Clinical characteristics of COVID-19 in children and young adolescents with inborn errors of immunity

To the Editor,
The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread across the globe, and the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic in mid-March of 2020.

In the pediatric age group, symptomatic COVID-19 has been mostly reported in children with inborn errors of immunity (IEI), chronic lung disease, and heart disease. Patients with IEI can be expected to have more severe illness. Moreover, due to weak cellular immunity and viral control, more severe disease is expected in patients with combined immunodeficiencies than in those with humoral defects. However, other authors have proposed that the opposite may be expected in immunocompromised patients. In children with IEI, the lack of the pro-inflammatory cytokine storm implicated in the pathogenesis of severe COVID-19 may protect these patients from multiple organ failure. Therefore, we aimed to determine the incidence and clinical severity of COVID-19 in IEI patients under follow-up in our hospital.

Patients who were followed up or newly diagnosed with IEI in our clinic between September 1, 2019, and October 1, 2020, were included in the study. The patients’ parents were called and asked whether the patient had COVID-19 or had contact with anyone with COVID-19. The patients’ results from viral tests including reverse transcription-polymerase chain reaction (RT-PCR) of a nasopharyngeal sample and IgM/IgG antibody testing for SARS-CoV-2 were recorded. Indications for hospitalization and treatment were determined based on the pediatric patient management and treatment guide from the Turkish Ministry of Health.

Statistical analyses were performed using IBM SPSS Statistics for Windows version 22.0 statistical software package (IBM Corp.). Numbers and percentages were reported for discrete variables; continuous variables were expressed as mean and standard deviation for data with normal distribution and as median and interquartile range (IQR) for non-normally distributed data.

The study included 371 IEI patients with a median age of 88 months (IQR: 36–156 months). Of these, 368 patients were under regular follow-up due to IEI and 3 patients were newly diagnosed with predominantly antibody deficiency after COVID-19 infection.

Of the 368 patients who were already under follow-up for IEI, 261 patients had predominantly antibody deficiency, 41 had combined immunodeficiencies with associated or syndromic features, 40 had congenital defects of phagocyte number or function, 8 had immunodeficiencies affecting cellular and humoral immunity, 7 had diseases of immune dysregulation, 7 had defects of intrinsic and innate immunity, 2 had autoinflammatory disorders, 1 patient had both predominantly antibody deficiency and complement deficiency, and 1 patient had phenocopies of IEI.

According to parent/caregiver reports, none of the patients had stopped taking prophylactic treatment and all patients had adhered to strict isolation, mask use, and social distancing measures during the pandemic.

The characteristics of the previously followed IEI patients who had COVID-19 infection are given in Table 1. Contact status and test results of the patients are presented in Figure 1.

The median age of the 32 patients (32/371; 8.6%) who were diagnosed with COVID-19 was 127 months (IQR: 71.25–183 months). Nine of the 29 previously known IEI patients diagnosed with COVID-19 required hospitalization, and 1 patient diagnosed with IEI after COVID-19 was hospitalized due to multisystem inflammatory syndrome in children (MIS-C). Therefore, a total of 10 (31.25%) of the 32 patients with confirmed SARS-CoV-2 infection were hospitalized. Among the hospitalized patients, 3 (30%) had predominantly antibody deficiency, 3 (30%) had congenital defects of phagocyte number or function, 2 (20%) had defects in intrinsic and innate immunity, 1 (10%) had combined immunodeficiencies with associated or syndromic features, and 1 patient (10%) had phenocopies of IEI. None of the patients died.

It has been reported in the literature that the incidence of COVID-19 in children is lower than in adults. Wu et al. reported that only 2% of 44672 COVID-19 confirmed cases were under 19 years of age. Therefore, the low confirmation rate in this study (7.88% [29/368] of patients who were already under follow-up for IEI) may also be attributed to the patients being in the pediatric age group.

High-risk contact was reported in only 59 (16.03%) of the 368 patients who were reached by phone, and of those, SARS-CoV-2 test results were negative in 5 patients and positive in 22 patients, and the other 32 patients had not been tested. The low rates of risky contact and COVID-19 in this patient group may be partly explained by the fact that families carefully followed strict isolation measures due to their experience with severe infections. However, PCR and
| Patient | IEI | Age (year) | Clinical manifestations of IEI | Routine prophylaxis | Contact with patient with COVID−19 | Symptoms | PCR/antibodies | Hospitalization | Treatment |
|---------|-----|------------|------------------------------|---------------------|-----------------------------------|----------|----------------|----------------|-----------|
| Predominantly antibody deficiencies |
| 1       | CVID | 15         | Recurrent otitis and mastoiditis | -                   | Family                            | No       | PCR (+)         | No             | No        |
| 2       | CVID | 18         | Fanconi aplastic anaemia, short stature, microcephaly, pituitary microadenoma, mental retardation | -                   | Family                            | Fever    | PCR (+)         | No             | No        |
| 3       | CVID | 7          | Dental abscess, recurrent pneumonia | TMP-SMX            | Family                            | Nausea   | PCR (+)         | No             | No        |
| 4       | CVID | 7          | Recurrent pneumonia, recurrent urinary tract infection | TMP-SMX            | Family                            | Fever    | PCR (+)         | No             | No        |
| 5       | CVID | 14         | Recurrent upper respiratory tract infections, recurrent pneumonia | -                   | Family                            | Nasal flow | PCR (+)        | No             | No        |
| 6       | CVID | 17         | Immune thrombocytopenic purpura, bronchiectasis, recurrent pneumonia | IVIG                | Family                            | Headache, arthralgia | PCR (+)         | No             | No        |
| 7       | CVID (the next-generation sequencing identified a germline heterozygous pathogenic variant in the exon 17 of the NFκB2 gene, c.1832G<A p.[Arg853Ter]) | 9          | Microcephaly, hepatosplenomegaly, chronic anemia, macrothrombocytopenia, hypothyroidism, joint hyperlaxity, short stature, recurrent pneumonia, recurrent urinary tract infections, inflammatory bowel disease | IVIG, TMP-SMX, Fluconazole | Family                            | Fever    | PCR not performed Ab (+) | No             | No        |
| 8       | CVID | 19         | Asthma, food allergy | -                   | Family                            | Fever, sore throat | PCR (+)         | No             | Faviapiravir, hydroxychloroquine |
| 9       | CVID | 14         | Asthma, recurrent upper respiratory tract infections, previous adenotonsillectomy, recurrent gingivitis, obesity, hypertension, factor deficiency | -                   | Family                            | Fever, headache, cough, dyspnea | PCR (+)         | Yes            | Oxygen |
| 10      | Selective IgA deficiency | 6          | Recurrent upper respiratory tract infections | -                   | Family                            | Fever, stomachache, vomiting | PCR (+)         | No             | No        |
| 11      | Selective IgA deficiency | 10         | G6PD deficiency, nasal polyposis, recurrent suppurrative otitis, hearing loss, hypertelorism, micrognathia, recurrent pneumonia | -                   | Family                            | Asymptomatic | PCR (+)         | No             | No        |
| 12      | Selective IgA deficiency | 20         | Asthma, allergic rhinitis, recurrent infections of gastrointestinal tract | -                   | Unknown                            | Fever, headache, myalgia | PCR (+)         | No             | No        |

(Continues)
| Patient | IEI | Age (year) | Clinical manifestations of IEI | Routine prophylaxis | Contact with patient with COVID−19 | Symptoms | PCR/antibodies | Hospitalization | Treatment |
|---------|-----|------------|--------------------------------|---------------------|----------------------------------|----------|----------------|-----------------|-----------|
| 13      | Selective IgA deficiency | 8          | Recurrent upper respiratory tract infections, recurrent pneumonia | -                   | Unknown                          | Fever, headache, malaise, loss of appetite, and anosmia | PCR (+) | No            | No            |
| 14      | Transient hypogammaglobulinemia of infancy | 3          | Recurrent bronchiolitis, antibiotic allergy | -                   | Family                           | Fever    | PCR (+) | No            | No            |
| 15      | Transient hypogammaglobulinemia of infancy | 4          | Recurrent upper respiratory tract infections, recurrent pneumonia | -                   | Unknown                          | Fever, vomiting, cough, diarrhea | PCR (+) | YES | Hydroxychloroquine |
| 16      | Partial IgA deficiency | 6          | Recurrent upper respiratory tract infections, recurrent pneumonia | -                   | Family                           | Conjunctivitis | PCR (+) | No            | No            |
| 17      | Decrease of IgM level | 14         | Recurrent bronchiolitis, allergic rhinitis | -                   | Family                           | Fever, headache, myalgia, arthralgia | PCR (+) | No            | No            |

**TABLE 1** (Continued)

**Combined immunodeficiencies**

| Patient | IEI | Age (year) | Clinical manifestations of IEI | Routine prophylaxis | Contact with patient with COVID−19 | Symptoms | PCR/antibodies | Hospitalization | Treatment |
|---------|-----|------------|--------------------------------|---------------------|----------------------------------|----------|----------------|-----------------|-----------|
| 18      | Wiskott-Aldrich syndrome (treated with gene therapy) | 11         | FMF, recurrent pneumonia, recurrent infections of gastrointestinal tract, persistent microthrombocytopenia, and recurrent suppurative infections despite gene therapy | -                   | Family                           | Asymptomatic | PCR not performed Ab (+) | No            | No            |
| 19      | Ataxia-telangiectasia | 12         | Previous non-Hodgkin lymphoma, recurrent pneumonia, chronic lung disease | IVIG                | Unknown                          | Fever, cough, dyspnea | PCR (+) | Yes | Oxygen |

**Congenital defects of phagocyte number or function**

| Patient | IEI | Age (year) | Clinical manifestations of IEI | Routine prophylaxis | Contact with patient with COVID−19 | Symptoms | PCR/antibodies | Hospitalization | Treatment |
|---------|-----|------------|--------------------------------|---------------------|----------------------------------|----------|----------------|-----------------|-----------|
| 20      | Kostmann disease (HAX−1 c.130-131insA., pW44X homozygous mutation) | 2          | Recurrent gingivitis, recurrent lower respiratory tract infections | TMP_SMX           | Unknown                          | Fever, herpetic stomatitis, diarrhea | PCR (-) | Ab (+) | Yes | Cefotaxime, acyclovir |
| 21      | Kostmann disease (HAX−1 c.130-131insA., pW44X homozygous mutation) | 14         | Recurrent cellulitis, recurrent lower respiratory tract infections, recurrent oral aphthous ulcers | GCSF              | Family                           | Asymptomatic | PCR not performed Ab (+) | No            | No            |
| 22      | Kostmann disease (HAX−1 c.130-131insA., pW44X homozygous mutation) | 20         | Recurrent cellulitis, recurrent lower respiratory tract infections, recurrent oral aphthous ulcers | GCSF              | Family                           | Cough     | PCR (+) | Yes | Oxygen |

(Continues)
# Table 1 (Continued)

| Patient | IEI                                                                 | Age (year) | Clinical manifestations of IEI                                                                 | Routine prophylaxis | Contact with patient with COVID-19 | Symptoms                     | PCR/antibodies | Hospitalization | Treatment            |
|---------|----------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------|---------------------|-----------------------------------|-----------------------------|----------------|-----------------|---------------------|
| 23      | Kostmann disease (HAX-1 c.130-131insA., pW44X homozygous mutation)   | 17         | Recurrent cellulitis, recurrent lower respiratory tract infections, recurrent oral aphthous ulcers | GCSF                | Family                            | Cough                       | PCR (+)        | No              | Favipiravir         |
| 24      | Congenital neutropenia                                               | 7 months   | Food allergy, atopic dermatitis, previous infantile sepsis, pyoderma                          | GCSF                | Family                            | Fever                       | PCR (+)        | Yes             | Ceftriaxone         |
| 25      | Chronic granulomatous disease                                        | 16         | Chronic ITP, recurrent infections of gastrointestinal tract, recurrent actinomyces, and staphyllococcal lymphadenitis | Itraconazole, TMP-SMX | Unknown                          | Fever, sore throat          | PCR (-) Ab (+) | No              | No                  |
| 26      | Chronic granulomatous disease                                        | 3          | Multiple liver abscess, necrotizing Aspergillus pneumonia, staphyllococcal pneumonia          | -                   | Unknown                          | Asymptomatic                | PCR (-) Ab (+) | No              | No                  |

**Defects in intrinsic and innate immunity**

| Patient | IEI                                                                 | Age (year) | Clinical manifestations of IEI                                                                 | Routine prophylaxis | Contact with patient with COVID-19 | Symptoms                     | PCR/antibodies | Hospitalization | Treatment            |
|---------|----------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------|---------------------|-----------------------------------|-----------------------------|----------------|-----------------|---------------------|
| 27      | Predisposition to severe viral infection                              | 13         | Kawasaki after MMR vaccination at 1 year old, recurrent viral interstitial pneumonia          | -                   | Family                            | Fever, cough, dyspnea, loss of appetite, bilateral conjunctivitis, erythema nodosum, hypotension, autoimmune hemolytic anemia | PCR (+)        | Yes             | Favipiravir, interferon alpha, oxygen, enoxaparin sodium, dexamethasone, teicoplanin, ceftriaxone, azithromycin |

**Phenocopies of inborn errors of immunity**

| Patient | IEI                                                                 | Age (year) | Clinical manifestations of IEI                                                                 | Routine prophylaxis | Contact with patient with COVID-19 | Symptoms                     | PCR/antibodies | Hospitalization | Treatment            |
|---------|----------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------|---------------------|-----------------------------------|-----------------------------|----------------|-----------------|---------------------|
| 28      | IL-21R deficiency                                                     | 21         | Asthma, Food-induced anaphylaxis, multiple food allergy, drug allergy                           | IVIG, TMP-SMX       | Family                            | Asthma attack               | PCR (+)        | Yes             | Favipiravir, methylprednisolone, salbutamol |

| Patient | IEI                                                                 | Age (year) | Clinical manifestations of IEI                                                                 | Routine prophylaxis | Contact with patient with COVID-19 | Symptoms                     | PCR/antibodies | Hospitalization | Treatment            |
|---------|----------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------|---------------------|-----------------------------------|-----------------------------|----------------|-----------------|---------------------|
| 29      | RAS-associated autoimmune leukoproliferative disease (SPRED1(NM_152594) C.684+50A>T homozygous) | 10         | Flattened nose, ptosis, hypertelorism, downsizing palpebral fissures and epicantil folds, low hairline, long philtrum, aplastic anemia, secondary HLH | -                   | Family                            | Fever, vomiting            | PCR (+)        | Yes             | No                  |

Abbreviations: Ab, antibodies; CVID, common variable immunodeficiency; FMF, familial Mediterranean fever; G6PD, glucose-6-phosphate dehydrogenase; GCSF, granulocyte-colony stimulating factor; HLH, hemophagocytic lymphohistiocytosis; IEI, inborn errors of immunity; IVIG, intravenous immunoglobulin; PCR, polymerase chain reaction; TMP-SMX, trimethoprim-sulfamethoxazole.
serology tests were not performed for 32 (54.24%) of the 59 patients with risky contact because they had no symptoms. These patients either were not infected with SARS-CoV-2 or had asymptomatic infection. The absence of test results for these patients is a limitation of our study.

A study from Turkey showed that children with COVID-19 tend to be asymptomatic or have mild symptoms. Only 1.5% of 1156 confirmed pediatric COVID-19 cases had severe disease, 56% had an underlying condition, and 2 patients died. In our study, there was no mortality. Of the 32 patients with confirmed COVID-19 in this study, 65.6% recovered with no treatment, and 11 (34.38%) received treatment for COVID-19 (Table 1). Ten of 32 patients were followed in hospital, while the other 68.75% of the patients did not require hospitalization due to COVID-19. All of the patients survived with no infection-related sequelae. In the literature, it has been reported that patients with IEI can either be expected to have more severe illness due to weak cellular immunity, or less severe disease due to the absence of a pro-inflammatory cytokine storm. Therefore, it is unclear whether IEI is a protective or predisposing factor for COVID-19. In our study, the lack of mortality may be attributed to ACE receptor levels and the absence of cytokine storm. This may support the theory that IEI patients may be less likely to develop severe manifestations of COVID-19 due to their immune system defect.

Some articles in the literature have included COVID-19 outcomes in IEI patients. A study from the United Kingdom reported that IEI patients with COVID-19 had a median age of 42 years and that older age was associated with mortality. In a study from Italy, 131 cases of SARS-CoV-2 infection occurred in patients with IEI, 33 of whom were aged 18 years or younger. The mean age of the patients who died was 48.5 ± 13.0 years. A high fatality rate was reported in Good’s syndrome and in Del 22q11, both conditions associated with a T-cell defect. Marcus et al. reported the clinical findings of COVID-19 in 20 patients with IEI. Their age ranged from 4 months to 60 years and 16 patients (80%) had humoral immunodeficiency. None of the patients suffered from hypoxemia, and none required hospital admission. In an international study, 94 COVID-19 patients with IEI (32 patients were <18 years old) were reported and 9 of them died. Two of the patients were in the pediatric age group; one had a phagocyte defect and another had immune dysregulation disorder. These studies suggest that there is significant heterogeneity in disease severity among these patients. However, it seems that older age is consistently associated with poorer prognosis. The literature also includes a few articles reporting COVID-19 outcomes in patients followed up due to antibody deficiency. Most of the patients with COVID-19 in our study were diagnosed with predominant antibody deficiency. In the literature, mortality was low in pediatric patients with IEI, similar to the other data related to children in our study.
In conclusion, mortality was not observed in any of the 32 patients (most with predominantly antibody deficiencies) diagnosed with COVID-19 in our study. All of the patients fully recovered with no infection-related sequelae. More information is needed about COVID-19 outcomes in patients with various IEI.

KEYWORDS
children, COVID-19, inborn errors of immunity

FUNDING INFORMATION
There is no financial support.

CONFLICT OF INTEREST
Authors indicate no such interest.

AUTHOR CONTRIBUTIONS
Ozge Yılmaz Topal: Data curation (equal); Formal analysis (equal); Methodology (equal); Resources (equal); Supervision (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal).
Ayşe Metin: Data curation (equal); Methodology (equal); Formal analysis (equal); Supervision (equal); Visualization (equal); Writing-review & editing (equal).
İlknur Kulhas Celik: Data curation (equal); Formal analysis (equal); Methodology (equal); Supervision (equal); Visualization (equal); Writing-review & editing (equal).
Selma Alim Aydin: Data curation (equal); Formal analysis (equal); Methodology (equal); Supervision (equal); Visualization (equal); Resources (equal).
Aslinur Ozkaya Parlakay: Data curation (equal); Formal analysis (equal); Methodology (equal); Supervision (equal).

DATA AVAILABILITY STATEMENT
Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data is not available.

REFERENCES
1. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145:e20200702.
2. Delavari S, Abolhassani H, Abolnezhadian F, et al. Impact of SARS-CoV-2 pandemic on patients with primary immunodeficiency. J Clin Immunol. 2021;41(2):345-355.
3. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034.
4. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10232):514-523.
5. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-1242.
6. Karbuz A, Akkoc G, Bedir Demirdag T, et al. Epidemiological, clinical, and Laboratory Features of Children With COVID-19 in Turkey. Front Pediatr. 2021;9:631547.
7. Babaha F, Rezaei N. Primary immunodeficiency diseases in COVID-19 pandemic: a predisposing or protective factor? Am J Med Sci. 2020;360(6):740-741.
8. Shields AM, Burns SO, Savic S, et al. COVID-19 in patients with primary and secondary immunodeficiency: The United Kingdom experience. J Allergy Clin Immunol. 2021;147(3):870-5 e1.
9. Milito C, Lougaris V, Giardino G, et al. Clinical outcome, incidence, and SARS-CoV-2 infection-fatality rates in Italian patients with inborn errors of immunity. J Allergy Clin Immunol Pract. 2021;9(7):2904-2906.e2.
10. Marcus N, Frizinsky S, Hagin D, et al. Minor Clinical Impact of COVID-19 Pandemic on Patients With Primary Immunodeficiency in Israel. Front Immunol. 2020;11:614086.
11. Meyts I, Buccioli G, Quinti I, et al. Coronavirus disease 2019 in patients with inborn errors of immunity: An international study. J Allergy Clin Immunol. 2021;147(2):520-531.
12. Fill LHL, Graven K, Persaud R, Hostoffer R. The clinical observation of a patient with common variable immunodeficiency diagnosed as having coronavirus disease 2019. Ann Allergy Asthma Immunol. 2020;125:112-114.
13. Quinti I, Lougaris V, Milito C, et al. A possible role for B cells in COVID-19? Lesson from patients with agammaglobulinemia. J Allergy Clin Immunol. 2020;146(1):211-3 e4.
14. Soresina AMD, Chiariini M, Paolillo C, et al. Two X-linked agammaglobulinemia patients develop pneumonia as COVID-19 manifestation but recover. Pediatr Allergy Immunol. 2020;31(5):565-569.

Ozge Yılmaz Topal, Ankara City Hospital, Division of Pediatric Allergy and Immunology, Ankara, Turkey.
Email: ozgeyilmazztopal@gmail.com

Editor: Fabio Candotti

CORRESPONDENCE
Ozge Yılmaz Topal
https://orcid.org/0000-0001-5245-2488
Azize Pınar Metbulut
https://orcid.org/0000-0001-8823-5960
Aslinur Ozkaya Parlakay
https://orcid.org/0000-0001-5691-2461

ORCID
Azize Pınar Metbulut
https://orcid.org/0000-0001-5245-2488
Ayşe Metin
https://orcid.org/0000-0001-8823-5960
İlknur Kulhas Celik
https://orcid.org/0000-0001-5691-2461
Selma Alim Aydin
https://orcid.org/0000-0001-5691-2461
Aslinur Ozkaya Parlakay
https://orcid.org/0000-0001-5691-2461

1 Division of Pediatrics Allergy and Immunology, Ankara City Hospital, Ankara, Turkey
2 Division of Pediatrics Allergy and Immunology, University of Health Sciences, Ankara City Hospital, Ankara, Turkey
3 Division of Pediatric Infectious Disease, University of Health Sciences, Ankara City Hospital, Ankara, Turkey

LETTER TO THE EDITOR