İSTANBUL UNIVERSITY PRESS

Çocuk Dergisi - Journal of Child 2023;23(3):9-14
DOI: 10.26650/jchild.2023.1059843

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Similarities and Differences Between SARS-Cov-2 and Influenza Infection from Symptom to Diagnosis in Childhood

Çocuklarda SARS-Cov-2 ve İnfluenza Enfeksiyonunda Semptomdan Tanıya Benzerlikler ve Farklılıklar

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Citation/Atıf: Demirbuğa A, Hançerli Törün S, Kaba Ö, Gümüş S, Yıldız R, Uysalol M, Et al. Similarities and differences between SARS-Cov-2 and influenza infection from symptom to diagnosis in childhood. Çocuk Dergisi - Journal of Child 2023;23(3):9-14. https://doi.org/10.26650/jchild.2023.1059843

ABSTRACT

Objective: The COVID-19 pandemic and annual influenza epidemic are responsible for thousands of deaths globally. This study was conducted to identify epidemiological aspects while demonstrating features that distinguish between influenza infection and COVID-19 disease in terms of clinical manifestations, laboratory, and prevention.

Methods: The patients hospitalized with confirmed influenza between October 2009-May 2014 (n=344) and with confirmed COVID-19 between April 2020-June 2021 (n=251) were enrolled in this study.

Results: The age of the patients with influenza infection was statistically significantly younger than the patients with SARS-CoV-2 infection (mean age 6 ± 5.3 years versus 13.0 ± 5.3 years, p <0.001). Fever, cough, and myalgia were the more common symptoms of influenza (p< 0.001; p<0.001, p=0.02). It was found that in cases of COVID-19 (n=55/251, 21.9%), headache complaints were more common at admission. Lymphopenia (n=89/251 35.4%) in COVID-19 and CRP elevation detected in influenza cases (n=201/344 58.4%) were statistically significant (p=0.01/ p<0.001). The mean hospital stay was 6±5 days (1-90 days) in influenza and 1±4 (1-64 days) in COVID-19 (p< 0.001).

The radiological investigations were less necessary in children with COVID-19 because of the lower overall incidence of infected, symptomatic, and severe cases and the lower presence of cough and respiratory symptoms compared to adults.

Conclusions: As the clinical and epidemiological features of COVID-19 have many parallels with influenza, it is important to ensure optimal management of both respiratory diseases as we expect that co-circulation will continue. Clinical findings in children are not sufficient for a definitive diagnosis, so it should be supported by a viral diagnosis test.

Keywords: COVID-19, influenza, children

ÖZ

Amaç: Bu çalışmada, çocuklarda klinik bulgular, laboratuvar tanısı ve hastalığı önleme açısından influenza enfeksiyonu ve COVID-19 hastalığı arasında ayrım yapan özellikleri gösterirken epidemiyolojik verileri de gözden geçirmek ve sentezlemek amaçlanmıştır.

Yöntem: Bu çalışmaya Ekim 2009-Mayıs 2014 yılları arasında hastanede yatan doğrulanmış influenza enfeksiyonu olan (n: 344) ve Nisan 2020-Haziran 2021 tarihleri arasında doğrulanmış COVID-19 (n: 251) nedeniyle yatan hastalar dahil edilmiştir.

Bulgular: İnfluenza enfeksiyonu olanlarda yaş, SARS-CoV-2 enfeksiyonuna göre istatistiksel olarak anlamlı küçük saptandı (ort. yaş 6 ± 5.3/13.0 ± 5.3, p <0.001). Ateş, öksürük ve miyalji influenzada en sık semptomlardı (p<0.001; p<0.001, p=0.02). Baş ağrısı hastaneye başvuruda COVID-19 olgularında daha sık bulundu (n=55/251, 21.9%). COVID-19 da lenfopeni, influenza olgularında ise CRP yüksekliği istatistiksel olarak yüksek bulundu(p=0.01/p<0.001). Ortalama hastanede kalış süresi influenzada 6±5 gün (1-90), COVID-19'da 1±4 gün (1-64) bulundu (p<0.001).

Erişkinlere kıyasla öksürük ve solunum şikayetlerinin daha az olması, semptomatik ve ciddi vakaların da daha az olması sebebiyle radyolojik görüntülemelere COVID-19 hastalarında daha az ihtiyaç duyulmuştur.

Sonuç: COVID-19'un klinik ve epidemiyolojik bulguları influenza ile paralellik göstermekle birlikte, her iki etkenin de dolaşımda devam edeceği düşünülürse her iki hastalığında optimal yönetimini sağlamak önemlidir. Ani başlayan ateş, öksürük, miyalji gibi bulgular influenza açısından uyarıcı olsa da tanı için yeterli olmadığından viral tanı testlerinin kullanımı önemlidir.

Anahtar Kelimeler: COVID-19, İnfluenza, çocuklar

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Submitted/Başvuru: 18.01.2023 • **Revision Requested/Revizyon Talebi:** 09.03.2023 • **Last Revision Received/Son Revizyon:** 15.03.2023 • **Accepted/Kabul:** 15.03.2023 • **Published Online/Online Yayın:** 05.09.2023

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INTRODUCTION

At the beginning of the 21st century, human public health was marked by the emergence of new viruses and pandemics. The World Health Organization (WHO) declared an influenza A H1N1 pandemic (pH1N1) on 11 June 2009 and a coronavirus pandemic known as COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), on 11 March 2020.

Children and young adults were more susceptible to pH1N1 infection than older persons. Dawood and colleagues reported that a total of 40% of patients were between the ages of 10 and 18 years, and only 5% of patients were 51 years of age or older. Although influenza is common all over the world, the annual attack rate is estimated at 5-10% in adults and 10-20% in children, and the first target in the community is considered to be childhood.

Children younger than 5 years old –especially those younger than 2– are at higher risk of developing serious flu-related complications such as lower respiratory tract infection. In older children and adults, sudden onset of high fever, chills, headache, sore throat and muscle pain, malaise, loss of appetite, and dry cough develop.

Clinical symptoms of children with COVID-19 generally were less severe than adults with COVID-19. Dong et al. reported that 43.1% of the confirmed cases were asymptomatic, and 12.9% had mild disease. In the United States, 22% of the population is made up of infants, children, and adolescents aged <18 years, reported 2,572 (1.7%) of all COVID-19 cases were among children aged <18 years. Among those with available information, 73% of pediatric patients had symptoms of fever, cough, or shortness of breath compared with 93% of adults aged 18-64 years during the same period and nearly one-third of reported pediatric cases (813; 32%) occurred in children aged 15–17 years, followed by those in children aged 10–14 years (682; 27%).

Because of the importance of epidemiological information regarding the last two pandemics, this study aims to synthesize epidemiological aspects that distinguish between influenza infection and COVID-19 disease in terms of clinical manifestations, laboratory diagnosis, and prevention.

METHODS

Pediatric patients under the age of 18 who were hospitalized at the Istanbul University, Pediatric Infectious Disease Department from October 2009–May 2014 with confirmed influenza and patients with confirmed COVID-19 during April 2020-June to 2021 were enrolled in the study. The study was approved by the Public Health Agency, Türkiye Ministry of Health (Number: 2021-09-08T09_20_16), and Istanbul University Ethics Committee (Number: 2021/1642).

On admission, nasopharyngeal swabs were collected using Virocult (Medical Wire & Equipment, UK) and along with tracheal aspirates sent to Istanbul Microbiology and Clinical

Table 1: Symptoms and abnormal laboratory findings of patients

Symptom	İnfluenza n (%)	COVID n (%)	p
Fever	317 (92 .1)	111 (44.2)	**< 0.001**
Cough	300 (87.2)	111 (44.2)	**<0.001**
Vomiting	77 (22.3)	12 (4.7)	0.177
Respiratory distress	66 (19.1)	20 (7.9)	0.108
Myalgia	86 (25)	54 (21.5)	**0.02**
Headache	42 (12.2)	55 (21.9)	**0.032**
Runny nose	48 (13.9)	23 (9.1)	0.147
Diarrhea	27 (7.8)	24 (9.5)	0.276
Throat ache	18 (5.2)	50 (19.9)	0.192
Convulsion	11 (3.2)	2 (0.8)	0.846
Rash	4 (1.2)	3 (1.2)	0.886
Loss of taste	-	22 (8.8)	
Loss of smell	-	24 (9.5)	
Abnormal laboratory findings			
CRP >5 mg/dL	201 (58.4)	66 (26.2)	**<0.001**
Lymphopenia <1000mm^3	61 (17.7)	89 (35.4)	**0.001**
Neutropenia<1500mm^3	28 (8.1)	5 (2)	0.618
Creatinine kinase > 300 IU	17 (4.9)	15 (5.9)	0.501
AST >38 UI	15 (4.3)	22 (8.7)	0.442

Microbiology Department Laboratory within the same day. All samples were transferred to cryo-tubes upon receiving and stored in a -80 °C freezer if not tested on arrival date.

EZ1 Virus mini kit V2.0 (Catalog number: 955134, Qiagen, Germany) was used for total nucleic acid extraction. Real-time PCR-based, multiplex FTDR Respiratory Pathogens 21 kit (fast-track DIAGNOSTICS, Luxemburg) was used for the detection of influenza virus such as on the RotorGene Q platform (Qiagen, Germany).

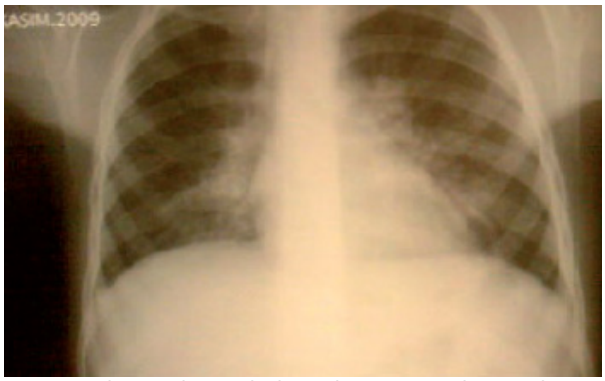

Figure 1: Chest radiograph shows hyperaerated parenchyma, interstitial infiltration in mid and lower zones of both lungs, and symmetric and central distribution.

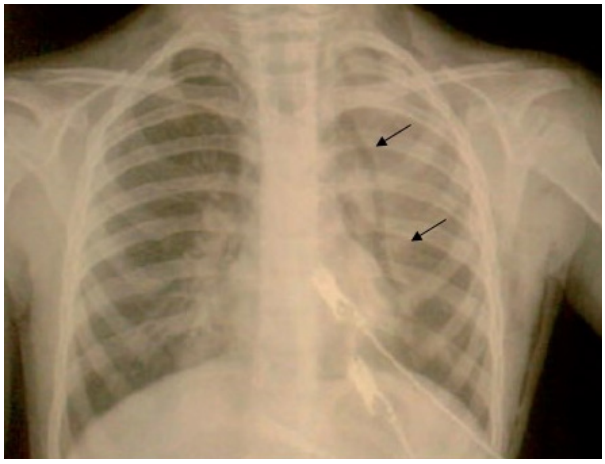

Figure 2: Pnömomediastinum

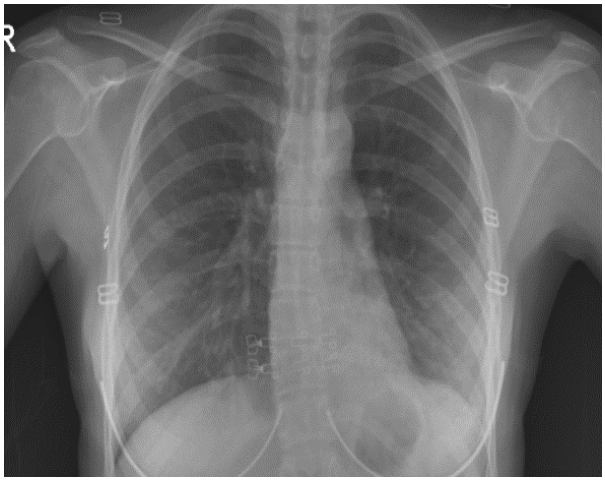

Figure 3: Ground-glass opacities with consolidation on chest radiograph

Extraction of viral RNA from nasopharyngeal swab samples for SARS-CoV-2 PCR testing was done manually with Bio-Speedy® Viral Nucleic Acid Isolation kit (Bioeksen the Co Ltd. R & D Technologies, Turkey). The SARS-CoV-2 PCR process was evaluated as positive by detecting the sample curve of SARS-CoV-2 ORF1ab Nucleocapsid gene regions by Rotor-Gene Q 5 Plex Real Time PCR application (Qiagen, Germany).

Five hundred ninety-five patients with positive SARS-CoV-2 and influenza virus nucleic acid test results were included. Demographic data of patients such as age and gender, admission symptoms, biochemical parameters, and radiological imaging findings were evaluated retrospectively.

Statistical Analysis

Clinical characteristics of patients and frequencies of complications were compared using the Chi-square test for categorical variables, and medians and distributions of continuous variables were compared using the Student T-test. All analyses were performed using IBM SPSS 21 (Statistical Package for Social Sciences, Chicago, IL, ABD) for Windows was used. P value $p < 0.05$ was considered significant.

RESULTS

During the study period, 251 patients with COVID-19 [127 male (50.6%), 124 female (49.4%); the mean age was 13.0 ± 5.3 years and 344 patients with influenza infection [206 male (60%), 137 female (40%) the mean age 6 ± 5.3 years] were enrolled in the study. The age of the patients followed up for influenza was younger than the patients followed up with COVID-19 ($p<0.001$).

Symptoms and abnormal laboratory findings of hospitalized patients are shown in Table 1. The mean hospital stay was 6±5 days (1-90 days) for influenza infection and 1 ±4 days (1-64 days) for COVID-19 ($p< 0.001$).

The 210 of 344 patients with influenza virus infection were evaluated with chest X-rays. Hyperaerated parenchyma (88/210, 41.9%), interstitial infiltration (84/210, 40%), atelectasis (18/210, %8.5), ground-glass opacities (15/210, 7.1%) and pneumothorax/pneumomediastinum (5/210, 2.3%) were imaging findings in these patients (Figure 1-2).

One hundred and five chest radiographs and 52 chest CT examinations of 251 children with COVID were evaluated. Ground-glass opacities with or without consolidation (24/52, 46.1%), feeding vessel sign (20/52, 38.5%), halo sign (12/52, 23,1%), pleural thickening (8/57, 14.0%), interlobular interstitial thickening (6/57, 10,5%) were detected by chest CT examination (Figure 3-6).

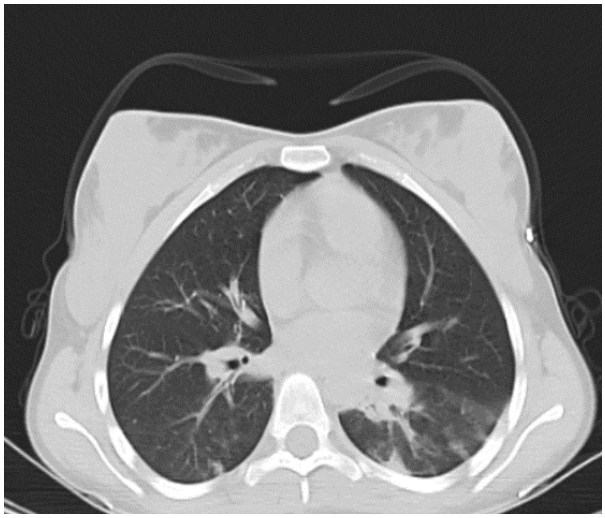

Figure 4: Ground-glass opacities with consolidation on chest CT

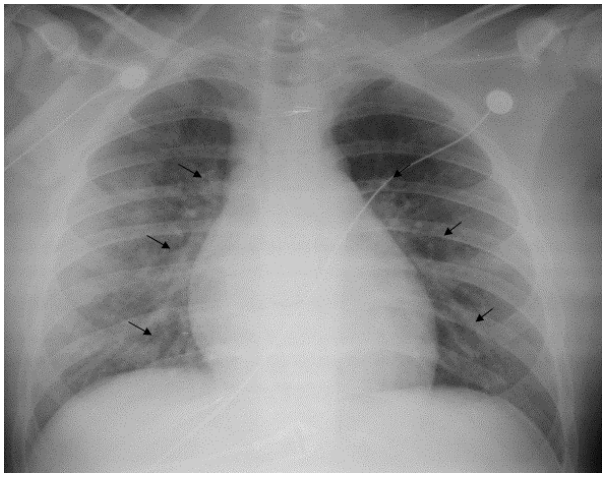

Figure 5: Ground glass density infiltrates in bilateral central and peripheral zones of both lungs on chest radiograph



Figure 6: Ground glass density infiltrates in bilateral central and peripheral zones of both lungs on chest CT

DISCUSSION

It was reported that in the first months of the pandemic, children were affected less by 2.2% in China, 1.2% in Italy, and 1.7% in the United States. With the widespread vaccination applied to adults in the second year of the pandemic, it has been determined that 15.5% of all cases (5.292.837/34.198.122) in the pediatric group where vaccination is not yet effective in the USA in September 2021. The reasons for the milder course of SARS-CoV-2 infection in children compared to adults have been investigated, but the reasons have not been clearly determined. Several theories have been discussed involving differences in the immune system, such as thymic function difference, cross-reactive immunity against other coronaviruses, as well as differences in the expression of the angiotensin-converting enzyme 2 (ACE2) receptor that the virus uses to enter the cell. In these studies, it was determined that the mean age of the patients was 7 years (2-13 y).

In our study, the mean age of the patients with COVID-19 was found to be 13.0 ± 5.3 years. This is significantly higher than the patients followed for influenza. It has been thought that this age difference may be caused by the fact that the influenza virus undergoes antigenic changes every year and the attack rate is higher in children, and younger children are more susceptible to this infection.

Although both SARS-CoV-2 and influenza virus are respiratory viruses, fever and cough were detected at high rates (92.1% versus 44.2%) as symptoms at admission to the hospital of patients with influenza infection.

Influenza illness is typically characterized by the abrupt onset of fever 39º to 40ºC and upper respiratory tract signs and symptoms (e.g., fever, chills, myalgia, headache, malaise, nonproductive cough). These symptoms of influenza can be predictive as a distinguishing symptom from other respiratory virus infections.

The major reported risk factors for pediatric COVID-19 cases were close contact with a SARS-COV-2 positive family member as a result of protective measures such as the closure of schools, and children being kept at home. Fever was detected in only 44% of children with COVID at admission to the hospital. Symptoms of pediatric patients with family contact were cough, vomiting-diarrhea, sore throat, convulsion, rash, and inability to taste and smell. In influenza-related upper respiratory tract disease, dry cough is most severe 3-4 days after the onset and continues for several weeks, even if other symptoms improve. In our case series, the cough was found to be a more frequent complaint at admission in influenza infection.

Myositis is classically occurring in children during the convalescent phase from febrile upper respiratory tract infections, most commonly after influenza B and can cause difficulty walking due to severe calf pain. Influenza B virus was detected in 83% of the children diagnosed with myositis in Poland during the influenza outbreaks in 2012/2013 and 2014/2015. In our study, myalgia was found to be a more

common symptom in patients with influenza virus infection than COVID-19, but it was not noticed in the creatinine kinase levels measured in laboratory tests.

There have been many reports of laboratory findings in pediatric COVID-19 patients. In a pediatric review, leukopenia and leukocytosis were present in 7.3% and 10.7% of cases, respectively. In another study, the most frequent abnormal laboratory findings were leukopenia/lymphopenia (28.9%, 95% CI = 19.5-39.2) and increased creatine kinase (20.1%, 95% CI = 1.3-49.9). It seems likely that COVID-19 has an effect in the direction of cytopenia, like other viral infections.

In the pediatric age group, radiological examinations were less necessary in children with COVID-19, due to the lower overall incidence of symptomatic and severe cases and the lower rate of cough-respiratory distress symptoms compared to adults. Foust et al. indicated that abnormal chest radiography findings in children with severe acute respiratory syndrome were unilateral and multifocal in one-third of cases with lower zone predominance. In our pediatric cohort, similar to previous studies, characteristic imaging findings were a peripheral and lower lobe dominant distribution pattern with multiple consolidative opacities.

It was reported that in children with viral pneumonia, 40 (49%) had alveolar changes on chest radiography. Although there are similar imaging features in chest X-rays taken due to both COVID-19 and influenza infection, hyperinflation (88/210, 41.9%) and ground-glass opacity and consolidation (84/210, 40%) were found to be higher in influenza. A different finding, pneumothorax, and pneumomediastinum, has been reported only in the influenza cases. Among all our patients, pneumothorax/pneumomediastinum was detected in 5 cases followed up due to influenza. With the increasing patient burden, the need for rapid diagnosis has made radiological methods, especially thorax computed tomography, frequently used in diagnosis. Chest radiography may be the first study that will be performed on pediatric patients with clinically suspected COVID-19. It makes more sense to consider computerized tomography in moderate or severe patients, to avoid exposure of this sensitive population to radiation.

The reopening of schools may cause an increase in the risk of some respiratory infections (such as influenza) in both children and adults in 2021-2022. In this period while the SARS-CoV-2 pandemic continues, it is essential to identify the infectious groups and to continue the isolation measures. However, COVID-19 has different epidemiologic characteristics from influenza. Influenza tends to be transmitted mainly from children to adults and therefore causes epidemics, and COVID-19 tends to be transmitted from adults to adults, or from adults to children. Although the sudden onset of symptoms such as high fever, cough, and myalgia is primarily a precursor of influenza infection and lymphopenia is primarily predictive of SARS-CoV-2 infection, these findings in children are not sufficient for a definitive diagnosis, so it should be supported by a viral diagnosis test.

Note: The editor in chief was not involved in the evaluation, peer-review and decision processes of the article, and these processes were carried out by the associate editors.

Ethics Committee Approval: This study was approved by the Public Health Agency, Türkiye Ministry of Health (Number: 2021-09-08T09_20_16), and Istanbul University Ethics Committee (Number: 2021/1642).

Informed Consent: Informed consent was not obtained as it was a retrospective study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- A.D., S.H.T., A.S.; Data Acquisition- S.M., Ö.K., S.G., R.Y.; Data Analysis/Interpretation- S.M., A.A., M.Ö., M.U.; Drafting Manuscript- A.D, S.H.T., A.S., Ö.K., S.M., S.G.; Critical Revision of Manuscript- R.Y., M.U., .A.A, M.Ö.; Final Approval and Accountability- A.D., S.H.T., A.S., R.Y., M.U. ,S.M., A.A., M.U., S.G., Ö.K.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support.

Not: Makalenin değerlendirme, hakem ve karar süreçlerinde baş editör yer almamış, ilgili yardımcı editörler tarafından süreçler yürütülmüştür.

Etik Komite Onayı: Etik komite onay Halk Sağlığı Kurumu, Türkiye Sağlık Bakanlığı (Sayı: 2021-09-08T09_20_16) ve İstanbul Üniversitesi Etik Kurulu'ndan (Sayı: 2021/1642) alınmıştır

Bilgilendirilmiş Onam: Retrospektif bir çalışma olduğu için bilgilendirilmiş onam alınmadı.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Çalışma Konsepti/Tasarım- A.D., S.H.T., A.S.; Veri Toplama- S.M., Ö.K., S.G., R.Y.; Veri Analizi/Yorumlama- S.M., A.A., M.Ö., M.U.; Yazı Taslağı- A..D, S.H.T., A.S., Ö.K., S.M., S.G.; İçeriğin Eleştirel İncelemesi- R.Y., M.U., .A.A, M.Ö.; Son Onay ve Sorumluluk- A.D., S.H.T., A.S., R.Y., M.U. ,S.M., A.A., M.U., S.G., Ö.K.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

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