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Original Article

Respiratory Viruses in Pediatric Patients with Suspected COVID-19 at the Early Stages of the Pandemic: A Single-center Experience

COVİD-19 Şüpheli Pediatrik Hastalarda, Pandeminin Erken Döneminde Diğer Solunum Yolu Virüs Enfeksiyonları: Tek Merkez Deneyimi

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ABSTRACT

Objective: This study aimed to report the respiratory tract viruses we detected in the respiratory polymerase chain reaction (PCR) samples taken from patients admitted to the Pediatric Emergency Service with suspicion of coronavirus disease-2019 (COVID-19) in the early stages of the pandemic, in addition to the clinical course, and laboratory features of the disease caused by these identified respiratory tract viruses.

Method: All upper respiratory tract PCR samples were taken simultaneously from patients suspected of having COVID-19 disease. All pediatric patients who came to the Pediatric Emergency Department with suspicion of COVID-19 disease between March and June 2020 were included in the study. We retrospectively compared the laboratory findings, clinical manifestations, and primary outcomes of the children aged between 1 month and 18 years infected with respiratory viruses (RVs) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus.

Results: Fifty-eight pediatric patients were tested. SARS-CoV-2 virus was detected in 27 (46.6%) patients and other RVs in 31 (53.4%) patients. The detection rate of SARS-CoV-2 was significantly higher in the older age group of children ($p<0.01$). We didn't detect co-infections with SARS-CoV-2 and other RVs in these patients. Compared to the children with COVID-19, those infected with other RVs required markedly higher rates of oxygen supplementation ($p<0.01$). There was no need for hospitalization in the COVID-19 patient group, and 23 of 31 critically ill children infected with other RVs were followed up in the pediatric intensive care unit.

Conclusion: RVs are common causes of childhood infections and may cause critical illness. Infections caused by other RVs progressed with more severe clinical findings than those of COVID-19 disease in pediatric patients. During the COVID-19 pandemic, other RVs that cause mortality and morbidity in children should be also kept in mind.

Keywords: Respiratory viruses, COVID-19, pediatric intensive care unit, pediatric emergency care

ÖZ

Amaç: Bu çalışmada, pandeminin erken döneminde koronavirüs hastalığı-2019 (COVİD-19) şüpheli hastalarda, diğer solunum yolu virüsleri açısından nazal sürüntü polimeraz zincir reaksiyonu (PCR) örnekleri çalışılarak; şiddetli akut solunum yolu sendromu koronavirüsü 2 (SARS-CoV-2) enfeksiyonu ve diğer solunum yolu virüsleriyle enfekte hastaların klinik ve laboratuvar özelliklerinin karşılaştırılması ve çocukluk yaş grubunda diğer virüslerin de patojen olarak akılda tutulması gerektiğini vurgulamak amaçlanmıştır.

Yöntem: Çalışmaya 11 Mart 2020 ve 30 Haziran 2020 tarihleri arasında Çocuk Acil Servise başvuran ve SARS-CoV-2 enfeksiyonu şüphesi olan 1 ay-18 yaş arası tüm hastalar dahil edilmiştir. COVİD-19 şüpheli tüm hastalardan diğer solunum yolu virüsleri açısından nazal sürüntü PCR örnekleri ve COVİD-19 PCR örnekleri eş zamanlı olarak alınmıştır. Solunum yolu virüsleri ile enfekte olan hastaların laboratuvar bulguları, klinikleri ve izlemdeki sonuçları SARS-CoV-2 enfeksiyonu olan hastalarla karşılaştırılmıştır.

Bulgular: Çalışmaya 58 hasta dahil edilmiştir. Bu hastaların 27'sinde (%46,6) SARS-CoV-2, 31'inde (%53,4) diğer solunum virüsleri saptanmıştır. Bu hasta grubunda COVİD-19 ve diğer solunum yolu viral etkenleriyle koenfeksiyon saptanmamıştır. COVİD-19 enfeksiyonu olan hastalarla karşılaştırıldığında diğer solunum yolu virüs enfeksiyonu olan daha küçük yaşlardaki hastalarda oksijen desteği alma oranı daha yüksektir ($p<0,01$). COVİD-19 ile enfekte olan hastalarda hastane yatışı gerekmemiştir. Solunum yolu virüsleriyle enfekte olan 31 hastanın 23'ü solunum sıkıntısı-solunum yetmezliği nedeniyle çocuk yoğun bakım ünitesinde izlenmiştir.

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Sonuç: Solunum yolu virüsleri çocuklarda sık görülen enfeksiyon etkenlerindendir ve kritik hastalığa neden olabilirler. Özellikle daha küçük yaş grubundaki çocuklarda diğer solunum yolu virüslerinin neden olduğu enfeksiyonlar, COVİD-19'a göre daha şiddetli klinik bulgularla seyretmektedir. Çocuklarda önemli mortalite ve morbidite nedeni olan diğer solunum yolu patojenleri, pandemi sürecinde de izolasyon önlemleri ve tedavi-izlem açısından önemli olup akılda tutulmalıdır.

Anahtar kelimeler: Solunum yolu virüsleri, COVİD-19, çocuk yoğun bakım, çocuk acil servis

INTRODUCTION

In December 2019, cases of pneumonia of unknown etiology were reported in Wuhan city of Hubei Province, China, which spread rapidly from Wuhan city to other provinces in China and abroad [1,2]. The name of the infection and the virus was determined as coronavirus disease-2019 (COVID-19) and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), respectively [3]. World Health Organization reported that COVID-19 had reached a pandemic on March 11, 2020 [4]. The clinical spectrum of COVID-19 disease can range from asymptomatic to critical illness. Milder symptoms are observed in children compared to adults, and the most common clinical findings in children, and adults are fever and cough [5,6]. Compared to adults, children have a better prognosis. Recovery in pediatric patients is possible within 1-2 weeks, and hospitalization is less often necessary in pediatric patients than adults [7].

The infection is transmitted human-to-human with respiratory droplets. Mainly, transmission occurs when infected person sneezes or coughs during close contact with people [8,9]. Laboratory findings, SARS-CoV-2 nucleic acid tests, serological tests, and radiological findings aid in the diagnosis [10]. Laboratory findings as lymphopenia, thrombocytopenia, and leukopenia, elevated erythrocyte sedimentation rate, C-reactive protein (CRP), and lactate dehydrogenase are more commonly seen [11]. Lung X-ray and computed tomography (CT) scanning can be used for diagnosis and assessment of disease progression. Lung X-ray is not recommended as the first choice diagnostic tool. In severe cases, a white lung pattern can be seen in plain chest X-rays [10]. Chest CT is more valuable than a plain chest X-ray. Ground-glass opacities and consolidations are the most common chest CT findings [5,12]. Nucleic acid amplification tests are the most commonly used method to confirm the diagnosis. SARS-CoV-2 was detected in nasopharyngeal and oropharyngeal samples obtained using the reverse-transcription polymerase chain reaction (RT-PCR) method [13].

Pneumonia caused by the other viral agents has also been seen in this period. Respiratory syncytial virus (RSV), influenza, parainfluenza viruses (PIV), human rhinovirus, adenovirus (ADV), and human metapneumovirus (hMPV) are the most common viral pneumonia agents in the child population [14]. Viral pathogens are responsible for pediatric emergencies and intensive care admissions because they cause acute respiratory infections, respiratory distress, and sepsis-like clinical presentation, especially in young children [15-18]. Pneumonia and bronchiolitis account for 20-50% of hospital admissions and lead to non-elective pediatric intensive care unit (PICU) admissions [19-20]. In children with comorbidities, the risk of mortality and morbidity significantly increases [21,22]. Molecular microbiological examination techniques enable the detection of many viruses that commonly cause acute respiratory infections in children, including influenza viruses RSV, ADV, PIV, and hMPV [23]. The recognition of SARS-CoV-2 infection is vital for appropriate infection control measures and potentially promising antiviral therapy. On the other hand, clinicians should also consider SARS-CoV-2 co-infection. SARS-CoV-2 co-infection rates with other respiratory viruses have been reported in the range of 0-20% [24]. COVID-19 protocols allowed us to test for the respiratory virus in all pediatric patients with suspected COVID-19 that attended our Pediatric Emergency Department in the early stages of the pandemic. In this study, we aimed to ascertain the respiratory virus (including SARS-CoV-2) present in respiratory samples of pediatric patients with suspected COVID-19 disease who attended to the Pediatric Emergency Department at the early stages of the pandemic. Our analysis compared diseases caused by SARS-CoV-2 and other viral agents detected in the pediatric population in terms of clinical features, and laboratory findings.

MATERIALS and METHODS

Patients who applied to the pediatric emergency department with respiratory system symptoms at the beginning of the pandemic were included in the study. Respiratory molecular PCR and SARS-CoV-2 PCR samples from these patients were taken in the pediatric emergency isolation room. The clinical manifestations of COVID-19 in children were not known clearly in the

early stages of the pandemic, so we performed necessary laboratory tests in all patients. The records of 58 patients aged between 1 month and 18 years taken to the pediatric emergency clinic in a tertiary care hospital between March 2020 - June 2020 were examined. All necessary data of the patients were obtained retrospectively from the electronic database records of the hospital. SARS-CoV-2-positive and other respiratory virus- positive patients were compared in two groups. The laboratory diagnosis of COVID-19 was based on a positive result obtained in the hospital laboratory via real-time (RT)-PCR testing of SARS-CoV-2 in nasopharyngeal swabs. The lung radiograms were evaluated in patients with respiratory distress who required hospitalization. The diagnosis of upper respiratory tract infection (URTI) and lower respiratory tract infections (LRTI) such as bronchopneumonia, pneumonia, and acute bronchiolitis was made by evaluating relevant disease symptoms, physical examination findings, and radiological findings in association. Mild symptomatic patients were followed up with isolation measures and discharged. The follow-up of the discharged patients was made via phone calls by the pediatric emergency physicians. Moderate to severe symptomatic patients were monitored in isolation rooms until the SARS-CoV-2 PCR examinations were concluded. Necessary permissions were taken from The Republic of Turkey Ministry of Health. Ethical approval was received from the Ethics Committee of Manisa Celal Bayar University Medical Faculty of Health Sciences (decision no: 465, date: 22.07.2020). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Patient Management

The Turkish Public Health Directive Guidelines prepared according to the recommendations of the COVID-19 advisory board were used as the main indications for PICU admission. Mild symptomatic patients were followed up with isolation measures and discharged from Emergency Department (ED). According to isolation measures, patients requiring respiratory and organ support were transferred to PICU until SARS-CoV-2 PCR results were obtained. Chest radiography was performed in patients who only needed respiratory support. None of the patients required CT. The standard definitions were used to evaluate chest radiographs at admissions, such as normal lung X-ray, bronchopneumonia, atelectasis, and air leaks (pneumothorax, pneumomediastinum, etc.). The respiratory conditions of the patients were evaluated clinically. Low- or high-flow oxygen delivery methods were chosen according to the SpO_2 levels of the patients. High-flow nasal cannula (HFNC) oxygen therapy was administered in patients with hypoxemic respiratory failure by wearing appropriate personal protective equipment due to the risk of aerosolization. These patients were closely monitored as for the progression of clinical deterioration. The most experienced physician intubated four patients with respiratory failure with a rapid sequence intubation protocol. Routine isolation measures in PICU were maintained until the SARS-CoV-2 PCR results of the patients were obtained. Fluid/electrolyte balance, antibiotics, nutrition, other supportive treatments, and weaning from invasive/noninvasive mechanical ventilation were arranged according to the PICU protocol.

Statistical Analysis

Study databases were evaluated using SPSS 20.0 (SPSS Inc, Chicago, Ill). Descriptive data were expressed as median (25-75 percentiles) for continuous variables. As appropriate, categorical variables were compared using the $\chi 2$ or Fisher Exact tests. Mann-Whitney U test was used for comparing nonparametric variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The records of 58 pediatric patients who were taken to our pediatric emergency clinic between March 2020 and June 2020 were examined retrospectively: SARS-CoV-2 was detected in 27 (46.6%) and other respiratory viruses in 31 (53.4%) patients. Twenty-eight (48.2%) male, and 30 (51.7%) female patients were included in the study. The median ages of patients with COVID-19, and those infected with other respiratory viruses were 108 (48-168), and 9 months (3-24), respectively. Co-infection with SARS-CoV-2 virus and other respiratory viruses was observed in any patient. The detection rate of SARS-CoV-2 was significantly higher in older children ($p<0.001$). In 27 pediatric patients, the way of transmission was identified as close contact with diseased family members or exposure to people infected with COVID-19. Twenty-seven children had symptoms of mild URTI such as sore throat, fever, and positive SARS-CoV-2 RT-PCR test results. There were no severe or critically ill patients. On admission, frequent symptoms were cough, fever, and myalgia in 14 (51.8%) of 27 SARS-CoV-2 positive patients. COVID-19 patient group had no severe clinical symptoms. Mild symptomatic patients were discharged home and followed up according to the protocols of our health ministry.

The clinical severity of patients infected with other respiratory viruses ranged from mild to severe respiratory distress. Twenty (64.5%) patients presented with moderate to severe respiratory distress due to acute LRTI were managed with HFNC oxygen therapy. Two patients who developed respiratory failure during the follow-up with HFNC and two patients admitted to the ED with respiratory failure were intubated and followed up on mechanical ventilation. Twenty-four (77.4%) patients were followed up in the intensive care unit. Inpatients were younger than outpatients (p=0.005). The patients with an underlying disease required more frequent hospitalizations (p=0.01). In terms of laboratory values, leukocyte, neutrophil and lymphocyte counts, CRP, and PCT values at admission were markedly higher in the other respiratory virus-infected inpatients. Moreover, eosinophil counts of the patients who required hospitalization were dramatically lower than those of outpatients (p=0.035) (Table 1).

The median white blood cell (WBC) count was 7670/μL (4300-10300) in COVID-19 patients, while it was 9750/μL, (7920-12640) in patients infected with other respiratory viruses, (p=0.013)., Median absolute neutrophil count/absolute lymphocyte (ALC) values were 2715/μL (1770-6710)/ 2005/μL (1331.5-3522.5); In COVID-19 patients, while they were 5280/μL (3250-8440)/2825/μL (2090-4270) in patients infected with other respiratory viruses (p=0.059/p=0.015). Serum aminotransferase (AST), serum alanine aminotransferase (ALT), CRP, procalcitonin (PCT), D-dimer values were statistically higher in the group infected with other viruses. The median fibrinogen level was determined as 260 (249.75-393.75) in COVID-19 patients and as 246 (171.5-368) in the group infected with other respiratory viruses (p=0.208). The median age of patients infected with respiratory tract pathogens was nine months (3-24) with a male dominancy (male:16; 51.6%) / female:15; 48.3%). Respiratory viruses identified in nasopharyngeal swab samples in order of decreasing frequency were as follows: RSV (13-22.4%), metapneumovirus (3-5.3%), rhinovirus (3-5.3%), influenza A (1-1.7%), ADV (1-1.7%), human parechovirus (1-1.7%), rhinovirus + ADV (2-3.4%), RSV + bocavirus (2-3.4%), RSV + ADV (1-1.7%), RSV + rhinovirus (1-1.7%), rhinovirus + enterovirus (1-1.7%), bocavirus + ADV (1-1.7%), parainfluenza + metapneumovirus (1-1.7%). LRTI and URTI were diagnosed according to clinical signs and symptoms. No mortality was observed in both groups (Table 2).

DISCUSSION

In this study, respiratory tract viruses and SARS-CoV-2 in children aged one month to 18 years attended to our pediatric emergency clinic between March 2020 and June 2020 with signs of respiratory tract infection and followed up as out- or in-patients were examined. Most studies indicate that children infected with COVID-19 have mild clinical manifestations characterized by relatively nonspecific symptoms such as cough, sore throat, nasal congestion, and fever. COVID-19 leads a much milder course than that seen in adults, and understanding the reasons for this may enable us to develop potential methods for treatment. The rates of hospital -including intensive care unit- admissions in adults have been reported as 10-33%, while the reported

Table 1. Demographic and laboratory variables

Variables	SARS-CoV-2 (+) (n=27)	Other RV (n=31)	p
Age (Months) (Median, 25-75 p)	108 (48-168)	9 (3-24)	<0.001
Sex (F/M)	15/12	15/16	0.586
WBC (Median, 25-75 p);	7670 (4300-10300)	9750 (7920-12640)	0.013
ANC	2715 (1770-6710)	5280 (3250-8440)	0.059
ALC	2005 (1331.5-3522.5)	2825 (2090-4270)	0.159
Eosinophil	40 (40-127.5)	5 (0-250)	0.035
AST (Median, 25-75 p)	22.5 (21-35.5)	38.5 (31.5-49.5)	<0.001
ALT (Median, 25-75 p)	20 (11-19.5)	14.5 (15.5-35)	0.006
CRP (Median, 25-75 p)	0 (0-0)	3.65 (2-17.9)	<0.001
Procalsitonin (Median, 25-75 p)	0.03 (0-0.05)	0.16 (0.1-1)	0.002
D-dimer (Median, 25-75 p)	125 (96.5-386.5)	719 (251.5-1358)	0.001
Fibrinogen (Median, 25-75 p)	260 (249.75-393.75)	246 (171.5-368)	0.208

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2, RV: Respiratory virüse, F: Female, M: Male, WBC: White blood cell, ANC: Absolute neutrophil, ALC: Absolute lymphocyte, AST: Aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein

rates of hospital, and PICU admissions in children have ranged between 5.7-20%, and 0.58-2%, respectively [25-28]. Among the pediatric patient population with COVID-19, the highest rate of hospitalization occurs in infants [29]. Our data have shown that the other respiratory tract infections might be more severe compared to COVID-19. In this study, the laboratory findings, including WBC, eosinophil counts, AST, ALT, CRP, PCT, D-dimer values, were different between these two groups. There was no need for mechanical ventilation support in SARS-CoV-2 -positive patients. While most of the other respiratory virus-positive patients required supplemental oxygen, HFNC, and mechanical ventilation (noninvasive/invasive) support. Laboratory findings are variable for laboratory - confirmed cases of COVID-19 in pediatric patients. In a systematic review of laboratory - confirmed COVID-19 cases in children, mostly normal complete blood counts, but lower WBC counts in 17%, and neutropenia or lymphocytopenia in 13% of the patients were indicated [30,31]. Also, eosinopenia (29.5%) was observed in another study [32]. Approximately 30% of the patients had elevated CRP (CRP was reported as >5 mg/L in most studies) or PCT (PCT was reported as >0.5 ng/mL). On the other hand, elevated inflammatory markers and lymphocytopenia may indicate multisystem inflammatory syndrome in children. AST values were elevated in 12% of the patients. In our study, WBC counts, AST, ALT, CRP, PCT, and D-dimer were statistically significantly higher in the group infected with other viruses. There is insufficient data on coagulation test results in children with COVID-19. A study of adult patients with COVID-19 showed increased D-dimer levels and prothrombin time in intensive care patients [33]. In the pediatric patients, an elevated D-dimer level was more frequent in infants than in the other age groups which may suggest that infants might become more seriously infected than older children during COVID-19 pandemic. Studies have shown that children with RSV have significantly lower lymphocyte counts and that severe stress reduces lymphocyte counts, especially CD4-positive T cells and CD8-positive T cells in septic patients requiring pediatric intensive care and ALC counts of patients decrease as well [34,35]. Although the most common viral agent in our study was RSV, lymphocyte counts were not statistically significant in the group infected with other viruses due to the limited number of patients and the presence of other viruses. Eosinophils make up only a small percentage of circulating leukocytes (1-3%) and potent pro-inflammatory cells [36,37]. In addition, eosinophils are involved in protective immunity, including antiviral responses. The pathophysiology of eosinopenia in COVID-19 is multifactorial, including direct eosinophil apoptosis caused by inhibition of eosinophil outflow from the bone marrow or by type 1 interferons released during acute infection [38]. Eosinopenia occurs in response to acute inflammation and sepsis. Studies have shown that lower eosinophil levels are associated with poor outcomes in critically ill patients [39]. In our study,

Table 2. Isolated respiratory viruses and oxygen delivery methods

RV type (n,%)	Simple O_2 mask (n)	Nonrebreathing mask (n)	HFNC oxygen therapy (n)	MV (n)
Adenovirus (1, 1.7%)	-	-	1	-
RSV (13, 22.4%)	2	1	9	1
Metapneumovirus (3, 5.3%)	-	-	1	2
Rhinovirus (3, 5.3%)	2	-	1	-
Influenza A (1, 1.7%)	-	1	-	-
Human parechovirus (1, 1.7%)	-	-	1	-
RSV + Adenovirus (1, 1.7%)	-	-	-	-
RSV + Bocavirus (2, 3.4%)	-	-	2	-
RSV + Rhinovirus (1, 1.7%)	-	-	-	1
Rhinovirus + Enterovirus (1, 1.7%)	-	-	1	-
Rhinovirus + Adenovirus (2, 3.4%)	-	-	2	-
Adenovirus + Bocavirus (1, 1.7%)	-	-	1	-
Parainfluenza + Metapneumovirus (1, 1.7%)	-	-	1	-
SARS-CoV-2 (27, 46.6%)	-	-	-	-

RV: Respiratory viruses, HFNC: High-flow nasal cannula, MV: Mechanical ventilation, RSV: Respiratory syncytial virus, SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2

eosinopenia was associated with severe disease in the group infected with other viruses. The chest X-ray appearance of LRTI due to other viruses was not specific. Chest X-ray was not performed in the COVID-19 patient group due to signs of URTI. In this study, almost all of the COVID-19- positive pediatric patients had mild upper airway infection symptoms, and they weren't hospitalized with COVID-19 infection. On the other hand, the COVID-19 receptor uses an angiotensin-converting enzyme (ACE). For input host cells, and angiotensin-converting enzyme-2 decreases with age. Pulmonary ACE concentration is still low in the children compared to that measured in adults. Children have a strong innate immune response due to trained immunity (secondary to frequent viral infections and live vaccines), possibly leading to early control of infection at the site of entry. However, young infants and children with underlying diseases may constitute high-risk groups and may need careful monitoring [40]. We think that respiratory failure may be more severe in infections caused by other respiratory tract viruses. Especially the youngest children (0-6 months) had higher RSV-related hospitalization rates than older children. A meta-analysis by Lansbury et al. [41] involving adults and children found that 3% of the patients hospitalized with COVID-19 were co-infected with another respiratory virus. This meta-analysis mainly detected RSV and influenza virus [41]. We attributed the absence of co-infection in our patients to the fact that the seasonal characteristics of influenza and other respiratory viruses were not observed during our study period and that isolation measures were implemented beginning from the early stages of the pandemic.

Study Limitations

This study has been performed on a limited number of patients due to a decrease in hospital admissions with the curfews in the early stages of the pandemic.

CONCLUSION

Respiratory viral infections are common in childhood and constitute important reasons for admission to the pediatric ED and hospitalization in pediatric intensive care, especially during the winter months. Interventions such as staying at home, complying with social distance, closing schools, travel restrictions; measures not specific to SARS-CoV-2 prevent transmission of other respiratory viruses. Detection of viral infections also plays an important role in the isolation and treatment of critically ill patients during the pandemic. Infections caused by other respiratory viruses in pediatric patients progressed with more severe clinical findings than COVID-19.

Ethics

Ethics Committee Approval: Ethical approval was received from the Ethics Committee of Manisa Celal Bayar University Medical Faculty of Health Sciences (decision no: 465, date: 22.07.2020).

Informed Consent: Since this study had a retrospective design, informed consent was not sought.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Concept: N.Z., A.B., S.A., S.Ş.B., S.Ak., Design: N.Z., A.B., Data Collection and/or Processing: N.Z., S.A., Analysis and/or Interpretation: N.Z., A.B., S.Ş.B., Literature Search: N.Z., A.B., Writing: N.Z.

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

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