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Original Article

A Comparison of Clinical Findings and Laboratory Test Results Between Hospitalized Children with COVID-19 and Influenza

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ABSTRACT

Aim: It can be challenging to distinguish between influenza and coronavirus disease-2019 (COVID-19) during the influenza season. Therefore, we aimed to compare the clinical symptoms, laboratory findings, and outcomes of these two diseases in children.

Materials and Methods: Thirty-two children with COVID-19 and 22 children with influenza who were hospitalized in our clinic were included in this study. The demographic, clinical, and laboratory findings of these patients were retrospectively reviewed.

Results: The median age of patients with influenza and COVID-19 was 1.4 and 15.3 years, respectively. Fever (77.3% vs 46.9%, p=0.02), nasal obstruction (27.3% vs 0%, p=0.003), wheezing (54.5% vs 3.1%, p<0.001), bilateral crackling sounds (63.6% vs 15.6%, p<0.001), prolonged expirium (63.6% vs 3.1%, p<0.001), tachycardia (36.4% vs 0%, p<0.001) and tachypnea (54.5% vs 0%, p<0.001) were significantly more frequent in those patients with influenza compared to COVID-19. Patients with influenza had significantly increased leucocyte count, lymphocyte count, and aminotransferase levels and lower albumin levels compared to those patients with COVID-19. In the influenza group, three patients needed intensive care, and one of them died. None of the patients with COVID-19 needed intensive care and there was no death in this group.

Conclusion: In hospitalized children, the clinical and laboratory findings were milder in those patients with COVID-19 compared to influenza.

Keywords: Children, coronavirus, COVID-19, influenza

Introduction

Influenza viruses and coronaviruses (CoVs) are common pathogens which cause respiratory disease in humans. CoVs cause intestinal and respiratory infections in humans and animals. Until 2019, six types [common CoVs, and severe ones such as severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) and middle east respiratory syndrome (MERS) CoV] which caused infection in humans were known. In December 2019, a new CoV, SARS-CoV-2, was identified in Wuhan, Hubei province of China (1-3). The disease caused by SARS-CoV-2 was officially named coronavirus disease-2019 (COVID-19) (1,2).

People of all ages have been affected in the global pandemic of COVID-19. Severe respiratory involvement requiring mechanical ventilation is more common in adults.

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Children are also affected by COVID-19, but their symptoms are milder than those of adults (4,5). During the COVID-19 pandemic, children experience symptoms that are observed in other viral infections such as fever, dry cough, rhinorrhea, sore throat, fatigue, diarrhea, and vomiting (1,4). Rarely, dyspnea or hypoxemia have also been described. Since routine blood tests and imaging have little value in viral infections, it is difficult to distinguish these symptoms from other viral diseases.

Influenza A and B viruses cause respiratory infections with cough and fever symptoms and affect many people each year. Symptoms of COVID-19 can be confused with respiratory diseases caused by influenza viruses (6-8).

The current polymerase chain reaction (PCR) tests for influenza and SARS-CoV-2 may be negative in some patients. However, recognizing these diseases at the time of admission to the hospital may enable healthcare professionals to take precautions quickly and determine the type of patient. For this reason, in this study, we aimed to determine any differences between these diseases by comparing the demographic, clinical, and laboratory findings of children with influenza and COVID-19. In the literature, there are a limited number of studies on children regarding this subject.

Materials and Methods

The study was carried out in accordance with the Helsinki Declaration. University of Health Sciences Turkey, İstanbul Haseki Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (date: 08/07/2020, number: 91-2020).

Patients

The study consisted of two patient groups: influenza and COVID-19. The medical records of 22 patients with influenza who were hospitalized in our hospital between January 1st, 2019, and February 1st, 2020, were retrospectively analyzed. Nineteen of these patients were Influenza A, and three were Influenza B. The patients with influenza infection were confirmed by a positive result for real-time reverse transcriptase-PCR (RT-PCR) multiplex via nasopharyngeal swab samples. Thirty-two patients who were hospitalized in our clinic between March 14th, 2020, and April 30th, 2020, were included in the COVID-19 group. The patients with COVID-19 were confirmed by a positive result for real-time RT-PCR via nasopharyngeal swab samples. Patients aged over 18 years were excluded. All patients had routine laboratory tests, including routine blood examination and biochemistry. No patient had had an influenza vaccine.

Sampling and Detection of Influenza and SARS-CoV-2 Viruses

Respiratory specimens were taken via Dacron-tipped swabs within 24 hours of admission. Influenza viruses were detected from nasopharyngeal specimens using RT-PCR multiplex testing (Qiagen, Germany). The kit also detects other human respiratory viral pathogens (human parainfluenza virus 1/2/3/4, respiratory syncytial virus A/B, human metapneumovirus, human CoV 229E/NL63/OC43, rhinovirus A/B/C, enterovirus, adenovirus, and human bocavirus 1/2/3/4) in addition to influenza A and B.

SARS CoV-2 was investigated using RT-PCR (Bioksen ArGe Teknik Co. Ltd, Turkey; Biospeedy®). If the first sample was negative for SARS-CoV-2 RNA at our clinic, a second specimen was sent for repeat-testing 24 hours after the first one. If the first or the second test was positive, the patient was accepted as a positive COVID-19 case.

Data Collection

Data regarding demographics, clinical and laboratory findings, treatments, and complications of the patients were recorded retrospectively from the medical records. The laboratory results of the patients on the day of admission were acquired.

Statistical Analysis

Statistical analysis was performed on SPSS 15.0 software. Numbers and percentages were used to express categorical variables; the median was used for numerical variables. The Mann-Whitney U test was used to compare median values between two groups, depending on the sample distribution. Categorical variables were compared using the chi-square test. $p<0.05$ was regarded as the alpha (α) significance level.

Results

The median age of those patients with influenza and COVID-19 was 1.4 and 15.3 years, respectively, which was significantly higher in the COVID-19 group. The COVID-19 group was comprised of 53.1% males (n=17), whereas the influenza group was comprised of 77.3% males (n=17), however this difference was not significant. Seven patients (31.8%) had underlying comorbidities in the influenza group, namely, four neurological, two cardiac, and one renal disease. Only two patients had comorbidity (6.2%) in the COVID-19 group, namely, one neurological and one renal disease. However, no significant difference was found between the two groups according to comorbidities (Table I).

At the time of admission, the mean duration of symptoms was three days (range: 1-8) in the influenza group and two days (range: 0-14) in the COVID-19 group, which was not statistically significant. Fever (77.3% vs 46.9%, p=0.02), nasal obstruction (27.3% vs 0%, p=0.003), and wheezing (54.5% vs 3.1%, p<0.001) were statistically more frequent in the influenza group than in the COVID-19 group. As for the findings of physical examinations, bilateral crackling sounds (63.6% vs 15.6%, p<0.001), prolonged expirium (63.6% vs 3.1%, p<0.001), tachycardia (36.4% vs 0%, p<0.001) and tachypnea (54.5% vs 0%, p<0.001) were also significantly more frequent in the influenza group than in the COVID-19 group (Table I).

Bronchodilator therapy, inhaled steroids and IV steroids were used at a higher rate in the influenza group than in the COVID-19 group. Those patients with influenza were hospitalized for a mean duration of 9 days (range: 4-28). During hospitalization, eight patients (36.4%) required nasal oxygen therapy and four patients (18.2%) needed high flow oxygen (HFO) therapy in the influenza group. Concerning the outcome, in the influenza group, three patients were admitted to the Pediatric Intensive Care Unit (PICU) for acute respiratory failure, and one of them died. No patient with COVID-19 required admission to the PICU (Table II).

A comparison of the blood tests showed that leucocyte count and lymphocyte count were significantly lower in those children with COVID-19 (5.5 vs 8.7x10^3/mm^3, p=0.02; 1.8 vs 2.7x10^3/mm^3, p=0.01, respectively) while hemoglobin and albumin were significantly lower in the influenza group (10.6 vs 13.3 g/dL, p<0.001; 39 vs 43 g/L, p<0.001).

Table I. Demographic and clinical characteristics of patients with COVID-19 and influenza infection

Variables	**Influenza (n=22)**	**COVID-19 (n=32)**	**p-value***
Age, years	1.4 (0.5;3.0) range: 0.2-4.5	15.3 (11.5;17.0) range: 0.1-17.1	**<0.001**
Male, n (%)	17 (77.3)	17 (53.1)	0.07
Days of symptoms	3 (1;7), (range: 1-8)	2 (1;3) (range: 0-14)	0.30
Fever, n (%)	17 (77.3)	15 (46.9)	**0.02**
Headache, n (%)	0	6 (18.7)	0.07
Myalgia, n (%)	1 (4.5)	1 (3.1)	1.0
Fatique, n (%)	0	2 (6.3)	0.5
Backache, n (%)	0	3 (9.4)	0.26
Artralgia, n (%)	0	1 (3.1)	1.0
Nazal obstruction, n (%)	6 (27.3)	0	**0.003**
Cough, n (%)	19 (86.4)	22 (68.8)	0.13
Wheezing, n (%)	12 (54.5)	1 (3.1)	**<0.001**
Shortness of breath, n (%)	10 (45.5)	8 (25)	0.12
Vomiting, n (%)	2 (9.1)	7 (21.9)	0.28
Diarrhea, n (%)	2 (9.1)	4 (12.5)	1.0
Abdominal pain, n (%)	0	2 (6.3)	0.5
Co-morbidity			0.07
Neurological	4 (18.2)	1 (3.1) 1 (3.1)	
Renal	1 (4.5)		
Congenital heart disease	2 (9.1)		
Crepitation, n (%)	14 (63.6)	5 (15.6)	**<0.001**
Prolonged expiration, n (%)	14 (63.6)	1 (3.1)	**<0.001**
Tachycardia, n (%)	8 (36.4)	0	**<0.001**
Tachypnea, n (%)	12 (54.5)	0	**<0.001**

*Mann-Whitney U test was performed for continuous data and $\chi 2$ testing was performed for the categorical data. Data are given as median (25^{th};75^{th} percentile) or n (%)
COVID-19: Coronavirus disease-2019

Table II. Treatment and outcome in patients with COVID-19 and influenza infection

Variables	Influenza (n=22)	COVID-19 (n=32)	p-value*
Antibiotic treatment, n (%)	20 (90.9)	32 (100)	0.16
Inhaler steroids, n (%)	9 (40.9)	1 (3.1)	**0.001**
IV steroids, n (%)	10 (45.5)	0	**<0.001**
Bronchodilators, n (%)	15 (68.2)	1 (3.1)	**<0.001**
Antiviral treatment, n (%)	15 (68.2)	20 (62.5)	0.23
Inotropic treatment, n (%)	1 (4.5)	0	0.40
Nasal O^2 treatment, n (%)	8 (36.4)	2 (6.3)	**0.01**
HFO, n (%)	4 (18.2)	0	**0.02**
Days of hospitalization	9 (7;11), range: 4-28	8 (6;9), range: 2-14	**0.04**
Outcome			**0.04**
PICU, n (%)	3 (13.6)	0	
Excitus, n (%)	1 (4.5)	0	

*Mann-Whitney U test was performed for continuous data and $\chi 2$ testing was performed for the categorical data. Data are given as median (25^{th};75^{th} percentile) or n (%)
COVID-19: Coronavirus disease-2019, HFO: High flow oxygen, PICU: Pediatric Intensive Care Unit

The median aspartate aminotransferase (AST) level was significantly higher in the influenza group than in the COVID-19 group (52 vs 24 IU/L, p<0.001). Urea and creatinine levels were significantly higher in those patients with COVID-19 than the influenza patients (17.9 vs 22.9 mg/dL, p=0.02; 0.26 vs 0.56 mg/dL p<0.001, respectively). The other markers had no significant difference between the two groups (Table III).

Discussion

In this study, we aimed to investigate the similarities and differences between COVID-19 and influenza in children. The differentiation between COVID-19 and influenza may be difficult in clinical practice, especially during the COVID-19 outbreak.

SARS-CoV-2 and influenza virus are transmitted similarly by respiratory droplets. In a study conducted in Hong Kong in January, the effects of interventions taken against COVID-19, such as social isolation, distancing, wearing masks, school closures, etc. on influenza transmission were investigated. As a result, the measures were shown to reduce influenza transmission as well as COVID-19 transmission significantly. That study showed that common factors are effective in the transmission of both diseases (9). Another study showed a decrease in influenza cases in China, Italy, and US, where the COVID-19 pandemic was seen as common and early. That result is attributed to the precautions taken against COVID-19 (10).

Unlike influenza, in children, the symptoms of COVID-19 are milder than in adults, and many children are asymptomatic (4). In our study, the most common symptoms in the COVID-19 group were fever, cough, vomiting, and headache, as in the medical literature (4). In a study by Qiu et

Table III. Laboratory findings of patients with COVID-19 and influenza infection

Variables	Influenza (n=22)	COVID-19 (n=32)	p-value*
Leucocytes, $\times 10^9$/L	8.7 (5.6;12.2)	5.5 (4.4;8.8)	**0.02**
Neutrophils, $\times 10^9$/L	4.2 (2.0;6.9)	2.9 (1.9;4.0)	0.19
Lymphocytes, $\times 10^9$/L	2.7 (1.5;4.5)	1.8 (1.3;2.3)	**0.01**
Hemoglobin, g/dL	10.6±1.6	13.3±1.5	**<0.001**
Platelets, $\times 10^9$/L	241 (130;381)	218 (195;262)	0.84
MPV, fL	9.9±1.06	10.2±0.90	0.17
PDW, fL	11.3 (10.2;12.4)	11.4 (10.1;13.0)	0.81
CRP, mg/L	8.9 (4.9;43.8)	3.8 (1.2;23.0)	0.12
Neutrophil/ lymphocyte	1.24 (0.42;1.89)	1.55 (1.01;2.43)	0.28
Platelet/ lymphocyte	78.7 (46.3;99.5)	124 (89.1;163)	**0.001**
SII	226 (119;599)	317 (212;621)	0.17
Albumin, g/L	39±4.3	43±2.6	**<0.001**
Urea, mg/dL	17.9 (12.1;23.2)	22.9 (17.9;26.6)	**0.02**
Creatinine, mg/L	0.26 (0.21;0.31)	0.56 (0.45;0.64)	**<0.001**
Uric acid, mg/dL	3.2 (2.5;4.5)	4.2 (3.5;5.0)	0.04
Sodium, mmol/L	138±4.4	137±3.3	0.74
Potassium, mmol/L	4.4±0.80	4.2±0.44	0.11
Chloride, mmol/L	105±4.5	103±3.2	0.08
Ca, mg/dL	8.8±2.2	9.5±0.42	0.18
AST, IU/L	52 (40;81)	24 (21;35)	**<0.001**
ALT, IU/L	21 (14;30)	14 (13;21)	0.054
Ph	7.38±0.06	7.39±0.06	0.69
pCO^2, mmHg	37±6.6	42.6±8.2	0.06
HCO^3, mmol/L	22.8±4.1	24.0±2.0	0.34

*Mann-Whitney U test was performed for continuous data. Data are given as mean ± standard deviation, median (25^{th}-75^{th} percentile)
COVID-19: Coronavirus disease-2019, MPV: Mean platelet volume, PDW: Platelet distribution width, CRP: C-reactive protein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase

al. (11), the most common symptoms were fever (36%) and dry cough. Other symptoms were sore throat, pharyngeal congestion, dyspnea or tachypnea, vomiting, and diarrhea (11). In our study, cough and fever were the two most common clinical symptoms of the influenza and COVID-19 groups. Headache was also a common symptom in children with COVID-19. Nasal obstruction was observed significantly more frequently in the influenza group than in the COVID-19 group. A study conducted in Wuhan reported that nasal obstruction was a common symptom in patients with both influenza and SARS-CoV-2 infection, but not common in patients with only SARS-CoV-2 infection (12). However, it was noted that the presence of this symptom alone would not be sufficient to rule out the possibility of COVID-19 (12). In a recent international study, the most common findings in children with influenza and COVID-19 were fever and cough (13). In that study, dyspnea, bronchiolitis, anosmia, and gastrointestinal system findings were observed more frequently in those children and adolescents with COVID-19 than in children with influenza. The authors reported that their findings are essential in distinguishing COVID-19 from influenza in children (13).

In a large-scale study from the US, children with COVID-19 and influenza did not differ in rates of hospitalization, PICU admission, or mechanical ventilator support (14). These results are not compatible with our study. In our study, the duration of hospitalization, PICU admission rates, requirements of nasal oxygen, and HFO support for those children with influenza were higher than for COVID-19 patients. However, in the aforementioned study, the median age of the patients with influenza was higher, in addition the number of patients with comorbidity was higher in the COVID-19 group when compared to our study.

In Zayed et al.'s (15) study, crackling sounds were statistically more frequent in an adult COVID-19 group than in an influenza group. In contrast to that study, we found that pulmonary auscultation findings were significantly more frequent in children with influenza. This difference may be attributed to the fact that involvement of the lungs is more common and the disease course is more severe in adult COVID-19 cases compared to children.

In our study, a higher rate of lymphopenia was observed in children with COVID-19. Lymphopenia is common in patients with COVID-19. We found leukocytosis, hypoalbuminemia, and elevated AST levels in children with influenza. These results were attributed to the more severe clinical course of the influenza group. In a study conducted in China, AST was found to be higher in children with influenza than in those with COVID-19 (16).

Li et al. (2) compared COVID-19 and influenza A patients under five years of age who had been hospitalized for pneumonia. They showed that the clinical course of COVID-19 patients was milder than that of influenza A patients (2). Similar to the results of their study, we observed that the clinical findings and prognosis for children with COVID-19 were milder than for children with influenza.

During the influenza season, influenza and COVID-19 co-infections have been reported in adults (6,17-19). This co-existence indicates the importance of investigating SARS-COV-2 in patients with respiratory findings even if the influenza virus has been detected. SARS-COV-2 RT-PCR can give false negative results. Therefore, suspicious cases need to be tested several times. Wu et al. (19) reported a senior case with COVID-19 and influenza A. After four negative nasopharyngeal swab specimens for SARS-CoV-2, the fifth sample taken from bronchoalveolar lavage fluid was found to be positive for SARS-CoV-2. In the beginning, when the patient's influenza A test was positive, his symptoms were attributed to influenza, and he was discharged to home. The patient was hospitalized again a few days later with signs of severe respiratory failure. False negative RT-PCR results make diagnoses rather challenging in the influenza season. However, the co-infection of these two infections must not be missed. In one study from Wuhan in China, throat swabs of 640 patients with influenza-like illnesses, of whom 142 were positive for an influenza test, from October 6th, 2019, to January 21st, 2020, were retrospectively investigated, and nine of these patients were found to be positive for COVID-19 (3).

Study Limitations

The first limitation of our study was the small sample size. Secondly, in our study, other viral agents could not be studied in the COVID-19 group as virology laboratories stopped other tests to focus on COVID-19 testing. An influenza antigen test was performed on eleven patients with COVID-19 and was found to be negative in all of them. In the months when the study was conducted, influenza was not common in our country.

Conclusion

In our study, children with COVID-19 had a milder clinical course than those with influenza. This result can be attributed to two factors; first, the median age was lower in our group of children with influenza. Influenza shows higher morbidity and mortality in younger ages. Second, the

children with COVID-19 had less comorbidity. Comorbidity of patients with COVID-19 leads to a worse prognosis. COVID-19 and influenza show similar symptoms in children. The role of symptoms in differentiating between these two diseases is rather limited.

Ethics

Ethics Committee Approval: Health Sciences Turkey, İstanbul Haseki Training and Research Hospital Clinical Research Ethics Committee approved the study protocol (date: 08/07/2020, number: 91-2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.A., A.A., N.S.D., Data Collection or Processing: G.A., N.S.D., Analysis or Interpretation: A.A., Literature Search: N.S.D., Writing: N.S.D.

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