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Evaluation of Clinical Symptoms and Laboratory Findings in Children with Coronavirus Disease 2019

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Abstract

Objective: The incidence of coronavirus disease 2019 infection in children is increasing. We investigated the relationship between the distribution of coronavirus disease 2019 on age, gender, clinical, and laboratory findings in children.

Methods: From March 2020 to March 2021, 192 pediatric patients with coronavirus disease 2019 (age: 0-18 years) were enrolled. Patients were divided into 5 groups as <1 age, 1-5 years, 6-10 years, 1-15 years, and 15-18 years. Coronavirus disease 2019 test were determined by the multiplex real-time polymerase chain reaction method. The demographic, clinical, laboratory, radiographic, and treatment data of the patients were obtained from the patients' files.

Results: Fever (44.79%), malaise (22.4%), and cough (19.27%) were the most common 3 symptoms seen in all coronavirus disease 2019 patients. Diarrhea (4.69%) and vomiting (4.17%) were the least common findings. C-reactive protein levels (19.63 ± 18.11 mg/L) were found to be above the normal limits, and procalcitonin values (0.03 ± 0.03 µg/L) were found within the normal limits in all of the patients. Family history was found in 96.35% of the patients, 51 (26.5%) were asymptomatic and 141 (73.5%) were symptomatic.

Conclusion: Most of the pediatric coronavirus disease 2019 patients had mild symptoms, and the most common symptoms of the patients were fever and malaise. Although the parameters associated with poor prognosis are similar in general, it should be known that laboratory and imaging findings typical for adults and children may not accompany the disease and may present with different presentations.

Keywords: COVID-19, children, fever, malaise, family history

Introduction

The highly infectious coronavirus disease 2019 (COVID-19), which emerged in Wuhan City of China in December 2019, has spread worldwide.[1,2] It turned out that this virus caused severe cases of pneumonia in China and was a very different enveloped RNA virus than usual. This virus was named COVID-19 on January 7, 2020 by the World Health Organization (WHO).[3] Later, the International Committee on Virus Taxonomy named the 2019-nCoV virus as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[4] The COVID-19 pandemic was declared by WHO on March 11, 2020. The first case in Turkey was seen on March 11, 2020.[5]

Coronavirus disease 2019, which causes severe respiratory tract infections such as SARS and the Middle East respiratory syndrome (MERS), has its epidemiological data and clinical symptoms.[6] It has been reported that there are many different symptoms and clinical presentations related to COVID-19, such as fever, cough, sore throat, headache, fatigue, muscle pain, and shortness of breath.[7] COVID-19 causes a long incubation period in adults, strong infectivity, atypical clinical symptoms, and high mortality in the elderly.[6] But, COVID-19 in children has milder clinical symptoms compared to adults.[8]

The aim of this study was to evaluate the clinical features, laboratory findings, and treatments of pediatric patients with COVID-19.

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Methods

Study Design and Participants

Ethical approval of this study was obtained by the Non-Interventional Ethics Committee of the Faculty of Medicine İstanbul Atlas University (Date: November 17, 2020, Number: 2020-11-17T11_56_32). The study was performed in accordance with the Helsinki Declaration.

In the study, the medical records of a total of 192 pediatric patients, 95 girls and 97 boys, aged 0-18, who applied to İstanbul Atlas University Medicine Hospital Pediatric Emergency and Pediatric Polyclinic (from March 2020 to March 2021) were diagnosed with COVID-19 were retrieved. Patients were divided into 5 groups as <1 age, 1-5 years, 6-10 years, 1-15 years, and >15 years. Sore throat, headache, loss of smell/taste were not detected at any age. Medical treatments for those who test positive for COVID-19 were initiated and proceeded with respect to our Ministry of Health guidelines.

Inclusion Criteria

- Patients with complaints have fever, weakness, cough, common body pain, loss of smell, sore throat, loss of taste, runny

nose, headache, abdominal pain, diarrhea, vomiting, skin rash, and diagnosis of COVID-19 with PCR positivity and patients under the age of 18.

Exclusion Criteria

- Patients who were not examined and had missing data in their files.

Combined pharyngeal and nasopharyngeal swab samples were obtained from patients who were admitted to the hospital with the suspicion of COVID-19. Diagnovital SARS-CoV-2 Multiplex Real-time Polymerase Chain Reaction (PCR) commercial kit was used for the diagnosis of COVID-19. Total RNA was extracted using the Generotex Full Automatic Rotary Nucleic Acid COVID-19 Extractor nucleic acid isolation device. Multiplex Real-time PCR testing was performed on Gentier 96 Real-Time PCR Detection device using Diagnovital® SARS-CoV-2 Multiplex Real-Time PCR kit. Diagnovital SARS-CoV-2 Multiplex is a real-time PCR-based detection system for SARS-CoV-2.

Collection of Clinical and Laboratory Data

Demographic information and clinical characteristics of each patient, including exposure history, anamnesis, symptoms, treatments, clinical results, and laboratory findings, were obtained from the electronic Medical Record System. Disease onset date, hospitalization dates, disease duration, and family history were recorded. All information was obtained and organized with a customized data collection form. Laboratory tests such as complete blood count (leukocytes, neutrophils, lymphocytes, platelets, and hemoglobin) and serum biochemistry [C-reactive protein (CRP), procalcitonin (PCT), and D-dimer) were requested at the time of admission. Chest posteroanterior (PA) radiographs were obtained from the patients' medical record.

Statistical Analysis

Statistical Package for the Social Sciences 23.0 (IBM SPSS Corp.; Armonk, NY, USA) package program was used in the study. Frequency and percentage values were given for categorical variables. Mean, SD, median, minimum, and maximum values were given for continuous variables. The normal distribution test of continuous variables was done with the Kolmogorov–Smirnov test. Chi-square analysis was used for the relationships between categorical variables. Categorical variables were evaluated with Fisher's exact test inappropriate situations. Independent sample *t*-test was used for the comparison of 2 groups in continuous independent variables with normal distribution, and 1-way analysis of variance was used for comparisons of more than 2 groups. The Mann–Whitney *U*-test was used in the comparison of 2 independent groups for the variables that did not fulfill the normal distribution assumption, and the Kruskal–Wallis *H*-test was used in the comparisons of more than 2 groups. Dunn's multiple comparison test with Bonferroni correction and Tamhane post-hoc test was used to determine the source of the significant difference. A $P < .05$ was considered statistically significant in the analyses.

Results

Of the 192 patients aged 0-18 years included in the study, 97 (50.52%) were male and 95 (49.48%) were female. The mean age of the cases was 11.56 ± 5.62 years, and when the distribution of age groups was examined, it was observed that 36.46% of the patients were in the >15 age group. There was a concomitant chronic disease in 4 (2.08%) patients. Fever (44.79%), malaise (22.4%), and cough (19.27%) were the most common symptoms. Age, gender, presence of chronic disease, and symptoms of the patients are shown in Table 1.

When the laboratory tests were evaluated, it was found that the CRP level was above the normal limits and the mean was 19.63 ± 18.11 mg/L in all of the patients who had blood tests, while the PCT values were within the normal limits and the mean was 0.03 ± 0.03 µg/L. Except for WBC, HGB, and HCT values, no statistically significant difference was found in other laboratory findings according to age groups. White blood cell levels were statistically significant between >15 years and 1-5 years ($P = .009$) groups, between >15 years and <1 ($P = .029$) groups, and between 11-15 years and 1-5 years ($P = .029$) groups. It was determined that the mean of the >15 age group was lower than the 1-5 age group and the <1 age group, and the mean of the 11-15 age group was lower than the 1-5 age group.

As a result of the analysis performed to determine whether HGB and HCT levels differ according to age groups, 1-5 age group and

Table 1. Demographic Features and Distribution of Clinical Findings of the Patients (N = 192)

		n	%
Age (year)	<1	8	4.17
	1-5	34	17.71
	6-10	31	16.15
	11-15	49	25.52
	15-18	70	36.46
Gender	Female	95	49.48
	Male	97	50.52
Chronic disease status	Absent	188	97.92
	Autism	1	0.52
	Asthma	2	1.04
	Rheumatic disease	1	0.52
	Hypertension	1	0.52
Initial symptoms	Fever	86	44.79
	Weakness	43	22.4
	Cough	37	19.27
	Common body pain	28	14.58
	Loss of smell	27	14.06
	Sore throat	25	13.02
	Loss of taste	24	12.5
	Runny nose	15	7.81
	Headache	15	7.81
	Stomach ache	9	4.69
	Diarrhea	9	4.69
	Vomiting	8	4.17
	Skin rash	0	0

Table 2. Comparison of the Laboratory Findings of the Patients According to Age Groups

	<1 age group	1-5 age group	6-10 age group	11-15 age group	15-18 age group	
	(n) Mean + SD Median (Minimum–Maximum)	(n) Mean + SD Median (Minimum–Maximum)	(n) Mean + SD Median (Minimum–Maximum)	(n) Mean + SD Median (Minimum–Maximum)	(n) Mean + SD Median (Minimum–Maximum)	*P*
WBC (/μL)	(n = 5) 9292 ± 4772 7290 (4700–16 820)	(n = 16) 7523 ± 2623 7505 (4020-14 340)	(n = 10) 6152 ± 1715 6330 (3500-8830)	(n = 13) 5641 ± 927 5620 (3160-6920)	(n = 15) 5489 ± 1111 5320 (4040-7750)	**.030***
HGB (g/dL)	(n = 5) 13.02 ± 3.17 12.9 (8.8-16.8)	(n = 16) 11.78 ± 0.74 11.95 (10.3-13.1)	(n = 10) 13.17 ± 0.52 13.15 (12.4-13.9)	(n = 13) 12.98 ± 1.11 12.7 (11.3-15.1)	(n = 15) 13.74 ± 1.39 13.8 (11.9-16.4)	**.003**
HCT (%)	(n = 5) 37.12 ± 7.22 39 (27.1-44.9)	(n = 16) 34.01 ± 1.89 34.15 (30.6-36.8)	(n = 10) 38.23 ± 1.52 38.25 (36.1 - 41)	(n = 13) 38.68 ± 2.96 39.5 (34.5–43.6)	(n = 15) 40.87 ± 3.88 40.9 (34.3-47.6)	**<.001**
PLT (/μL)	(n = 5) 247 360 ± 133 608 283 000 (58 800-418 000)	(n = 16) 230 438 ± 58 354 237 500 (133 000-318 000)	(n = 10) 229 900 ± 46 964 233 000 (150 000-309 000)	(n = 13) 212 169 ± 62964 221 000 (33 200-287 000)	(n = 15) 209 933 ± 41 907 221 000 (124 000-263 000)	.715
LYMP (10^3/μL)	(n = 5) 4.47 ± 3.81 2.34 (1.05-8.62)	(n = 16) 2.85 ± 1.61 2.8 (0.69-6.82)	(n = 10) 1.92 ± 1.04 1.7 (0.74-3.73)	(n = 13) 1.89 ± 0.96 1.61 (0.79-3.59)	(n = 15) 1.58 ± 0.9 1.59 (0.54-4.25)	.086*
NEU (×10^3/μL)	(n = 5) 3.11 ± 1.68 2.82 (0.96-5.61)	(n = 16) 3.78 ± 2.42 3.69 (0.81-8.8)	(n = 10) 3.43 ± 1.59 3.22 (1.6-5.82)	(n = 13) 3.07 ± 0.78 3.34 (1.3-4.16)	(n = 15) 3.14 ± 1.45 2.71 (1.54-5.73)	.790
MONO (×10^3/μL)	(n = 5) 1.43 ± 0.61 1.14 (0.76-2.28)	(n = 16) 0.8 ± 0.31 0.8 (0.35-1.3)	(n = 10) 0.66 ± 0.29 0.58 (0.34-1.31)	(n = 13) 1.54 ± 2.39 0.57 (0.3-7.2)	(n = 15) 0.66 ± 0.21 0.61 (0.39-0.97)	.211
CRP (mg/L)	(n = 0) – –	(n = 6) 23.45 ± 24.05 10.01 (5.5-56)	(n = 2) 12.96 ± 9.09 12.96 (6.53-19.38)	(n = 5) 14.72 ± 9.49 14.21 (5.48-29.59)	(n = 3) 24.61 ± 24.6 11.26 (9.56-53)	.944*
PCT (μg/L)	(n = 3) 0.07 ± 0.02 0.07 (0.05-0.08)	(n = 0) – –	(n = 0) – –	(n = 4) 0.02 ± 0.01 0.01 (0.01-0.03)	(n = 1) 0.01 ± 0 0.01 (0.01-0.01)	.057*
D-Dimer (μg/L)	(n = 1) 1.83 ± 0 1.83 (1.83-1.83)	(n = 0) – –	(n = 1) 0.27 ± 0 0.27 (0.27-0.27)	(n = 2) 0.23 ± 0.02 0.23 (0.21–0.24)	(n = 1) 0.19 ± 0 0.19 (0.19-0.19)	.284*

1-Way analysis of variance.
*Kruskal–Wallis *H*-test.
CRP, C-reactive protein; HCT, hematocrit; HGB, hemoglobin; LYMP, lymphocyte; MONO, monocyte; NEU, neutrophil; PCT, procalcitonin; PLT, platelet; WBC, white blood cells.
Bold values indicate significance.

6-10 age group ($P < .001$, $P < .001$, respectively), 11-15 age group ($P = .033$, $P < .001$, respectively) and >15 age groups ($P < .001$, $P < .001$, respectively). It was determined that the mean HGB and HCT levels of the 1-5 age group were lower than the 6-10 age group, 11-15 age group, and >15 age group (Table 2).

maging methods were needed in 34 (17.7%) patients, and findings consistent with pneumonia were found in 2 of 23 patients who underwent PA chest x-ray. Strikingly, 185 (96.35%) patients had a family history of COVID-19 in their families. Six of the patients (3.14%) were hospitalized and treated. The mean hospital stay of these patients was 7.83 ± 1.72 (minimum–maximum: 6-10) days. Other patients were followed up and treated on an outpatient basis. When the treatments they received were examined, it was found that antibiotic treatment was administered to 52 (27.08%) in total, 45 patients once and 7 patients more than once. It was observed that azithromycin (16.15%) and amoxicillin–clavulanic acid (9.38%) treatments were the most frequently used antibiotics. In addition, it was determined that 10 (5.21%) of the patients used oseltamivir, 23 (11.98%) favipiravir, and 21 (10.94%) hydroxychloroquine (Table 3).

Discussion

Many studies are being conducted on the symptoms and laboratory findings of COVID-19, mostly in adults, in order to illuminate the ignorance of the coronavirus disease, which is spreading rapidly all over the world. Although children seem to be less affected than adults, data on the epidemiological features and clinical features of COVID-19 in the pediatric age group are very weak and limited.[9,10] In a report published by the Chinese Center for Disease Control and Prevention, it was reported that approximately 2% of all patients were <19 years old, but there was no specific clinical information about the patients.[11]

Coronavirus disease 2019 in children is still an incompletely elucidated topic, the clinic and prognosis of SARS-CoV-2 infection and the epidemiological role of children in the pandemic still require further studies. In current study, fever (44.79%), fatigue (22.4%), and cough (19.27%) were the most common findings; diarrhea (4.69%) and vomiting (4.17%) were the least common findings. As compared to a normal cough, a COVID-induced cough is characterized by 2 factors, i.e., dry and a persistent cough. A dry cough usually occurs without any phlegm or mucus and may have a hacking sound. It has a consistent, rough sound to it since it comes with no mucus. Other things that separates it from a normal cough is that COVID cough is usually persistent and can linger on for weeks and sometimes even months. Our results were compatible with other studies.[12,13] In all of our patients who had a blood test, the CRP level was above the normal limits, while the PCT values were within the normal limits. The high rates of CRP (18.8%) were observed in the study of Cui et al[14] is similar to our study. In the same study, it was reported that PCT levels increased in 40.8% of pediatric patients, but it was observed to be normal in some other cases. We can attribute the normal PCT values in our study to the fact that PCT examination was performed in a few patients and secondary bacterial infections were very underdeveloped. On the other hand, although there was a statistically significant difference when WBC, HGB, and HCT values were compared according to age groups in our study, this suggests that this situation is related to the physiological changes of the patients according to age. We believe that these values do not show any significant feature or relationship with COVID-19 disease. Besli et al[12] found the most common abnormal laboratory finding to be lymphopenia with 21%, while Cui et al[14] found the rate of lymphopenia as 9.8%. In our study, the most common abnormal laboratory finding was lymphopenia with a rate of 50.8%, which is similar to other studies.

In a multinational European study, approximately one-third of the patients diagnosed with COVID-19 had chest x-rays, and it was reported that half of them had findings consistent with pneumonia.[15] Besli et al[12] found findings consistent with pneumonia in 12% of chest x-rays taken in symptomatic patients in their study. In our study, chest x-rays of 23 patients were examined and pneumonia was found in 2 (8.6%). The low rate of our study may be due to the fact that chest x-rays are not taken for every patient in order to prevent unnecessary radiation exposure of patients without examination findings, early admission of patients or early diagnosis by performing extensive PCR testing on patients. However, in other studies conducted in China, findings consistent with pneumonia were found in almost two-thirds of the cases in the pulmonary tomography of mild and moderate pediatric cases diagnosed with COVID-19.[9,16,17] In our study, lung tomography was performed in 11 patients, and findings consistent with pneumonia were found in only 2 (18.18%) of the patients. The reason for this difference between studies may be due to the fact that chest tomography was not taken for every patient in order not to expose patients with coughing complaints or no signs of listening in the lungs on examination, or that we did not have as many patients as the number of patients in other studies.

One of the main reasons for the rapid spread of COVID-19 is the history of contact. It has been reported that 75%-90% of children have a family contact history in COVID-19 studies conducted in China,[9,16] and family contact history is reported as 50%-60% in studies conducted in Europe.[15,18] In our study, it was found that 96.35% of the cases had a family history. We think that this high rate in our study is due to the fact that the schools were closed at that time, and the families were crowded or Turkish family structure. Besli et al,[12] in parallel with our study, reported that 75%-90% of the patients had a family history in their study. In addition, 7 (7%) of the patients were asymptomatic and 97 (93%) were symptomatic.[12] However, in our study, 51 (26.5%) of the patients were asymptomatic and 141 (73.5%) were symptomatic. The different rates between the 2 studies can be attributed to the fact that the studies were conducted in different groups of patients with different sociodemographic characteristics at different times, that a good and sufficient history was not taken from the family and the patients, that the families did not explain their complaints clearly enough, that the COVID-19 infection is constantly mutating and that different variants have different effects.

Table 3. Distribution of Drugs Used in the Treatment of Patients (n = 192)

		n	%
Antibiotic	Azithromycin	31	16.15
	Amoxicillin–clavulanic acid	18	9.38
	Cefixime	2	1.04
	Cefuroxime axetil	2	1.04
	Ampicillin	2	1.04
	Cefotaxime	2	1.04
	Cefdinir	1	0.52
	Ceftriaxone	1	0.52
Antiviral	Favipiravir	23	11.98
	Oseltamivir	10	5.21
Antimalarial	Hydroxychloroquine	21	10.94

Hospitalization rates of patients diagnosed with COVID-19 also differ. In studies conducted in some countries, differences were observed between hospitalization rates, it was reported that the rate of hospitalization varied between 5.7%-62% and the rate of hospitalization in the pediatric intensive care unit was 0.6-9.7%.[15,16,19-21] In a study conducted in Turkey, 8% of the patients were hospitalized and 4% of the children were found to be hospitalized in the intensive care unit.[12] In our study, 6 (3.14%) of the patients were hospitalized and treated. A total of 5 (83%) of these patients were newborns and one of them was a patient with a chronic disease. The mean hospitalization duration of the patients was 7.83 ± 1.72 (minimum–maximum: 6-10) days. The reason for the variability of hospitalization rates in studies conducted in different countries can be explained by the fact that the treatment regimen of pediatric patients diagnosed with COVID-19 varies according to the age groups and severity of the patients. Different treatment regimens are applied according to countries and age groups in patients diagnosed with COVID-19. In a study conducted in China, different treatment regimens were recommended according to the age of the patients, and various regimens ranging from supportive treatment to different antiviral treatments were suggested.[22] In Turkey, some agents such as oseltamivir, azithromycin, chloroquine, and favipiravir were applied in the treatment of pediatric patients in line with the recommendations of the Coronavirus Scientific Committee convened under the Ministry of Health.[23] In our study, when the treatments received by the patients were examined, it was seen that antibiotics were used in a total of 52 (27.08%) patients and

azithromycin treatment was most frequently used in 31 (16.15%) patients. However, oseltamivir was used in 10 (5.21%) patients, hydroxychloroquine in 21 (10.94%) patients, and favipiravir in 23 (11.98%) patients. The treatment regimens used were used in accordance with the recommendations of the appropriate age and dose according to the guideline prepared in the light of current data in line with the recommendations of the Ministry of Health Coronavirus Science Committee. We think that antibiotics used other than azithromycin are mostly given with unnecessary concerns, without evidence of secondary bacterial infection in patients and because the COVID-19 disease is not fully known.

There are some limitations to this study. Some patients with complaints and family history were refused samples by their families for different reasons (lack of drug in case of positive detection, difficulty in sampling, financial reasons). Therefore, the number of patients is low. Also this study, which we evaluated as a single-center, retrospective study, may differ from regional studies. For this reason, there is a need for more comprehensive studies to be carried out with the participation of larger masses about the clinical findings of pediatric patients who have not yet been fully clarified. In addition, we think that laboratory values such as creatine kinase, lactate dehydrogenase, ferritin and International Correction Rate (INR) that show the course of COVID-19 disease should be examined.

Conclusion

It was understood in our study that most of the pediatric COVID-19 cases had mild symptoms, and the most common symptoms of the patients were fever and fatigue. It has been observed that patients can also show extrapulmonary symptoms, but the rate is low. It was thought that if the infected patients had a chronic disease and were under the age of 1, the patients required more careful care. In addition, we think that more attention should be paid to measures such as family contact, mask, distance, and hygiene in order not to increase the number of COVID-19 cases in children and society with the opening of schools in our country.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of University of İstanbul Atlas University (Date: November 17, 2020, Number: 2020-11-17T11_56_32).

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

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