Predictive factor for first wheezing episode

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The aim of study was to evaluate various risk in patients who were hospitalized with moderate to severe virus-induced wheezing. Infants hospitalized with virus-induced wheezing were enrolled in the study. Respiratory viruses were detected in nasopharyngeal swab and total IgE levels and skin prick tests were performed in all patients. The mean age of the patients was 11.2±9 months. The most common detected viral agents were Respiratory Syncytial Virus, (33.6%), Influenza virus (16.3.%). Children with positive family history of atopy had their first virus-induced wheezing at an earlier age (9.0 ±7.8 months) than the others (14.2±10.8 months), (p=0.007). Atopy and viral etiology did not significantly influence clinical severity of the disease. Although children with positive parental history of atopy experience first virus-induced wheezing at an earlier age, personal atopy was not found as a risk factor for predicting the severity of the first virus-induced wheezy episode.

Key words: atopy, respiratory virus, children, virus-induced wheezing.

Viral respiratory infections are the most common causes of wheezing in infants and young children less than three years of age. Hospital admissions for wheezing continue to be a significant health care problem in many countries.

Although, almost 50 percent of children are reported to have wheezing in the first year of life, only 20 percent will experience continued wheezing symptoms in later childhood[1]. Wheezing phenotypes have been defined to identify the characteristics and risk factors associated with children that experience wheezing[2]. There is some variability in age cutoffs differentiating these phenotypes in which some risk factors such as maternal tobacco use during pregnancy, having siblings, and daycare attendance, family history of atopy are associated with each phenotype. Atopy in early childhood is a strong predictor for asthma in adulthood[1]. A number of epidemiologic studies have investigated these risk factors for wheezing with respiratory infections and their effects on these illnesses[3-5].

The aim of our study was to describe and evaluate various risk factors including personal atopy and family history of atopy together with clinical and laboratory findings in patients who were hospitalized with moderate to severe virus-induced wheezing.

Material and Methods

Study setting and procedures for the patients

The patients 0-36 months of age who presented to the Pediatrics wards, in Istanbul Medical Faculty during September 2013 and May 2014 with a wheezing episode were evaluated. Patients with toxic appearance, poor feeding, lethargy, dehydration, moderate to severe respiratory distress, apnea, hypoxemia and having parents who were unable to care for them at home[6,7] were hospitalized after an average of 12 hours observation period at emergency unit.

Patients' demographic information was obtained from the hospital records, and included onset date of disease, age at onset, gender, family

Table I. Clinical and Laboratory Characteristics of Patients on Admission

n(total) =92	n	%
Age (month; mean±SD)	11.2±9.0	
Sex (M)	57	
Days of hospitalization	6±4	61.9
Birthweight	2900±794	
Fever	20	21.7
Flu vaccination	2	2.1
Breastfeeding	7.1±5.9	
Recent history of respiratory tract disease in the household	43	46.7
Clinic stage of wheezing illness		
Moderate		65.2
Severe		34.7
	60	
Passive smoking	32	32.6
Parental history for atopy		32.6
Blood eosinophilia at admission		10.8
	30	
	30	
	10	Mean±SD
Blood leukocyte (/μL)		10779±5227
Blood lymphocyte (/μL)		3963±2139
Blood neutrophills(/μL)		5548±3800
CRP (mg/L)		13±25

and personal history of atopy, family smoking habits and recent history of respiratory tract disease in the household and flu vaccination. Also clinical data for assessment of the disease severity, length of hospital stay and laboratory data including whole blood count, C-reactive protein (CRP), and detected virus in the nasopharyngeal swap were also obtained. Patients with chronic disease were excluded from the study.

The disease severity of each patient was estimated and scored according to a severity scoring system, as described previously[8,9]. Patients were divided into three groups as mild, moderate and severe based on clinic symptoms, and severity.

On admission, nasopharyngeal swap specimens or tracheal aspirate material were obtained from patients. Samples were sent to the virology laboratory located at the Istanbul Faculty of Medicine by commercial viral transport medium (ViroCult, Medical Wire & Equipment Co., England), respiratory viruses were detected after RNA/DNA extraction (Qiagen GmbH, Germany) and using real-time reverse transcriptase-polymerase-chain-reaction (RT-PCR) technique (Fast-track Diagnostics, Luxembourg). RT-PCR amplification was performed for the detection of Respiratory *Syncytial Virus* (RSV), Influenza (Inf), Parainfluenza (PIV), Rhinovirus (RV),

Table II. Severity Scoring System for Clinical Stage

	Mild	Moderate	Severe
Apnea	No	No	Yes
Respiratory rate (/min)	<50	50-70	>70
Pulse rate (/min)	<140	140-160	>160
Retraction	Mild	Moderate	Severe
SaO2	>%93	% 86-92	% < 85
Cyanosis	No	-	Yes
Fio2 required for SaO2 93%	-	0.21-0.4	>0.4

* The patient, who had the most severe criteria was considered in the severity of that clinical stage.
+References[8,9]

Table III. The Relation Between Atopy, Clinical Stage and Detected Virus

Factors	Sole RSV n=31	Sole Inf n=15	Sole RV n=12	Sole Other viruses n=17	Multiple virus n=17	P value
Age (mean±SD) months	9.5±8.2	18.9±13.1	9.7±9.7	14.7±9.2	9.9±7.5	0.007
Sex (male) n(%)	23(74.1%)	8(53.3%)	7(58.3%)	10(58.8%)	9(52.9%)	0.530
Severe cases n(%)	9(29.0%)	3(20%)	2(16.6%)	9(52.9%)	9(52.9%)	0.073
Positive skin prick test n(%)	4(12.9%)	2(13.3%)	0(0%)	0(0%)	0(0%)	0.164
Blood eosinophilia n(%)	5 (16.1%)	2(13.3%)	0(0%)	1(5.8%)	2(11.7%)	0.474
IgE levels >100 kU/L n(%)	4(12.9%)	2(13.3%)	2(16.6%)	1(5.8%)	1(5.8%)	0.789
Atopy n(%)	6(19.3%)	1(6.6%)	2(16.6%)	1(5.8%)	1(5.8%)	0.485
CRP	8.0±13.7	13.7±20.6	11.0±19.2	18.1±35.0	18.6±31.0	0.534

OneWay ANOVA (Brown-Forsythe) Post Hoc Test: Games Howell Kruskal Wallis Test Post Hoc Test: nonparametric posthoc test (Miller(1966) * Mean±SD **Median ± IQR (Inter Quartile Range)

Human Bocavirus (HBoV), coronavirus (CoV), human Metapneumovirus (hMPV), Adenovirus (AV).

Potential risk factors for respiratory infections including passive smoking, birthweight, duration of breastfeeding, flu vaccination, recent history of respiratory tract disease in the household and atopic status of the child and family were evaluated by using a questionnaire.

Oxygen saturation was measured during the child's hospital admission. A disposable SpO2 sensor (Nihon Kohden BSM-2701K, Tokyo, Japan) was applied to the right hand or wrist before switching on the pulse oximeter (Nihon Kohden BSM-2701K, Tokyo, Japan).

A pediatric radiologist interpreted chest X-rays of the patients; the patients who had different radiological images other than typical findings such as: hyperaeration, bronchial infiltration, peribronchial markings were excluded from the study.

Serum total IgE levels and skin prick tests were performed within 3 months after the recovery, at the outpatient visit. Skin prick tests were performed by using a panel of common allergens including house dust mite, mold mix, tree mix, grass mix, weed mix, cat, dog, cockroach, cow's milk, and egg (Stallergenes, Paris, France). A positive skin prick test was defined as a wheal with a diameter that exceeded the negative control by at least 3 mm. Serum total IgE values were measured by the CAP radioallergosorbent technique according to the manufacturer's instructions (UniCAP; Pharmacia and Upjohn, Uppsala, Sweden). Children with a positive reaction to any of the allergens tested and/or with IgE levels above 100 kU/L were considered atopic.

Ethics: This study was approved by Ethical Commitee Consent of Istanbul Medical Faculty: 2014/703

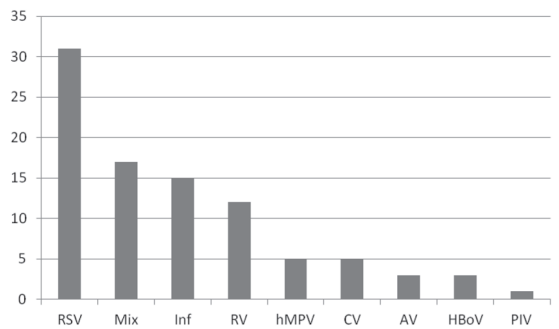

Fig. 1. Detected viruses in wheezy infants with lower respiratory infection

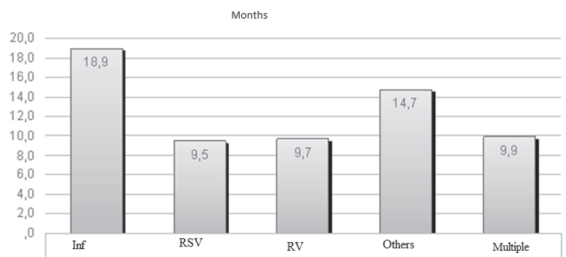

Fig. 2. The age distribution of patients infected with various viruses

Table IV. Comparison of the Characteristics of Nonatopic and Atopic Patients

n= 92	Nonatopics (n=81)	Atopics (n=11)	P value
Age (months)*	11.1±8.9	11.6±10.0	0.890
Sex (male) n (%)	48 (59.2%)	9 (81.8%)	0.196
Days of hospitalization*	5.7±3.8	8±4.5	0.034
Birthweight (gr)*	3059±1061	2882±757	0.493
Severe cases n (%)	27 (33.3%)	5 (45.4%)	0.509
Fever n(%)	22 (27.1%)	2(18.1%)	0.506
Recent history of respiratory tract disease of household n(%)	38(46.9%)	5 (45.4%)	0.593
Breastfeeding (month)*	6.9±5.9	8.1±5.9	0.537
Flu vaccination n (%)	2 (2.4%)	0	0.774
Passive smoking n (%)	34 (41.9%)	4(36.3%)	0.495
Parental history of atopy n(%)	25(30.8%)	5(45.4%)	0.260
Complete blood count			
Leukocyte (mm3)**	10498±5225	12047±4988	0.163
Neutrophills (mm3)**	5361±3819	6921±3966	0.209
Lymphocyte (mm3)**	3859±2094	4732±2416	0.206
Eosinophil(mm3)**	99±64	184±460	0.004
CRP (mg/L) *	14.7±25.7	2.8±2.9	0.011

Pearson Chi-Square Test (Exact) - Independent T Test - Mann Whitney U Test (Exact)
Ss. Standart deviation * Mean±SD **Median ± IQR (Inter Quartile Range)

Statistical analysis

Statistical analysis were performed with Statistical Package for the Social Sciences (SPSS) software, version 21 for Windows and PAST. Confidence intervals were stated at the 95% confidence level and $p < 0.05$ was considered significant. Correlations between parameters were assessed by using the Spearman's rho tests and for comparison of categorical data were used by Pearson Chi-Square and Fisher Exact tests. Numerical variables were reported as means ± SDs, median ± IQR (Interquartile Range) and non-numerical parameters were reported as n(number), percent(%).

Results

Patients' characteristics and risk factors

During the study period, 92 pediatric patients (≤3 years of age) hospitalized with wheezing and detected with viral lower respiratory infections were enrolled in the study (Table I). The mean hospital stay was 6±4 days (2-20 days), and the mean age of the patients was 11.2±9.0 months (1-36 months). Fifty-seven of the patients (n=57, 61.9%) were male. Clinical findings of atopic disease such as atopic dermatitis, food allergy and allergic rhinitis were not detected in any of the patients.

The mean number of household was 4±1 (2-10 persons), and the percentage of recent history of respiratory tract disease in the household was 46.7 (n=43). Parental history was positive in 32.6% of the patients for smoking and for atopy. Flu vaccination rate of the patients was very low (n=2; 2.1%).

The mean level of total IgE was 25.9±52 kU/L. Of the patients, 10.8 % (n=10) had IgE levels above 100 kU/L, and 10.8 % (n=10) had eosinophilia on admission. At the outpatient appointment, all patients evaluated with skin prick tests and blood eosinophil counts. Of them 6.5 % (n=6) had positive skin prick tests for at least one allergen and 10.8 % (n=10) had eosinophilia.

On admission, most of the hospitalized patients had moderate disease according to the severity classification (Table II). Among them, patients with severe symptoms were transferred to the pediatric intensive care unit. When we compared clinical parameters between the

cases with moderate and severe disease, severe cases had more frequent recent history of respiratory tract disease of the household (63.6 %, p=0.017 OR=2.78 CI=1.18-6.59) and longer hospitalization periods (7.3±4.3 days, p=0.022). The mean serum CRP level was significantly lower in severe cases (8.4±12 mg/dL p=0.02) than moderate ones. Other clinical parameters did not differ significantly between the two groups.

Virus identification

The most common detected virus was RSV with 33.6% (n=31), and the second, Inf virus with 16.3% (n=15) of the patients. RV, hMPV, CV, AV, HBoV and PIV were detected in 13.0% (n=12), 5.4% (n=5), 5.4% (n=5), 3.2% (n=3), 3.2% (n=3) and 1% (n=1) patients, respectively. Co-infections were detected in 17 (16.5%) patients [AV+RV(n=4), RSV+RV+HMPV (n=3), AV+CV(n=2), Inf+RSV(n=1), AV+HMPV(n=1), RSV+RV(n=1), AV+CV(n=1), RSV+RV+CV(n=1), RV+CV(n=1), RSV+RV+HMPV(n=1), RV+PIV(n=1)] (Fig 1).

The age distribution significantly differed among patients with various viruses. The mean age of children infected with Inf, RSV and RV were 18.9±13.1, 9.5±8.2 and 9.7±7.5 months, respectively. Children infected with influenza were significantly older than others (p=0.007). We also compare age of patients with sole virus and age of patients with influenza. The difference was more obvious (Inf: 20.2±13, sole virus: 11.3±9.1 months p=0.001) (Fig. 2).

The mean age of children infected with sole virus and multiple viruses were 13.2±10.1, 11.3±7.9 months (p=0.043).

Atopic characteristics, age, clinical severity of the patients and sole virus infection were negatively associated with sole viral etiology (Table III).

Risk factors for atopy

In the whole group, children with positive family history of atopy had their first virus-induced wheezing at an earlier age (9.0 ±7.8 months) with respect to others (14.2±10.8 months), the difference was found significant (p=0.007). When we classified them according to atopic status, clinical characteristics and laboratory findings. Days of hospitalization of atopic patients was longer than nonatopics patients (8.0±4.5 days p=0.0349. The mean serum CRP level of atopic patients was significantly lower than nonatopics' (2.8±2.9 mg/dl p=0.011) and serum eosinophil level was higher than atopics', respectively (184 mm^3 p=0.004) (Table IV).

Discussion

Atopy is a known risk factor for virus-induced wheezing[10]. Although atopy has been investigated thoroughly in children with recurrent wheezing, data on the role of atopy in the first virus induced wheezing attack is quite limited. In the present study, we tried to assess various risk factors including atopy together with clinical and laboratory findings in patients who were hospitalized with moderate to severe first wheezy attack.

There are a lot of studies investigating the role of laboratory tests and risk factors such as: premature birth[11], breast feeding[12], and birthweight[13] on severity of virus-induced wheezing in early age. In the current study we did not find any relationship between these risk factors and severity of the wheezing illness.

Respiratory symptoms with viral infections most likely result from virus-induced damage of the airway epithelium, followed by airway inflammation in a predisposed individual. Respiratory viruses such as RSV cause cytopathic damage to airways, or can activate epithelial cells to secrete a wide variety of chemokines and cytokines[14]. Cytokines are important in the development of fever. Uyar et al.[15] showed that fever was present in 33.9% of patients, aged between 0-2 years old, with the initial diagnosis of acute bronchiolitis, which was similar to our results.

In the current study, RSV and Influenza were the dominant viruses detected among children with first virus-induced wheezy attack. RSV and RV were detected with a higher rate in the group of children aged ≤12 months than in the children of 1–3 years of age, which was in agreement with other studies[16,17]. Patients with an allergic predisposition presented neither with specific respiratory virus distribution nor with any other clinical or laboratory features. This study suggests that risk factors listed above may not have any influence on the first virus-induced wheezing attack. Of the children, 32.6 % were exposed to environmental tobacco

smoke at home and 46.7% had recent history of respiratory complaints in the household. It is clear that passive smoke exposure aggravates airway hyperresponsiveness and the frequency and persistence of symptoms[18]. The prevalence of virus-induced wheezing may be decreased by raising awareness about effects of passive smoke on children and infection control in the household.

A comparison of presenting age between viral pathogens revealed that patients with Influenza are significantly older than patients with RSV, RV and others. The vaccination rate is very low in Turkey[19]. The reason for detection of Influenza at a relatively later age in respect to other viral agents may be due to transplasental transfer of maternal IgG antibodies from the mothers of patients who had passed influenza infection recently. Vaccination is important for children especially above 12 months old and we think that the following are the recommended vaccinations for Turkey is influenza**.**

Data on the link between atopy and viral wheeze is limited. Subrata et al.[20] suggested that interactions between innate antiviral and allergic inflammatory pathways may lead to severe viral illnesses in atopic children. In the current study, one-third of patients who had parental history of atopic disease had their first virus-induced wheezy episode younger than the others without parental history of atopy. On the other hand, personal atopy due to high IgE levels and/or skin prick test positivity existed in only 11.9 % of children. Clinical findings of atopic disease such as atopic dermatitis, food allergy and allergic rhinitis were not detected in any of the patients. This may be explained that our study center is a tertiary referral center for the region so severe cases usually admitted. The study showed that atopy alone should not be accepted as a risk factor for predicting the severity of first virus-wheezy episode. We found that atopic children had significantly lower CRP response in wheezing illness than non-atopics. This may be attributed to different pathways and cytokine formation in atopic individuals. RSV also can play an important role in this finding. Franz et al.[21] reported a significant negative correlation between the absolute viral load in RSV infections and an elevated CRP. Our study showed that RSV was the predominant virus among our patients and CRP levels in patients with RSV infection was lower than that of patients with other viruses. But this difference could not reach significant level. Although RSV was also the most frequently observed virus among non-atopics, serum CRP levels did not show similar low levels.

Although children with positive parental history of atopy experience their first virus-induced wheezing at an earlier age, personal atopy was not found as a risk factor for predicting the severity of the first virus-induced wheezy episode. Atopy only effected the day of hospitalization. Atopic patients tend to be hospitalized longer than nonatopcs'.

This study had some limitations. Although a large group of patients was studied, the number of patients in the subgroups of atopics and nonatopics were small.

The strength of our study was ability to diagnose viral agents precisely with PCR technology, and the presence of allergy skin prick test one month after discharge from the hospital when immune system has been restored.

In conclusion, our results suggest that first virus-induced wheezing in 0-36 month aged children were not associated with personal atopy and children with positive family history of atopy had their first virus-induced wheezing at an earlier age. And also severe cases had more frequent recent history of respiratory tract disease of the household. The most detected viruses were RSV and Inf. The number of infants with severe wheezing may be decreased by developing and sustaining effective strategies to increase influenza vaccination rate.

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