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Wheezing Phenotypes in Preschoolers

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ABSTRACT

The incidence of wheezing is very high during the first years of life. Up to 25-30% of the infants have at least one episode of wheezing. The diagnostic approache should start with the differentiation between congenital or inherited wheezing, and subsequently the diagnosis of acute, chronic or recurrent wheezing (RW).

In children with RW or chronic wheezing the somatic development is relevant. If the child presents a good nutritional status and a good general state, the most frequent diagnosis would be asthma. In children with failure to thrive the investigation plan will start with cystic fibrosis and gastroesophageal reflux.

There are two major classification of RW in children: according to symptoms and to the clinical course. Wheezing phenotypes based on symptoms are: 1) episodic wheezing, in which the duration of symptoms is short, without any symptoms between episodes, and they associate other sings of viral infection; and 2) wheezing with multiple triggers (beside infections they present wheezing during exercise, or after allergen exposure, or during emotional changes). According to clinical course there are three main RW phenotypes: 1) transient wheezing with early onset, during infancy; 2) persistent wheezing with the onset during the first 3 years of life and persistence of symptoms after 6 years, and 3) RW with late onset, after the age of 3 years. The last two may be related to atopy. In these children we use the Asthma Predictive Index (API) to identify the future patients with asthma that require lonf term therapy.

Keywords: Wheezing; Prescholers; Phenotype

INTRODUCTION

Acute respiratory tract infections in prescholers that associates wheezing are very common. By the age of 6 years old half of the children presented already at least one episode of wheezing. Several structural and functional particularities of the respiratory tract are responsible of the higher prevalence of wheezing in children as compared with adults. One of the reasons is the smaller caliber of the airways in children and a higher resistance to the airflow [1]. Another risk factors could be a lower pulmonary compliance in children, and a lower tissular elasticity which increases the risk for airways obstruction and also for athelectasis.

DIAGNOSIS APPROACH

Whenever we assess a child with wheezing we have to begin with the answer of two relevant questions:

a. Is wheezing due to congenital disorder or does it have an aquired origine?

b. How is the clinical course of wheezing: acute, chronic persistent or reccurent wheezing.

If we are facing chronic persistent or reccurent wheezing, the diagnosis aproach will start with two significant aspects: nutritional status and the general status of the chlild during the episode [1].

INTERNATIONAL CONSENSUS APPROACHING PRESCHOOL WHEEZING

During the past two decades numerous studies cntributed with major clarifications on recurrent wheezing (RW). Several documents where elaborated on this topic pursuing management consensus of RW which embodies the concerns of pediatricians, pulmonologists and allergologists on this topic [2]. Among these we mention only Global Initiative for Asthma (GINA) published initial in 1995 and the last version in 2019 [3].

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WHEEZING PHENOTYPES IN CHILDREN

In 2008, ERS Task Force described two temporal models of wheezing (phenotypes): episodic or viral wheezing and wheezing with multiple triggers [1-3]. In 2014 Brand PL, et al. published an up-to-date analysis of wheezing phenotypes in preschoolars reiterating the idea of the two wheezing phenotypes, with the same characteristics, bringing new arguments in favor of the long-term therapeutic approach in patients with recurrent symptoms [4].

Based on the current data that are available in the guidelines and consensus on RW we may clasify it either according to the triggers and symptoms, or to clinical course [2,5].

Several large cohorts of preschool children were published recently, each of them comprising one or more episodes of bronchoconstriction, with wheezing. These longitudinal studies provided data that allowed the development of clinical scores with some paraclinical investigations which are useful for the prediction of the clinical course towards asthma.

The ALSPAC Study (Avon Longitudinal Study of Parents and Children) included 14,702 children. The authors described 6 clinical wheezing phenotypes, defined on clinical criteria: a) children with rare or without episodes of wheezing (59% of the analised children); b) persistent wheezing, regardless the onset and the duration of persistent symptoms; two cathegories of c) early onset wheezing (during the first 18 months of life), one with transient course, d) the second one with prolonged wheezing; and two phenotypes based on the age at the onset, respectively e) wheezing with intermediate onset (between 18 months and 3.5 years); or f) RW late onset (after 3.5 years). The authors described different characteristics for each of these 6 phenotypes at the age of 7.5 to 8.5 years as referred to the pulmonary function, the association of atopy, and the allergologic assessment [6].

The PIAMA Study (Prevention and Incidence of Asthma and Mite Allergy) published by Dutch authors which monitored 4146 neonates (out of them 2877 remaining preschoolars that were completely assessed) until the age of 8 years, described only 5 wheezing phenotypes [7]. The main difference as compared with ALSPAC cohort is that PIAMA study does not recognize d) phenotype of early onset and prolonged clinical course. The other five phenotypes described in ALSPAC classification have similar traits and designations [7,8].

The ELFE cohort (French Longitudinal Study of Children) followed 18,041 newborns and revealed a high percentage of infants with their first episode of wheezing during the first 2 months of age [9]. The authors assessed the presence of wheezing at two months and at one year of life and described four slightly different wheezing phenotypes: a) non-wheezers; b) intermittent wheezing (with an intial episode of wheezing at two months and no other recurrence); c) persistent (if the infant had wheezing at two months and also at one year) and d) incident (when the first episode of wheezing occured after the age of two months). In this cohort several risk factors were related to persistent wheezing, such as: nocturnal cough, productive cough, signs of respiratory distress, maternal smoking [10], delivery by caesarian section, parental asthma [11] or other allergies like eczema or allergic rhinitis [12], and being the first child in the family.

Oksel used latent class analysis (LCA) and reported a series of 3167 adults aged 23 to 24 years, that were followed-up starting infancy. These participants completed reports of wheeze initially twice a year, and after 2 years of age, yearly, until the age of 16.5 years old [13]. The authors used the same 6 wheezing phenotypes from ALSPAC study. The assessment was based on questionnaires aplied to mothers and spirometry with bronchodilator test at the end point. The highest proportion of subjects with current asthma was in the persistent wheeze phenotype (99.7%), and in late-onset (school-age) phenotype (88.4%), while preschool-onset remitting phenotype revealed no asthma (94%), althought these subjects presented some spirometry abnormalities. Lung function was significantly less in the persistent wheezing and early-onset preschool remitting wheeze phenotypes compared with the never/infrequent wheeze phenotype.

WHEEZING - ASTHMA RELATIONSHIP

Worldwide numerous concerns on wheezing phenotyping and the identification of evolution patterns reflects the attempt of pinpoint the risk of developing asthma in these children.

The clinical course: wheezing

The diagnosis of wheezing is based on the anamnesis [1]. As the child ages, the great majority of infants and preschoolers become asymptomatic. The relationship between wheezing episodes with the onset during the first years of life and the development of asthma in older ages and during adulthood represents one of the main questions regarding the prognosis of these patients. The identification of risk factors and of triggers that correlates with the clinical course towards asthma represents the premise of early active intervention in the primary prevention of asthma. The majority of current guidelines and scores that attempt to define the risk for asthma in prescoolars with episodes of wheezing are based on the cohort assesed by Martinez F. during early 1990 known as Tucson's Children Respi¬ratory Study [10]. It comprised 1246 children that were followed from birth up to 15 years of age. The analyses of the data suggested that risk factors may be recognized and may induce the atopic response, type Th-2, when the infant or young child is exposed to some factos that associates bronhoconstriction and wheezing. Martinez F. was the first author that suggested that early onset, before the age of 3 years is correlated with good outcome [10]. This phenotype was designated as early transient wheezing. The association of atopy and late onset, after 3 years old is correlated with a higher risk of persistent wheezing and with a possible clinical course towards asthma after the age of 6 years.

All longitudinal studyes described two main evolution patterns of wheezing with the onset during preschools years, according to the association of risk factors. Among these factors maternal smoking, low births weight and male gender, in correlation with the onset of wheezing during acute viral respiratory tract infections seems to have a good outcome and remission in older ages in 80% of the patients. Several more recent studies revealed that these patients have a very high risk to present chronic obstructive pulmonary disease (COPD) during adulthood.

The second pattern of clinical course reffers to those that associate atopy, young mothers, being the first child in the family and which present wheezing in correlation with multiple triggers, both viral infections and allergens. The risk for asthma development in these patients is up to 50-60%.

Prediction score

The diagnosis and treatment of asthma meets an active dinamics due to numerous studies on many features, stating with genetcs,

chronic inflammation and remodeling of airways, up to educational aspects, adherence to long term medication and new pharmacological approches. In 2014 GINA consensus included informations on The Asthma Predictive Index (API) in children below the age of 5 years old with the diagnosis of asthma. Initially API was published by Castro-Rodriquez JA in 2000, and it became a very valuable tool for the prediction of clinical course in children with recurrent symptoms at young age [14]. The API score includes minor and major criteria based on which the diagnosis of asthma may be suspected in preschoolers. If a child presents at least 3 episodes of wheezing lasting at least one day, and interferes with sleep quality, in correlation with one major criterion and /or two minor criteria is consistent with the diagnosis of asthma.

According to Castro-Rodriquez major criteria are: 1) family history of asthma in at least one parent and 2) the diagnosis of atopic dermatitis confirmed by a physician. Minor criteria are: 1) prior diagnosis of allergic rhinitis, 2) hypereosinophilia over 4% and 3) wheezing without symptoms of acute respiratory tract infection.

Many authors have proposed changes of API during the past decade. Among these, Guilbert TW and colab formulated a modified API (mAPI) in which the minimum of four episodes of wheezing is required, and added the results of allergic skin prick tests, while the role of allergic rhinitis is ignored [15]. Thus, hypersensitivity for at least one environmental allergen becamed a major criterion and the hypersensitivity for food allergens (egg, milk or peanuts) represents a minor criterion.

API

After publishing API the follow-up of preschoolers proved that thiose with a higher value of API had a higher risk of long-term duration of symptoms up to 4 to 10 folds as compared with those without major or minor criteria for asthma. A negative API score is correlated with a good outcome, without asthma symptoms in 95% of the patients.

Castro-Rodriguez published during the past years several analyses of the evolution of predictive scores of early onset wheezing in preschoolars towards the onset of asthma. In 2017 he published a systematic review of the studies on these scores [16]. The premise of this review was that the heterogeneity of clinical symptoms and of mechanisms explains the need for multiple algorithms in approaching RW. The results of this analysis allowed us to formulate the role of risk predictors and protective factors for asthma, that may be summarized [2,5].

Other risk factors included in this analysis are: high frequency of wheezing episodes during the first 5 years of life, ethnicity (higher risk for Hispanics), high gestational age (over 42 weeks of pregnancy), low or medium level of parental education, passive smoking in the first 3 years of life and maternal smoking as an independent risk factor, or recurrent abdominal pain due to either food allergy or gastroesophageal reflux.

The protective factors that were identified are: breastfeeding at least 3 months, the child's rank (rank 3 is accompanied by a significantly lower risk for the persistant wheezing), the presence of pets in the house during infancy.

Duijts and Colab published their results on the pulmonary function tests in RW [17]. They showed that persistent wheezing is associated with lower levels of FEV1 and lower FEV1/FVC, as compared with infrequent wheeze in early childhood. Their study revealed that children with late onset, intermediate-onset, and persistent wheezing have higher bronchodilator reversibility of FEV1 than transient early or prolonged early wheeze. The same wheezing phenotypes proved higher FeNO during adolescence.

Genetic polymorphism

The heterogeneity of clinical features in preschool children with RW has been the basis of concerns for the identification of some factors, including genetical, that may be used in the prediction of clinical course of RW. The involvement of genetic factors in the pathogenesis of asthma is outlined by recent studies. The role of chromosome 17 and especially the ORMDL3 region is proved. Numerous genes are involved in the immunological mechanisms that are reponsible for inflammation, airway hyperreactivity, and bronchial remodeling [18]. An association of an ORMDL3 variant with different wheezing phenotypes was revealed.

Among the genes that increases the susceptibility for asthma, the most studied are: ADAM, myelopeptidase domain, that consists in 33 gene correlated with the occurence of some atypical clinical features of asthma and RANTES (Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted).

In children with wheezing there were already identified 67 genes. Several genes are related to immunity, some of them having variable clinical expression in transient or persistent wheezing. Only six of them are currently validated (ANXA1, STAT1or signal transducer and activator of transcription, TLR7, GPR18, GZMH or granzyme H, and PTGER2).

The genetic profile might be responsible for the heterogeneity of wheezing. On the other hand, in different wheezing phenotypes similar genetic expressions may occur [5,18].

In children with transient wheezing it seems that ANXA1, STAT1 and TLR7 play a key role. In patients with persistent wheezing 19 genes were identified, each of the playing different roles: 13 genes are upregulated (6 of them correlated with immunity, 7 genes being involved in proteins transport) and 6 genes are downregulated (3 of them correlated with immunity, including PTGER2).

Regarding the clinical course from wheezing towards asthma, 33 candidate gene were discovered, as well as 47 types of genetic variants (SNPs, single nucleotide polymorphism). Beside these genes the current studies are focused also on the role of IL8, VEGFA, MBL2 and IKBKB gene [18].

Endotypes

The efforts for wheezing phenotyping are in close relationship with current concerns for distinguishing between different asthma endotypes. Identifying specific biomarkers even during the first episode of wheezing that may predict a long term outcome with persistent symptoms is a constant topic. Since wheezing occurs early in life, during infancy, and children present recurrent episodes during preschool age, one goal for these biomarkers is to find some that do not imply invasive approache of the patient.

The potential biomarkers were initial serum eosinophilia and total serum IgE. Afterwards different API's included tests for specific allergen identification (skin prick tests and serum specific IgE). Recent studies investigated non-volatile inflammatory markers in exhaled breath [15]. Some of these biomarkers are cytokines and chemokines, or the fraction of exhaled nitric oxide (FeNO). In older children the sampling of exhaled air or different

techniques for measuring FeNO as a marker of Th2-type airway inflammation are now available and the studies proved their value [17]. In preschoolers, these techniques are neither standardized, nor generally available, and involves many challenges. The era of proteomics and genomics is now a current area of research [19].

CONCLUSION

The main aim of wheezing phenotyping is based on that the prediction of asthma and asthma endotyping should be targeted on implications for clinical practice and identifying the best treatment strategies. In pediatric pneumology the current trend is the switch from "one size fits all" approach to personalised strategies. A better understanding of pathophysiological mechanisms, including genetics will provide a better recognition of a possible outcome, in order to a better anticipation of different endotypes that will afford us to apply a more adequate treatment strategy.

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