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COVID 19 in Patients With Primary Immunodeficiency

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Research Article

Keywords: SARS-CoV2 infection, COVID 19, primary immunodeficiencies, metaanalysis

Posted Date: February 15th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-164902/v1

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Version of Record: A version of this preprint was published at Journal of Clinical Immunology on July 6th, 2021. See the published version at https://doi.org/10.1007/s10875-021-01065-9.

Abstract

The results and the complications following SARS-CoV2 infection in individuals with primary immunodeficiency(PID) remain unclear. The objective of this study is to report the course, follow-up, outcome of COVID 19 in 26 patients with PIDs from a tertiary PID center in Turkey. Infection mortality rate was found to be %7.69 which is eight times higher than infection mortality rate (%0.97) in general population in Turkey. Although it is clear that mortality in patients with PID is higher than in the normal population, it is difficult to suggest a more risky group among primary immunodeficiencies for COVID-19 with a complicated course according to the data published so far. The groups are quite heterogeneous regarding age, sex and comorbidities, but it is remarkable that patients who underwent HSCT with curative treatment had an uncomplicated course despite comorbidities. Future studies as metaanalysis getting data together may help to get a more reliable conclusion.

Introduction

In December 2019, a new human pathogen, a single-stranded RNA virus named 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), appeared in Hubei province of China(1). SARS-CoV-2 enters human cells by the help of angiotensin converting enzyme 2 receptor expressed predominantly in lung and intestinal epithelial cells, alveolar cells and vascular endothelial cells and causes an infectious disease (coronavirus disease 2019 [COVID-19]) characterized commonly with pneumonia and acute respiratory distress. The virus mainly spreads through droplet transmission among people causing increased number of infections and death in the population each day(2). Risk factors such as advanced age, male gender, hypertension, obesity, cardiovascular disease have been identified in patients with severe SARS-CoV2 infection(3).

Primary immunodeficiencies (PID) result from more than 430 identified genetic defects affecting at least one component of humoral or cellular immunity, causing susceptibility to certain pathogens(4).

In patients with PID, the course of COVID-19 may vary from mild disease to death. There are studies both on the course of COVID-19 in patients with PID and the genetic predisposition or underlying inborn errors of immunity in the patients with severe and complicated course of COVID-19(5-9). However, these studies are very few and the results are far from proving a clear relationship between PID and severe SARS-CoV2 infection.

In this study, we report the course, follow-up, outcome and distribution of PIDs among the patients with COVID-19 from one of the leading PID centers in Turkey with the aim of contributing information regarding the course of the disease in PID patients with COVID-19.

Methods

We retrospectively analyzed primary immunodeficiency patients in our center, Hacettepe University, Department of Pediatric Immunology, who had SARS-CoV2 PCR positivity in nasopharangeal swap sample. Only cases confirmed with PCR were included in the study. All patients were diagnosed before COVID-19, and the underlying genetic defects were given. In the patients with ongoing genetic research, clinical diagnosis was made in accordance with European Society of Immunodeficiencies (ESID) guidelines (10). A questionnaire surveyed either by phone interview or chart review to collect the patients' demographical data, clinical complications related to their PID disease, treatments for PID and symptoms, transmission route, clinical manifestations of COVID-19. Lung computed tomography (CT) findings were noted in patients who were evaluated with lung CT.

Information about the place of treatment, the agents used for treatment, and the outcome were given for each patient.

This study was approved by the Ethics Committee of Hacettepe University and Turkish Ministry of Health. Written informed consent was taken from all patients and/or their parents as well.

Results

Patient Characteristics

Twenty-six patients with PID from a single center had been involved in this cohort. Only patients confirmed by PCR were enrolled in the study. 14 (53.8 %) of the patients were male. The median age of the patients is 20.5 (IQR: 9.41-39) years, (min: 15 months, max: 46 years). 15 of the 26 patients were over 18 years of age. The distribution of patients according to sex and age is shown in Figure 1. The median duration of follow-up for PID was 3.5(IQR: 1-12) years (min:6 months, max: 17 years). The distribution of the diagnosis of the patients was as combined immunodeficiency(9), CVID(5), immunodeficiencies with immunedysregulation(4), other antibody deficiencies(4), agamaglobulinemia(3), congenital neutropenia(1). Detailed information on demographical findings, comorbidities of the patients and transmission route, course and treatment of COVID 19 are given in Table 1.

Comorbidities Related with PID

Fifteen patients (57.7%) had history of recurrent pulmonary infections and 4 patients had bronchiectasis and 4 patients had asthma. Autoimmune diseases [OIHA (4), SLE (3), Hashimoto thyroiditis (3), DM (1), JIA (1), autoimmune encephalitis (1), mixed connective tissue disease (1), vitiligo (1), PAN (1)] were present in 12 patients (46.2%). Twelve patients (46.2%) had gastrointestinal complications including diarrhea, hepatitis or cirrhosis. 3 of five patients with history of malignancy, cured with chemotherapy; one patient had low grade lymphoproliferative disease ; one patient had relapsing non-Hodgkin lymphoma with ongoing chemotherapy.

Treatments for PID and Comorbidities

Three of the patients were not using any prophylaxis or treatment. 14 patients were using both immunoglobulin replacement therapy (IGRT) and antibiotic prophylaxis, 3 was using only antibiotic prophylaxis and 5was using only IGRT. Nine of the patients were using immunomodulatory and immunosuppressive drugs including mycophenolate mophetile (MMF), corticosteroid, hydroxychlorokine, sirolimus, abatacept, azathiopurine and methotraxate. Two of the patients (P1, P22) were transplanted for RASGRP1 (+4 years post-HSCT) deficiency and LRBA deficiency (+2 years post-HSCT).

Clinical Information and Outcome of COVID19

Sixteen of the patients (61.5%) became COVID-19 by house contact transmission. 21 patients(80.8%) had fever , 7 patients had cough and 6 patients had headache at presentation. 15 patients were treated as outpatients, 9 patients were hospitalized and 2 patients were treated in the intensive care unit. There were patients who received Favipiravir (16), antibiotics (12), low molecular weight heparin (7), hydroxychloroquine (6), antiviral (3), and IVIG treatment (4) for treatment. Two patients had bacterial coinfection and *H. influenza* was detected in sputum culture. The median time to recovery was 8 (IQR: 7-16) days. Recovery time extended to 60 days in a patient with a diagnosis of XLA. Ten patients were evaluated by Thorax CT, 7 had parenchymal ground-glass areas and consolidations consistent with COVID-19 pneumonia.

A 46-year-old female patient (P23) with a diagnosis of LRBA deficiency and a 39-year-old female patient (P6) with combined immunodeficiency, receiving chemotherapy for EBV (+) relapsed non-Hodgkin lymphoma died. Mortality rate was found to be 7.69% in our PID-COVID-19 cohort.

Discussion

At the beginning of the pandemic, our patients with primary immunodeficiency were more anxious and sheltered with exhibiting appropriate behaviours such as using masks, social distancing, and strict self-isolation. So, we did not have any patients with COVID-19 among our PID patients at the beginning. With the loosening of the protective measures in summer and the exhaustion of the population, with the change in the attitude our PID patients we started to treat PID patients with COVID-19 since July. Here we report the course, follow-up, outcome and distribution of 26 patients with PID and COVID 19 so far.

Among our 26 patients, 11 patients were hospitalized (42.3%) and two patients died. Infection mortality rate was found to be %7.69 which is eight times higher than infection mortality rate (%0.97) in general population in Turkey. In a study conducted in the United Kingdom, hospitalization rate was found to be 53.3% among 60 PID patients. 12 patients died and the infection mortality rate was reported as 20%(11). An international study with 94 patients with PID documented death of 9 (9.57%) patients during follow-up(5). In a study conducted in Iran, which is located in a similar geographical region with our country, 8 of 19 PID patients died, and the mortality rate was found to be 42.1% that is 10 times higher than the normal population in Iran similar to our findings(12). This diversity of hospitalization and mortality rates in different studies may be associated with the fact that primary immunodeficiencies are a highly heterogeneous group of diseases, and disease severity varies quitely with PID-related comorbidities. Another factor affecting the difference between mortality rates among studies may be the number of pediatric patients included. None of our patients were above 50 years of age, 11 out of 26 were children in our study group which may be one of the explanations of lower mortality than other studies.

In our study, there were 5 patients with CVID, 3 patients with X-linked and autosomal recessive agamaglobulinemia. None of our patients with CVID or XLA died, and hospitalization rates were similar in both CVID and agamaglobulinemia. It was stated that among the primary antibody deficiencies, CVID patients had a more severe course than those with XLA (13, 14). On the contrary, in our cohort, two XLA patients had a more severe course with longer hospital stay which extended to 60 days.

Combined immunodeficiency was the most common PID in this study(n=8). Hospitalization rate of patients with combined immunodeficiency was 50%. A 39-year-old patient with CID and EBV + relapsing lymphoma developed COVID-19 while receiving active chemotherapy at hospital and died in ICU due to secondary HLH. A patient with combined immunodeficiency due to RASGRP1 deficiency with comorbidities, pulmonary bronchiectasis and a history of lobectomy showed favorable outcome. It was noteworthy that this patient had attained curative treatment with HSCT 4 years ago.

Five of our patients had immunodeficiency with immunedysregulation. Among them a 46 year old female patient (P5) with LRBA deficiency died. She had history of neuroendocrine tumor of the stomach(cured), autoimmune hemolytic anemia, SLE, bronchiectasis and recurrent diarrhea as comorbidity and was using abatacept and IGRT. However, another 30-year-old patient with LRBA deficiency, with comorbidities such as hypertension, BK virus nephropathy, vitiligo, low grade lymphoma history, and bronchiectasis was treated at home without any complication due to COVID-19. It was also noteworthy that this patient had attained curative treatment with HSCT 2 years ago.

Both patients who died in our cohort had a potential of uncontrolled immune response due to CID and immunodeficiency with immunedysregulation. The study from Iran also revealed that the most lethal COVID-19 was seen in patients with SCID and familial hemophagocytic lymphohistiocytosis with 150 folds higher risk of mortality(12). In the case of combined immunodeficiency, disease severity will be increased due to the impaired cellular immunity and viral control and in the case of immunedysregulation, uncontrolled inflammatory responses may also make the patients more susceptible to the COVID-19(15).

One of the most striking points in our study is the outcome of 2 male patients who transplanted for RASGRP1 deficiency and LRBA deficieny. Although they had variety of comorbidities (history of bronchiectasis and lobectomy, hypertension, BK virus nepropathy), outcome was favorable.

Conclusion

Although it is clear that mortality in patients with PID is higher than in the normal population, it is difficult to suggest a more risky group among primary immunodeficiencies for COVID-19 with a complicated course according to the data published so far. The groups are quite heterogeneous regarding age, sex and comorbidities, but it is remarkable that patients who underwent HSCT with curative treatment had an uncomplicated course despite comorbidities. Future studies as metaanalysis getting data together may help to get a more reliable conclusion.

Declarations

Acknowledgments

We thank all physicians and nurses for their invaluable support and care for patients with PID and COVID 19.

Author Contributions:

All authors contributed to the study conception and design. MO, HNB, AA collected the data. SE performed the analysis and wrote the first draft of the manuscript. DC, ATI and IT commented on the manuscript and improved the discussion

All authors read and approved the final manuscript.

Data Availability:

On a reasonable request, the data supporting the findings of the study are available from the corresponding author.

Compliance with Ethical Standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical Approval:

This study was approved by the Ethics Committee of Hacettepe University and Turkish Ministry of Health.

Consent to Participate:

Informed consent was taken from all patients and/or their parents as well.

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Tables

Table 1. Characteristics of Patients with PID and COVID19

Patient ID	Age	Sex	Diagnosis	PID comorbidity	Treatments for PID and comorbidities	Clinical signs of COVID 19	Organ involvement	Treatment place	Medic
1	20y	M	CID (*RASGRP1* deficiency)	NHL history, bronchiectasis, history of lobectomy, bronchiolitis obliterans after HSCT, undifferentiated connective tissue disease	HSCT+ hydroxychlorokine	Fever, cough, malaise	-	Hospital	Favipi antibi
2	21y	M	CID	Asthma, plastic bronchitis, epilepsy	IGRT, antibiotic px, inhaled steroids	Dyspnea, cough	Pneumonia	Hospital	Favipi antibi LMWH IVIG, o suppo
3	2y	F	CID	OIHA, giant cell hepatitis, epilepsy	IGRT, MMF	Headache	-	Home	
4	4.5y	F	CID	Neonatal giant cell hepatitis, AIHA	IGRT, Azathiopurine	Fever	-	Home	-
5	9.5y	M	CID (STAT1 GOF)	Mycotic calcification in aortic Wall, esophagitis	IGRT, antibiotic px	Fever	-	Hospital	Favipi antibi
6	39y	F	CID, EBV+	SLE, autoimmune thyroiditis, NHL	Chemotherapy, IGRT, antibiotic px	Sore throat, runny nose	Secondary HLH	ICU	Favipi antibi IVIG, M ventila
7	46y	F	CID(CARD11 deficiency)	Nodules in lung, Asthma, DM, Hashimoto thyroiditis, low grade lymphoproliferation	IGRT	Fever, Chest pain, back pain,cough, headache, lethargy	-	Hospital	Favipi antibi
8	15y	M	AT	GERD	IGRT, antibiotic px	Runny nose, sneezing	-	Home	Favipi antibi
9	10y	F	AT	-	Antibiotic px,	Muscle pain	-	Home	-
10	41y	F	CVID	HSM, AIHA, nodular lesions in lung	IGRT, antibiotic px, steroid	Fever, headache, abdominal pain	-	Home	Hydrox Favipi
11	22y	M	CVID	HSM, bronchiectasis, mediastinal LAP, nodular lesions in lung, History of splenectomy	IGRT, antibiotic px	asymptomatic	Pneumonia	Hospital	Favipi
12	31y	M	CVID	Cirrhosis	IGRT, antibiotic px	asymptomatic	-	Home	Favipi
13	46y	F	CVID	Bronchiectasis, autoimmune thyroiditis, alopecia universalis, onicomycosis	IGRT, antibiotic px	Muscle pain, headache, malaise	-	Home	Hydrox
14	37y	F	CVID	-	IGRT, antibiotic px	Fever	-	Home	Hydrox Favipi
15	19y	M	XLA	Chronic diarrhea, PAN	IGRT, antibiotic px, MMF,steroid	Fever	Pneumonia, resistant fever	Hospital	Hydrox Favipi antibi
16	18y	M	XLA	-	IGRT, antibiotic px	Cough, diarrhea	Pneumonia	Hospital	Favipi antibi LMWH IVIG, o suppo

17	3y 9 months	F	Agammaglobulinemia	Recerrent lung infections, JIA	IGRT, antibiotic px, Methotrexate	Fever, wheezing, hoarseness	-	Home	-
18	39y	M	Hypogamma-globulinemia	-	-	Headache, sore throat, loss of taste and smell	-	Home	Hydrox Favipi
19	6y	M	Hypogamma-globulinemia	-	Antibiotic px	Sore throat, fever, hoarseness	-	Home	-
20	9y	M	Selective IgA deficiency	Asthma	Inhaled steroid, antibiotic px	Fever, malaise, tiredness	-	Home	Antibi
21	39y	F	Partial IgA deficiency	-	-	sneezing, gum pain, runny nose, inability to walk, weakness	-	Home	Favipi
22	30y	M	LRBA deficiency	Hypertansion, BK virüs nephropathy, GVHD, vitiligo, low grade lymphoma history, bronchiectasis	HSCT+ IGRT,Sirolimus	Fever, headache, backache	-	Home	ASA, e
23	46y	F	LRBA deficiency	Hypogonadotrophic hypogonadism, neuroendocrine tumor of the stomach, AIHA,SLE, Evans syndrome, bronchiectasis, recurrent diarrhea	IGRT, Abatacept	Malaise, diarrhea, cough	Pneumonia	ICU	Hydrox Favipi antibi IVIG, m ventila
24	27y	M	Immune-dysregulation EBV+	Ankylosing spondilitis	IGRT	Muscle pain, dyspnea	-	Home	Favipi antibi
25	13y	F	ID	Castleman disease, myastenia gravis, paraneoplastic pemphigus, SLE	IGRT, Hydroxychlorokine, piridostigmin, sirolimus	Nasal congestion	-	Home	-
26	15months	M	Congenital neutropenia	-	G-CSF	Fever, cough, nasal congestion	-	Hospital	Favipi antibi

ASA: Acetylsalicylic acid, AT: Ataxia-telangiectasia, CID: Combined immunodeficiency, CVID: Common variable immunodeficiency, HSCT: Hematooetic stem cell transplantation, ICU: Intensive care unit, IGRT: Immunoglobulin replacement therapy,JIA: Juvenile idiopathic arthritis, LMWH: low molecular weight heparin, MMF: Mycophenolate mophetile, px: prophylaxis, SLE: Systemic lupus erythematosus, XLA: Xlinked agammaglobulinemia

Figures

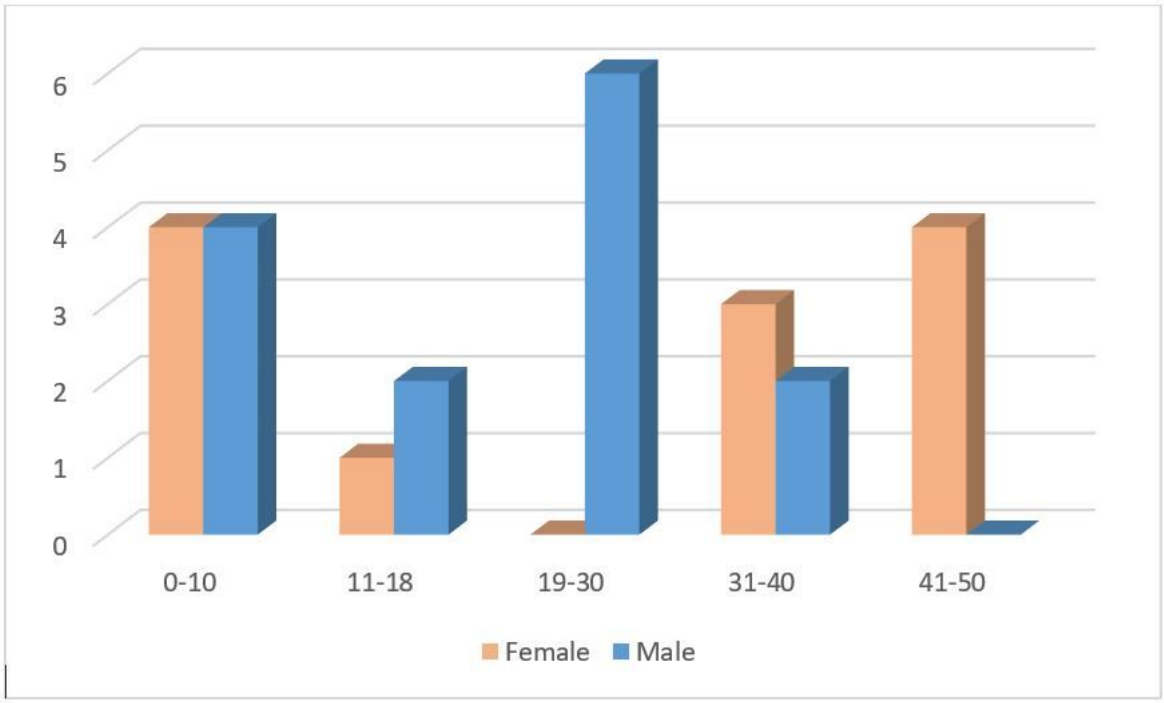

Figure 1

Distribution of age and sex among patients