Symptom-pattern phenotype and pulmonary function in preschool wheezers

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Background: Pulmonary function in preschool wheezing phenotypes based on wheeze onset and duration and atopic status has been extensively described but has not been studied in symptom-pattern phenotypes of episodic (viral) and multiple-trigger wheeze.

Objective: We investigated whether multiple-trigger wheezers were more likely to have abnormal pulmonary function and increased fraction of exhaled nitric oxide (FeNO) than episodic (viral) wheezers and whether multiple-breath wash-out was more sensitive at detecting abnormal pulmonary function than specific airways resistance (sR_{aw}) in preschool wheezers.

Methods: FeNO, multiple-breath wash-out indices (lung clearance index [LCI] and conductive airways ventilation inhomogeneity [S_{cond}]) and sR_{aw} were measured in healthy children and those with recurrent wheeze aged 4 to 6 years. Subgroup analysis was performed according to current symptom-pattern (multiple-trigger vs episodic [viral]), atopic status (atopic vs nonatopic), and wheeze status (currently symptomatic vs asymptomatic).

Results: Seventy-two control subjects and 62 wheezers were tested. Multiple-trigger wheezers were associated with an average increase of 11% (95% CI, 7% to 18%; $P < .001$) in LCI, 211% (95% CI, 70% to 470%; $P < .001$) in S_{cond}, and 15% (95% CI, 3% to 28%; $P = .01$) in sR_{aw} compared with episodic (viral) wheezers. Pulmonary function in episodic (viral) wheezers did not differ significantly from control subjects. The presence of current atopy or wheeze was associated with higher FeNO ($P = .05$) but did not influence pulmonary function significantly. On average, LCI was abnormal in 39% (95% CI, 32% to 45%), S_{cond} was abnormal in 68% (95% CI, 61% to 74%), and sR_{aw} was abnormal in 26% (95% CI, 16% to 35%) of multiple-trigger wheezers.

Conclusions: Multiple-trigger wheeze is associated with pulmonary function abnormalities independent of atopic and current wheeze status. S_{cond} is the most sensitive indicator of abnormal pulmonary function in preschool wheezers. (J Allergy Clin Immunol 2010;126:519-26.)

Key words: *Children, episodic (viral) wheeze, multiple-trigger wheeze, phenotype, preschool wheeze, pulmonary function, symptom-pattern*

Studies suggest that most asthma originates in early childhood. Nearly 30% of children have at least 1 episode of wheezing before their third birthday, and by 6 years, the figure is almost 50%.[1] Although wheeze resolves spontaneously in some children, it persists in those at risk of asthma.[1]

The natural course of preschool wheezing disorders is heterogeneous, and objective distinction between wheezing phenotypes is clinically important because etiology, pathophysiology, potential for therapy, and outcome might differ.[2] Phenotypes based on wheeze onset and duration (transient, persistent, and late-onset wheeze)[1,3-7] and atopy[8-10] have been validated by pulmonary function tests (PFTs) and measures of airway inflammation, such as fraction of exhaled nitric oxide (FeNO). Although these phenotypes have improved our understanding of preschool wheezing disorders and are useful in epidemiologic studies, they are of limited use in clinical practice.[11] Hence the use of episodic (viral) and multiple-trigger wheezing phenotypes based on symptom-pattern (also referred to as temporal phenotype) has been recommended.[11,12] However, symptom-patterns of wheeze have not been objectively validated by PFTs or markers of airway inflammation.

Despite specific challenges posed by preschool children, a number of pulmonary function techniques, including plethysmographic specific airways resistance (sR_{aw}), have gained popularity in recent years.[13,14] Nevertheless, such measurements might not be sensitive enough to detect early airways disease in young children.[15] In preschool children with cystic fibrosis, the lung clearance index (LCI), a measure of overall ventilation inhomogeneity derived from the multiple-breath wash-out (MBW) technique, has been shown to be more sensitive than spirometry and sR_{aw} measurement in detecting pulmonary function abnormalities.[15] Ventilation inhomogeneity in asthmatic subjects is clinically important because it can impair both gas exchange efficiency and the distribution of inhaled medications.[16,17] However, it is not known whether indices of ventilation inhomogeneity in preschool wheezers are abnormal compared with those in healthy children, irrespective of whether they are more sensitive in detecting pulmonary function abnormalities than conventional PFTs and whether symptom-pattern phenotypes of preschool wheeze are associated with abnormal pulmonary function.

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Abbreviations used
BDR: Bronchodilator reversibility
FeNO: Fraction of exhaled nitric oxide
FRC: Functional residual capacity
ICS: Inhaled corticosteroid
LCI: Lung clearance index
MBW: Multiple-breath wash-out
PFT: Pulmonary function test
S_{acin}: Acinar airways ventilation inhomogeneity
S_{cond}: Conductive airways ventilation inhomogeneity
SPT: Skin prick test
sR_{aw}: Specific airways resistance

We tested the hypothesis that preschool children with multiple-trigger wheeze were more likely to have abnormal pulmonary function and airway inflammation (by using FeNO as a surrogate) compared with episodic (viral) wheezers and healthy control subjects and that MBW indices were more sensitive at detecting pulmonary function abnormalities than sR_{aw} in preschool wheezers.

METHODS

This prospective cross-sectional study was conducted at the UCL Institute of Child Health, London, United Kingdom. The Joint UCL/UCLH Ethics Committees and the local hospital ethics committees approved the study. Parents provided informed written consent for their children to participate.

Subjects

Preschool children with wheeze. Children aged 4 to 6 years with physician-diagnosed recurrent wheeze (defined as >3 episodes in 12 months) before age 3 years (irrespective of current wheezing status) were included. Children with wheeze were recruited from a cohort of preschool wheezers previously studied at the Royal Brompton Hospital[18] and from outpatient clinics at Royal London Hospital and Great Ormond Street Hospital for Children. Children with radiologically documented lower respiratory tract infection, ventilation or oxygen supplementation in the neonatal period, and congenital cardiac disease surgically repaired or requiring medical therapy and those who were born before 36 weeks' gestation and small for gestational age were excluded. PFTs were performed when children were well (ie, no clinical evidence of upper respiratory tract infection and no acute exacerbation in the previous 3 weeks). In addition, parents were requested to withhold short-acting bronchodilators for 8 hours and long-acting bronchodilators for 24 hours before PFTs.

Healthy control subjects. Healthy control subjects were recruited from 2 sources: (1) children previously enrolled as infants in an epidemiologic study at the Institute of Child Health who were mainly of white origin[19,20] and (2) children from the community, including friends or siblings of children with wheeze, so that the healthy control group reflected the ethnic diversity of the wheezers. Children were ineligible if they had been hospitalized for any respiratory illness (eg, croup, pneumonia, and bronchiolitis), had physician-diagnosed asthma, were currently using inhaled bronchodilators, or had ever used inhaled steroids. Other exclusion criteria were similar to those of the wheezing group.

Assessments

All children had anthropometric measurements and a clinical respiratory examination to ensure the absence of acute wheeze or upper respiratory tract infection. Baseline FeNO values, MBW indices (LCI, conductive airways inhomogeneity [S_{cond}], acinar airways inhomogeneity [S_{acin}], and functional residual capacity [FRC]), and sR_{aw} were measured in all subjects in that order. In the wheezers only, bronchodilator reversibility (BDR) was assessed by measuring MBW and sR_{aw} 20 minutes after administration of 200 μg of salbutamol through a spacer. Full reversibility was defined as pulmonary function reverting to normal after bronchodilator administration (ie, postbronchodilator MBW indices and sR_{aw} significantly better than baseline values and not significantly different from the baseline values in healthy control subjects). Part reversibility was defined as postbronchodilator MBW indices and sR_{aw} being significantly better than baseline values but significantly worse than baseline values in healthy control subjects. Atopic sensitization (skin prick tests [SPTs] to house dust mite, cat, dog, grass, tree, and *Aspergillus fumigatus* [Soluprick SQ; ALK-Abelló A/S, Horsholm, Denmark]) was ascertained in all participants; sensitization was defined as a wheal at least 3 mm greater than that elicited by the negative control.

FeNO values were measured at an expiratory flow of 50 mL/s by using the single-breath online method according to American Thoracic Society guidelines,[21] with computerized equipment and a chemiluminescence EcoMedics AG analyzer CLD 88 (EcoMedics, Durnten, Switzerland). MBW was performed as previously described in preschool children.[13,15] Sulfa hexafluoride was the inert marker gas used for calculation of gas-mixing indices reported in this study, as measured with a respiratory mass spectrometer (AMIS 2000; Innovision A/S, Odense, Denmark). LCI was calculated by dividing the cumulative expired volume by the FRC, and S_{cond} and S_{acin} were estimated by calculating phase III slopes, as previously described.[22] The mean LCI, S_{cond}, S_{acin}, and FRC values from 3 technically acceptable wash-outs are reported. sR_{aw} was measured with a constant-volume body plethysmograph (Master Screen Body Plethysmograph, version 5; VIASYS Healthcare, Hochberg, Germany). Children sat alone in the plethysmograph wearing a nose clip. They were guided to breathe at a rate of 30 to 45 breaths per minute through the mouthpiece; 3 trials of 10 loops were recorded. Results were excluded if fewer than 5 technically acceptable loops were obtained. The mean total sR_{aw} values from the 3 trials are reported.

All wheezers were categorized according to the following:

1. Current symptom-pattern (episodic [viral] or multiple-trigger wheeze). Episodic (viral) wheezers were defined as those children who wheezed only with discrete viral respiratory tract infections and were asymptomatic between episodes. Multiple-trigger wheezers were defined as those who wheezed with viral respiratory tract infections but were also symptomatic between episodes with other triggers, such as dust allergy, tobacco smoke, exercise, and cold air.[11]
2. Current atopic status (atopic: positive SPT response, current eczema, or both; nonatopic: negative SPT response and no eczema).
3. Presence or absence of wheeze in the previous 12 months. Those with at least 1 wheezing episode were defined as currently symptomatic and those without wheeze as currently asymptomatic.

Healthy control subjects were compared with all wheezers, and subgroup analysis was performed according to the phenotypes described above.

Statistical analyses

The study was powered to detect group differences between episodic (viral) and multiple-trigger wheezers, with MBW as the primary outcome. It was assumed from our previous studies that body size might account for 20% to 40% of the MBW indices' variability, particularly LCI and FRC.[23] Furthermore, ethnicity is considered an independent predictor of pulmonary function as differences in pulmonary function between Asian and white children persist even after correction for body size.[24,25] A sample size of 56 subjects for each ethnic group (28 in each group) would be sufficient to detect an additional 10% variability in MBW indices caused by disease, with at least 80% power at the 5% significance level.[26]

Data are presented as geometric means (95% CIs) or medians (interquartile ranges). Baseline characteristics of healthy control subjects and wheezers were compared by using χ^2, Mann-Whitney *U*, or *t* tests, as appropriate. Demographic differences and unadjusted FeNO values and pulmonary function results between healthy control subjects and the subgroups of episodic (viral) and multiple-trigger, nonatopic and atopic, and currently asymptomatic