground-glass opacity
Lymphocyte count ($\times 10^9$ cells/L)	1.55	0.55	1.82	1.51	1.85	0.32
Ferritin (ng/dL)	821	1557	755	482	661	1250
D-dimer (mg/L)	0.71	0.59	0.35	0.28	0.32	0.80
Mechanic ventilation	No	No	No	No	No	Yes
COVID-19 treatment	Favipiravir	Favipiravir, steroid	Favipiravir	Favipiravir	Favipiravir	No
Complication	No	No	No	No	No	Exitus

CNS, central nervous system; COVID-19, coronavirus disease 2019; CT, computed tomography; GIS, gastrointestinal system; NFRT, non-factor replacement therapy.

bleeding (in 3 patients), 2 patients had lower gastrointestinal system, and 1 had lung bleeding. Bleedings were controlled with additional factor replacements. The patient with lung bleeding was hospitalized when he had hypotension on the sixth day of COVID-19 positivity. On the sixth day of hospitalization, he had hemoptysis and the thorax CT showed patch-like shadows (Figure 1). He received an additional dose of FVIII replacement and steroid therapy. Then, hemoptysis did not recur. Another hemophilia patient developed intracranial bleeding when he was receiving leukemia treatment. He was 9 years old when he was diagnosed with high-risk B precursor acute lymphoblastic leukemia. The factor VIII prophylaxis was continued 3 times a week and he received additional factor replacements when he had intrathecal treatments. After delayed intensification therapy, he had gram-negative bacterial sepsis and also COVID-19 swab was positive. He was transferred to the intensive care unit and intubated due to respiratory insufficiency. After blood culture negativity was obtained, COVID-19 PCR positivity continued. Then, he passed away due to sudden intracranial bleeding.

During the study period, hemophilic arthropathy councils and elective orthopedic surgeries were postponed in the first 12 months of the pandemic. Fortunately, due to emergency regulations by the Ministry of Health to provide factor concentrates, none of the patients experienced difficulty in treatment and prophylaxis during the pandemic.

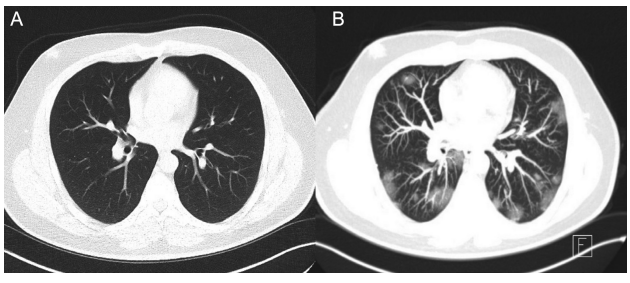

Figure 1. Chest computed tomography images of patient 2. (A) Admission to the hospital. (B) Bilateral patch-like shadows and pulmonary hemorrhage lesions.

DISCUSSION

At the beginning of the COVID-19 pandemic, recommended preventive measures by the World Federation of Hemophilia to reduce COVID-19 infections in patients with hemophilia were to limit routine clinical visits.[3] There was scant data on whether the patients with IBD were prone to severe infection or complications at that time. However, consecutive studies reported that patients with hemophilia and other IBD were not at high risk for COVID-19 infection.[5,8] Besides, Dorgalaleh et al[8] argued that patients with IBD had protection against COVID-19-related hypercoagulability. Continuation of regular factor prophylaxis and maintaining trough factor levels >3% are essential to protect joint health in patients with hemophilia.[3] It has been recommended that patients on prophylaxis should be continued regular treatment during COVID-19 disease. In case of thromboembolic events, they have recommended to be treated with standard prophylactic doses of anticoagulants. Patients are also recommended to participate in physical activity or self-physiotherapy programs to prevent loss of muscle mass and joint stiffness during the pandemic.[9] In the first 3 months period of the pandemic, the lockdown period, clinical visits were limited; however, 97.6% of our patients with IBD received their prophylaxis regularly at home or in the hospital thanks to the regulations by the Ministry of Health. Likewise, Cuesta-Barriuso et al[10] reported adherence to prophylaxis as 86% during the lockdown period in adult patients with hemophilia in Spain. They also noted no changes in the frequency of knee bleeding; however, the frequency of ankle bleeding was significantly reduced which may be related to a sedentary lifestyle during the lockdown. All of our patients who had significant bleeding were accessed to

our centers and were treated with factor replacement therapy in the hospital.

Coronavirus disease 2019 infection was mostly asymptomatic in childhood and children were reported to be 7.2% of all cases with COVID-19 in Turkey.[11,12] Likewise, adults comprised most of our study population (75%). Although most of the patients with IBDs developed mild or moderate symptoms of COVID-19, a limited number of patients were reported to exhibit severe inflammatory responses and thromboembolic complications.[13,14] The well-defined risk factors for severe COVID-19 infection are comorbidities including older age (>65 years), pulmonary or cardiovascular disease, hypertension, obesity, or diabetes mellitus.[15] Sixteen of our patients had comorbidities; however, only 1 patient with leukemia and sepsis developed intracranial bleeding and passed away. None of our hospitalized patients experienced thrombosis. Likewise, the Italian MECCOVID-19 study reported that 13 IBD patients with confirmed COVID-19 infection had mild/moderate respiratory symptoms, 4 of them had severe disease and needed hospitalization, and 1 of them died.[16] Dorgalaleh et al[8] also reported that none of their patients with IBD who developed COVID-19 infection nor died neither had a thrombotic event.

Limitations of our study are related to its retrospective design and scant laboratory data. In addition, our study population comprised mostly adult patients, because COVID-19 infection was mostly asymptomatic in childhood. The other limitation is psychosocial outcomes of the patients with chronic diseases like IBDs could not be assessed.

CONCLUSION

In conclusion, patients with IBD and COVID-19 infection mostly had a mild/moderate course of the disease and the COVID-19 pandemic did not disrupt the follow-up and treatment of patients with IBD so far.

Ethics Committee Approval: The study was approved by the medicalethics committee of İstanbul Faculty of Medicine (No. 05.04.2022/837020)

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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