Solunum Yolu Virüs Enfeksiyonu Nedeni ile Hastaneye Yatan Çocukların Klinik ve Epidemiyolojik Olarak Değerlendirilmesi

Clinical and Epidemiological Evaluation of Hospitalized Children With Respiratory Virus Infections

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ÖZET

Giriş: Solunum yolu virüsü enfeksiyonları, özellikle bebeklerde ve küçük çocuklarda hastaneye yatışların en sık nedenidir. Multipleks PCR ile solunum yolu virüslerinin saptanması hasta yönetimini kolaylaştırmış ve yeni virüslerin tanımlanmasına izin vermiştir. Bu çalışmanın amacı, hastanede yatan çocuklardaki viral ajanların insidans ve epidemiyolojik özelliklerini belirlemek ve tek virüs ile çoklu virüs enfeksiyonlarının klinik bulgularını karşılaştırmaktır.

Hastalar ve Metod: Solunum yolu enfeksiyonu nedeni ile hastanede yatan çocukların verileri geriye dönük olarak araştırıldı. Hastaların demografik özellikleri, başvurdukları ay / mevsim, klinik ve laboratuvar bulguları, yatış süresi, nazofaringeal sürüntü örnekleri incelendi. Solunum yolu virüsleri için Multiplex PCR kullanıldı. Tek virüs enfeksiyonu olan hastalar ile çoklu virüs enfeksiyonu olan hastalar karşılaştırıldı.

Bulgular: Eylül 2014 - Nisan 2016 tarihleri arasında hastanede yatan çocuklardan alınan toplam 114 nazal sürüntü örneği multipleks PCR ile değerlendirildi. Hastaların 94'ünde (% 83.3) en az bir solunum patojeni tespit edildi. Hastaların 29'unda (% 30.9) koenfeksiyon tespit edildi. RSV (% 28.7) en sık görülen patojendi ve RSV-Rhinovirus en sık görülen birliktelikti (% 31, 9/29). Birden fazla virüs enfeksiyonu sıklıkla daha küçük çocuklarda saptandı ($p = 0.022$). İki grup arasında cinsiyet, erken doğum, mekanik ventilasyon öyküsü, kronik hastalık varlığı, ailede sigara içimi öyküsü, ailede üst solunum yolu enfeksiyonu varlığı, hastalığın ciddiyeti (solunum skorlaması, oksijen hastanede kalış süresi, yoğun bakım ihtiyacı) ve laboratuvar bulguları açısından anlamlı fark saptanmadı. ($p> 0.05$).

Sonuç: Hastaların% 83.3'ünde en az bir solunum yolu virüsü ve hastaların üçte birinde birden fazla solunum yolu virusu tespit edildi. RSV hem tek hem de çoklu virüs enfeksiyonlarında en sık rastlanan patojendi. Hastalığın şiddeti açısından tek virüs ve çoklu virüs enfeksiyonları arasında bir ilişki saptanmadı.

Anahtar Kelimeler: Akut solunum yolu enfeksiyonları, solunum yolu virüsleri, çocuk, PCR

ABSTRACT

Introduction: Respiratory virus infections are the most common cause of hospitalization particularly in infants and young children. Detection of the respiratory viruses with multiplex PCR has recently facilitated patient management and allowed for the identification of new viruses. The aim of this study was to determine the incidence, epidemiology of viral agents in hospitalized children and to compare the clinical manifestations of single virus versus multiple virus infections.

Material and Method: Data of hospitalized children with respiratory infections were retrospectively investigated. Demographic characteristics of the patients, month/season they admitted, clinical and laboratory findings, duration of hospitalization, nasopharyngeal swab samples were investigated. Multiplex PCR was used for respiratory viruses. Patients with a single virus infection and those with multiple virus were also compared.

Results: A total of 114 nasal swab samples from hospitalized children during September 2014-April 2016 were evaluated by multiplex PCR. At least one respiratory pathogen was detected in 94 (83.3%) of the patients. Coinfections were identified in 29 (30.9%) of the patients. RSV (28.7%) was the most common single pathogen and RSV-Rhinovirus was the most common coexistence (31%, 9/29). Multiple virus infections frequently detected in younger children (p = 0.022). There was no difference between children with multiple versus single virus infections in terms of gender, premature birth, mechanical ventilation history, presence of chronic illness, family history of smoking, upper respiratory tract infection in the family, severity of disease (respiratory scoring, oxygen requirement), hospitalization stay, need for hospitalization in the intensive care unit and laboratory findings (p> 0.05).

Conclusion: In 83.3% of the patients, at least one respiratory virus and in the one third of the patients more than one respiratory virüs was detected. RSV was the most common pathogen in both single and multiple virus infections. There was no relationship between the single and multiple virus infections for the disease severity.

Keywords: Acute respiratory tract infections, respiratory tract viruses, children, PCR

1.1. Introduction

Respiratory infections are the most common infectious diseases worldwide and cause significant morbidity and mortality (1). Viruses are the most common cause of respiratory infections in childhood. Respiratory tract viruses can cause very different clinical manifestations, ranging from asymptomatic upper respiratory tract infections to severe infections, which can result in multi-organ failure, although they often cause self-limiting, milder infections (1).Although viral respiratory infections affect all age groups, they most commonly cause recurrent infections throughout the year in younger age groups. With the new molecular methods such as polymerase chain reaction (PCR) developed in recent years, many viruses in etiology can be displayed quickly and easily. Respiratory syncytial virus (RSV), rhinovirus (RV), influenzae, influenza B, coronaviruses (CoV), parainfluenza viruses (PIV), adenoviruses (AV) and also Human metapneumovirus (HMPV) and human bovavirus (HBoV) which have been recently identified as causative agents, are the most common viruses (2,3).

The most common agents responsible for hospital admission in young age groups are RSV and Influenza viruses. RV that are believed to cause mild infections in recent years but cause infection in

both upper and lower respiratory tracts, bronchiolitis and pneumonia are the most common cause of respiratory tract infections in children worldwide, especially in the increasing proportion of patients under 5 years of age (4,5,6).

In this study, clinical features of the patients who were admitted due to lower respiratory tract infection between 2014 and 2016 and the epidemiology of respiratory tract viruses detected nasopharyngeal swab specimens were investigated. Clinical characteristics between children with multiple versus single virus infections were also compared.

2.1. Material-Method

We retrospectively evaluated the data of 114 children between the ages of 0 and 18 who were admitted to the Department of Pediatric Infectious Diseases of Ege University School of Medicine between September 2014 and April 2016 with a diagnosis of lower respiratory tract infections and a sample of nasopharyngeal swab was taken considering viral respiratory tract infection. Demographic characteristics of the patients, month/season they admitted, clinical and laboratory findings, duration of hospitalization, nasopharyngeal swab samples were investigated. The samples were sent to Clinical Virology Laboratory of Medical Microbiology Department of Ege University. Multiplex PCR was used for Influenza A and B, RSV, Rhinovirus, Adenovirus, Parainfluenza type 1-3, HMPV, Bocavirus.

3.1. Statistical Analysis

All analyzes were performed using the SPSS17.0 package program. The normal distribution suitability of the numerical variables was tested with the Shapiro-Wilk Test. Categorical variables were described using frequency and percentage, numerical variables are described using median and minimum-maximum values. Chi-square test (Fisher Exact Test / Exact Test) was used to analyze the relationship between the two categorical variables. Two independent sample medians were compared with the Mann Whitney U test. $P < 0.05$ was considered statistically significant.

4.1. Results

A total of 114 children between the ages of 0 and 18 who admitted to the Department of Pediatric Infectious Diseases of Ege University with a diagnosis of lower respiratory tract infection between September 2014 and April 2016 and a sample of nasopharyngeal swab was sent for viral agent identification were included in the study. Forty one (35.9%) of the cases were and 73 (64.1%) were

male. Median age was 13.4 months (33 days-144 months); There were 54 (46.9%) patients between 0-6 months, 41 (35.6%) between 6-24 months, 17 (14.7%) between 2-5 years and 2 patients (2.6%) above 5 years. 83.3% of the cases were found to be under 2 years of age (Fig 1). Sixty three (54.7%) patients in the 2014-2015 season and 51 (45.3%) patients in the 2015-2016 season were hospitalized. Mean hospital stay was 6 (2-26) days. Fifty four (47%) of the patients were admitted to hospital in February and March. At least one respiratory pathogen was detected by polymerase chain reaction in 94 (83.3%) of the patients. Of these, 65 (69.1%) were found to have single pathogen while 29 (30.9%) were multiple. It has been observed that RSV is most often found to be positive in January-February-March (Fig 2). The distribution of viruses between 2014 and 2016 were as ; Twenty-seven (28.7%) patients had RSV (RSVA 17, 18% -RSV B, 10, 10.7%), 21 (22.3%) Rhinovirus, 6 (6.4%) Bocavirus, 5 (5.3%) Influenzae, 3 (3.2%) HMPV, 2 (2.1%) adenovirus and 1 (%1) parainfluenza type 1-3. RSV and Rhinovirus was the most common coexistence (9/29, 31%).

In both seasons, 98% of cases (n = 112) were not affected by influenza vaccination and there were no significant differences between cases with and without causative factors in terms of premature birth, mechanical ventilation and chronic disease history (p> 0.05).

When single and multiple virus infections are compared; There was a significant age difference between the two groups. Median age was 10 months in the single virus infections while it was 5 months in multiple virus infections (p = 0.022). When both groups were compared for the following reasons; gender, premature birth, mechanical ventilation history, presence of chronic illness, family history of smoking, upper respiratory tract infection in the family, severity of disease (respiratory scoring, oxygen requirement), hospitalization stay, need for hospitalization in the intensive care unit, There was no significant difference between the groups (p> 0.05). When laboratory results are evaluated; White blood cell, C-reactive protein, blood sodium level were not different between the two groups (p> 0.05) (Table 1).

5.1. Discussion

Respiratory viruses are the most common cause of respiratory infections in children (7). A wide spectrum of clinical manifestations can ocur due to respiratory viruses ranging from mild upper

respiratory tract infections to serious illnesses with multi-organ failure (1). In developed countries pediatric mortality due to respiratory viruses is low but in developing countries annual death is 66.000-199.000 for RSV and 28.000-111.500 for influenza in children younger than 5 years of age (8,9). The predicted mortality due to acute lower respiratory infections among children younger than 5 years of age is 1.3 million deaths each year (10). RSV and influenza are the most common viruses in hospitalized children worldwide. Rhinovirus which is considered to cause mild upper respiratory infections, can also cause serious infections in children. With the emerging molecular methods including polymerase chain reaction (PCR), several new viruses and viral species such as HMPV and HBoV (11,12) are identified. In the studies performed, the sensitivity and specificity of RT-PCR were reported as 94.4% -100% for RSV, 100% -91.3% for RV, 98% -98% for influenza virus and 100% -95% for PIV, 96-98.8% for HMPV (13).

The distribution and frequency of respiratory tract viruses can vary depending on many different factors such as; age, season, socioeconomical status, underlying disease, diagnostic test used (PCR, culture, coverage..). Molecular PCR testing for respiratory viral pathogens has resulted in increasing detection of dual or multiple viruses in respiratory secretions of children. At least one viral respiratory tract pathogen detection rate has been found to range between 41.8% and 78.6% in several studies in our country (14,15,16). The overall detection rate of a respiratory virus was 48% in the study of Brittain-Long et al (17). In our study involving children between the ages of 0-18 years who were hospitalized because of lower respiratory tract infection in the period of 2014- 2016, viral agent was detected in 83.3% of the patients (n = 94) with molecular method (multiplex PCR). Of these, 65 (69.1%) were found to have a single agent while multipl viruses were identified in the remaining 29 (30.9%) patients. RSV was the most common agent while RSV-rhinovirus coexistence was most common in the multipl infections. Similarly to our study, higher rates have been reported from different countries; it was reported to be 85.3%in Japan and 88.7% in France (18,19).

There are few studies comparing the difference between single and multiple virus infections and the impact of multiple viruses on the severity of illness is unclear. There are several studies showing increased hospitalization and intensive care requirement in the presence of RSV and/or HMPV (20,21). At least one virus was detected in 63 % of hospitalized children and more than one virus was detected in 18%of the study population of Martin et al (22); RSV was the most frequently detected

agent and the most common combinations among the multipl infections were RSV/adenovirus and RSV/coronavirus in their work. They reported that multiple viruses were more common in children aged 6-24 months (%27), children with single virus illnesses had higher rates of severe clinical disease compared with children with multiple virus infections and children with multiple virus detections were less frequently admitted to the intensive care unit, required oxygen, required longer hospital stays compared with the group of children with single viruses. Cebey-López M et al (23) also reported that the presence of more than one virus in hospitalized children with respiratory infection is very frequent but it does not seem to have a major clinical impact in terms of severity.

The viral detection rate was 457/560 (81.6%) of which 331/560 (59.1%) were single infections and 126/560 (22.5%) were multiple infections in the study reported by Wishaupt JO et al (24). They found out that disease (severity), management and outcome are not associated with a specific virus. Single and multiple viral respiratory infection do not significantly differ with regard to clinical outcome and patient management. There was no difference on the disease severity or outcome between single virus and multiple virus infections in our study similar to these reports but some other reports argue against it. Richard N et al (25) reported ; A viral agent was identified in 96.1% of infants with bronchiolitis. RSV was the main detected respiratory virus in hospitalized infants. Infants with coinfections were 2.7 times (95% CI: 1.2-6.2) more at risk for pediatric intensive care admission than those with a single infection. RSV and rhinovirus were the viruses most frequently identified in mixed infections in infants hospitalized with bronchiolitis. Cilla G et al (26) reported; at least one virus was detected in 66.9% of the episodes and simultaneous detection of two or more viruses was frequent (27% of the episodes with viral detection). The most frequently detected virus was RSV, followed by human bocavirus and rhinovirus. Children with viral coinfection more frequently required hospital admission than those with single viral infection. The age distribution of infections caused by single and multiple viruses also varies. Viral coinfections were reported to be more frequent in children aged less than 12 months in the study of Cilla G et al (26). Canducci et al (27) reported a lower prevalence of multiple virus infections in the youngest infants in contrast to our study.

In conclusion; RSV was the most common agent and RSV and Rhinovirus was the most common coexistence in our study population. Infections with multiple viruses were more frequent in small age

groups but we observed that the severity of the disease was not different in single or multiple virus infections.

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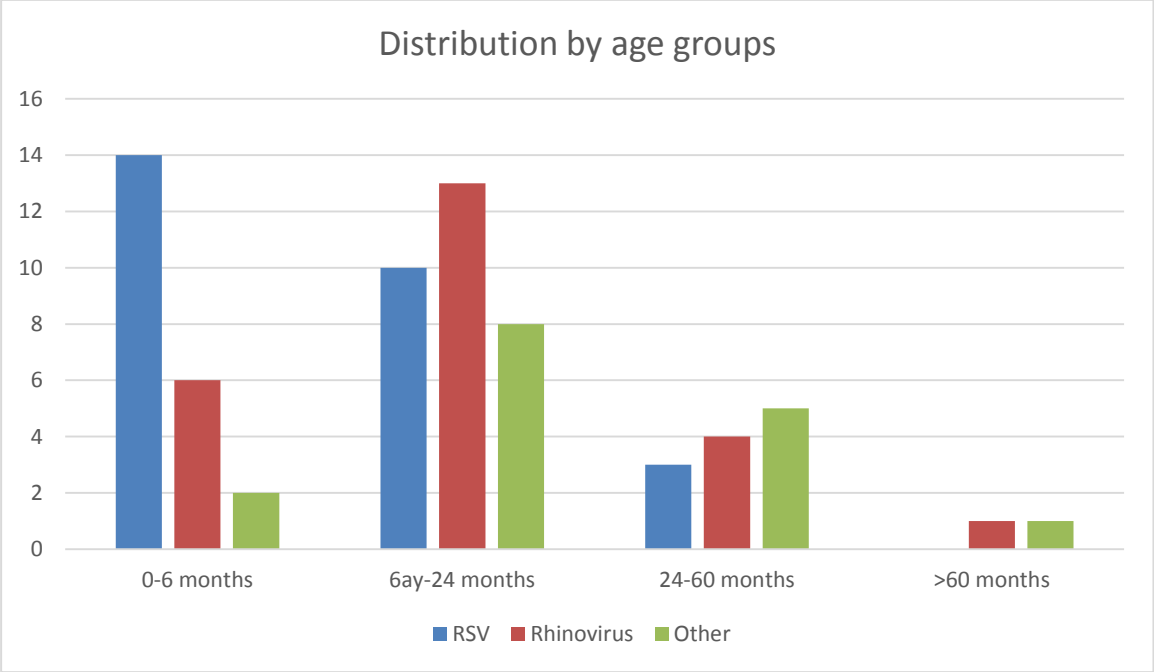

Figure 1. Distribution of the respiratory viruses by age groups

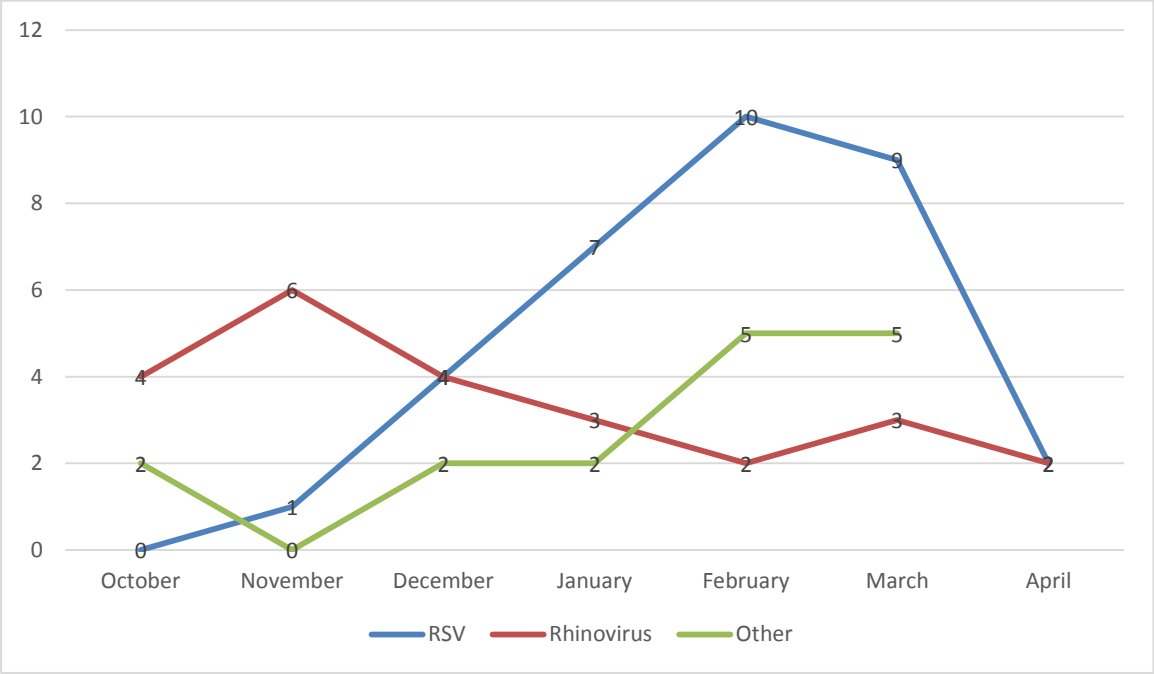

Figure 2. Seasonal distribution of respiratory viruses

Table 1: Characteristics of the patients, by single or multiple virus infections

	Single virus (n=65)	**Multipl viruses (n=29)**	**p**
age (median)	10(26)	5(10)	0.022
gender (female/male) n (%)	22 / 43 (33.8/66.2)	10/19 (34.4/65.6)	0.91
age n(%) **0-6 months** **6-24 months** **24-60 months** **>60 months**	 28(43) 25(38.6) 10(15.4) 2(3)	 16(55.1) 11(37.9) 2(6.9) 0(0)	0.39
Smoking in the family n(%)	20(30.7)	8(27.5)	0.78
Prematurity n(%)	16(24.6)	10(34.4)	0.30
Mechanical ventilation n(%)	13(20)	6(20.6)	0.91
Chronic disease n(%)	16(24.6)	8(27.5)	0.73
Respiratory tract infection in the family n(%)	19(29.2)	8(27.5)	0.90
Disease severity (respiratory score) n(%) **mild** **moderate** **severe**	 6(9.2) 51(78.4) 8(12.3)	 3(10.3) 25(86.2) 1(3.5)	0.41
Hospitalization day (median)	5(3)	5(2.5)	0.909
O2 requirement	31(44.9)	10(34.4)	0.25
Systemic steroid use n(%)	37(53.6)	21(72.4)	0.13

Admission to intensive care unit n(%)	5(7.2)	1(3.4)	0.44
Laboratory			
Leukocyte count (/mm^3) (mean+SD)	11400(±4512)	9623(±4153)	0.074
Crp(median+IQ)	0.4(2.75)	0.6(1.15)	0.776
Sodium (median+IQ)	137(3.1)	136.7(4.5)	0.565

Student's T test, Mann-Whitney U test, Chi-Square test are used; Data are given as mean ± SD or median (IQR)