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Study on Human Metapneumovirus and Atopy as Risk Factors of Wheezy Chest in Infants and Young Children.

Hanan M. Hamed[1]*, Sally Ahmed Farid El-Sahrigy[1], Nadia Ahmed Amin Moustafa[2], Nihal Mohamed El Sayed El Rifai[3], Nehal S. Hasan[4], and Sherif Moustafa Abdel Aziz[5].

[1]Professor of Pediatrics, Pediatrics Department - National Research Centre, Dokki, Cairo, Egypt.
[2]Professor of Pediatrics. Faculty of medicine - Cairo University, Dokki, Cairo, Egypt.
[3]Lecturer of Pediatrics. Faculty of Medicine - Cairo University, Dokki, Cairo, Egypt.
[4]Professor of Clinical Pathology. Clinical pathology Department - National Research Center, Dokki, Cairo, Egypt.
[5]Assistant Lecturer of Pediatrics .Pediatrics Department .National Research Centre, Dokki, Cairo, Egypt.

ABSTRACT

Wheezing in children is a common problem encountered by family physicians. Identify young children with wheezy chest at risk of developing asthma later in life using asthma predictive index (API) and study the association of human metapneumovirus (hMPV) and atopy as risk factors for wheezy chest in these children. 50 infants and children complained of wheezy chest were included. They were subjected to the following : Full history taking with stress on atopic history, physical examination; absolute eosinophil count ;skin prick test and direct Immunofluorescent-antibody test (DFA) of nasopharyngeal mucus specimens for the diagnosis of hMPV infections. 64% of our patients were at high risk for asthma development by API. The prevalence of atopy was 42%. Separate univariate analysis examining risk factors for atopic wheeze showed significant associations with, allergic rhinitis (OR, 6.5 ;95%,CI ,1.23-36.9 ;P=0.02), eczema(OR, 5.11 ;95%,CI 1.29-20.22 ;P=0.02), and Parental asthma(OR, 7.08 ;95% CI ,1.72-21.49 ;P=0.004). Human metapneumovirus were found in 6% of the patients. According to API, 64% of our patients were at high risk for asthma development, where atopy was the prominent risk factor while infection with hMNV was less important risk factor.

Keywords: infants; young children, human metapneumovirus, atopy, wheezes, asthma predictive index.

Corresponding author

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INTRODUCTION

During the first years of life, pulmonary and non- pulmonary diseases can manifest as recurrent episodes of wheezing, which can be called the "wheezy baby syndrome" [1]. Wheezing results from any pathophysiologic process leading to impaired airflow and mediated by a reduction in airway diameter [2]. The narrowing of the airways can be caused by inflammation from asthma, an infection, an allergic reaction, or by a physical obstruction, such as a tumor or a foreign object that's been inhaled [3].

The incidence of wheezing in Egyptian infants and children under five concluded to be 55% for acute wheezing and 12% for recurrent ones [4].

Much attention has been focused on the strong association between atopic tendency and childhood wheezing [5]. Numerous studies showed a higher frequency of asthmatic symptoms in atopic children than in non-atopic children [6].

Many common respiratory viral infections can trigger recurrent wheezing, which in turn can have an impact later on in childhood. The most often identified viruses in the first episode of wheezing in infants are respiratory syncytial virus (RSV), rhinovirus, parainfluenza, and human metapneumovirus (hMPV) [3].

The hMPV has been identified in many countries as one of the leading causes of lower respiratory tract infections in young children [7], which is responsible for 5–10% of acute respiratory tract infections in neonates and children[8].

The hMNV is an enveloped non- segmented RNA virus belonging to genus Metapneumovirus, family Paramyxoviridae [9]. Two major genetic lineages have been identified termed subtypes A and B, which are further subdivided into four subgroups (A_1,A_2, B_1 and B_2) subtype A is the most dominant one [10].

The prevalence of atopic diseases continues to rise in modernized countries, without a clear explanation for this increase. One potential cause identified from epidemiologic studies of children is respiratory RNA viral infections leading to development of recurrent wheezing, asthma, and allergic sensitization [11]. Therefore, the aim of this work is 1) To identify young children with wheezy chest at risk of developing asthma later in life using asthma predictive index (API). 2) To study the association of human metapneumovirus (hMPV) and atopy as risk factors for wheezy chest in these children.

PATIENTS AND METHODS

This cross-sectional study was conducted on (50) infants and children with wheezy chest recruited from the Pediatrics Pulmonary Outpatient Clinic, Specialized New Children Hospital, Cairo University. The study was carried out in the period from April to June 2012.The study was approved by the ethical committee of the National Research Centre and Cairo University. Children less than 6 months and more than 6 years as well as children with pre-existing chronic chest disorder as tuberculosis and cystic fibrosis excluded from this study, as well as those who manifest with parasitic infestation.

They were subjected to: Full history taking with stress on wheezing apart from colds (frequency, its duration and methods of treatment), parental history of asthma, parental smoking, eczema, allergic rhinitis and allergic sensitization to egg, milk, or peanut. Thorough clinical examination for the patients. Complete blood picture (CBC) total, differential leukocyte counts and absolute eosinophil count. Chest X-ray (Antero-posterior).

Direct Immunofluorescent-antibody test (DFA) of nasopharyngeal mucus specimens for the diagnosis of hMPV infections in children [12] ,where it is prevalent in the period of the study.

Skin prick test were performed for the most Common 11 allergen (8 aeroallergens and 3 food).According to them we classified the patients into atopic and non-atopic groups.

Asthma Predictive Index (API) as noted by Castro-Rodriguez, 2010[13], was calculated in the all patients and atopic and non-atopic sub groups .A positive API score requires recurrent episodes of wheezing during the first 3 years of life and 1 of 2 major criteria (physician-diagnosed eczema or parental asthma) or 2 of 3 minor

criteria (physiciandiagnosis allergic rhinitis, wheezing without colds, or peripheral eosinophilia >4%). A loose index (<3 episodes/y and 1 of the major or 2 of the minor criteria) and a stringent index (>3 episodes/yand 1 of the major or 2 of the minor criteria) .

Allergy skin prick test

The method used was the prick method. The following allergen extracts were used: Aeroallergens(Dermatophagoides Farinae;Dermato pteranyssinus ;Hay Dust; Alternaria tenuis ;Moulds II ;Candida albicans; Cat epithelia; Dog epithelia)Food sensitization (Hen's egg; Grasses / cereals; Cow's milk) plus histamine and physiological saline which acted as positive and negative controls, respectively. An allergen skin test reaction with a mean wheal diameter of at least 3 mm more than the negative control would be regarded as positive and the subject would be defined as atopic.

No children received any antihistamines, ketotifen or corticosteroids for at least one week before skin prick testing.

All reagents obtained from Allergopharma D21462 Reinbek (Germany).

Diagnosis of hMPV infections

Sample collection

Nasopharyngeal mucus specimens were collected using a #5 Fr feeding tube attached to a 10 ml syringe. Briefly, a maximum volume of 1 ml of sterile saline was administered to the subject's nostril by gently pushing the piston of the syringe; the fluid was then suctioned back into the syringe to obtain the washings of the nasal secretions. The specimens were temporarily stored on wet ice in a cooler and transported within 8 hours of collection to the laboratory where they were separated into 4 aliquots and stored at -70°C until the time of analysis [14].

Principle of Test

The IMAGEN hMPV test contains monoclonal antibodies conjugated to fluorescein isothiocyanate (FITC). The conjugated antibodies bind specifically to viral antigens present in all strains of hMPV**.** The reagent is used in a one-step direct immunofluorescence technique. The stained area is mounted and viewed microscopically using epifluorescent illumination. If hMPV antigen is present, characteristic bright apple green fluorescence is seen in infected cells [15].

Statistical Analysis

The SPSS package system version 14.0 for windows (SPSS, Chicago and IL., USA) was used for data management and analysis. Quantitative data was presented as median and range. Qualitative data was expressed as frequency (absolute numbers and percent %). Pearson chi-square test was used for statistical analysis of the qualitative data. Fisher's exact test used to frequencies between studied groups. Statistical analysis considered significant when P-value was ≤0.05. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to estimate the strength of the association.

RESULTS

The patients' age , ranged from 6-72 months with median age 32months ,70% were males and 30% were females. The seasonal distribution of the patients was 38% in April, 34% in May and 28% in June.76% of the patients from urban areas and 24% were from rural areas.

Eosinophilia (≥ 4 %) found in 38%. The median absolute eosinophilic count was 164 (112.5 -270.8) and median relative eosinophilic count was 2 (2- 4).

According to Asthma Predictive Index (API), 64% of all the patients were of high risk for asthma development.

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The demographic and clinical data of the all cases are shown in table 1.

Table 1: The demographic and clinical data of the all cases

Variable	Frequency(%)
Age < 36 moths	29(58%)
Urban area	38(76%)
Parental smoking	23(46%)
Parental asthma	26952%)
History of eczema	13(26%)
Allergic rhinitis	9(18%)
Wheezing apart from cold	28(26%)
Treatment with steroids	24(48%)
High risk for developing asthma by API	23(46%)
Eosinophilia (≥ 4 %)	19(38%)
Increase in bronchovascular markings in the chest plain x-ray.	50(100%)

The Patients were classified to have atopy as defined by at least one skin prick test allergen positive response into 2 groups atopic group (42%) and non-atopic group(58%) (Table 2).

Table 2: Univariate analysis of risk factors for atopic wheeze

	Atopic wheezer	Non Atopic wheezer	OR	95% CI	P value
Number	42%(21)	58%(29)			
Age<=36months	57.1%(12/21)	17/29	0.94	0.3-2.93	0.9
Male	37.1%(13/21)	62.9%(22/29)	0.517	0.152-1.76	0.29
Urban	44.7%(17/21)	55.3%(21/29)	1.3	0.36-4.7	0.48
Fever	42.9%(9/21)	41.4%(12/29)	1.06	0.34-3.31	0.9
Sibilant wheeze	76.2%(16/21)	72.4%(21/29)	1.22	0.33-4.44	0.76
Allergic rhinitis	(7/21)	(2/29)	6.75	1.23-36.9	0.02
Wheezing apart from cold	47.6%(10/21)	62.1%(18/29)	0.56	0.18-1.7	0.31
History of eczema	42.9%(9/21)	(4/29)	5.11	1.29-20.22	0.02
Parental smoking	57.1%(12/21)	37.9%(11/29)	2.18	0.69-6.85	0.18
Parental asthma	76.2%(16/21)	34.5%(10/29)	6.08	1.72-21.49	0.004
Recurrent	61.9%(13/21)	41.4%(12/29)	2.3	0.73-7.27	0.15
Treatment with Steroids	61.9%(13/21)	37.9%(11/29)	2.66	0.84-8.46	0.09
Eosinophilia≥ 4 %	47.6%(10/21)	31%(9/29)	2.02	0.63-6.46	0.23

OR:odd ratio
95%CI: confidant interval

Among the atopic group 6% gave positive results to all 11 allergens, the highest allergen (36%) was for cat epithelia and the lowest (10%) for cow's milk (figure 1).

Figure 2 showed the distribution of food sensitization and aeroallergen according to SPT.

Separate univariate analysis examining risk factors for atopic and non-atopic wheeze are shown in (table

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2). There were significant association between atopy and allergic rhinitis,eczema, and Parental asthma (P=0.02, P=0.02,and P=0.004)respectively.

Risk of asthma development according to API was significantly higher in atopic cases in comparison to non atopic cases(85.7% vs 48.3%, p=0.006) figure 3.

Among the all cases, hMPV were found in three cases(6%). They were two boys and a girl, their age ranged from 30 to 66 months and two lived in an urban residence. The three cases were atopic, had family history of parental asthma and two of them had history of parental smoking.

Figure 1 :Frequency of allergen by Skin prick test in atopic group

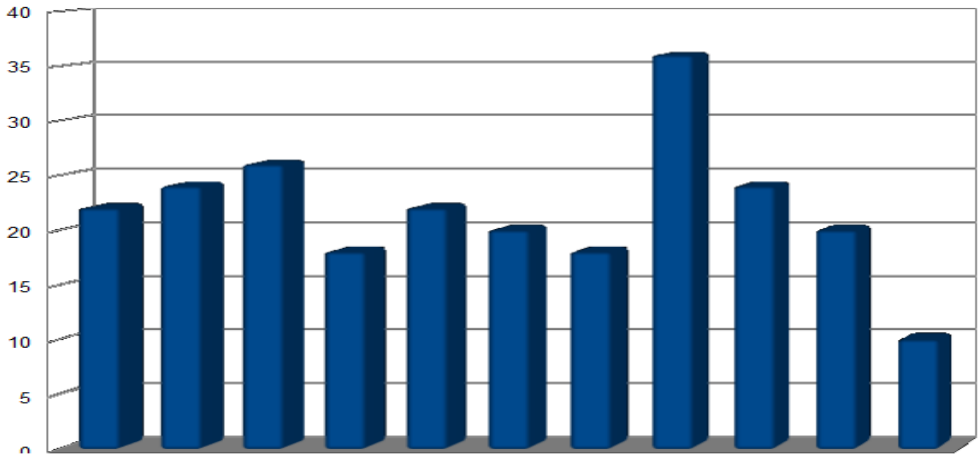


Figure 2: Distribution of allergic sensitization by skin brick test (SPT) according to food and areo-allergin

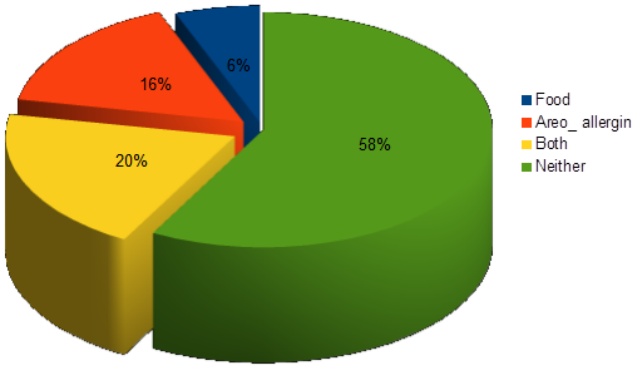
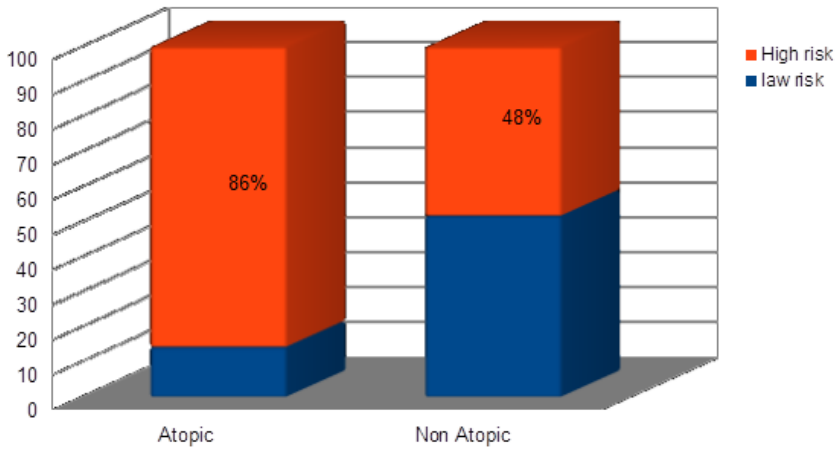


Figure 3: Risk for asthma development according to asthma predictive index (API) for atopic and non-atopic wheezers.



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DISCUSSION

Most cases of asthma begin during the first years of life, so identification of young children at high risk of developing the disease is an important public health priority. The aforementioned considerations have suggested that identification of symptomatic infants and young children who are prone to develop asthma may be very important for the development of a strategy for early intervention aimed at changing the natural course of the disease [15].

The patients in the current study had a median age of 32 months, These results came in agreement with many studies [16,17]. They reported high prevalence of wheezing in developing countries in the same age range. Gupta et al [18] clarified that young children have smaller airways, decreased respiratory reserve, increased oxygen consumption and metabolic demands, and less robust compensatory mechanisms. It is important to be cognizant that this population can progress to severe respiratory failure more quickly than their older counterparts [18].

In the present study, male gender was 70% ,these results were in agreement with Lima et al, and Chong Neto et al, [19,20] showing that the majority of the wheezing chest patients were males and considered male gender to be a major risk factor for wheezing. The reasons for the higher prevalence of asthma in boys may be that their airways develop relatively slowly compared with lung volume (dysanapsis) and are easily sensitized to indoor allergens such as house dust mites and cat dander[21].

Seventy six percent of the patients were from urban areas . Our results coincided with Ali et al [22] who reported that urban areas showed high rate of wheezing compared to rural areas . This may be due to the fact that urbanization with its high levels of vehicle emissions and Westernized lifestyle parallels the increase in respiratory allergy in most industrialized countries ; which was explained by the hypothesis that childhood farm environment seems to have a protective effect against allergic rhinitis.

The blood picture of our patients showed eosinophilia (≥ 4 %) in 38% . This was in agreement with Castro-Rodriguez [13] he also considered normal eosinophilic count in wheezing infants is a better predictor for wheezing remission by the age of 6 years than measurements of allergic sensitization.

In the present study,the asthma predictive index (API) showed that 64% were of high risk for asthma development. These results coincided with Suh and Koh [23]who used the same index ,they added that this index is a useful for early-stage discrimination between those who are likely to develop asthma and those who are not, in order to avoid over-diagnosis and/or over-treatment, and more importantly, to provide proper management and medical resources to those at risk. Beigelman et al [24] reported that the API, is used to predict asthma in longitudinal studies In most health care settings, it is easy, cheap, and probably reliable method.

Forty-two of our patients are atopic according to Skin prick test (SPT). They gave positive results for ≥1 allergen and 6% gave positive results to all 11 allergens. This was similar to results of De Vera et al., 2003[25] as a total of 37% of the children demonstrated positive skin test results for ≥1 allergen.

The most common allergen found was for cat epithelia (36%) and the least common was for cow's milk (10%). This was in agreement with Chinoy et al [26] who found sensitizations to cat epithelium is common, even in subjects who claimed no direct exposure.

Allergic sensitization to foods alone was 6% while 14% had aeroallergen and 22% had both . These results are in agreement with Guilbert el al [27] who found allergic sensitization to foods alone was uncommon (7%) compared with sensitization to aeroallergens (28%). They concluded that the high prevalence of aeroallergen sensitization suggests that aeroallergens might have an important role in the early development of asthma. Early intervention with an inhaled corticosteroid can significantly attenuate, or perhaps even prevent, the allergic march from the initial stages of allergic sensitization to the subsequent development of asthma in toddlers with episodic wheezing.

Eczema , rhinitis and Parenteral asthma, were independently significant risk factors for atopy in our patients that go parallel to Guilbert al, and Kurukulaaratchy et al [27,28]. However they also found positive

association with male sex and eosinophilia (≥ 4 %) that were in disagreement with our result.

The atopic group of patients showed a highly significant elevation of allergic rhinitis percentage compared to the non-atopic group. This was in agreement with Van Bever, and Castro-Rodriguez, [29,13] who found allergic rhinitis was one of the important tools in the Asthma Predictive Index (API). On the contrary, Castro-Rodriguez et al [30] reported that no one with positive API suffered from allergic rhinitis.

The atopic group of patients showed a highly significant elevation of eczema percentage compared to the non-atopic group. Sangsupawanich et al, and Chipps [31,32]showed that patients with atopic dermatitis have an increased risk of respiratory symptoms such as wheeze and cough. Graziella et al, [33] reported that atopy is generally believed to be a crucial determinant in the future development of persistent asthma.

Parentral asthma was significant positive in atopic compared to non atopic ,this result coincided with Chong Neto et al, Castro-Rodriguez et al, and Maksimovic et al [20,30,34], who reported that strong family history of allergic disease was the strongest risk factors for development of atopy

Kurukulaaratchy et al [28] illustrated an important role for asthmatic family history in the manifestation of wheeze, regardless of whether or not the subject is atopic. Thus, even in the absence of personal atopy, they have found that maternal asthma is independently associated with wheezing at 10 years of age. The mechanism behind such relationship remains obscure but, it may involve in utero factors.

According to API, our results revealed 85.7% of the atopic study group was of high risk for asthma development, which was of high significance compared to the non-atopic group. Graziella et al [33]reported that atopy is generally believed to be a crucial determinant in the future development of persistent asthma. Wheezy infants who have a positive asthma predictive index (API) or are atopic are more likely to respond to treatment than episodic viral wheezers [35].

We studied the frequency of hMPV as the second most common cause of wheezing in children after RSV. Our results revealed a frequency of 6% , their ages were 30 to 66 months. Similar findings by an Egyptian study [36] who found prevalence of 8% in infants and children with wheezy chest aged from 2-24 months. Essam et al [37] found that hMPV may be responsible for 5 to 15% of cases of URI in Egyptian children . Our results coincided with the fluctuating incidence of its infection that has been reported by groups from different areas, varying from 2.2% to 43% in respiratory tract samples from patients with acute respiratory infections in Chinese and American patients [38,18].

The prevalence of hMPV may differ according to geographical distribution, or by other factors such as social, environmental, or climate conditions may be involved [36].

The all three hMPV cases belonged to the atopic classified patients. This coincided with Kusel et al., 2007[39] who reported that viral infections interact with atopy in infancy to promote wheezing and asthma later on.

Dorothy and Mitchell [11], demonstrated that respiratory infections by RNA viruses may be sufficient to drive the development of atopic disease. This mechanism initiated through the initial production of anti-viral IgE. They added that mechanistic and epidemiologic studies are still needed to tease out the actual role that viruses play in the development of clinical atopic disease, and we await these future studies with much anticipation.

CONCLUSION

Male sex, young age <36 months and urban area frequently distributed in our wheezy patients. The atopy was the prominent risk factor while infection with hMNV was less important risk factor, however all positive hMPV were atopic. A study on large scale is needed to clarify the relation between atopy and virus infection.

There is a strong association between atopy and parenteral asthma, eczema and rhinitis. Consequently, intervention strategies to prevent atopic sensitization by allergen avoidance in early life must be applied in an attempt to modify the development of childhood allergy, wheeze, and asthma.

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