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Mini-Symposium: Asthma Phenotypes

Episodic Viral Wheeze and Multiple Trigger Wheeze in preschool children: A useful distinction for clinicians?

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SUMMARY

Accumulating evidence suggest that splitting preschool recurrent wheezing disorders into Episodic (Viral) Wheeze (EVW) and Multiple Trigger Wheeze (MTW) is an oversimplification. There is little evidence that the EVW and MTW phenotypes are related to the longitudinal patterns of wheeze, or to different underlying pathological processes. As the clinical response to inhaled corticosteroids and montelukast varies considerably between individual children with EVW, and between individual patients with MTW, the clinical usefulness of the EVW-MTW approach is doubtful.

Based on the currently available evidence, we propose to describe preschool wheeze symptoms not only in terms of temporal pattern, but also in terms of frequency and severity, and age of onset. Relevant associated clinical parameters like atopy and eczema should be described with recognition of age of onset, pattern, and severity. Comparing these data to biomarkers and histopathology may help to improve our understanding of preschool wheezing disorders in the future.

Until phenotypes can be described that are associated with different pathobiological process, are related to different longitudinal outcomes, or are clearly different in terms of response to therapy, clinicians are encouraged to take a trial and error approach of different therapeutic agents in preschool children with troublesome recurrent wheeze.

INTRODUCTION

Preschool wheeze is generally thought to consist of different phenotypes, or different disease entities. The differentiation between phenotypes is potentially important in order to effectively study different underlying disease processes, to target appropriate intervention, and to predict clinical course. Various techniques have been applied to differentiate between different preschool wheeze phenotypes, making use of lung function,[1,2] exhaled nitric oxide,[3,4] broncho-alveolar lavage, bronchial biopsy,[5] and metabolomics.[6] The above have greatly aided our understanding of preschool wheeze, but as yet have failed to accurately differentiate between phenotypes that are clinically useful or pathobiologically discernable.

PURPOSE OF THIS REVIEW

In daily practice, most clinicians can only rely on symptoms obtained through history taking and physical examination; lung function testing is not routinely available to characterize preschool age patients. Clinically, different phenotypes based on temporal wheeze patterns can also be recognized [7]; specifically, Multiple Trigger Wheeze (MTW) and Episodic (Viral) Wheeze (EVW) (Box 1).

Clinicians have long recognised the large inter-patient variation in temporal wheeze patterns. Separation of patients with ongoing low grade wheeze symptoms followed by exacerbations from patients who report no wheeze in between exacerbations seems intuitive. Realising that this distinction into separate clinical phenotypes would appear logical to clinicians in daily practice, and because the available evidence at the time suggested that this distinction might also have therapeutic consequences, the European Respiratory Society (ERS) Task Force on the classification and management of preschool wheezing disorders proposed to use this classification system for clinical purposes.[7] The Task Force Report stressed, however, that this recommendation was based on

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Box 1. Definitions of episodic (viral) wheeze and multiple trigger wheeze.

Episodic (viral) wheeze is defined as ''wheeze in discrete episodes, with the child being well between episodes'', and is usually diagnosed in children who wheeze only in the presence of coryzal symptoms.
Multiple trigger wheeze is defined as wheezing that shows discrete exacerbations, but also symptoms in between episodes, and the name implies that wheeze is triggered by factors other than viruses i.e. mist, crying, laughter, exercise, or allergens. MTW is therefore diagnosed in children who wheeze in the presence and absence of coryzal symptoms.

very limited evidence, and that it was likely to change when additional evidence became available.

In this article, we will review a number of studies that have added to the body of knowledge on the pathophysiology of preschool wheezing disorders, and argue that the ERS Task Force recommendations to distinguish only EVW and MTW is an oversimplification of a complex spectrum of wheezing phenotypes in this age group. We will propose a more comprehensive and unifying approach to characterizing these patients.

DIFFERENTIATION BY SEVERITY AND FREQUENCY OF SYMPTOMS, AND BY OTHER RESPIRATORY SYMPTOMS

A drawback of classifying preschool wheeze into EVW and MTW is that the classification does not allow for differentiation between wheeze of different severity and frequency. For example, patients with episodic wheeze exacerbations and occasional mild wheeze during exercise or exposure to cold air would be classified as MTW with patients who suffer from continuous low grade wheeze between more severe exacerbations. Patients who frequently require hospitalisation for shortness-of-breath and wheeze following corysal symptoms with little or no wheeze in between episodes will be classified as having EVW, together with patients who have mild wheezing during some cold episodes (EVW). When considering wheeze only, there may be more temporal patterns of preschool wheeze than can be described by EVW and MTW (Figure).

Another drawback of the EVW-MTW approach is that it fails to take other respiratory symptoms into account, such as cough, colds and chest congestion. In the Manchester birth cohort study, adding such additional symptoms to the pattern of wheeze by principal component analysis in three and five year olds improved the correlation to lung function and risk factors for asthma, and were

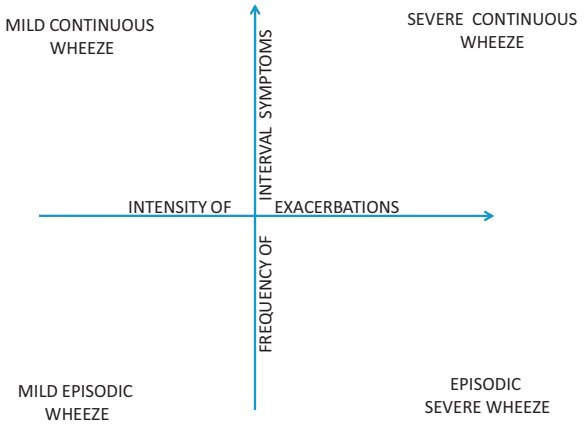

Figure 1. Visual illustration of the range of wheezing symptoms seen in preschool aged children.

Box 2. Longitudinal wheeze phenotypes of childhood as described in the Tucson study.

Transient wheeze that resolves by the age of three years and is associated with reduced lung function at birth but not associated with atopy
Atopic wheeze/asthma which starts later and is associated with atopy and bronchial responsiveness
Non-atopic wheeze which is less severe, less persistent, and less prevalent than atopic asthma in developed countries

therefore considered to ''more likely reflect underlying pathophysiologic processes.[8]''

LONGITUDINAL OUTCOMES OF EARLY CHILDHOOD WHEEZE

Birth cohort studies have shown that there are different longitudinal patterns of wheeze. The classic Tucson study identified three longitudinal phenotypes (Box 2).[1]

These and subsequent data have suggested that transient wheeze early in childhood was caused by virus infection in children born with small airways. Transient wheezing is associated with decreased lung function at birth, maternal smoking during pregnancy,[9] male gender, the presence of older siblings, the attendance of day care,[10–12] and the absence of atopy.[13] However, it should be stressed that these relationships were based on group data, and that the distribution of such risk factors overlapped considerably between transient wheezing and other wheezing phenotypes.

In the Leicester cohort, cluster analysis was used to analyse data from children who were assessed between birth and five years of age, and followed up two to four years later.[14] Parental answers to questions about attacks of wheezing in the presence or absence of colds were analysed, together with lung function and allergy skin prick test results. This analysis yielded three wheeze phenotypes [Box 3].

The authors subsequently proposed that the longitudinal phenotypes described in the Tucson study[1] (transient wheeze and persistent wheeze) may correspond with EVW and MTW.[14] However, with closer inspection of the Leicester data, subjects in the transient viral wheeze group had a probability of 0.28 for 1-2 episodes of wheezing, and a 0.63 probability of no wheeze at all in the year before the first survey. The same limitation applies to the Tucson data, where the wheeze phenotypes are based on children who *ever* wheezed before the age of three years.[1] In population studies, approximately half of preschool children with wheezing have recurrent wheeze, and the other half most of these children have only had one single wheezing episode ever.[15] Arguably, few

Box 3. Longitudinal phenotypes of childhood wheeze as described from the Leicester cohort.

Atopic persistent wheeze: Lung function was reduced and bronchial hyper responsiveness was greater than in healthy children. ''Attacks'' of wheeze occurred with and without colds and were accompanied by shortness of breath. Almost a third of subjects in this category experienced more frequent attacks in summer.
Non-atopic persistent wheeze: Atopy was rare and infrequent attacks of wheeze were accompanied by shortness of breath, wheeze was more common in winter and more severe at night.
Transient viral wheeze: In which infrequent wheeze occurred mostly with colds, and had mostly subsided by the second survey two to four years later.