CASE SERIES
Iran J Allergy Asthma Immunol
October 2022; 21(5):594-599.
Doi: 10.18502/ijaai.v21i5.11046

The Uncomplicated Course of COVID-19 in Primary Immunodeficiency Patients: A Report of 14 Common Variable Immunodeficiency Patients

Mohammad Nabavi[1], Faezeh Mohammadi[2], Saba Arshi[1], Mohammad Hasan Bemanian[1], Morteza Fallahpour[1], Fatemeh Atashrazm[1], and Sima Shokri[1]

[1] Department of Allergy and Clinical Immunology, Rasool e Akram Hospital, Iran University of Medical Sciences, Tehran, Iran
[2] School of Medicine, Iran University of Medical Sciences, Tehran, Iran

Received: 14 December 2021; Received in revised form: 14 April 2022; Accepted: 24 April 2022

ABSTRACT

Coronavirus disease 2019 (COVID-19) affects millions of people worldwide. Clinical manifestations range from asymptomatic to severe viral pneumonia. CVID patients with COVID-19 infection are not adequately studied. In some studies, CVID patients had higher mortality rates, although other studies showed that CVID patients might have an uncomplicated COVID-19 infection. We describe 14 cases of COVID-19 infection in Iranian CVID patients in this study, including clinical manifestations, laboratory findings, and treatment strategies. There were 29% of patients with mild disease, 43% with moderate disease, and 29% with severe disease in this study. A critical case and a death occurred in none of our patients. There were six cases of infection more than two weeks after receiving the second dose of Sinopharm BIBP COVID-19 vaccine; all had mild to moderate disease. Among these patients, Remdesivir was the most frequently prescribed medication. According to this study, most of our patients presented with an uncomplicated disease course.

Keywords: Common variable immunodeficiency; COVID-19; COVID-19 Vaccines; Primary immunodeficiency

INTRODUCTION

In December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, Hubei Province, China.[1] It has quickly spread across the world and was declared a pandemic by the World Health Organization on March 11, 2020.[2] The clinical phenotypes of coronavirus disease 2019 (COVID-19) are variable, including asymptomatic infection in most cases to severe pneumonia with ongoing respiratory failure.[3] The most common symptoms of COVID- 19 are fever, cough, myalgia, or fatigue; atypical symptoms include sputum, headache, hemoptysis, vomiting, and diarrhea.[4] Laboratory manifestations of the disease are lymphopenia, thrombocytopenia, and leukopenia. Most of the patients had elevated levels of C-reactive protein (CRP); less common were elevated levels of alanine aminotransferase (ALL), aspartate aminotransferase (AST), creatine kinase, and D- dimer.[5] Common variable immunodeficiency (CVID) is characterized by

Corresponding Author: Sima Shokri, PhD;
Department of Allergy and Clinical Immunology, Rasool e Akram Hospital, Iran University of Medical Sciences, Tehran, Iran. Tel: (+98 21) 8670 4681, Fax: (+98 21) 8862 2533, E-mail: mohsenzadegan.m@iums.ac.ir

low immunoglobulin levels, recurrent infections, and auto-immunities.[6] Patients with CVID are generally expected to present severe COVID-19 diseases because of their underlying immune defect.[3] But some other articles suggest that because of poor B lymphocyte response and loss of Interleukin-6 receptor, CVID patients are protected against cytokine storm consequences and severe forms of the disease.[7] A review of published case reports and case series showed that the rate of severe and fatal forms of COVID-19 in CVID patients is increased compared to the general population. Still, this estimation had the limitation of lacking systematic cohort studies to identify mild and asymptomatic cases.[8]

CVID patients have trouble fighting off infections because antibody production is impaired. Therefore, secondary bacterial infections may be the more concerning issue in CVID patients, especially in upper and lower respiratory tracts.[9] Moreover, bacterial respiratory infections can lead to chronic pulmonary disease and potentially life-threatening complications.[6,9]

Science December 2020 that the first prophylactic vaccines for COVID-19 were developed, but there is scarce data about vaccine efficacy in CVID patients. A study on 15 CVID patients vaccinated using Pfizer-BioNTech (BNT162b2) showed that 73% of patients had protective titers of SARS-CoV-2 S1 IgG.[10] There is no evidence about other vaccines' efficacy in CVID patients.

Due to insufficient information, further studies are needed to obtain a general overview of the association between CVID and the severity of COVID-19 disease. Therefore, we decided to share our experience with clinical manifestations, laboratory features, and treatment strategies of 14 Iranian COVID-19 cases with a history of CVID.

CASE PRESENTATION

Out of 95 patients registered as primary immunodeficiency diseases (PID) patients in the department of allergy and clinical immunology in Rasoul Akram Hospital, 40 had confirmed diagnosis of CVID. We reviewed medical recordings and televised all of these 40 patients to evaluate symptoms suspected of COVID-19 infection and documented the treatment regimens they received. Among all PID patients, 22 months after the COVID-19 outbreak in Iran, 14 patients had confirmed COVID-19 diagnosis with positive COVID-19 PCR. Some other patients had possible symptoms of COVID-19, but their PCR test was negative. These patients are not included in this study. Due to low experience in the management of COVID-19 in immunodeficient patients, in the first few months, patients with moderate symptoms of CVID were also admitted to the hospital. They received maximal treatment regimens, which were available for managing COVID-19 infection at that time. The treatment regime for COVID-19 was based on Iran's national protocol for diagnosing and treating COVID-19. During the study time, eight updated versions of the protocol were published. About 17 months after the beginning of the COVID-19 outbreak in Iran in April 2021, all PID patients registered in our database were vaccinated using the Sinopharm BIBP COVID-19 vaccine. Out of 14 cases of COVID-19 presented in this paper 6 patients (42.9%) were infected with COVID-19 two weeks after the second dose of the vaccine. These cases are considered vaccine breakthrough infections, and none of them had severe symptoms.

Table 1 shows the clinical characteristics of CVID patients with COVID-19 infection. 7 patients (50%) were male, and 7 patients (50%) were female. The mean age of the patients was 39.35±12.6. Six patients (42.9%) had been hospitalized, but none were admitted to ICU or required mechanical ventilation, and there was no mortality (0%) in these patients. NIH severity of illness categories was used to show the severity of clinical manifestation. Patients are divided into five groups on this scale: asymptomatic, mild, moderate, severe, and critical. Symptomatic patients with standard imaging and no shortness of breath have mild illness. Patients with evidence of lower respiratory disease in clinical or imaging with Sat O2 $\geq$ 94% are considered to have moderate disease. In patients with Sat O2 < 94% or lung infiltration, more than 50% have severe disease;[11] in our study, four patients had a mild illness (28.6%), six patients had a moderate illness (42.9%), and four patients had a severe illness (28.6%). In this study, we did not have asymptomatic or critical patients. The medications used for COVID-19 treatment for each patient are shown in Table 1. The most used medication was Remdesivir which five patients (35%) received. The other antiviral drug Favipiravir was prescribed for two of our patients (14%). Four patients (28%) only received supportive treatments like acetaminophen and diphenhydramine for muscle pain and cough. Two patients (14%) were treated; using Hydroxychloroquine

and antibiotics. Hydroxychloroquine was recommended for COVID-19 treatment in older versions of the national protocol. Also, one patient (7%) received Dexamethasone and Atazanavir. All patients were on immunoglobulin (IG) replacement therapy for CVID, and none were on biological therapies. The mean dose of IVIG they received was 621.4±188.8 mg/Kg monthly, and the mean serum IgG level was 663.3±371.9 mg/dL. Four of 14 patients had baseline lymphopenia with total counts less than 1500 cells/mm^3 none had severe lymphopenia. Peripheral blood cell immunophenotyping results are shown in Table 2.

Table 1. Clinical characteristics and comorbidities of 14 CVID patients with COVID-19 infection

Patient number	Age	Gender	COVID-19 severity	Hospitalization	vaccine breakthrough infection	Medications for COVID-19	Comorbidity
1	63	Male	Severe	+	-	Remdesivir	DM - HTN – CAD - Multiple Myeloma
2	56	Male	Moderate	-	+	Favipiravir	History of Gastrointestinal Lymphoma–Bronchiectasis
3	35	Female	Moderate	-	+	Remdesivir	-
4	54	Male	Mild	-	-	Supportive treatment	Bronchiectasis
5	21	Female	Moderate	-	-	Favipiravir	-
6	49	Male	Severe	+	-	Remdesivir	Bronchiectasis - Autoimmunity (cytopenia)
7	21	Male	Mild	-	+	Supportive treatment	-
8	34	Female	Mild	-	+	Supportive treatment	Bronchiectasis
9	38	Male	Severe	+	-	Hydroxychloroquine-Meropenem	-
10	32	Female	Severe	+	-	Hydroxychloroquine-Clarithromycin	History of Lymphoma
11	28	Female	Moderate	+	-	Remdesivir	Bronchiectasis
12	35	Male	Mild	-	+	Supportive treatment	Autoimmunity (cytopenia)
13	43	Female	Moderate	+	-	Dexamethasone-atazanavir	IBD
14	42	Female	Moderate	-	+	Remdesivir	Bronchiectasis

DM, Diabetes mellitus; HTN, Hypertension; CAD, coronary artery disease; IBD, inflammatory bowel disease)

Table 2. Summary of immunologic data in 14 patients with CVID (the flow-cytometry data are for the time of CVID diagnosis, but the IgG level and the dose of IVIG are for the time of COVID-19 infection)

Patient Number	Absolute lymphocyte count(cells/ µL) (Nl:1000-4800)	CD3 count (cells/µL) (Nl: 900-2400)	CD4 count (cells/ µL) (Nl: 430-1800)	CD8 count (cells/µL) (Nl: 330-980)	CD19 count (cells/µL) (Nl: 110-570)	CD20 count (cells/µL) (Nl: 74-440)	CD56 count (cells/µL) (Nl: 100-670)	CD16 count (cells/µL) (Nl: 100-670)	CD4/CD8 (Nl: 0.80-6.71)	IgG level (mg/Dl (NL:700-1600)	IVIG (mg/kg)
1	2240	1411	560	695	76	50	179	336	0.81	1260	400
2	2184	1375	720	699	174	-	480	-	1.03	460	800
3	2280	1054	980	479	501	501	250	273	2.05	556	400
4	2100	1932	399	1512	52	63	42	84	0.26	635	700
5	1645	1398	674	658	32	-	-	213	1.02	525	500
6	1438	949	388	563	172	186	259	259	0.69	494	700
7	4450	2314	1513	756	667	-	934	-	2.00	1030	500
8	1560	1123	593	530	203	218	195	249	1.12	870	600
9	1368	1067	191	848	-	136	-	109	0.23	90	900
10	1352	973	405	446	202	202	91	120	0.91	1400	500
11	2516	1635	528	1031	452	503	478	427	0.51	190	700
12	1457	859	495	364	466	-	65	72	1.36	500	1000
13	1702	1259	868	357	102	-	170	221	2.43	780	400
14	6500	5135	2600	2535	325	455	585	715	1.03	497	600

(CD, cluster of differentiation; IgG, Immunoglobulin G; IVIG, Intravenous Immunoglobulin)

DISCUSSION

This study reported 14 cases of Iranian CVID patients with confirmed COVID-19 infection. There was no gender difference in the incidence of COVID-19 infection. About 28% of subjects had severe disease, and no one had a critical disease. We had no mortality in our study population. In this study, we had the limitation of asymptomatic infection diagnosis because a PCR test was performed when the patient had possible symptoms or a history of contact with a confirmed COVID-19 case. A review article of 68 CVID patients reported with COVID-19 infection showed that 29% of patients were moderate to severely infected. In contrast, around 10% of cases were critically infected patients. the mortality from COVID-19-related complications they reported in CVID patients was 13%, but this could be an overestimation due to the study types of the articles included in the review.[8] A meta-analysis showed that the infection fatality rate (IFR) for COVID-19 in the general population is 0.68%.[12] Conducting cohort studies will help estimate the IFR of COVID-19 in CVID patients. All of our patients received IVIG before and during the COVID-19 infection period. A case report showed IVIG could also positively affect COVID-19 treatment.[13] Seven patients in our study received Remdesivir and Favipiravir, which have antiviral effects and are indicated as COVID-19 treatment in the current version of the national protocol for diagnosis and treatment of COVID-19 in Iran. Two hospitalized patients with severe symptoms received antibiotic therapy to prevent secondary infection. A case series of 10 CVID patients with COVID-19 reported that half of their patients received antibiotics for the same reason.[14] Six patients in this study were infected with COVID-19 for more than two weeks and less than six months after the second dose of the Sinopharm BIBP COVID-19 vaccine. None of these patients had severe or critical illnesses. This can suggest that the vaccine was effective in preventing the severe forms of the disease. Still, the high rate of vaccine breakthrough infection shows the necessity for further studies to evaluate Sinopharm BIBP COVID-19 vaccine effectiveness in immunodeficient patients.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ACKNOWLEDGEMENTS

This study was supported by Iran University of Medical Sciences.

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
2. Yousefzadegan S, Rezaei N. Case Report: Death due to COVID-19 in Three Brothers. Am J Trop Med Hyg. 2020;102(6):1203-4.
3. Meyts I, Bucciol G, Quinti I, Neven B, Fischer A, Seoane E, et al. Coronavirus Disease 2019 in patients with inborn errors of immunity: an international study. J Allergy Clin Immunol. 2020;147(2):520-31.
4. Singh R, Kang A, Luo X, Jeyanathan M, Gillgrass A, Afkhami S, et al. COVID-19: Current knowledge in clinical features, immunological responses, and vaccine development. FASEB J. 2021;35(3):e21409.
5. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13.
6. Chapel H, Lucas M, Patel S, Lee M, Cunningham-Rundles C, Resnick E, et al. Confirmation and improvement of criteria for clinical phenotyping in common variable immunodeficiency disorders in replicate cohorts. J Allergy Clin Immunol. 2012;130(5):1197-8.e9.
7. Petricau C NI, Deleanu D. Surprising protective mechanisms against severe forms of COVID-19 infection among common variable immunodeficiency patients—one center experience. Research Square. 2021.
8. Weifenbach N, Jung A, Lötters S. COVID-19 infection in CVID patients: What we know so far. Immun Inflamm Dis. 2021;9(3):632-4.
9. Abbott JK, Gelfand EW. Common Variable Immunodeficiency: Diagnosis, Management, and Treatment. Immunol. Allergy Clin North Am. 2015;35(4):637-58.
10. Abo-Helo N, Muhammad E, Ghaben-Amara S, Panasoff J, Cohen S. Specific antibody response of patients with

common variable immunodeficiency to BNT162b2 coronavirus disease 2019 vaccination. Ann Allergy Asthma Immunol. 2021;127(4):501-3.
11. Andersen JB, Midttun K, Feragen KJB. Measuring quality of life of primary antibody deficiency patients using a disease-specific health-related quality of life questionnaire for common variable immunodeficiency (CVID_QoL). J Patient Rep Outcomes. 2019;3(1):15-9.
12. Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. Int J Infect Dis. 2020;101(14):138-48.
13. Aljaberi R, Wishah K. Positive outcome in a patient with coronavirus disease 2019 and common variable immunodeficiency after intravenous immunoglobulin. Ann Allergy Asthma Immunol. 2020;125(3):349-50.
14. Cohen B, Rubinstein R, Gans MD, Deng L, Rubinstein A, Eisenberg R. COVID-19 infection in 10 common variable immunodeficiency patients in New York City. J Allergy Clin Immunol Pract. 2021;9(1):504-7.