Research Article / Araştırma Makalesi

COVID-19 Pandemisi Öncesi Kanserli Çocukların Akut Solunum Yolu Viral Enfeksiyonlarının Epidemiyolojisi

Epidemiology of Acute Respiratory Viral Infections of Children with Cancer Before the COVID-19 Pandemic

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Abstract: Children with cancer became a major high-risk group during the COVID-19 pandemic. It has become difficult for patients to reach practical and safe care and treatment all over the world. The late diagnosis of many childhood cancers was driven by limited access to healthcare due to the pandemic and fears of COVID-19 that prevented parents from making an early medical assessment of their child's symptoms. Acute respiratory diseases are an important cause of morbidity and mortality in children with cancer, regardless of the COVID-19 pandemic and were seen less frequently in the pandemic during the lockdown and distant education period in comparison to the time before the pandemic in children with cancer. Acute respiratory viral infections frequently cause febrile neutropenia attacks in children under five years of age. A three year retrospective cross-sectional study was performed in a tertiary care university hospital. Children with cancer who presented to the Department of Pediatric Hematology and Oncology with the diagnosis of acute respiratory viral infection were included in the study if they had available results of multiplex polymerase chain reaction (PCR) of nasopharyngeal aspirate samples. The qualitative detection of 18 respiratory viruses and four bacterias were detected by the real-time multiplex polymerase chain reaction. Sixty-six patients with 93 acute respiratory viral infection were included in this study. Seventy of 93 (75%) samples were positive for at least one pathogen. The most common three viruses were HRV, Influenza H1N1, and Influenza H1N3, respectively. Other than COVID-19, the risk of severe acute respiratory viral infections are always important in children with cancer and during the pandemic, hygiene measures and social restrictions caused a reduction in the number of acute respiratory viral infection. This study is critical because it shows the distribution of agents in children with cancer who had acute viral upper respiratory tract infections in the near term before the pandemic.
Keywords: COVID-19, Childhood Cancers, Febrile Neutropenia, Respiratory İnfections

Özet: COVID-19 pandemisi sırasında kanserli çocuklar yüksek riskli gruplardan biri oldular. Hastaların kolay vegüvenli hasta bakımına, daha önemlisi tedaviye ulaşması tüm dünyada zorlaştı. Pandemi nedeniyle sağlık hizmetlerine sınırlı erişim ve ebeveynlerin çocuklarındaki semptomların erken tıbbi değerlendirilmesini engelleyen COVID-19 korkusu birçok çocukluk çağı kanserinin geç teşhisine neden oldu. Akut solunum yolu enfeksiyonları, COVID-19 pandemisinden bağımsız olarak kanserli çocuklarda önemli bir hastalık ve ölüm nedenidir. Bu enfeksiyonlar, pandemi öncesine göre pandemi döneminde sokağa çıkma yasağı ve uzaktan eğitim nedeniyle daha az görüldü. Akut solunum yolu viral enfeksiyonları beş yaşın altındaki çocuklarda sıklıkla febril nötropeni ataklarına neden olur. Üç yıllık retrospektif kesitsel nitelikte olan bu çalışma üçüncü basamak bir üniversite hastanesinde yapıldı. Çocuk Hematoloji ve Onkoloji Bilim Dalı'nda akut solunum yolu viral enfeksiyonu tanısı alan kanserli çocuklar, nazofaringeal aspirat örneklerinde multipleks polimeraz zincir reaksiyonu (PCR) ile etken saptandıysa çalışmaya dahil edildi. Multipleks polimeraz zincir reaksiyonu ile on sekiz solunum virüsünün ve dört bakterinin kalitatif tespiti için test çalışıldı. Akut viral üst solunum yolu atağı geçiren 66 hasta bu çalışma dahil edildi. Doksan üç örneğin 70'i (%75) en az bir patojen için pozitifti. En yaygın üç virüs sırasıyla HRV, Influenza H1N1 ve Influenza H1N3'dü. COVID-19 dışında, kanserli çocuklarda ciddi akut solunum yolu viral enfeksiyonu riski her zaman önemlidir ve pandemi sırasında hijyen önlemleri ve sosyal kısıtlamalar, akut solunum yolu viral enfeksiyonu sayısında azalmaya neden olmuştur. Bu çalışma pandemi öncesi yakın dönemin akut viral üst solunum yolu enfeksiyonu geçiren kanserli çocuklarda etken dağılımı göstermesi nedeniyle önemlidir.
Anahtar Kelimeler: COVID-19, Çocukluk Çağı Kanserleri, Febril Nötropeni, Solunum Yolu Enfeksiyon

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1. Introduction

The first case of COVID-19 was detected in Turkey when the World Health Organisation (WHO) proclaimed a COVID-19 pandemic on March 11, 2020. Children with cancer are among the high risk groups for COVID-19 because of immunosuppression treatment due to anti-cancer therapy. The current outbreak of COVID-19 caused an unheard-of global threat to the practical and safe care for children with cancer. Moreover, the late diagnosis of many childhood cancers were due to limited access to healthcare due to the pandemic and fear of infection which prevented parents from seeking early medical evaluation of symptoms in their child (1-3).

Febrile neutropenia (FN) is one of the most common acute side effects of pediatric cancer treatment and the mortality due to FN has dramatically declined due to the widespread use of broad-spectrum antibiotics. Acute respiratory viral infections (ARVIs) frequently cause FN attacks in children under five years of age. Even if cancer patients are not neutropenic, due to the ongoing immunosuppression, infections are likely to be severe (4-6). Acute respiratory diseases are an important cause of morbidity and mortality in children with cancer, regardless of the COVID-19 pandemic. The non-COVID-19 ARVIs were seen less frequently in the pandemic during the lockdown and distant education period in comparison to the time before the pandemic in children with cancer (7,8).

This study aimed to evaluate the distribution of respiratory viruses which caused ARVI in children with cancer before the COVID-19 pandemic.

2. Materials and Method

A three year (January 2019 to February 2020) retrospective cross-sectional study was performed in a tertiary care university hospital in Turkey after obtaining approval from the local ethics committee. Children with cancer who presented to the Department of Pediatric Hematology and Oncology with the diagnosis of acute respiratory viral infection were included in the study if they had available results of multiplex polymerase chain reaction (PCR) of nasopharyngeal aspirate samples. The clinical records were obtained from the medical records.

Acute respiratory viral infection (ARVI) was described as the presence of cough with fever (fever; at least one episode of fever, measured or reported, with axillary temperature> 38°C (based on one measurement) or 37.5°C (based on two measurements with a 1-hour interval) for less than two weeks with at least one or more of the following signs or symptoms: coryza, cough, sore throat, and/or gastrointestinal symptoms.

Respiratory samples taken from each nasopharyngeal aspirate and one from the nasopharyngeal swab were collected from all patients enrolled in the study. Within an utmost period of 4 hours after collection, the specimens were blended and annexed to a ringer lactate solution to a total of 4 mL. After homogenization, the specimens (approximately 1 mL) were allocated into aliquots in cryotubes, previously identified and stored in liquid nitrogen, and stored at -80 ◦C. In the Medical Microbiology Laboratory, the DNA, and total RNA nucleic acids were extracted from samples using the extraction Kit.

The sensitivity and specificity were followed up by standard quality control for molecular diagnostics. The qualitative detection of 18 respiratory viruses (adenovirus (ADV), coronavirus (NL63, 229E, OC43, and HKU1), human metapneumovirus (hMPV A/B), human rhinovirus (HRV), enterovirus; influenza A (H1, H1N1, and H3), influenza B, Middle East Respiratory Syndrome–related Coronavirus (MERS-Cov), parainfluenza (PIV1, 2, 3, and 4), respiratory syncytial virus (RSV A/B), and four bacterias (*Bordatella Parapertussis, Bordatella Pertussis,Chlamydia Pneumoniae, and Mycoplasma Pneumoniae)* were detected by the real-time multiplex polymerase chain reaction.

Data were analysed using the Statistical Package for the Social Sciences (SPSS)

program, version 17.0 (SPSS Inc., Chicago, IL, USA). Non-parametric descriptive statistics were calculated. A p-value<0.05 was considered significant. Approval for the study was obtained by Eskisehir Osmangazi University Non-interventional Clinical Research Ethics Committee.

3. Results

Sixty-six patients (44 males, M: F= 2:1) with ARVI were included in this study. Forty-one (62%) of them were diagnosed with hematologic malignancy (leukemia or lymphoma), 14 (21%) of them were with solid tumors and 11 (17%) of them were with bone marrow failure (isolated neutropenia or pancytopenia). The most common complaints in 93 episodes of 66 patients were cough, coryza, and fever. Seventeen applications were only due to fever. Patients were admitted to the hospital with a mean of 1.8 ± 1.4 days (range 0-6 days) following the onset of fever.

Seventy of 93 (75%) samples were positive for at least one pathogen. The most common three viruses were HRV, Influenza H1N1, and Influenza H1N3, respectively (Table 1). The coexistence of two pathogens were detected in 15 (16%) samples (Table 2). A bacterial agent was not detected in any of the samples. The mean age of patients was 5.3 ± 4.3 years (range, 6 months to 17.5 years).

Adenovirus (ADV), Coronavirus (Cor-NL63, Cor-229E, Cor-OC43, Cor-HKU1), Human metapneumovirus (hMPV A/B), Human rhinovirus (HRV), Enterovirus; Influenza A (H1, H1N1, and H3), Influenza B, Middle East Respiratory Syndrome–related Coronavirus (MERS-Cov), Parainfluenza (PIV1, 2, 3, and 4), Respiratory syncytial virus (RSV A/B). months to 17.5 years). The distribution of positive tests by season were 46 (66%) in winter, 12 (17%) in spring, 1 (1%) in summer, and 11 (16%) in autumn.

As an antiviral agent, oseltamivir was utilized in 42 of the 93 (45%) episodes of ARVI. In 28 of 42 (66%) episodes, influenza was the causative agent (influenza A H1N1 n:17, H3 n:6, and influenza B n:5). Also, four cases with a negative nasale sample had used oseltamivir. Seventeen (18%) cases were supported with the replacement of intravenous immunoglobulin (IVIg). Pulmonary findings as increased respiratuar rate, breath sounds louder than normal, crackles, and other anormalities in physical examination were detected in 35 (38%) of the 93 episodes. Oxygen therapy, admission to an intensive care unit, and need for mechanical ventilation were not required in any of the episodes.

4. Discussion

The pandemic of COVID-19 is one of the most critical global challenges faced in the last months. However, other than COVID-19, the risk of severe ARVIs are always important in children with cancer (10, 11). In this study, we evaluated the distribution of respiratory viruses which caused ARVI in children with cancer before the COVID-19 pandemic. Patients with fever were admitted to the hospital within an average of 48 hours. The most common symptoms (cough, coryza and fever) of patients were similar to that observed in the previous studies (12,13).

In Marcone et al study (14), viral diagnosis was achieved in 361 (83.2%) hospitalized patients and 115 (61.8%) outpatients. Aydin Koker et al (15) reported that they detected an agent for acute viral respiratory infections in 219/560 (39.1%). Also, coinfection with two viruses was detected in 45/219 (20.5%) of episodes (8). In another study, coinfections were reported 36 out of 326 (5.5%) severe acute lower respiratory tract infections (16). In our study, we obtained 70 out of 93 (75%) samples which were positive for at least one pathogen and the coexistence of two pathogens were detected in 15 (16%) samples. The ARVIs are frequent in cold seasons; autumn and winter (13). Similar to previous studies, the most common test positivity was detected during the winter months in this study.

Table 1. Distribution of pathogens identified by moleculer tests

Pathogens	Cases with single detection	Cases with co-detection	Total number of cases (%)
ADV	4	-	4 (5)
Cor-NL63	1	1	2 (3)
Cor-229E	1	-	1 (1)
Cor-OC43	3	-	3 (4)
Cor-HKU1	2	-	2 (3)
HMPV A/B	4	-	4 (5)
HRV	21	3	24 (27)
Entero V.5	-	-	-
InfA-H1	19	1	20 (23)
InfA-H1N1	-	1	1 (1)
InfA-H3	6	1	7 (8)
InfB	5	-	5 (6)
MERS-Cov	-	-	-
PIV-1	1	-	1 (1)
PIV-2	-	-	-
PIV-3	-	1	1 (1)
PIV-4	1	2	3 (4)
RSV-A/B	2	5	7 (8)

Adenovirus (ADV), Coronavirus (Cor-NL63, Cor-229E, Cor-OC43, Cor-HKU1), Human metapneumovirus (hMPV A/B), Human rhinovirus (HRV), Enterovirus; Influenza A (H1, H1N1, and H3), Influenza B, Middle East Respiratory Syndrome–related Coronavirus (MERS-Cov), Parainfluenza (PIV1, 2, 3, and 4), Respiratory syncytial virus (RSV A/B).

Table 2. Combination of identified combinations among co-detection of all respiratory pathogens

	ADV	Cor-NL63	Cor-229E	Cor-OC43	Cor-HKU1	HMPV A/B	HRV	Entero V.	InfA H1	InfA H1N1	InfA H3	InfB	MERS-Cov	PIV1	PIV2	PIV3	PIV4	RSV A/B
ADV	NA	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
Cor-NL63	-	NA	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-
Cor-229E	-	-	NA	-	-	-	1	-	-	-	1	-	-	-	-	-	-	-
Cor-OC43	-	-	-	NA	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cor-HKU1	-	-	-	-	NA	-	-	-	-	-	-	-	-	-	-	-	-	-
HMPV A/B	-	-	-	-	-	NA	-	-	-	-	-	-	-	-	-	-	-	-
HRV	-	-	-	-	-		NA	-	-	-	-	-	-	-	-	-	-	-
Entero V.	-	-	-	-	-	-	-	NA	-	-	-	-	-	-	-	-	-	-
InfA-H1	-	-	-	-	-	-	1	-	NA		-	-	-	-	-	-	-	-
InfA-H1N1	-	-	-	-	-	-	1	-	-	NA	-	-	-	-	-	-	-	-
InfA-H3	-	-	-	-	-	-	-	-	-	-	NA	-	-	-	-	-	-	-
InfB	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-	-	-	-
MERS-Cov	-	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-	-	-
PIV-1	-	-	-	-	-	-	-	-	-	-				NA	-	-	-	-
PIV-2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-
PIV-3	-	-	-	-	-		1	-	-	-	-	-	-	-	-	NA	-	-
PIV-4	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	NA	
RSV-A/B	-	-	-	1	-	1	-	-	1	1	-	1	-	-	-	-	-	NA

Adenovirus (ADV), Coronavirus (Cor-NL63, Cor-229E, Cor-OC43, Cor-HKU1), Human metapneumovirus (hMPV A/B), Human rhinovirus (HRV), Enterovirus; Influenza A (H1, H1N1, and H3), Influenza B, Middle East Respiratory Syndrome–related Coronavirus (MERS-Cov), Parainfluenza (PIV1, 2, 3, and 4), Respiratory syncytial virus (RSV A/B).

The three viruses most frequently detected in children with ARVI were unsorted HRV, RSV, and influenza subtypes (14-16). In this study, we most frequently detected HRV, influenza subtypes, and RSV, respectively.

The seasonal prevalence of influenza infections in children with cancer, closely parallels the community wide prevalence. However, influenza infection remains a significant cause of morbidity and mortality in these patients. As a well known precept, respiratory infection management occurs with providing the patient with supportive care and utilizing antiviral therapy to whose in need. Neuraminidase inhibitors are recommended as a first-line medication for the treatment or prophylaxis of influenza infections in the immunocompromised population(17-19). Also, as an adjuvant treatment, intravenous immunoglobulin (IVIG) are used to support the immune system in some severely ill patients (20). In this study, 45% of the cases were given oseltamivir, while 18% were given IVIG.

In Marcone et al. (14) study, the clinical findings were significantly serious in the inpatients than the outpatients. Aydin Koker et al. (15) reported that the pulmonary findings were seen in 28% of the patients and patients with acute leukemia were more vulnerable to pneumonia than children with solid tumors. In this study, pulmonary findings were detected in 38% of the cases. This may be related to the higher number of patients with acute leukemia compared to other diagnoses. But we are happy that oxygen therapy, admission to an intensive care unit, and need for mechanical ventilation were not required in any of the episodes.

In summary, we have seen a decrease in ARVI due to viral factors other than COVID-19 in patients during the pandemic. In this period, hygiene measures and social restrictions caused a reduction in the number of ARVI. Before the pandemic, we found that influenza subtypes and HRV were the most commonly detected viruses in children with cancer similar to the healthy population. The lack of a need for intensive care and the absence of patient loss was pleasing. This study is critical because it shows the distribution of agents in children with cancer who had acute viral upper respiratory tract infections in the near term before the pandemic.

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Ethics

Ethics Committee Approval: The study was approved by Eskisehir Osmangazi University Non-interventional Clinical Research Ethical Committee (Decision no: 04, Date: 14.07.2020).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis**.**

Author Contributions:

Idea/concept: E.T., Z.C.Ö., Ö.K., Design: E.T., T.U., G.D., Ö.B. Data Collection: U.T, B.A. Data Processing: E.T., U.T. Analysis/Comment: T.U., G.D., Ö.B, Literature research/review: E.T., Ö.K. Writing: E.T., B.A.

All authors discussed the results and contributed to the final manuscript.

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