Evaluation of the novel coronavirus disease in Turkish Children; Preliminary Outcomes

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Abstract

Background: The novel coronavirus disease (Covid-19) can progress with mild to moderate or self-limiting clinical findings in children. The aim of this study was to investigate the disease features of Covid-19 in Turkish children. Methods: Children diagnosed by the method of RT-PCR for Covid-19 at the Dicle University Department of Pediatric, between April and June 2020, were evaluated. Hospital records were investigated retrospectively. Results: One hundred and five patients children with the mean age of 108.64 \pm 65.61 were enrolled in this study. The most common cause of transmission in pediatric patients was contacting with a family member diagnosed with COVID-19 (n=91, 86.7%). The most common admission complaints were dry cough (n=17, 16.2%), fever (n=16, 15.2%), lassitude and fatigue (n=14, 13.3%) respectively. More than 95 % of all children with Covid-19 had asymptomatic, mild, or moderate cases. CRP was identified only independent factor associated with long duration of hospitalization. Conclusion: The results of this study show preliminary results of a study investigating the effect of Covid-19 on Turkish children. A clear understanding of the local epidemiology of corona virus infections and identification of risk factors is critical for the successful implementation of the prevention and control program.

Introduction

Coronaviruses (CoVs) are the single-chain, positive-stranded and enveloped RNA viruses that related to human disease had been determined (1). The virus responsible for novel coronavirus disease (COVID-19) is located under the Sarbecovirus subspecies in the genus betacoronavirus, which it contains in severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). The new nomenclature of the virus has been accepted as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2).

Among the coronaviruses causing disease in humans, HCoV 229E, NL63, OC43, and HKU1 are the most frequently isolated. Despite all of the coronaviruses can infect subjects of all ages, these subtypes are the cause of endemics of upper respiratory tract infections in adults. However, many coronavirus subtypes can cause severe disease settings in humans (3, 4, 5).

Coronaviruses are capable of mutation leading to novel CoVs that can be transmitted from animals to

humans. At first, SARS-CoV is transmitted from bearcats to humans in 2002 and resulted hundreds of people to lose their lives in 37 countries. After 10 years, in 2012 MERS-CoV, was first described in humans which was transmitted from dromedary camels to humans and caused 858 fatalities (6, 7).

In December 2019, the novel SARS-CoV-2 was reported in Wuhan, China. After this date, the number of patients increased rapidly, and the disease was observed common all over the world. A number of studies of the total burden of novel COVID-19 have demonstrated that, although generally more dangerous in adults at risk of COVID-19 related complications because of chronic underlying diseases such as cardiovascular and cerebrovascular diseases and diabetes (8).

COVID-19 is also seen common in otherwise healthy children, a considerable number of whom experience severe disease leading to hospitalisation, increased outpatient visits and pharmaceutical medication prescriptions, and (although rarely) even death (9). The first COVID-19 infected child patient in the world was reported from Shenzen on January 20, 2020 (10).

The management of the disease is not very clear and no reliability and effectiveness-proven treatment are yet available for COVID-19. The drugs used to treat it frequently cause adverse effects. Although there are previous studies on possible prognostic drugs in the treatment of pediatric COVID-19, there is no consensus for treatment (11-17).

To our knowledge, there is no major published study on pediatric COVID-19 in Turkish children. Therefore, in our study, we aimed to evaluate the clinical, radiological and laboratory features of the disease in Turkish children. Another objective of this retrospective study was to compare the pediatric COVID-19 disease characteristic in Turkey to those found in other countries. In our study, we also aimed to identify risk factors associated with coronavirus in Turkish children.

Material and Methods

This study included 105 pediatric patients between the ages of 0-18 years, who were diagnosed with COVID-19 in Dicle University, Faculty of Medicine, Department of Pediatric which is the main center for management of pediatric Covid-19 patients in southeastern Turkey, between April 2020 and June 2020. The diagnosis of COVID-19 was made by the method of real-time reverse transcription-polymerase chain reaction (RT-PCR) in samples obtained with nasopharyngeal swab. During the diagnosis, BUN, creatinine, Alanine amino transferase (ALT), Aspartate amino transferase (AST), Lactate dehydrogenase (LDH), serum electrolytes, Prothrombin time (PT), Activated partial thromboplastin time (aPTT), International normalized ratio (INR), C-reactive protein (CRP), procalcitonin, troponin I, CK-MB and D-Dimer were studied in all patients. Posterior-anterior (PA) chest radiography was performed in every patient included in the study and in cases of pathological findings on radiography or clinically severe cases. The data that include patient demographics, laboratory and clinical results, and the previous treatments of the patients were retrospectively taken from patient files and computer-based patient records.

The severity of the disease was classified as asymptomatic, mild, moderate, severe, and critical according to the clinical characteristic, laboratory results, and chest radiography findings (18).

- Asymptomatic: Cases with a positive RT-PCR test without any clinical and radiological findings
- Mild: Cases with upper respiratory tract infection symptoms such as fever, fatigue, myalgia, cough, sore throat, nasal flow with normal espiratory system examination
- Moderate: Cases with pneumonia with complaints of fever and cough but without the symptoms of dyspnea and hypoxemia or cases with findings of COVID-19 on chest CT scan without any symptoms
- Severe: Cases with fever and cough in the early period who develop dyspnea and central cyanosis within a week (arterial oxygen saturation of <92%)
- **Critical:** Cases who develop acute respiratory distress or respiratory failure rapidly, and who tend to develop shock, encephalopathy, myocardial affection, coagulation dysfunction, and acute kidney injury

The patients were divided into three age groups and the data were compared. These groups were as follows: Group 1, patients aged 0 to 1 year (0-12 months); Group 2, patients aged 1 to 10 years (13-120 months);

Group 3, patients aged 10 to 18 years (130-216 months).

Patients over 18 years of age and suspected of having COVID-19 with clinical, laboratory, and radiological findings, but with negative RT-PCR test results were excluded from the study.

The approval was taken from the Republic of Turkey Ministry of Health and the Ethics Committee of Dicle University, Faculty of Medicine.

Statistical Analysis

Data analyses were examined by using Statistical Package for Social Sciences (SPSS), Version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov test) whether or not they were normally distributed. Normally distributed variables were shown by using means and standard deviations, and non-normaly distributed variables were shown by using median and range (maximum and minimum). The chi-square test was used to analyze of categorical variables. Correlations of parameters were studied using Pearson or Spearman correlations. Multiple groups were compared using one-way analysis of variance (ANOVA) with a post-hoc Bonferroni correction and Kruskal-Wallis test for the normally and non-normally distributed variables, respectively. The independent variables for duration of hospital stay were investigated by using stepwise multiple linear regression analysis. P values <0.05 were considered statistically significant.

Results

The mean age of the patients was 108.64 ± 65.61 months (1.5 months-18 years). Of the patients, 51.4% (54/105) were male. There were 13 patients in Group 1, 46 patients in Group 2, and 46 patients in Group 3. The most common cause of transmission in pediatric patients was contacting with a family member diagnosed with COVID-19 (n=91, 86.7%).

Four of our patients (3.8%) had an accompanying disease at the time of diagnosis. A 16-year-old patient had more than one comorbid factor (Diabetes Mellitus + Beta thalassemia major + chronic respiratory disease). A 5.5-month-old patient was followed-up for Primary Hemophagocytic lymphohistic to before the diagnosis. One of whom with Down syndrome and Acute lymphoblastic leukemia, and the other with the diagnosis of epilepsy and was on anti-epileptic drugs.

The most common admission complaints were dry cough (n=17, 16.2%), fever (n=16, 15.2%), lassitude and fatigue (n=14, 13.3%) and headache (n=12, 11.4%), respectively. The admission complaints of the patients were summarized in Table 1.

Chest CT was performed on 48 patients. Pulmonary ground-glass opacities (n=11, 10.4%) were the most common chest CT findings detected in these patients (**Fig. 1, 2**). Other common findings were local patchy shadow (n=5, 4.7%) and bilateral patchy shadow (n=4, 3.8%), respectively. Pleural effusion was also seen in one of our patients.

A significant number of patients were clinically asymptomatic (n=59, 56.2%). Three patients required intensive care. The classification based on clinical severity was summarized in Table 1. The mean length of hospital stay was 4 (range 1-19) days in the patients who required hospitalization. No mortality was observed in any of our patients.

Antibiotics and antiviral agents were used to treat the patients. The most commonly used drugs were the combinations of azithromycin (n=72, 68.6%), hydroxychloroquine (n=21, 20%), antibiotics (n=10, 9.5%), oseltamivir (n=8, 7.6%), lopinavir-ritonavir (n=4, 3.8%). Only 3 of our patients required the use of oxygen. High flow oxygen was administered to a patient who required intensive care.

The clinical and laboratory findings of the patients were summarized in Table 2.

According to the differences between Groups 1, 2, and 3, the contact history was significantly lower in Group 1 than in other two groups (p<0.001). The frequency of male gender was significantly higher in Group 2

(p=0.032) than in other two groups. Besides, sore throat and cough complaints were significantly higher in Group 3 than in other two groups (p=0.004, p=0.008) (Table 3).

The distribution of the clinical severity of the patients by age groups was shown in Table 4.

The Wbc and D-dimer levels, lymphocyte, and platelet counts were significantly higher in the patients in Group 2 compared to other two groups (p=0.007, p<0.001, p0.001, p=0.005). The creatinine levels were lower in the patients in Group 1 than in other two groups (p<0.001), and the blood urea levels were lower in the patients in Group 1 than in the patients in Group 3 (p=0.048). The parameters that showed significant differences among the groups regarding the evaluation of the laboratory findings were shown in Table 5.

There were significant positive correlations between length of hospitalization and CRP, ferritin, fibrinogen, Body temperature (r=0.871, r=0.400, r=0.648, r=0.585, p<0.001, p=0.021, p<0.001, p<0.001, respectively) and negative correlations with oxygen saturation, (r=-0.765, p<0.001). We modelled a multiple linear regression analysis with enter model to define the independent variables of duration of length of hospital stay. Gender, CRP, ferritin levels, fibrinogen, oxygen saturation were included into the analysis. CRP was only independently factor associated longer duration of hospitalization (p<0.001, table 6).

Discussion

Children can carry the heaviest burden of viral respiratory diseases. However, corona virus related infections also vary widely among pediatric individuals. Studies from China and America recommend, that children with COVID-19 might be less serious than in adults and that pediatric cases might knowledge various symptoms than do adults (19, 20); nevertheless, disease characteristics among pediatric patients in the Turkey have not been described. The aim of this study was to determine the epidemiological characteristics of pediatric COVID-19 patients during the first 3 months (April - June) of the disease that occur in Turkey.

Our study included positive pediatric cases confirmed with the RT-PCR method. The male/female ratio in COVID-19 varies between studies. In previous reports from China and America, boy outnumbered girls (11, 19-21). The present study showed a male (51.4%) predominance, similar to what has been described in the Chinese and American populations (22-24). In previous studies, ages ranged between 1 day and 18 years (19, 20, 22). In our study, the mean age of the patients was 108.64 ± 65.61 months and the age range of patients is between 45 days to 18 years. These results suggests that all ages of childhood were sensitive to COVID-19.

In a Chinese study, the most common symptoms in children with COVID-19 were reported as fever and dry cough (36%, 19%, respectively) (22). Also in an another previous large-scale study, fever and cough were reported more frequently in pediatric COVID-19 cases (56%, 54%, respectively), too. In our study, the most common symptoms on admission were cough (16.2%), fever (15.2%), lassitude and fatigue (13.3%). In American study the frequency of sore throat, headache, and diarrhea have been found to be quite less in pediatric patients (20). The present study found the symptoms including; sore throat, headache, diarrhea, loss of taste, anosmia and vomiting (8%, 20%, 4%, 2%, 3% and 6% respectively). These findings are in line with other studies from other countries. These results suggests that children do not always have fever or cough as reported signs and symptoms.

Comorbidities were present in 3.8% of the patients. The comorbidities were as follows: diabetes mellitus, beta thalasemia major, chronic respiratory disease, Down syndrome, acute lymphoblastic leukemia and epilepsy (25).

A 17-year-old girl with insulin-dependent type one diabetes (HbA1C: 8.6) and bone marrow transplantation due to beta thalassemia major and who developed bronchiolitis obliterans presented to the emergency department with shortness of breath and two weeks of a cough. On physical examination, there was tachycardia and high fever. Also, there was bilateral crepitan ral and roncus in auscultation. Laboratory workup was significant for white blood count (WBC) of $7.74 \times 103/\mu$ L with 0.99 % eosinophils, blood glucose of 220 mg/dL, elevated C-reactive protein, and normal venous blood gas. Initial blood and sputum cultures with gram stain were negative. Computed tomography (CT) of the chest showed ground glass, peribronchial consolidation areas and mosaic pattern in both lungs (**Fig. 3**). Despite initial treatment with oseltamivir, azithromycin and hydroxychloroquine treatment, the patient developed respiratory distress, so that lopinavir–ritonavir and favipiravir were added to the treatment. The PCR tests for SARS-COV-2 on the 9th and 11th days of treatment were negative. The patient was discharged on the 17th day with healin.

A 6-month-old male patient infected with COVID-19 in April 2020, while receiving Hemophagocytic Lymphohistiocytosis (HLH) 2004 chemotherapy protocol with the diagnosis of familial (Genetic / Primary) HLH. In our patient, which was accompanied by defective perforin gene defect in primary HLH pathogenesis, COVID-19 infection with the presence of fever and hyperferritinemia, was evaluated in favor of reactivation and the patient was given both the HLH-2004 chemotherapy protocol treatment and COVID-19 therapy as recommended by the guidelines. Our patient improved clinically and in terms of laboratory test results at the end of the 15-day hospitalization period and was discharged. It should be remembered that COVID-19 can be seen with different clinical manifestations in the pediatric age group, and COVID-19 test should be recommended, especially in children with immunosuppression and fever.

In a previous report covering 2135 pediatric patients with COVID-19, the disease followed an asymptomatic, mild, moderate, severe and critical. Regarding the severity, 4.4%, 51.0%, and 38.7% cases were diagnosed as asymptomatic, mild, or moderate, respectively (totally 94.1% of all cases) (19). In another study found that children with COVID-19 had milder clinical manifestations and nearly half of pediatric patients were asymptomatic (22). In our study, 56.2 % of the cases were asymptomatic, 30.5% were mild, 10.5% were moderate, 2.9 % were severe and none of our patients were critical. The percentage of the patients requiring ICU admission was 2.9%.

Laboratory findings in pediatric COVID-19 patients are generally similar to those in other coronavirus infections. The number of white cells is often normal or low; neutropenia and / or lymphopenia may accompany. Thrombocytopenia may develop. C reactive protein and procalcitonin values are generally normal. In severe cases, liver enzymes and lactate dehydrogenase may increase, and abnormal coagulation and high D-dimer levels have been reported in these cases (26). In our study, we found the elevated level of lactate dehydrogenase and D-dimer in 3 cases with severe disease.

Thoracic tomography findings in children are bilateral multiple patchy, nodular ground glass opacities and / or infiltrations in the middle and outer zones of the lung or under the pleura. In the present study, pulmonary ground glass opacities (n = 11, 10.4%) were found as the most common finding in chest tomography. Other common findings were; local patchy shadow (n=5, 4.7%) and bilateral patchy shadow (n=4, 3.8%), respectively. In one of our patients, pleural effusion was seen. These results are consistent with other reports (11, 21, 27). The radiological findings are non-specific and milder than adults (17, 21, 27, 28).

To date, there are no published controlled clinical trials on pediatric COVID-19 specific drug therapy. As with other age groups, there is insufficient evidence for any drug that can be used in the treatment of COVID-19 in children. Therefore, suggested treatments for COVID-19 in child patients should be evaluated in accordance with the studies on adults and should be planned in specific to a child patient. World Health Organization and the American Center for Disease Control and Prevention does not recommend a specific drug for the treatment of children with COVID-19 (29, 30). In our country, the management of pediatric patients with COVID-19 is also evaluated by the Scientific Board of Ministry of Health at frequent intervals and revisions are made (31, 32). Probable adverse effects of drugs must be taken into consideration in the decision for treatment in child patients. Treatment should be evaluated in specific to each child patient, and medication may be planned for patients, respectively; azithromycin (n = 42, 40%), hydroxychloroquin (n = 21, 20%), empirical antibiotic (n=10, 9.5%), oseltamivir (n = 8, 7.6%), lopinavir-ritonavir (n = 4, 3.8%) and Favipiravir (n = 1, 0.9%). Only 3 patients needed oxygen therapy. High flow humidified oxygen was applied to a patient who was followed up in the intensive care unit.

There were some limitations to our study. First, this study was hospital-based, second it is possible the data may be incomplete and incorrect due to the retrospective study design.

Conclusion

To our knowledge, this study is the largest reported cohort of children with pediatric patients with COVID-19 in Turkey. A clear understanding of the local epidemiology of corona virus infections and identification of risk factors is critical for the successful implementation of the prevention and control program. Long and prospective studies are needed to provide a clear understanding of the local epidemiology of respiratory tract infections and identification of risk factors, the successful implementation of a prevention and control program, and to clarify the role of respiratory pathogens.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Figures



Figure 1. Bilateral ground glass and consolidation areas in a 7- month old girl with fever and cough



Figure 2. The CT image of a 9- month old girl with a history of fever, cough and close contact with a family member, revealing peripheral ground-glass areas in both lungs



Figure 3. Computed tomography (CT) of a A 17-year-old girl with dyspnea and cough revealing ground glass and peribronchial consolidation areas

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