

Evaluation of Children with Infantile Wheezing at The Age of Six: A New Asthma Predictive Index

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Abstract: Recurrent wheezing is a common problem in young children. It is difficult to diagnose real asthma in children under 6 years of age because of different phenotypes of wheezing related disorders in this age group. This study was performed in the outpatient clinic of Pediatric Allergy and Immunology Department. This study includes 208 children who visited at least three times during the first three years of their lives with the complaints of wheezing attacks. Those who visited the department with the diseases such as congenital malformation, gastro esophageal reflux, tracheobronchial fistula, aspiration syndrome, heart failure, cystic fibrosis and immunodeficiency were eliminated and excluded from the study. Transient early wheezing 107 (51,4%), non atopic wheezing 28 (13,5%), atopic wheezing 73 (35,1%) have been detected. Sixty five (31,3%) of the children were females and 143 (68,7%) were males. After the separate and together evaluation of the risk factors we have developed an asthma prediction index. The values of the index have been found as it is written below. The sensitivity 83%, specificity 90,7%, positive predictive value 89,2%, negative predictive value was 85,2%. It might be possible to distinguish which of the children who comes to the department with the complaints of recurrent wheezing might suffer from asthma by using the asthma prediction index. It might also be possible to change the natural course of the disease by developing early intervene strategies.

Keywords: wheezing, child, wheezing phenotypes, asthma predictive index.

INTRODUCTION

Wheezing is a sound produced when air passes through the narrowed bronchial airways due to inflammation, bronchospasm and mucosal edema. Wheezing is generally produced in the lower airways. One out of every three children presents with at least one wheezing attack by the age of three. This ratio increases to 50% by the age of six [1]. Wheezing may start and subside as a single attack. It can last for a long time or it can be seen as recurrent attacks. Three or more wheezing attacks in children who are less than two years old is defined as recurrent wheezing [2]. There are many reasons for recurrent wheezing during the nursing period, which are inflammatory events such as asthma, infections, congenital malformations, gastroesophageal reflux, tracheobronchial stenosis, upper respiratory infections, extrathoracic diseases, and aspiration syndromes. [3].

According to the data obtained from longstanding prospective cohort studies starting from birth, there are different phenotypes of wheezing in children [4]. The first birth cohort that helped define different phenotypes in the preschool age group was performed by Martinez et al. in Tucson. At the end of this study, using phenotypes were defined as transient early wheezing, non-atopic wheezing, atopic

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wheezing, and children with no wheezing [5]. Using phenotypes based on the data of the aforementioned study is still well accepted. Children who had at least one wheezing attack in the first three years of their lives but no wheezing by the age of six are defined as temporary early wheezing phenotype. It is speculated that these children have narrow airways after birth that would result in a tendency to wheeze [6]. However, wheezing attacks are related to viral infections in non-atopic wheezing phenotype. It is told that there may be an alteration in the control of respiratory airways which may cause airway obstruction during viral infections. Children with atopy who had wheezing attacks in the first three years of their lives and who still had wheezing by the age of six are grouped as atopic wheezing [1]. Children who have atopic wheezing can be symptomatic at any age. However, at least one symptom is noticed before the age of six and they become sensitized to at least one respiratory allergen [1, 7]. Early allergic sensitization is the important risk factor that will result in severe disease and serious loss in pulmonary function. Early allergic sensitization can produce a genetic tendency toward future asthma development [1, 8, 9]. It is difficult to diagnose asthma in children less than six years of age because of different phenotypes of wheezing. This is why it is of great importance to reevaluate children after six years of age who presented with recurrent wheezing in the early childhood period.

MATERIALS and METHOD

In this study, we included children who presented with at least three wheezing attacks in the first three years of their lives in Pediatric Allergy and Immunology Polyclinic during a 10-year period (2001-2011). Patients who had congenital malformations, gastroesophageal reflux, tracheobronchial stenosis, aspiration syndromes, heart failure, cystic fibrosis and immune deficiency were excluded. Medical charts of children who were involved in the study were evaluated after six years of age retrospectively. A course of wheezing is based on a patient's demographic features in clinical and laboratory data. In this study, our aims were to determine the risk factors for wheezing in children and the incidence of wheezing phenotypes and to develop an asthma predictive index that is valid and appropriate for our patients.

Three different recent phenotypes which are the basis for our study have been previously defined in the literature. Wheezing in children was defined as temporary early wheezing if it was seen before three years of age but no later than six years of age. However, it was defined as persistent wheezing if wheezing attacks kept happening after six years of age. The persistent wheezing group was also divided into atopic and non-atopic wheezing based on the presence or absence of atopies. Atopy is defined as positive skin test reactivity to common aeroallergens and/or raised total serum IgE or specific IgE radioallergosorbent test and/or the presence of eczema.

A new form was generated for each and every case suitable or eligible for this study, which included clinical features of the patient, past medical history, family history along with laboratory data were included.

LABORATORY

Peripheral blood samples were obtained from patients in this study before the age of three and after six, and eosinophil levels, serum IgE levels, specific IgE levels and skin prick tests were recorded. Children older than six years of age and cooperative were administered respiratory function tests. Reversibility test positivity was accepted as an increase in FEV1 of 12% and an increase of 15% in PEF after the application of appropriate doses of beta-2 agonists. In our hospital, total IgE and specific IgE levels

were studied by ELISA (Beckman coulter, immage 800, immunochemistry system). Absolute eosinophil count of 450 per microliter or more than 5% was accepted as eosinophilia. Prick skin test was done in our allergy and immunology laboratory after an appropriate time of discontinuation of antihistaminic anti-influenza medications and cough syrups. It was performed by dropping a droplet of standard allergen solvent on the skin and infiltrating the epidermis via a lancet. During the skin test, different allergens were used, including pollens, fungal spores, house dust mites, animal feathers, and wide variety of food substances (Stallergenes S.A. France, Allergopharma solutions). Twenty minutes after this test was done, skin reactions were evaluated. The edema that developed on the skin was compared with negative (antigen dilution solution) and positive (histamine hydrochloride 1 mg per milliliter) controls, and indurations at least 3 millimeter larger than the negative control group were accepted as positive.

STATISTICAL METHODS

Data was analyzed by using a statistical package for social sciences (SPSS for Windows 11) Chicago, USA. The Kruskal-Wallis test risk analysis was performed for numerical data. For meaningful results, the Mann-Whitney U test was performed. The Chi-square test was used to compare categorical data. Fallibility was accepted as $P < 0.05$. The asthma predictive index was created by the multivariate logistic regression method.

RESULTS

Sixty five of the children (31.3%) were female, 143 (68.7%) were male. The male sex was higher in all wheezing phenotypes. Among different wheezing phenotypes, early wheezing was detected in 107 (51.4%) of children. Twenty eight of the children had non-atopic wheezing (13.5%) and atopic wheezing was detected in 73 (35.1%) of children [Figure 1].

Detected risk factors were allergic rhinitis, asthma in a first-degree relative, owning a pet at home, IgE levels of more than 50 IU per milliliter at the time of presentation (before three years of age), sensitization by respiratory airway allergen detected by prick test or specific IgE levels, number of wheezing attacks being more than five in the first three years of life, age at start of wheezing after nine months of age ($P < 0.05$) [Table 1]. In our study, sensitization to food allergens, birth via cesarean section, and premature birth were detected as risk factors for early wheezing. However, male sex, asthma in second-degree relatives, exposure to cigarette smoke, smoking during pregnancy, allergic rhinitis in the family, atopic dermatitis in the child or in his/her family, visiting or staying in a daycare center, or mechanical ventilation treatment in the neonatal period were not detected as risk factors ($P > 0.05$). It was found that having at first-degree relative with asthma is a risk factor; however, asthma in the mother, father or siblings or sensitization to multiple allergens did not influence asthma development in the future ($P > 0.05$).

Creation ff Our Asthma Predictive Index

All the risk factors that we detected for permanent wheezing were analyzed by the multivariate logistic regression method step by step and an asthma predictive index was created for our patients [Table 2].

In this index, sensitization to respiratory airway allergens was considered as the major risk factor as it increases the risk of asthma development 31.6 times compared to the control population. A total IgE of more than 50 IU per milliliter, wheezing starting after nine years of age and number of wheezing attacks being more than five in the initial three years of life, which increase the risk of asthma 5.6, 3.3, and 2.2

times respectively, were accepted as minor risk factors [table 3]. The asthma predictive index (API) that we created had a sensitivity of 83%, specificity of 90%, possible predictive value of 89.2%, and negative predictive value of 85.2% [Table 4].

DISCUSSION

Recurrent wheezing in early childhood that presents with different phenotypes is very common and should be defined precisely. In this study, we tried to discover the risk factors and create an asthma predictive index (API) that is valid for outpatients.

In children who present with recurrent wheezing before three years of age, sensitization to allergens (rejected by prick test or specific IgE level) was found to be a risk factor for the persistent or future development of asthma compatible with the current literature ($P<0.05$) [10, 11, 12, 13, 14, 15]. When children presented with recurrent wheezing in the initial three years of age and had sensitizations to allergens were evaluated, it was found that sensitization to food was related more to early wheezing. However, sensitization to respiratory airway allergens was found to be risk factor for atopic wheezing and asthma development ($P<0.05$). The prevention of early asthma in kids (PEAK) modified the original asthma predictive index (API) by accepting aeroallergens defined as sensitization to aeroallergens as a major risk factor and replaced the allergic rhinitis in the physical examination to food sensitization as a minor risk factor [4, 16]. Similar to current literature, we found the early sensitization to respiratory allergens as the most important risk factor for asthma development. Contrary to the literature in our study, sensitization to food has not been associated with asthma development, as this type of sensitization was related more to transient early wheezing in children ($P<0.05$).

In the literature, there are publications which accept the IgE levels being more than 100 IU per milliliter as a risk factor for atopic wheezing [5,17]. There are no studies in the literature which accept IgE levels of more than 50 IU per milliliter as a risk factor for atopic wheezing. In this regard, our study is a pioneer study. In our study, IgE levels above 50 IU per milliliter and 100 IU per milliliter under three years of age were determined to be related to feature asthma development ($P<0.05$).

Given the data of our study, recurrent wheezing that develops after nine months of age can be predictive of positions of wheezing after six years of age and asthma development in the future ($P<0.05$). In fact, Tucson detected markedly high IgE levels at the age of nine months in children with atopic wheezing phenotype in this study. Nevertheless, there was no relation found between IgE levels in umbilical cord blood and atopic wheezing. IgE mediated sensitization in the first year of life was deemed to be responsible for the situation [1]. Similar to our study, the study that was done by Inal et al. showed that the age of the initial wheezing attack of children with early, temporary wheezing was lower than the children with atopic wheezing (18). The fact that there is a tendency to airway obstruction in the initial months of life due to anatomic and physiologic reasons support the idea that wheezing in the initial months of life is less related to asthma development [6, 19].

There was no observation of meaningful difference in terms of the wheezing attack numbers in the presentation between early temporary wheezing and atopic wheezing. The number of attacks in the atopic wheezing group increased continuously by the age of three, and hence this group was markedly different statistically from early temporary wheezing groups in terms of increases in the frequency of wheezing attacks. It was found that having more than five wheezing attacks in the initial three years of

life is a big risk factor for the persistence of wheezing ($P < 0.05$). In the study in Oslo (URECA) a new scale was discovered or created to predict asthma development by the age of 10 years by scoring the number of wheezing attacks in the initial two years of life, the number of months with continuous wheezing, and the number of wheezing attacks that required hospitalization (20). The relation between asthma and higher numbers of attacks in the first years of life in our study also supports the aforementioned study in Oslo.

The original asthma predictive index (API) was developed as a simple and useful method clinically based on the data of the TCRS study to predict the prognosis of wheezing in playschool children [1, 4, 5]. API is considered positive if there is frequent wheezing attack in the initial three years of life and any major risk factors or two positive minor risk factors out of three [Table 4]. Children who had positive API developed asthma at a rate of between 47.5 and 51.5% between six and 13 years of age. Five percent of children with negative ATI developed asthma between six and 13 years of age [4, 21]. The progression of early asthma in kids (PEAK) modified the original ATI by changing the aeroallergens as a major risk factor and replacing sensitization to food with allergic rhinitis in the physical examination as a minor risk factor [4, 16]. The Urban Environment in Childhood Asthma (URECA) discovered a new scale for predicting asthma development by age of 10 years according to the degree of wheezing in the initial two years of life in their study in Oslo. By scoring the number of wheezing attacks, the number of months with continuous wheezing, and the wheezing attacks that required hospitalization, a maximum score of 12 was developed. A positive correlation between asthma development and increasing score was detected. Sensitivity was 52% and specificity was 87%, above a score of five [4, 20]. The disadvantage of using or relying on these indexes is that they have a positive predictive value around 50% although they have a good negative predictive value [4].

In a study by Razi et al. in our country, no relation was detected between asthma in parents and the development of wheezing in children [17]. In the large cohort studies in the literature (1, 8, 22), the history of asthma in the family has been shown to be a risk factor for wheezing during childhood. We can deduce that the literature [1, 8, 22] of atopic dermatitis was not a risk factor for asthma development in our study. According to the available genetic evidence, asthma is a complex disease with an oligogenic or polygenic basis. Environmental factors have importance in the development of disease [23]. This disease does not show Glasgow Mendelian single gene defects although there are some genes shown to provide a tendency toward atopy [24]. The fact that our index did not include a family history of asthma or atopic dermatitis as criteria, which were major criteria in the original asthma predictive index, made us think that environmental and genetic factors were influential in this situation. Moreover, similar sample size compared to the Tucson study may be a factor for us not being able to determine a second major criterion. In our index, if major criteria is positive, API can be leading; however, if the major criteria is negative, the sensitivity of our API is 23.6% specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 61.4%. In other words, sensitivity becomes very low and specificity and the positive predictive value become 100%. This actually shows that factors other than sensitivity to airway allergens are inadequate in predicting the course of the disease.

The disadvantage of using these indexes is the fact that although they have a positive predictive value of around 50%, although they have a good negative predictive value, they will have a positive predictive value just run 50%. Therefore, predicting asthma development in the future is very difficult. We think that the API has a better positive predictive value compared to the original asthma predictive index and the other indexes. Hence, it is more appropriate to use our asthma predictive index as a screening test

for children presenting with recurrent wheezing. By doing this, we believe that by predicting the future asthma development in these children it is possible to change the natural course of the disease by developing early intervention strategies.

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