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Wheezing Disorders in Childhood

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Abstract

Children can present wheezing episodes very early on life. Among pediatric population this is a very common respiratory symptom of can evolve into severe life-endangering episodes. Wheeze can be found in all pediatric age groups; however, infants and preschoolers are mostly affected. The appropriate characterization and management of this higher risk group is crucial to improve quality of life. At least one third of children under 5 years are affected and nearly 30% of wheezing children will experience complete remission of symptoms before 6 years of age [1], thus making wheezing a different respiratory illness in contrast with asthma in older children and adults. As a means of finding associations between clinical features, risk factors, and clinical outcomes, several wheezing phenotypes are based on prospective birth cohorts have been described. These population studies have improved understanding of epidemiology and pathophysiology of wheezing, allowing for the creation of asthma predictive indices that help distinguish those children with episodes of wheeze who will develop asthma in later childhood. Numerous viruses are implicated in the pathophysiology of wheezing and are proposed as one of the main triggers for acute episodes during early childhood.

Keywords: Wheezing, Children; Episodes; Asthma; Virus

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Introduction

Definitions and epidemiology

Wheezing is caused by an obstruction of the lower respiratory tract that implies turbulent airflow which can result in severe complications and life threatening acute events. Due to its complex and diverse clinical presentation, it has been classified into various overlapping phenotypes. To define wheezing we need to visualize it as a symptom that makes up the clinical picture of various respiratory diseases; however, in infants and young children, in whom the physiopathology of wheezing is poorly understood; the term has been utilized to define a respiratory disease by itself. The diagnosis and management in young children becomes a challenge because of the different underlying diseases that can predispose to wheezing [1,2]. The high medical costs in the inpatient and outpatient settings become a heavy burden for healthcare services [3]. Most of the episodes of wheeze in infants and young children are tightly associated with viral respiratory infections [4]. It is well known that in the very first 2 years of life the first wheezing episode reports as Respiratory Syncytial Virus (RSV) bronchiolitis [5,6]. Bronchiolitis and asthma are the most diagnosed respiratory diseases in preschool and school-age children in whom episodes of wheeze are the chief respiratory complain; another significant number of wheezing children in developing countries are misdiagnosed with pneumonia, thus remaining under diagnosed and receiving inappropriate management [7]. Other less frequent causes of wheeze in children include structural anomalies, tracheomalacy, cystic fibrosis, congenital heart diseases, immune deficiencies and gastro esophageal reflux [8]. Whatever the etiology, wheezing in children is a very common problem and population studies have shown that one third of children under 3 years of age report at least one episode of wheeze and by the age of 6 the cumulative prevalence of wheeze increases to nearly 50% [2,9,10]. Since 2008 the European Respiratory Society Task Force recognized wheezing in preschool children as a condition with different pathophysiological features compared to asthma seen in older children and adults and underscored the importance of addressing them as different diseases. Furthermore, it has been published that many wheezing young children will reach full resolution of their symptoms after 6 years of age [10]. Given the difficulty of performing pulmonary function tests in children under

Table 1: Characteristics of preschool children with wheeze [19].

Frequency of Episodes	Occasional or frequent
Severity of Episodes	Mild, severe or life-threatening
Temporal Pattern	Wheezing with viral colds or in response to other triggers
Long Term Outcome of Symptoms	Transient versus persistent wheeze

6 years to assess airway obstruction reversibility and due to the lack of technique standardization, the diagnosis of asthma in preschoolers is controversial and based solely on clinical criteria. Moreover, identifying wheezing children that will go on to develop asthma after 6 years of age is a challenging task and the aim of ongoing research [11]. Therefore, we deem appropriate to propose different etiologic and pathophysiological mechanisms, albeit not independent, to better understand wheezing in children less than 6 years in contrast to the asthmatic older children or adult [8]. The ESR Task Force conducted a survey and described a standardized nomenclature of lung sounds in six different languages that has been acknowledged by an expert panel; according to their report wheezing is defined as a continuous high-pitched whistling or hissing musical sound [12]. There is not an accurate way to record it. Clinically, diagnosis is achieved by means of a thorough medical history and examination and relies on the sensitivity of parents and clinicians to recognize it [10]. This respiratory sound is audible through chest auscultation during expiratory time, although depending on the severity of the airway obstruction it can be heard from a distance in up to 30% of cases [13]. Aguilera-Zamarroni specifies that "wheeze has duration of 250 milliseconds and can be monophonic if there is airway obstruction of large calibre bronchi or polyphonic whenever there is diffuse small calibre airway obstruction." Recurrent wheezing is defined as 3 or more episodes of wheeze within the last year [14]. Due to the lack of precise clinical instruments for the systematic identification of wheezing children, the International Study of Wheezing in Infants (EISL) developed a validated written questionnaire addressed to children's parents or guardians to recognize episodes of wheeze by asking for the presence of whistling or wheezing of the chest during their children's first 12 months of life [15]. Wheezing is very common in children. It has been published that one third of children aged 3 years or less will report wheezing symptoms and that nearly half of the pediatric population will have suffered from wheezing at the age of 6 [2,9,10]. Mallol et al. [3] reported that 40% to 45% of children worldwide had at least one episode of wheezing in their first year of life and 23% had recurrent wheezing [3]. The prevalence varies depending on the specific location; multicenter studies from the International Study of Asthma and Allergies in Childhood (ISAAC) and the EISL have demonstrated the highest prevalence in Latin America [3,16]. In Latin America 21.4% of children within their first year of life had recurrent wheezing and 47.3% reported at least one episode of wheeze[3]. In six South American countries the EISL showed that 16.6% of children had recurrent wheezing [17]. In a meta-analysis that encompassed population studies carried out up to 2016 documented that the prevalence of children aged 0 to 2 years with a single wheezing episode and recurrent wheezing was 40.55% and 19.27% respectively [18]. The clinical presentation of wheezing in children is quite variable and it has been difficult to link the exact genetic and environmental factors that determine its etiology. The pathophysiology is poorly understood and it has been considered that given its multifactorial nature, diverse mechanisms of disease underlying bronchial obstruction might be encountered. There is considerable heterogeneity in the clinical spectrum of this disease regarding frequency, grade of severity, temporal pattern and duration of episodes (Table 1) [19].

Phenotypical view of wheezing children

Ever since the end of the 20th century, efforts were made to classify wheezing children according to phenotypes that would predict their clinical evolution and degree of therapeutic response (Table 2). The first phenotypical classification of wheezing children was published by the Tucson Children's Respiratory Study (TCRS) after a 6 year follow up of 1,246 neonates [20]. This classification was the result of the detailed observation of epidemiological features of wheezing children and focused on duration of wheezing episodes and risk factors associated. Subsequently the ESR Task Force and PRACTALL consensus published their own phenotypical classification with special attention to the temporality of wheezing episodes. The latter classification claimed to be more useful in the clinical context compared to the longitudinal phenotypes formerly described by the TCRS, which can be only recognized retrospectively [1,19,21]. One of the major contributions of the TCRS was the description of wheezing phenotypes based on the presence or absence of wheezing in children up to 3 years and its persistence beyond 6 years, they also studied lung function associated to respiratory tract disease in young children and helped to introduce the first Asthma Predictive Index (API). Through this follow up it was possible to subdivide children into 3 groups: transient early wheezers, persistent wheezers and late onset wheezers [1]. Transient early wheezers were found to have at least one episode of wheeze related to respiratory infections in the first 3 years of life with no further episodes reported after 6 years of age. These children were unlikely to report a history of atopic disease such as asthmatic mother, cutaneous hyper-reactivity, or high IgE serum levels. They also presented decreased lung function at birth and at 6 years with normalization by the age of 16. Children with persistent wheeze suffered from wheezing before and beyond 3 years of age up until 6 years. These children were highly associated to family history of asthma, high IgE serum levels and decreased lung function from preschool age until adulthood. Features in the late onset wheezer encompassed a significant association with maternal asthma, allergic rhinitis and variable respiratory function. This group included children with the first wheezing episode after 3 years of age and recurrent wheeze at the age of 6. In this birth cohort 51.5% never reported wheezing within their first 6 years of age [20]. According to a classification from the ESR Task Force, pre-school children fit into two groups: those with episodic (viral) wheeze and those with multiple-trigger wheeze. Episodic wheezers simultaneously suffer from viral lower respiratory tract infections with repeated wheezing episodes that keep a seasonal pattern with absence of wheeze between episodes. They report complete remission of symptoms by the age of 6. Multiple-trigger wheeze is associated with infections, tobacco smoke, traffic air pollution and indoor allergens and show discrete flare up´s but also symptoms between episodes [19]. As an effort to improve the characterization and classification of wheezing children, the ALSPAC and PIAMA birth cohorts observed 14,062 and 3,963 children respectively. These studies recorded important atopic data

Table 2: Wheezing phenotypes in children [1,10,22].

Study group	Phenotypes
TCRS(Tucson Children's Respiratory Study Group) [1]	Transient early wheeze
	Persistent wheeze
	Late onset wheeze
PIAMA(Prevention and Incidence of Asthma and Mite Allergy) and ALSPAC (Avon Longitudinal Study of Parents and Children) [22]	Never/infrequent wheeze
	Transient early wheeze
	Prolonged early wheeze
	Intermediate onset wheeze
	Late onset wheeze
	Persistent wheeze
ERS (European Respiratory Society) [10]	Episodic viral wheeze
	Multi-trigger wheeze

Table 3: Asthma predictive indices.

Cohort	API-TCRS [27] (n=1,246)		PIAMA [30] (n=3,963)		Isle of Wight [28] (n=1,456)	
Age of asthma prediction	13-6		8-7		10	
Parameters	Major criteria Physician diagnosis of asthma Physician diagnosis of atopic dermatitis at age 2 or 3 Minor criteria Physician diagnosis of allergic rhinitis at age 2 or 3 Wheezing apart from colds Peripheral eosinophilia >4%		Male sex Post-term delivery Low parental educational status Parental history of inhaler medications Wheezing frequency Wheezing/dyspnea apart from colds Physician-diagnosed eczema		Family history of asthma Recurrent chest infection at 2 years Atopy skin prick test at 4 years Nasal symptoms at 1 year	
Positive score	3 episodes/year plus 1 mayor criteria or 2 minor criteria		Cut off value >35 points		Presence of 4 risk factors	
Clinical Performance	Sensitivity 22%	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
		97%	7%	99%	10%	98%

prospectively (skin prick test, airway hyper reactivity, serum IgE leves and atopic history) and agreed with the phenotypes already described by the Tucson and the ESR groups; however, they went further and described the intermediate-onset wheezer: an additional phenotype who presented symptoms after 2 years of age [22]. The Multicenter Allergy Study (MAS) was a German study that enrolled 1,314 infants and collected information periodically until the age of 13 years. Through the measurement of specific IgEs to specific allergens and lung functioning MAS recovered important data to establish relationships between sensitization and wheezing in early childhood [23]. In the UK 1,186 infants were followed up by the Manchester Asthma and Allergy Study (MAAS). Lung function tests, skin prick tests and serum IgE levels were recorded prospectively and as a whole helped to establish associations between preschool wheeze phenotypes and lung function results [24]. In spite of these distinctive features, a high grade of overlap exists between phenotypes, to such an extent that the clinical applicability of phenotypical classifications has been called into question. This is due to the variable natural history, interchangeable risk factors, different therapeutic approaches and the lack of full standardized data collection in these cohorts. Evidence suggests that these phenotypes poorly predict long term clinical outcomes since up to 55% of these patients will fit in more than one phenotype during their clinical course and that both severity and frequency of episodes summon better prognostic power and serve a much stronger predictor of asthma in later years. Additionally, these phenotypes have no utility in directing therapeutic approach as it has been demonstrated that they do not predict response to treatment [19,25,26].

Wheeze persistence assessment

The phenotypes developed by the prospective cohorts aforementioned supplied with the launch pad for the development of prognostic tools aimed at prediction of asthma in older children (Table 3). Using the risk factors found in children less than 3 years from the TCRS (using univariate analysis on an unselected ethnic mix cohort), Castro-Rodríguez et al. coined the first Asthma Predictive Index (API). This index takes into account the age of onset of wheeze and frequency of episodes (children must have recurrent episodes of wheeze within the first 3 years of life), family history of asthma, atopic dermatitis, wheeze apart from colds, allergic rhinitis and eosinophilia. Children under 3 years with a negative API have few risk factors associated with the development of asthma and are classified as transient wheezers, meanwhile children with a positive stringent API have a 77% probability of developing asthma at 6 to 13 years old [27]. The Dutch PIAMA cohort results also led to the creation of predictive indices to identify preschoolers that would develop asthma at the age of 6 to 10 years. Odds ratios for individual predictors determined from multivariate analyses were calculated from the PIAMA cohort (a non-ethnic mix select cohort based on allergic screening results) and revealed that male sex, post-term delivery, parental education, inhaled medication, wheezing frequency, wheeze/dyspnea apart from colds, number of respiratory tract infections and eczema were independent risk factors for asthma. Each of these factors has a different weight which makes the scoring system much more complicated for the

Table 4: Viral etiology of wheeze in children [37,38].

Respiratory syncitial virus type A and B
Human rhinovirus
Para influenza virus
Human metapneumovirus
Corona virus
Adenovirus
Influenza virus A and B
Enterovirus (Echovirus and coxsackie)

clinician than the major and minor criteria system of the API [28]. Kurukulaaratchy et al. [29,30] used the birth cohort from the Isle of Wight study to identify risk factors associated with persistence of wheezing up until age 10 years; independent risk factors observed were positive family history of asthma, recurrent lower respiratory infections at 2 years of age, atopic skin prick test at 4 years of age, and nasal symptoms at 1 year of life. The latest 2017 GINA guidelines reaffirm the utility of the API from Castro-Rodriguez as an asthma risk profile tool for children under 5 years old, nonetheless its applicability and validation in other contexts needs more study [8]. Despite all these population studies, identifying those young children who will become persistent wheezers and asthmatics continues to be a difficult task. Effective techniques for measuring airway obstruction alongside the introduction of reliable inflammatory airway markers and the better understanding of the pathophysiological role of infections and atopy will allow strengthening correlation between phenotypes, clinical outcomes and therapeutic response in wheezing children.

Viral etiology of wheezing

Children under 6 years old register the highest incidence of viral respiratory infections, with bronchiolitis being on top of the list [31-33]. Likewise, the incidence of wheezing is high in this age group [34]. Even though wheeze is the respiratory symptom more often reported in children, it is no longer reported in 60% to 66% of children reaching age 6 years; these children will remain asymptomatic at age 16 when respiratory viral infections are less frequent [35,36]. Regardless of multiple etiological factors associated with wheeze, cohort studies have identified a strong association between viral respiratory infections and transient wheeze. Both the TCRS and the ESR Task Force acknowledge a group of young children with transient wheezing episodes caused by viral respiratory infections that will overcome the disease after age 6 years [19,35]. In recurrent wheezers with transient episodes appearing seasonally, up to 60% cases were associated with respiratory viral infections [1]. Single viral isolation has been documented in 66% to 90% of wheezing preschoolers with positive history of atopy [37,38]. A higher risk of wheezing and asthma is expected in children who have suffered from RSV bronchiolitis and Rhinovirus respiratory infections [39,40]. In a prospective cohort from Spain, children with severe viral respiratory infections posed a higher risk to develop recurrent wheeze during the first year of life [41]. Observational studies define day-care attendance and contact with siblings as important risk factors for wheeze in preschoolers; this association has been explained by the augmented exposure to respiratory viruses in those settings which consequently raises the likelihood of having wheezing episodes [42]. It should be noted that the presence or absence of respiratory infections is a criterion taken into account by the predictive indices for asthma that have been published so far [27,28,30,43]. It has been pointed out that, in developing countries, children with acute respiratory infections present with high mortality, poor response to antibiotic treatment and high viral isolation rates, suggesting that wheezing might be underreported and mistreated in this population [7]. Although causality has yet to be determined, the above-mentioned data outline the strong association between viral respiratory infections and wheeze in children less than 6 years of age. Several studies call attention to the fact that certain virus like Rhinovirus or RSV are isolated during respiratory infections in children whose symptoms persist as described by the persistent wheeze phenotype with the possibility of evolving into asthma in later childhood [37,38,44-47]. In a prospective cohort Lemanske et al. [37] established that a single episode of wheeze caused by Rhinovirus during the first year of life was a strong predictor of wheezing at 3 years of age with an OR of 6.6; this study also noted that at least one infection by RSV increased the risk of wheezing at age 3 years (OR 3). Similarly other viruses such as Parainfluenza type 1, Influenza A and B, Adenovirus and non-Rhinovirus Picornavirus raised the risk of wheezing (OR 3.9) after adjusting for other noninfectious risk factors [37]. Jackson DJ et al. [37] reinforced the hypothesis of viral-induced wheeze in the longer term with a cohort of children that showed wheezing illnesses caused by RSV and Rhinovirus during the first, second and third year of life were strong predictors of the subsequent evolution to asthma at 6 years old [38]. Sigurs et al followed up prospectively 47 children aged <1 year with RSV lower respiratory tract infection and reported an increased prevalence of asthma and recurrent wheeze at age 18 years in comparison with an age and gender matched control group [48]. This association strongly supports the fact that viral respiratory infections play an utterly important role both as causative agents and prognostic long term factors in wheezing children. It is of utmost relevance to identify the viral isolates involved in wheeze exacerbations during early childhood, especially in children under 6 years whose airway obstruction can turn into acute life threatening events. The most frequently reported viruses which can trigger wheezing episodes and asthma exacerbation in children vary among countries and medical care centers depending on geographical distribution, age, ethnicity, seasons and viral outbreaks. It has been published that the most important viral triggers for acute asthma exacerbations are Rhinovirus, RSV, Coronavirus, Human Metapneumovirus, Parainfluenza and Adenovirus [49]. RSV, Rhinovirus and Influenza virus are the most often reported initiators of acute respiratory events in asthmatic children [50]. According to prospective cohorts the major viruses isolated from wheezing children are Rhinovirus, RSV, Parainfluenza, Influenza, Metapneumovirus, Coronavirus, Adenovirus and Enterovirus (Table 4) [37,38]. Although the relative contribution of each single respiratory virus to episodic wheeze is hard to establish and goes beyond the scope of this review, several studies render conclusive evidence that supports the association between wheezing episodes and respiratory viruses. Experimental studies explain the mechanisms by which certain viruses cause airway obstruction. Evidence in murine models demonstrates inflammation and bronchial hyperresponsiveness induced by single- and double-stranded RNA respiratory viruses with a predominant Th2 response at bronchial epithelium [51-53]. Suggestions are made that RSV infections predispose to recurrent wheezing by the induction of the Th2 pathway mediated by IL-4 and IL-10 and the consequent shift in the immune system response towards allergic stimuli [54,55]. Influenza virus activation of a Th1 response by enhancing the production of IFN-gamma which in turns promotes dendritic

cells activation via IFN-gamma bolstered Th2 type immunity leads to boosting of allergen response [56]. Although the exact etiology of wheezing during childhood is difficult to ascertain, the microbiological determination of wheezing episodes is important to give way to continuous epidemiological surveys that can help clarify the causative association between viral infections and wheeze in children. Furthermore, introduction of preventive measures for viral respiratory disease and measurement of its impact on the prevalence of wheezing in children will improve our understanding of viral-induced wheezing in children.

Conclusion

Wheezing in young children is a highly prevalent respiratory illness whose diagnosis is based solely on clinical examination. Due to its broad clinical spectrum, it is difficult to diagnose and laborious to predict clinical outcomes. Although 30% of wheezing children will experience complete remission of symptoms after 6 years of age, it is important to identify those who will suffer from asthma in subsequent years. Clinicians must bear in mind that a thorough history is cornerstone to determine both a precise diagnosis and reliable prognosis. In order to identify those children who will have recurrent and persistent symptoms we have to pay special attention to the presence of atopic history and define the likelihood of having respiratory symptoms caused by either allergic recurrent responses or transient triggers such as viral infections. While several viruses predispose to wheezing episodes in children, research is yet to determine the specific mechanisms by which they may cause asthma in later childhood. More studies are necessary to establish the efficacy of prevention of viral infections as a way of diminishing wheezing in early childhood. Considering the heterogeneity of childhood wheezing and its multiple underlying causes, it is unlikely to have a 100% sensitive and specific tool to assess the probability of developing asthma in later childhood. Even so, the predictive indices aforementioned help us approach the wheezing child in the healthcare setting in a practical, cost-efficient and systematic way. The API continues to be the most reliable, extensively validated and highly specific tool for the identification of children at greater risk for developing asthma later in life.

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