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ORIGINAL ARTICLE

Is there an association between wheezing and pneumonia?

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Abstract
Objective: The aim of this study was to investigate whether there is a relationship in school aged children between wheezing and pneumonia prior, during, or following the pneumonia episode.
Patients-Methods: One hundred and three children with community acquired pneumonia who were hospitalised were recruited along with 55 controls.
Results: During hospitalisation wheezing was audible in 11/103 (10.6%) patients with pneumonia and in none of the controls (p=0.009). Wheezing ever or asthma was elicited in 29/103(28%) patients with pneumonia and in 8/55 (14.5%) of the controls and this difference was not significant. Two years after the hospitalisation with pneumonia, wheezing episodes occurred in 12/103 with pneumonia and 1/55 of the controls (p=0.034). Among those who developed asthma following pneumonia 11/12 also had wheezing prior to pneumonia.
Conclusion: There is an excess of wheezing prior, during, and after an episode of pneumonia in school aged children and therefore children with pneumonia should be followed up carefully.

Introduction

Pneumonia is among the most common infections affecting the respiratory tract in childhood.[1,2] There is evidence that wheezing episodes predispose to pneumonia in pre-school aged children,[3,4] but the evidence is not so strong for their school aged counterparts.[3,4] Conversely, children with pneumonia during the first three years of life were more likely to have physician diagnosed asthma and current wheezing at the age of 6 or 11 years.[5] Furthermore, wheezing is associated with right middle lobe syndrome which is a type of persistent pneumonia,[6–8] although such a strong association has never been disclosed for uncomplicated community acquired pneumonias, particularly at school age. Population risk factors such as indoor air pollution, poor socioeconomic status, parents' smoking and urban residence have been suggested as risk factors for pneumonia, especially in early childhood.[9]

All these relations imply a potential link of asthma and pneumonia which has nevertheless not definitely defined, especially for older children. Of note is the fact that although the prevalence of pneumonia is similar, in developed

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countries the same is not true for asthma. According to the International Study of Asthma and Allergies in Childhood (ISAAC) study, Greece has an asthma prevalence lower than 5%[11] whereas American cities as well as Australian, British and Scandinavian ones have an asthma prevalence rate much higher than that of Greece.[10] Therefore conclusions in the latter countries may not be relevant for the former as we have similar prevalence of pneumonia but very different asthma prevalence. The aim of this study was to investigate whether asthma or a history of asthma was a predisposing factor for all cause community-acquired pneumonia requiring hospitalisation in children older than six years of age, and conversely whether pneumonia is a triggering factor for wheezing following the pneumonia episode.

Patients and methods

All children, older than six years of age, admitted to our department with radiographically ascertained unilateral lobar or segmental community-acquired pneumonia during a two-year period were recruited. They had not been taking antibiotics or inhaled corticosteroids prior to the diagnosis and they had not been vaccinated for pneumococcal infections with conjugate or polysaccharide vaccines and had no history of recurrent pneumonia. For the purpose of the study, a paediatric radiologist reassess blindly and independently the type of consolidation. Patients' eligibility was determined by the absence of anatomic abnormalities of the respiratory tract, immunological defects, congenital heart disease, chronic diseases or other concurrent infections, progressing neurological conditions or psychomotor retardation. For every two patients one control patient was assigned to the study, hospitalised during the same period with either urinary tract infection or gastroenteritis and matched for age and gender. The age of the controls was the mean age of the respective patients +/− 1 year. All patients' parents were contacted by telephone and a structured questionnaire was asked. One part of the questionnaire was filled in using the chart data (age, gender, pneumonia characteristics, laboratory findings, history of prematurity, breast feeding) and the remainder was filled out over the telephone. The information provided concerned demographic characteristics such as socioeconomic status (with questions asking about living or not in their own house, the size of the house, educational level of the parents, parental smoking at home) the history of current asthma, during the last two years after pneumonia, or asthma in the past prior to hospitalisation with pneumonia, as well as the history of allergic rhinitis and eczema. Questions were also answered for history of previous infectious diseases.

Statistics

The relationship between pneumonia and each potential risk factor or adverse outcome of post-pneumonia wheezing was studied using separate univariate analysis with chi-square test. Each risk factor was treated as a categorical variable. The variables that constituted the core of the study design were also tested jointly in order to adjust for mutual confounding in multivariate logistic regression analysis. Laboratory findings which were continuous variables were tested using t-test or Mann Whittney depending on the data distribution.

Socioeconomic status was assessed by the parents' educational status, the ownership of house and the crowding of the house as represented by the number of m^2 per subject.

Two equations of multiple logistic regression analysis were tested. Both had as dependent variable pneumonia or control group. The first had as independent variables wheezing ever, taking inhaled medications ever and wheezing on auscultation during hospitalisation. The second has wheezing ever, wheezing after the hospitalisation and inhaled medications after the hospitalisation.

Results

The study population consisted of 110 patients with lobar or segmental pneumonia and 55 controls. Seven patients with pneumonia declined to answer the questionnaire and therefore the final study population consisted of 103 patients with pneumonia and 55 controls. There was no difference with respect to gender as the pneumonia group consisted of 55 boys and 48 girls and the control group included 27 boys and 28 girls. There was also, as expected because of matching, no difference with respect to age. There was also no difference among factors which affect the prevalence of wheezing, such as prematurity, breast feeding, and parental smoking at home. The mean age of the pneumonia group at the time of admission was 8.7 +/− 1.4 years and the respective age for the control group was 9.1+/− 1.8 years.

Among the clinical characteristics during hospitalisation, wheezing was more prevalent in pneumonia group as it was noticed in 11/103 patients whereas wheezing was not audible in any child of the control group (p=0.009). Similarly, inhaled bronchodilator was administered in 15/103 patients with pneumonia and in none of the control group (p=0.001). The laboratory findings of the pneumonia and the control group are shown in the Table 1. The blood culture was positive for pneumococcus in only 3/103 patients with pneumonia and in neither child of the control group. Parapneumonic effusion was noticed in 12/103 patients with pneumonia. The duration of hospitalisation for the pneumonia group was (mean 4.56+/−2.8 days) not significantly different from that of the control group.

Parents' educational status and the ownership of house were not significantly different between pneumonia patients and controls. However, the crowding of the house as represented by the number of m^2 per subject was significantly different (pneumonia group 23.7 +/− 8.2 versus control group 20.6+/−7.8, p=0.03).

The history of previous infection was not indicative for the development of pneumonia with the exception of previous lower respiratory tract infections, which was significantly higher in the pneumonia group ($p<0.001$).

Wheezing ever or asthma diagnosed ever by the physician or administration of inhaled pharmaceutical agent was not a risk factor for pneumonia group (wheezing ever 21/103 patients with pneumonia versus 8/55 control group). It should be noted that among the eleven children with

Table 1 Laboratory findings of the pneumonia and the control group

	Pneumonia		Control		
Variable	Mean	SD	Mean	SD	P
Hb (g/dl)	12.07	1.16	12.42	1.14	NS
Wbc (cells/ml)	18322	16909	11234	5610	0.003
Neutrophils (cells/ml)	13913	2566	7863	1842	0.034
Platelets (cells/ml)	300806	100040	293370	70043	NS
CRP(mg/l)	117	92	48	56	<0.001
ESR (mm/h)	94	13.7	46	14.9	<0.001

NS: not significant.

audible wheezing on auscultation during hospitalisation only 3/11 had experienced wheezing before. Similarly, allergic rhinitis; atopic dermatitis; and family history of atopy were not associated with the pneumonia group as they were analogously distributed in patients with pneumonia and in the control group.

Two years after the hospitalisation of pneumonia, wheezing episodes occurred in 12 children with pneumonia and in one child of the control group (p=0.034). Inhaled agents for asthma were given to 11/103 children with pneumonia after the hospitalisation and in none of the control group (p=0.008). Only 3/12 children of the pneumonia group who developed asthma after pneumonia had wheezing during hospitalisation and 11/12 also had wheezing prior to pneumonia.

No equation of logistic regression analysis showed a statistical significant parameter.

Discussion

Our data suggest that there is clearly a relationship between pneumonia and wheezing but this association should be interpreted cautiously in different periods, during hospitalisation, prior to pneumonia and following pneumonia.

The finding that in 11/103 children with pneumonia there was wheezing during hospitalisation and in 8/11 this was the first time that they had wheezing according to the parents. Wheezing was audible by the doctor and therefore was not further evaluated by spirometry test. That means that this was infectious induced wheezing during pneumonia. However, in children older than 6 years viral pneumonia does not usually require hospitalisation and therefore one could argue whether bacterial respiratory infection could induce wheezing. It is estimated that in about 16%–25% of children with pneumonia there is a mixed bacterial–viral infectious etiology[11,12,14] and therefore viral induced wheezing would be plausible. Furthermore viral infection of the upper respiratory tract often precedes symptoms of pneumonia and therefore could also have caused viral induced wheezing. It is also known that pneumococcus and mycoplasma are the most common bacteria that cause pneumonia in this age.[11,13,14] Pneumococcal disease among children is associated with isolation of RSV, influenza virus and adenovirus.[15] Mycoplasma except from pneumonia causes airway hyperreactivity which clinically becomes overt with wheezing.[13,15] The majority of the cases had the inflammation indices much higher with respect to the control group (white blood cells, neutrophils, CRP, ESR) which indicate that the majority of pneumonia may be of bacterial origin given that their consolidation was either segmental or lobar.

Prior to hospitalisation, wheezing was elicited in 29/103 children with pneumonia. This does not reached a statistically significant level compared to controls but the proportion of 30% wheezing in pneumonia patients is much higher than the respective 5% which is the asthma prevalence in Greece according to the previously mentioned ISAAC study.[10] It is also double the wheezing-ever prevalence in the control group and therefore in a larger sample may have reached statistical significance. To our knowledge there are two more studies which investigate whether wheezing-ever is a risk factor for pneumonia in school aged children, both of which were conducted in developed countries.[3,4] Both studies showed a significant association between wheezing ever and the development of pneumonia. However, the country origin of the corresponding studies was Finland[3] and Australia;[4] areas with asthma prevalence 4–6 times higher to that of Greece, according to the ISAAC study.[10] Therefore it is mathematically more plausible in countries with high asthma prevalence to depict wheezing as a significant risk factor for pneumonia which does not show a substantial variation of prevalence among developed countries. Furthermore, in the aforementioned studies, controls were healthy children and not children with disease of a system other than the respiratory system as was our case. Their design involved all the community acquired pneumonia of their area irrespective of hospitalisation whereas our study involved only hospitalised children with community acquired pneumonia and therefore our controls should also have been hospitalised children.

Lower respiratory tract infections were a factor that predisposed significantly to pneumonia. This finding is in agreement with Heiskanen et al[3] who also revealed that not only in preschool aged children but also in their school aged counterparts recurrent lower respiratory infection was a risk factor for pneumonia. Otitis media was a risk factor for pneumonia in early childhood but not in school age which is also in agreement with our study.

Socioeconomic status as represented by the parental educational level and the ownership of a house was not associated with pneumonia. However, the lack of an association may be attributed to the homogeneity of the study population with respect to their parental educational level. In fact, household crowding was a significant factor

for the development of pneumonia. This finding is in accordance with Cardoso et al.[16] who found that household crowding put children at increased risk for acute respiratory tract infections, but may protect against asthma.

Our study also tested the prevalence of wheezing episodes following pneumonia. Wheezing was significantly more common among children with pneumonia compared to the control group. The proportion of children with wheezing following pneumonia was 12% which was more than double compared to that expected in the general population. However, the majority of these children had also wheezing prior to the pneumonia incident. This is a point that has also been observed by Clark et al.[17] who concluded that a high proportion of children hospitalised with pneumonia either already have unrecognized asthma or subsequently develop asthma. It should be noted that this is not uncommon even in early childhood as an excess of wheezing was shown, which was not significant, after infantile pneumonia.[18,19]

Among the drawbacks of our study was that there was a lack of data regarding the infectious etiology of pneumonia. Nevertheless, our design was to investigate whether there was an association of wheezing with all cause community acquired pneumonia which required hospitalisation and therefore the lack of infectious identification did not influence our results. Furthermore, our study was retrospective and the diagnosis of wheezing prior to pneumonia was based on parental recall. However, retrospective parental report for memorable events is likely to be valid and for that reason international epidemiological studies have used this tool to identify asthma prevalence.[10] It should also be argued that there is no information regarding the atopy status of the participating children. Atopy status may not be different between patients and controls and therefore the excess of wheezing in the pneumonia group could not be explained on the grounds of atopy surrogates. Nevertheless even an excess of atopy markers in the pneumonia group would not alter our observation, indicating, in such a case, that children with atopy are more prone not only to wheezing but also to pneumonia. Such speculation cannot be made on the basis of our data.

In summary, there is an excess of wheezing prior, during, and after pneumonia incidents. This excess, which was as high as 2–3 times the prevalence observed in general population, reached a significant level for the period during and after pneumonia. Therefore these cases need a careful follow up in order to unmask any type of latent asthma with the appropriate medical history.

Conflict of interest

The authors have no conflict of interest to declare.

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