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Prevalence of Viruses in Acute Asthma Exacerbations in Childhood in a Hospital in West Part of Turkey

Selime Ozen Boluk[1], Ilke Taskirdi[1], Omer Akcal[2], Mehmet Sirin Kaya[1], Idil Akay Haci[1], Ozgen Soyoz[1], Figen Celebi Celik[1], Canan Sule Karkiner[1], Fahri Yuce Ayhan[3], Nesrin Gulez[1], Ferah Genel[1], and Demet Can[4]

[1] Division of Allergy and Immunology, Department of Pediatrics, Dr Behcet Uz Children's Education and Research Hospital, University of Health Sciences Izmir, Izmir, Turkey
[2] Division of Allergy and Immunology, Department of Pediatrics, Gaziantep Cengiz Gökçek Maternity and Children's Hospital, Gaziantep, Turkey
[3] Department of Microbiology, Dr Behcet Uz Children's Education and Research Hospital, University of Health Sciences Izmir, Izmir, Turkey
[4] Departments of Pediatrics, Balıkesir University Faculty of Medicine, Balıkesir, Turkey

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ABSTRACT

Acute asthma exacerbations (AAE) are episodes characterized by potentially life-threatening and rapidly deteriorating asthma symptoms. Viral respiratory infections are one of the major triggers in the pathophysiology of childhood asthma exacerbations. In this study, we aimed to determine the distribution of viral agents among pediatric AAE patients.

One hundred and three AAE patients, aged 5 or older, hospitalized between from February 2017 through February 2020 at Pediatric Immunology and Allergic Diseases Unit were included in this study. Fifty patients (48.5%) were female, and the mean age of the patients was 108.2 months. Viruses were detected in 58 (%56.3) of the patients, in 5 of whom more than one virus type was detected. The most commonly detected virus was human rhinovirus (n=43, 67.1%).

Other types included respiratory syncytial virus (n=8; 12.5%), influenza (n=6; 9.3%), human metapneumovirus (n=4; 6.2%), adenovirus (n=1; 1.5%), enterovirus (n=1; 1.5%), and parainfluenza (n=1; 1.5%). Viral agents were detected in 29 out of the 47 patients with allergic asthma, with human rhinoviruses comprising the majority (18 patients). The mean length of hospital stay was 7.89 days.

Human rhinovirus is the most common virus that triggers AAE, with similar distributions in allergic and non-allergic asthma. We found no correlation between virus type and the length of hospital stay.

Keywords: Acute asthma exacerbations; Polymerase chain reaction; Viruses

Corresponding Author: Selime Ozen Boluk, MD, Division of Allergy and Immunology, Department of Pediatrics, Dr Behcet Uz Children's Education and Research Hospital, University of Health Sciences Izmir, Izmir, Turkey. Tel: (+ 90 507) 3805 156, Fax: (+ 90 232 489 2315), E-mail: yarenseli85@hotmail.com

INTRODUCTION

Viral respiratory infections (VRI) play a significant role in all wheezing illnesses from bronchiolitis to asthma.[1] Viral infections are responsible for nearly %80-85 of acute asthma exacerbations (AAE) among school-age children.[2] Viruses act as a triggered factor for AAE and cause an increase in the healthcare cost of asthma.[3] Asthma exacerbations constitute a serious burden of treatment all over the world. AAE is a frequent cause of admission to the emergency unit and hospitalization for children.[4] The prevalence of hospitalization due to AAE for children is 495 per 100.000, compared with adults (92 per 100.000) is a bigger problem in childhood.[4] It is accepted that the AAE role is a key to defining the severity of the disease. Prevention of AAE is an important criterion for evaluating the accomplishment of asthma treatments.[4] Viral respiratory infections seem as common triggers that's determination rate reaches nearly 100% for wheezy children and 80% for adults.[5] Viral infections are more important when children return to their school after the summer-spring breaks. Circulation times of the respiratory viruses were related to more serious asthma symptoms and more frequent asthma loss of control.[6] Knowledge about the viruses' patterns among asthmatic children can help the prevention and treatment of AAE and help decrease the burden on patients.[3]

Respiratory viruses during AAE include human rhinovirus (HRV), respiratory syncytial virus (RSV), adenovirus (AdV), parainfluenza virus (PiV), human coronavirus (HCoV), influenza virus (IfV), human metapneumovirus (HMpV), bocavirus (BoV), enterovirus (EnV), cytomegalovirus (CMV), herpes simplex virus (HSV), HRV, EnV, HMpVand RSV were more prevalent in children, whereas, AdV, IfV, PiV, HCoV, and BoV are more frequent among adults.[7] HRV which is a common cold virus is the most common single trigger of AAE. It covers 76% of wheezy children's AAE and 83% of adults with asthma.[5]

The most sensitive method for determining the viral agent is the Polymerase chain reaction. Determination of the viral respiratory tract infections noticeably improved during the last 20 years because of improving PCR techniques. Some new respiratory viruses and subgroups were defined and the diagnosis of HRV was clarified.[4]

We aimed to determine the distribution of viral agents by polymerase chain reaction (PCR) that can cause AAE in children who needed hospitalization.

MATERIALS AND METHODS

Participants

The patients with acute asthma exacerbations (AAE) older than 5 years who were needed to hospitalize (n=108) at Pediatric Immunology and Allergic Diseases Unit between February 2017-2020 were enrolled. Three patients were excluded because of insufficient clinical and laboratory data and 2 patients were excluded because of inappropriate nasopharyngeal samples. As a result, a total of 103 patients' data was included in the analysis.

Study Design and Ethical Approval

This retrospective cross-sectional study was approved by the SBU Izmir Dr. Behcet Uz Education and Research Hospital Clinical Research Ethics Committee on 2021/496, 2021 (decision no.02-04).

Asthma Definition

We included studying the adolescents and children over 5 years who met the criteria for asthma according to GINA.[8] Acute asthma exacerbations were defined as worsening symptoms that needed changes in medications according to the American Thoracic Society/European Respiratory Society statement.[9] The patients with acute asthma exacerbations older than 5 years who were required to hospitalize were included in to study. Children under 5 years were not included because it was difficult to differentiate asthma from other wheezing etiologies among young children. When AAE was classified as mild, moderate, severe, and life-threatening according to GINA updated at 2020, patients with severe and life-threatening exacerbations were directly hospitalized and patients with moderate exacerbations that were insufficiently responsive to management in primary care were also hospitalized. Patients with mild exacerbations or moderate exacerbations that were well-responded to management in primary care were not included. According to GINA asthma severity of exacerbations classification, agitation, respiratory rate over 30/min, talking with short words, preferring to sit in hunched positions, needing accessory muscles, pulse rate over 120 bpm, O2

saturation below 90%, and best or predicted PEF 50% are criteria defined as severe exacerbation. Talking with sentences, prefer sitting to lying, having no agitation, increased respiratory rate, no need for accessory muscles, pulse rate between 100-120 bpm, O2 saturation between 90-95% on air, and best od predicted PEF over 50% are criteria for mild or moderate asthma exacerbation.[8]

Data and Virus Detection

For each child included in the study, data on age, sex, type of asthma (allergic, nonallergic), and the duration of hospitalization, was recorded. Nasopharyngeal samples were collected from all patients at the first 24-hour followed-up hospitalization. nasopharyngeal swabs were obtained from 2-3 cm depth and then put at a vial for virus transport.

Nasopharyngeal samples were tested by multiplex real-time PCR assay for respiratory pathogens. Two different commercial diagnostic kits were used in consecutive years, FTDRP 21 Plus (Fast-Track Diagnostics, Luxembourg) before 2018 and Bosphore Respiratory Pathogens Panel Kit (Anatolia Gene works, Turkey) in 2019-20. Besides the viral pathogens, mycoplasma pneumonia and Haemophilus influenza were also investigated with both kits.

Statistical Analysis

Categorical variables were expressed in number and percentage (%). Comparisons between groups of qualitative variables were determined using the chi-square test, numerical variables were compared; using the student's t-test and one-way analysis of variation (ANOVA). Multiple logistic regression analysis was used to investigate potential independent risk factors. All analyses were performed using SPSS 18 (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.).

RESULTS

Participants' Characteristics

Fifty of the patients were female (48.5%). The median age of the patients that were included in the study was 108.2±37 months. Forty-seven patients (45.6%) had allergic asthma. Clinical and laboratory data of the patients were summarized in Table 1.

Four patients had a cardiac disease (Operated Patent Ductus Arteriosus, Supraventricular tachycardia, and mitral valve prolapse). Three patients had epilepsy, a patient had vitamin B12 deficiency and a patient had Familial Mediterranean Fever.

The mean white blood count of patients at admission was 11229±4667/mm^3. This value was 10671±4617/mm^3 for patients with allergic asthma and 11861±4694/mm^3 for patients with allergic asthma. There was no statistical significance (p=0.28).

The mean C reactive protein (CRP) level of patients at admission was 1.4±2.6mg/dl and there was no significance between allergic and nonallergic patients. (Respectively 1.2±2.3 and 1.54±2.88, p=0.61).

There was a statistical significance in mean total IgE level and absolute blood eosinophil level between allergic and nonallergic patients. The mean total IgE level of nonallergic patients was 220±320 kIU/L and 598±646 kIU/L for allergic patients (p=0.001). The mean Blood Eosinophil level was 169±252/mm^3 for nonallergic patients and 434±529/mm^3 for allergic patients (p=0.002).

24 patients with the diagnosis of allergic asthma had indoor aeroallergen sensitivity, 10 patients had outdoor aeroallergen sensitivity and others of them had both indoor and outdoor aeroallergen sensitivity.

Table 1. Characteristics of clinical and laboratory data

	Mean±SD	Min-Max
Age (months)	108.2±37	60-204
Hospitalization (day)	7.8±3.1	2-17
WBC (/mm^3)	11229±4667	1930±24180
CRP (mg/dl)	1.4±2.6.	0.02-14
Total IgE (kIU/l)	392.4±521.9	1-2852
#Blood eosinophil (/mm^3)	293±425	0-2030

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Prevalence of the Detected Viral Pathogens in Patients with Acute Asthma Exacerbation

At least one viral agent was observed in 58 patients. Fifty-three of patients (51.4%) had a single viral pathogen. Therefore, 5 patients had super infection of two or three viruses (4.8%). HRV (n=43; 67.1%) was the most commonly detected viral pathogen in patients with AAE, followed by RSV (n=8; 12.5%). Respectively, IfV (n=6; 9.3%), MPV (n=4; 6.2%), PiV (n=1; 1.5%), EnV (n=1; 1.5%), AdV (n=1; 1.5%) were determined. Mycoplasma pneumonia positivity for one patient was determined.

The studied patients were collected in all 3-year seasons. Sixty-four percent of attacks (n=66) were in the cold season (between October-March). Sixty-nine percent of attacks (n=30) related to human rhinovirus were in the same season (between October-March) (Table 2).

Comparisons of HRV and non HRV/without Detected Pathogen Groups

Data of 103 patients with a single viral pathogen and without detected pathogen was summarized in Figure 1. The mean WBC level was significantly high for the HRV group (p=0.00) (Table 3). Significant differences between the two groups among mean CRP, total IgE or mean blood eosinophil levels were not determined.

Comparisons of HRV and non HRV/without Detected Pathogen Groups

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Table 2. Distribution of exacerbations according to the months

Number of exacerbations	**6**	**6**	**10**	**17**	**10**	**10**	**13**	**6**	**8**	**8**	**3**	**6**	**n=103**
	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	July	Aug	
Number of exacerbations related to HRV	4	3	6	9	2	5	5	1	3	2	2	1	n=43

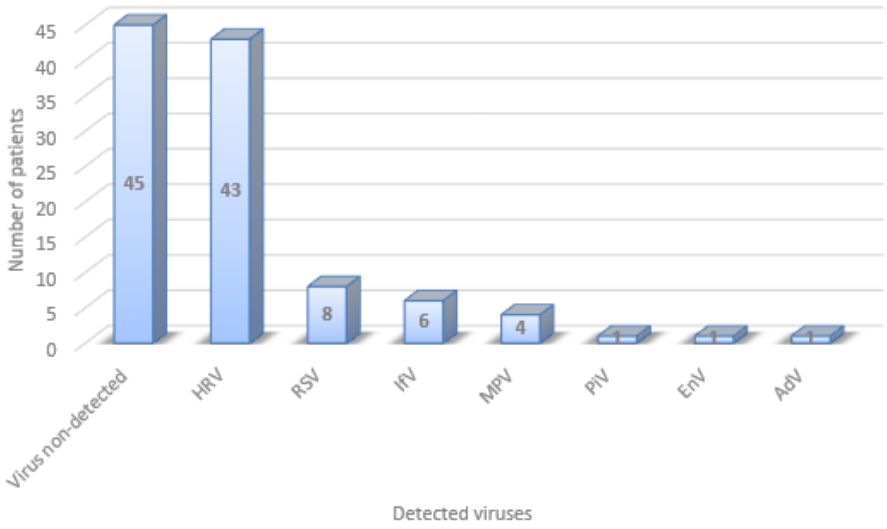

Figure 1. Distribution of viral pathogens in patients with an acute asthma attack. Human rhinovirus (HRV), respiratory syncytial virus (RSV), influenza (IfV), human metapneumovirus (MPV), parainfluenza (PiV), adenovirus (AdV) enterovirus (EnV)

Table 3. Comparisons of Human rhinovirus and non-Human rhinovirus/without detected pathogen groups

	HRV (n=43)	non-HRV/without detected pathogen (n=60)	*p*
Male gender	23 (53.4%)	30(50%)	0.72
Mean age±SD (months)	105.9±35.8	109.8±38.1	0.60
Mean hospitalization day±SD	7.6±2.8	8.05±3.3	0.54
Present of atopy	20 (46.5%)	27 (45%)	0.87
Mean WBC level±SD (/mm3)	13220±9140	4457±4218	**0.00**
Mean CRP level±SD (mg/dl)	1.5±2.07	1.3±3.04	0.77
Mean total IgE level±SD (kUI/L)	498±602	299±424	0.90
Mean blood eosinophil level±SD(/mm3)	317±471	274±388	0.62

Human rhinovirus (HRV), standard deviation (SD), white blood cell (WBC), C reactive protein (CRP)

Comparison of Clinical Characteristics among Allergic and Nonallergic Groups

There was no difference between allergic and nonallergic groups among gender. Forty- five point six patients (n=47) had allergic asthma and a viral pathogen was determined in 29 (61.7%) of them. Rhinovirus was a responsible trigger at 18 of them (41%). The ratio of allergic asthma was 38.2% for patients who had no viral trigger. Significant differences between hospitalization days and the allergic and nonallergic groups were not determined ($p>0.05$).

Comparison of Duration of Hospitalization

There was no difference between the comparison of duration of hospitalization among HRV and non-HRV groups. Mean hospitalization time was 7.7±2.8 days for HRV and 8.01±3.28 days for non-HRV groups ($p=0.62$). The mean duration of hospitalization was 7.79±2.9 days. There were no statistically significant differences between the duration of hospitalization and allergic/nonallergic groups (respectively 7.9±3.4 and 7.8±2.8 days, $p>0.05$).

DISCUSSION

At least one viral agent was observed in 58 of 103 patients who hospitalized due to AAE. Single viral pathogen was identified at 51.4% of patients (n=53). Five patients had super infection with more than one virus (4.8%). HRV (n=43; 67.1%) was the most frequent virus detected in participants with asthma exacerbation and followed by RSV (n=8; 12.5%). Respectively, IfV (n=6; 9.3%), MPV (n=4; 6.2%), PiV (n=1; 1.5%), EnV (n=1; 1.5%), AdV (n=1; 1.5%) were determined.

The prevalence of common respiratory viruses related to AAE was exposed in this study. HRV was the most frequent viral pathogen similar to the other studies.

Acute asthma exacerbations are characterized by respiratory distress, dyspnea, and worsening cough. Aeroallergens, air pollution, and respiratory tract infections may be trigger factors for AAE. Management of AAE related to these respiratory tract infections is a serious health problem.[10] Because respiratory tract infections are now considered the most frequent reason for AAE.[11]

These exacerbations are the most common causes of approval to hospitals for children diagnosed with asthma. The cost for the patients with uncontrolled asthma and frequent exacerbations is 3.5 times higher than the patients with controlled asthma.[12,13] As a result, asthma exacerbations related to respiratory tract infections constitute a burden for both patients and health systems.

Although clinicians have observed the relationship between viral respiratory infections and AAE for many years, the viral etiology of asthma attacks could not always be proved because of the low sensitivity of determining techniques of viruses.[14] With the technical improvements in laboratory and microbiology, rapid developments are experienced in the diagnostic sense, as in many other fields of medicine. This development was also observed in the field of RT-PCR and allowed the researchers to reveal the relationship between viral respiratory infections and AAE. In our study, nasopharyngeal swab specimens were taken for each patient at admission to the hospital, and Multiplex PCR analysis was performed to the identification of viruses.

As in our study, the other studies display that there was a detected viral agent in almost two-thirds of children

with AAE. This ratio was almost fifty percent of adults with AAE.[3] It is seen that the rate of viruses triggering asthma attacks decreased somewhat as the age group of patients gets older according to literature. In a pediatric and adults studies meta-analysis that used analysis of meta-regression, the determination rate of the viral agents was higher in children than in adults.[3] School-aged children were included in our study. So, because of the narrow range of age, the correlation between age and virus-induced AAE could not be determined.

Determination rate of the viral agents was 52%-65% of cases and HRV was most often detected (51–71%), followed by RSV (8–18%), IfV (7–15%), PiV (4–11%) and HMpV (3–9%).[3] The distribution of the viral agent was found with similar order amongst children; HRV was detected most frequently with 68.53%, followed by RSV 16.23%, IfV 7.93%, PiV 5.81%, and HMpV 5.02%.[2] Similar to recent studies, HRV was as most often detected virus in our study (67.1%), followed by RSV (n=8; 12.5%) and respectively, IfV (n=6; 9.3%), HMpV (n=4; 6.2%), PiV (n=1; 1.5%), EnV (n=1; 1.5%), AdV (n=1; 1.5%).

HRV is now considered as the major risk factor for children at school-age and related with the cofactors like aeroallergen sensitization Odds Ratio reaches 45 .[5] HRV infections stimulate the respiratory epithelial cells to produce IL-25 and IL-33, so that TH2 inflammation may present like exposure to the aeroallergen.[15,16] Therewith epithelial damage may occur and due to remodeling, airway hypersensitivity and mucus hypersecretion may develop. HRV is an RNA virus and three types (HRV-A, HRV-B, HRV-C) are defined HRV may locate in both the upper and lower respiratory tract.[5] HRV-A and HRV-C are the most common types of HRV that are responsible for asthma exacerbations and may cause more serious respiratory diseases than HRV-B.[17] In addition, HRV-C is the most frequent type of HRV determined among patients hospitalized and in intensive care units because of asthma.[18] Unfortunately, we could not determine the types of RSV in our study.

In a study that showed the relation between asthma exacerbation and triggered viruses and/or mycoplasma pneumonia, Mycoplasma DNA was determined at 4% of samples by RT-PCR.[1] This ratio was 0.97% in our study. Mycoplasma prevalence might show seasonal variation or some might be found temporary as an epidemic, so longer-term and wide-ranged analyses are needed.

Inappropriate antibiotic usage is so high for asthma exacerbations because clinical manifestations may be considered related to pneumonia by clinicians.[19] It is known that viral respiratory infections are more common for both adults and children with asthma. As a result, inappropriate antibiotic usage is present for treatment. As a result, inappropriate antibiotic usage is present for treatment. Antibiotics for seconder bacterial infections related to viral-induced asthma exacerbations may also cause symptom worsening because of increasing bacterial lysis.[20] Therefore, determining the viral etiology of AAE may prevent unnecessary usage of antibiotics and support the control of the viral illness and at the same time may help to decrease of burden related to AAE. Determination of the viral etiology may be more important when the antiviral specific treatments like TLR3 and IFN-B agonists and IL 25 and IL-33 antagonists.[21]

It is defended that variable inflammatory response to viral infections in asthma may be related to the atopic ground of the patients. Viral infections activate eosinophils and may release major basic proteins that connect M2 receptors and blockade their functions in atopic patients.[22] In our study, the association between atopy and virus-induced exacerbations was prominent (55.8%) but not significant statistically. Again, allergen sensitization is thought to be significantly related to HRV-associated asthma exacerbation.[1] Like this study, Rhinovirus was responsible for 41% of children with allergic asthma in our evaluation.

When it is critically evaluated, this study has several limitations. Firstly, we could not perform the identification of HRV types. Especially, it is known that HRV-C may be responsible for severe exacerbations when compared to other HRV types.[1] Data of the study reflects the experience and outcomes of a single center. Multicenter studies covering different regions may provide more precise data because regional differences can be seen. Finally, patients with severe asthma exacerbation that were hospitalized were only included in the study. Mild asthma exacerbations and patients who are treated at home are not included so it could not provide clear information about the viral etiology of all asthma exacerbations.

Viruses may be a triggered agent for AAE for patients diagnosed with both allergic and non-allergic asthma. HRV has been identified as an important cause of AAE. Whether asthma is allergic or not, it does not affect the type of virus that triggered AAE. Prevention and identification of viral respiratory infections may decrease the burden of disease-related asthma and unnecessarily usage of antibiotics.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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