

Letter to the Editor

Exhaled nitric oxide measurement confirms 2 severe wheeze phenotypes in young children from the Trousseau Asthma Program

To the Editor:

Recurrent wheezing in young children is a heterogeneous disease principally related to viral infection, genetic background, and environmental features. Fraction of exhaled nitric oxide (FENO) measurement is a noninvasive test of bronchial eosinophilic inflammation, and FENO values are known to be correlated with atopic features in school-aged children. FENO values also serve as an objective parameter of asthma control and could be useful in managing asthmatic children.¹

However, the relevance of FENO values in the young child remains to be defined. Studies have shown that FENO measurement could be used to monitor recurrent wheeze in young children and possibly to identify a population of children at risk of early-onset asthma.^{2,3}

We have recently identified the novel severe wheezing phenotypes of atopic multiple-trigger wheeze and nonatopic uncontrolled wheeze, as opposed to mild episodic viral wheeze in young children by means of cluster analysis.⁴ We set out to confirm these wheezing phenotypes and approach a physiopathologic mechanistic approach using FENO measurements.

An unsupervised statistical method was used on a new population of recurrent wheezing young children (<36 months of age) included in the Trousseau Asthma Program. All children with more than 3 episodes of reversible bronchial obstruction documented within the previous 6 months were considered for inclusion. Exclusion criteria were the presence of another chronic obstructive pulmonary disease, episodes of exacerbation or acute respiratory illness within the previous 3 weeks, and administration of anti-inflammatory treatment within the previous 2 weeks.

The clinical parameters included in the cluster analysis were defined in the same way as our previous work,⁴ especially for the atopic parameters with a standardized questionnaire from the International Study of Asthma and Allergies in Childhood (sex, body mass index, eczema, allergic rhinitis, food allergy, maternal or paternal asthma, asthma severity and control, hospitalization for exacerbation, triggers, and chest radiographic results),⁵ but all the specific and nonspecific blood inflammatory markers performed in the previous work⁴ were replaced by FENO measurement only. FENO levels were measured offline during tidal breathing, as recommended by the American Thoracic Society, with a chemiluminescence NO analyzer (NIOX; Aerocrine AB, Solna, Sweden).

The study included 79 consecutive children with recurrent wheezing seen in outpatient consultation that met the inclusion criteria. The average age of the participants was 22 ± 9.2 months (mean $\pm$ SD), and there were more boys (66%) than girls. Sixty-one percent of the children had uncontrolled or partially controlled asthma; 24% of them were receiving high doses⁴ of inhaled corticosteroid, and 37% were receiving low doses.⁴

The cluster approach revealed 3 clusters of children with shared phenotypic characteristics (see Fig E1 in this article's Online Repository at www.jacionline.org).

Cluster 1 was the largest group, comprising 43 children 19.2 ± 10.5 months old (mean $\pm$ SD, Table I and Fig 1). This

cluster had the greatest number of children with mild disease according to Global Initiative for Asthma classification (96%). In this population recurrent wheeze was more often controlled without high doses of inhaled corticosteroids than in the other clusters (40%), and the children had fewer atopic features, such as eczema, allergic rhinitis, or food allergy. Children mostly wheezed only during colds (episodic viral wheeze, 51% of cases). Thus this phenotype shares the same characteristics as the previously described mild episodic viral wheeze phenotype.⁴ FENO values were lowest in this cluster (6.6 ± 4.6 ppb, mean $\pm$ SD).

Cluster 2 comprised 10 children 23.8 ± 9.0 months old (Table I and Fig 1). Children in this cluster had several features of severity. They all had moderate-to-severe asthma, and their symptoms were frequently uncontrolled despite high doses of inhaled corticosteroids (50%). Most of the children had been hospitalized at least once for asthma exacerbation (90%). Apart from parental asthma, this phenotype has the same characteristics as the previously described nonatopic uncontrolled wheeze phenotype.⁴ FENO values were highest in this cluster (17.7 ± 10.0 ppb).

Cluster 3 comprised 26 children 22.1 ± 9.0 months old (Table I and Fig 1). Asthma severity of children in this cluster was intermediate compared with that in the 2 other clusters, with 66% having moderate-to-severe asthma. A significantly higher frequency of multiple-trigger wheeze (92%) characterized this cluster, along with atopic features, such as allergic rhinitis (88%) and eczema (54%). This phenotype shares all the clinical characteristics of the previously described atopic multiple-trigger wheeze phenotype⁴ and had intermediate FENO values (11.5 ± 10.7 ppb).

This article not only provides objective and physiologic validation of our previous data⁴ with the same 3 phenotypes but also a new approach, including FENO determinants together with severity and atopy by means of cluster analysis. Increased FENO values were associated with the more severe phenotypes, especially nonatopic uncontrolled wheeze, compared with mild episodic viral wheeze ($P = .002$). By taking into account numerous inclusion and exclusion criteria, we obtained a small but homogeneous sample size. Most of the variables were distributed in the same way as our previous study, thus proving the reliability of our data. There were a few discrepancies, however, which were probably due to the lack of power of the small sample size (eg, only a tendency for male sex and food allergy associated with cluster 3).

In young children with recurrent wheeze, FENO values are known to be correlated with asthma severity³ and multiple-trigger wheeze with abnormal lung function.⁶ Ghdifan et al⁷ showed that for FENO values of greater than 15 ppb, the predictive positive and negative values for uncontrolled disease were 65% and 90%, respectively, in a population of infants with recurrent wheeze. Moreover, FENO values are known to be positively correlated with various clinical and biological atopic features in young children. Values are increased in atopic wheezy young children,⁸ and FENO measurements could thus differentiate between children with and without allergic sensitization independently of allergic symptoms.⁹ Finally, in accordance with the literature, our study suggests that in young children FENO values appear to be

TABLE I. Clinical features of children according to cluster analysis in the entire population (n = 79)

	Total cohort (n = 79)	Cluster 1 (n = 43), mild EVW	Cluster 2 (n = 10), nonatopic UW	Cluster 3 (n = 26), atopic MTW	P value*
Patients' characteristics					
Male sex	66	58	70	77	.27
BMI (kg/m ²), z score	0.17	0.09	−0.16	0.43	.27
Allergic comorbidities					
Eczema	34	19	50	54	.006
Allergic rhinitis	53	37	30	88	<.001
Food allergy	9	7	10	12	.80
Maternal or paternal asthma	20	12	0	42	.002
Asthma severity†					
Mild	63	96	0	35	
Moderate	30	2	80	58	<.001
Severe	6	2	20	8	
Controlled without high dose of ICS	29	40	30	12	.003
Uncontrolled with high dose of ICS	24	7	50	42	
≥1 Hospitalization for asthma exacerbation	22	16	90	4	<.001
Triggers					
EVW	38	51	60	8	<.001
MTW	62	49	40	92	
Chest radiograph					
Bronchial syndrome and/or pulmonary distension	42	39	60	38	.46
Alveolar syndrome and/or atelectasis	8	11	0	4	
FENO (PPB), mean ± SD	9.6 ± 8.6	6.6 ± 4.6	17.7 ± 10.0	11.5 ± 10.7	.002

All variables are expressed in percentages except body mass index z scores and FENO values. Boldface values indicate statistical significance. High doses of inhaled corticosteroids were defined as 250 µg/d fluticasone equivalent or greater.

BMI, Body mass index; EVW, episodic viral wheeze (wheezing only during colds and asymptomatic between episodes); ICS, inhaled corticosteroid; MTW, multiple-trigger wheeze (wheezing during colds and with other triggers, such as house dust, grass, pets, tobacco smoke, exercise, or cold air); Uncontrolled, not or partially controlled; UW, uncontrolled wheeze.

*ANOVA or χ^2 tests were used when conditions were respected, and Kruskal-Wallis or Fisher exact tests were used otherwise.

†According to the Global Initiative for Asthma.

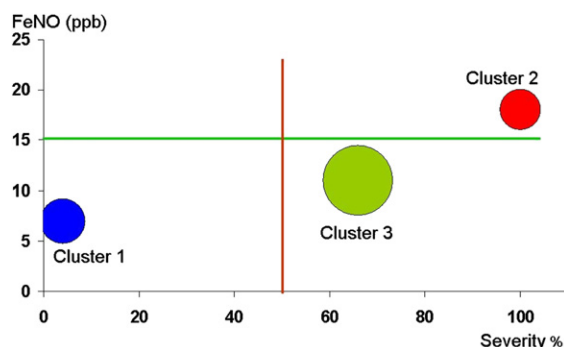


FIG 1. Representation of the 3 clusters according to FENO value, severity, and percentage of allergic rhinitis for the entire population (n = 79). FENO values are expressed in parts per billion. Severity is defined as the percentage of moderate-to-severe asthma according to Global Initiative for Asthma classification. *Circled areas* represent the percentage of atopic rhinitis according to the International Study of Asthma and Allergies in Childhood.

influenced by poor asthma control and disease severity and then by atopic features.

Rahel Gouvis-Echraghi, MD^a
Philippe Saint-Pierre, PhD^b
Amir-Abbas Besharaty, MD^a
Agnès Bernard, MD^a
Jocelyne Just, MD, PhD^a

From ^aCentre de l'Asthme et des Allergies, Hôpital d'Enfants Armand Trousseau, APHP, and ^bLaboratoire de statistiques théoriques et appliquées, Pierre et Marie Curie University, Paris 6, Paris, France. E-mail: jocelyne.just@trs.aphp.fr.

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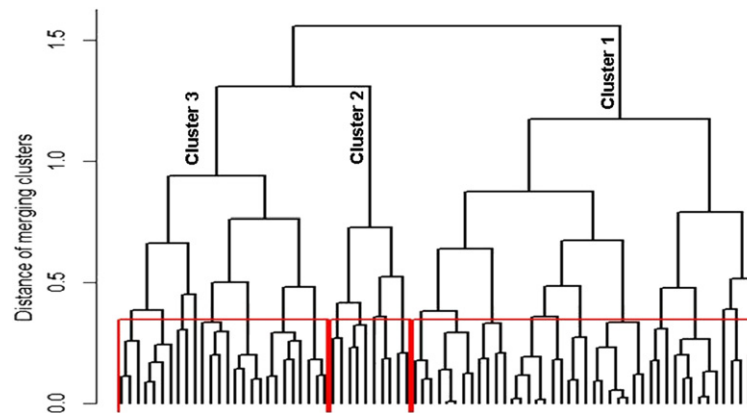


FIG E1. Dendrogram for the entire population ($n = 79$) obtained by using a hierarchic bottom-up clustering method. Three clusters emerged. This agglomerative approach begins with each subject as a separate cluster and merges them into successively larger clusters. By using Ward linkage, samples were merged into larger clusters to minimize the within-cluster sum of the square.