

Original article

Objective assessments of allergic and nonallergic rhinitis in young children

Background: Allergic and nonallergic rhinitis are common childhood disorders. **Objective:** To study nasal eosinophilia and nasal airway patency in young children with allergic and nonallergic rhinitis to assess the pathology behind such diagnoses.

Methods: We investigated 255 children at six years of age from the Copenhagen Prospective Study on Asthma in Childhood birth cohort assessing rhinitis history, specific immunoglobulin E relevant to rhinitis symptoms, nasal eosinophilia and nasal airway patency by acoustic rhinometry before and after decongestion. Associations were studied in a multivariate graphical model corrected for gender, height and nasal steroid usage.

Results: Allergic rhinitis was significantly and directly associated with irreversible nasal airway obstruction (reduced decongested nasal airway patency) ($P = 0.004$), whereas nonallergic rhinitis was not. Both allergic rhinitis ($P = 0.000$) and nonallergic rhinitis ($P = 0.014$) were directly and significantly associated with nasal eosinophilia, but this association was stronger for allergic rhinitis.

Conclusion: Allergic rhinitis and nonallergic rhinitis are of different pathologies as suggested from their different associations not only to allergy but importantly also to irreversible nasal airway obstruction and eosinophilic inflammation. Allergic rhinitis was significantly associated with nasal eosinophilia and irreversible nasal airway obstruction suggesting chronic inflammation and structural remodeling of the nasal mucosa in children at the age of 6 years. Nonallergic rhinitis exhibited no change in the nasal airway patency, but some nasal mucosal eosinophilia albeit less than children with allergic rhinitis.

B. L. K. Chawes, E. Kreiner-Møller, H. Bisgaard

Danish Pediatric Asthma Center, Copenhagen University Hospital, Gentofte Copenhagen, Denmark

Key words: acoustic rhinometry; allergic rhinitis; children; nasal eosinophilia; nonallergic rhinitis.

Hans Bisgaard
Copenhagen Studies on Asthma in Childhood
Danish Pediatric Asthma Center
Health Sciences, University of Copenhagen
Copenhagen University Hospital, Gentofte
Ledreborg Allé 34
DK-2820 Gentofte
Copenhagen, Denmark

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Allergic rhinitis is the most common chronic disease in children (1). Although usually not considered a severe disease, allergic rhinitis has a major impact on quality of life (2), sleep and school performance (3) as well as a considerable socio-economic impact due to health care utilization, treatment costs and loss of work (4).

Allergic rhinitis is traditionally defined from sensitization in combination with 'a significant problem with sneezing, blocked or runny nose in the past 12 months in periods without accompanying cold or flu' (5). Sensitisation is simple to determine (6, 7), while symptom history is nonspecific, as it is difficult to separate a history of viral symptoms from nonviral symptoms (8). Specificity improves if the family is interviewed by a doctor over simple questionnaire data, but remains imprecise.

Objective assessments may further improve our understanding of the pathologies of allergic and nonallergic rhinitis (9). Therefore, we have measured nasal airway patency and nasal eosinophilia in young children with doctor defined allergic and nonallergic rhinitis to assess the pathology behind such diagnoses.

Nasal congestion is a key symptom in both allergic and nonallergic rhinitis (10) and therefore rhinitis phenotyping is improved from objective measure of nasal airway patency. Acoustic rhinometry is a simple and noninvasive method for objective measurement of nasal airway patency (11), which has been validated against computed tomography (12). The technique is well tolerated by children (13–15) and provides assessment of cross-sectional area against distance (11).

Eosinophilic inflammation is a hallmark of the allergic diseases (16) and nasal eosinophilia is associated with severity of allergic rhinitis in children and teenagers (17, 18). Therefore, objective assessment of

nasal eosinophilia should further improve childhood rhinitis phenotyping.

We investigated 255 six-year-old children from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) birth cohort to analyse the associations between rhinitis symptoms and objective measures of allergic sensitisation, nasal airway patency and nasal eosinophilia to investigate the pathology driving allergic rhinitis and nonallergic rhinitis.

Methods

The study is reported in accordance with recognized guidelines (19).

Design

The COPSAC is a single-centre, prospective clinical birth cohort study of 411 children born to asthmatic mothers, which was previously described (20–22). The children were enrolled at 1 month of age and attended the COPSAC clinical research unit every 6 months for scheduled clinical investigations according to standard operating procedures (20–22).

Ethics

The study was conducted in accordance with the Declaration of Helsinki and was approved by The Copenhagen Ethics Committee (KF 01-289/96) and The Danish Data Protection Agency (2008-41-1754) (22).

Objective end-points

Nasal airway patency was assessed by acoustic rhinometry performed twice in the child's 6th year of life both in and out of the pollen season. Measurements were made by trained research assistants at the COPSAC clinical research unit using the SRE 2100 continuous wide-band acoustic rhinometer with a small-sized adult anatomical nose adapter (RhinoMetrics, Interacoustics AS, Assens, Denmark). The subject was seated facing the examiner and stopped breathing for about 5 s with the probe tube applied to the nostril. Three independent measurements with a standard deviation less than 5% were obtained from each nostril before and 15 min after decongestion with one puff of intranasal xylomethazoline 1 mg/ml (Fig. 1).

Nasal airway patency end-points:

- 1 Baseline nasal airway patency: absolute nasal volume 1–4 cm into the nasal cavity.
- 2 Decongested nasal airway patency: absolute decongested nasal volume 1–4 cm into the nasal cavity.
- 3 Nasal responsiveness from topical α -agonist:

$$\frac{\left(\frac{\text{Decongested nasal airway patency} - \text{baseline nasal airway patency}}{\text{baseline nasal airway patency}} \right) \times 100\%}{\text{baseline nasal airway patency}}$$

We selected the lowest values from the two observations to adjust for seasonal variation due to pollen season. The variables analysed were categorized in quartiles. Selection of nasal airway patency end-points is described in the on-line repository.

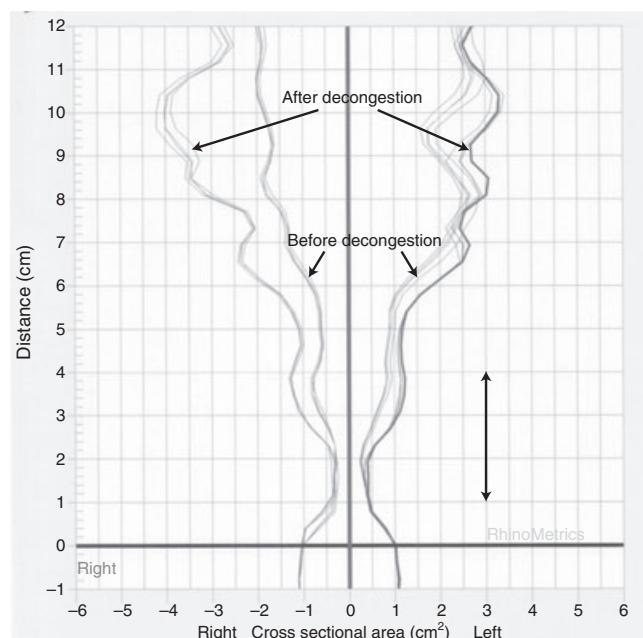


Figure 1. Acoustic rhinometry before and after decongestion with local α -agonist. The inner curves show measurements before decongestion, the outer curves measurements after decongestion. The vertical arrow represents the part of the area-distance curve which is integrated as the nasal volume 1–4 cm into the nasal cavity.

Nasal eosinophilia was assessed by nasal scraping performed twice in the child's 6th year of life both in and out of the pollen season. Nasal mucosal specimens were obtained by gently scraping the anterior part of the inferior turbinate with Rhinoprobes (Arlington Scientific Inc, Arlington, TX, USA). The specimens were transferred onto glass slides, air-dried for 30 min, fixed in 95% ethyl alcohol for 3 min and stained by May-Grünwald-Giemsa method. Eosinophils were counted by light microscopy at high-power (oil immersion, $\times 1000$) by two experienced cytologists, blinded to the rhinitis diagnosis. Rating was done according to Meltzer's semi-quantitative scale evaluating the mean number of eosinophils per 10 high-power field: (0) 0 cells, ($\frac{1}{2}$ +) 0.1–1.0 cells, (1+) 1.1–5.0 cells, (2+) 5.1–15.0 cells, (3+) 15.1–20.0 cells, (4+) > 20.0 cells (16). Specimens without respiratory epithelium or specimens with less than 10 high-power fields were excluded. Nasal eosinophilia was defined as $\geq 1+$ and analysed as a dichotomized variable. The subjects were judged to have eosinophilic inflammation if any one of the two specimens showed nasal eosinophilia.

Rhinitis diagnosis

Rhinitis was diagnosed at 6 years of age by the doctors at the COPSAC clinical research unit based on parent interviews on history of symptoms in the child's 6th year of life. Rhinitis was defined as a significant problem with sneezing, blocked or runny nose in the past 12 months in periods without accompanying cold or flu (23). Significance of symptoms was judged by severity, length of periods and time of year.

Allergic sensitisation. The levels of specific immunoglobulin E (IgE) at 6 years of age against eight common inhalant allergens (cat, dog, horse, birch, timothy grass, mugwort, house dust mites and moulds)

were determined by ImmunoCAP (Pharmacia Diagnostics AB, Uppsala, Sweden). Values of specific IgE ≥ 0.35 kU/l were considered indicative of sensitisation (6, 7) and were analysed as a dichotomized measurement.

Allergic sensitisation was only considered relevant when rhinitis symptoms were predominant during the appropriate exposure: birch (April–May), grass (May–August), mugwort (July–August), moulds (May–October), house dust mites (October–February) and animals (when exposed).

Allergic rhinitis and nonallergic rhinitis. Allergic rhinitis was defined as rhinitis with relevant allergic sensitisation against ≥ 1 inhaled allergens (i.e. symptoms during exposure); nonallergic rhinitis as rhinitis with irrelevant sensitisation (i.e. no symptoms during exposure) or no sensitisation. Control group consisted of subjects without rhinitis symptoms and no sensitisation. Nasal steroid usage was defined as intranasal steroids applied within the month prior to acoustic rhinometry and nasal scraping.

Statistics

Inter- and intraobserver variations of the two cytologists were analysed by weighted kappa values. The associations between allergic rhinitis, nonallergic rhinitis, acoustic rhinometry variables and nasal eosinophilia were analysed by graphical models, distinguishing first between direct, indirect and spurious relationships and secondly adjusting for confounding and effect modification of direct relationships by estimation of conditional relationships. Chi-squared statistics and partial gamma coefficients were used during the analysis. All *P*-values reported are Monte-Carlo approximations of exact conditional *P*-values; a *P*-value ≤ 0.05 was considered significant.

Graphical models (24) are multivariate statistical models applied to analyse high-dimensional contingency tables and are employed here to reveal complex interactions between several outcomes. A graphical model is defined by a Markov graph where variables are presented as nodes and significant associations between variables by lines. Associations between outcomes are described by gamma correlation coefficients and *P*-values by Monte-Carlo approximations (25). All analyses were made using DIGRAM version 1.65 (<http://staff.pubhealth.ku.dk/~skm/skm/index.html>) and SAS version 9.1 (SAS Institute Inc, Cary, NC, USA) for Windows.

Results

Baseline

We investigated 255 of the cohort of 411 infants by doctor interview on rhinitis symptoms and measurements of specific IgE, nasal eosinophilia and acoustic rhinometry. The study group was characterized by significantly more eczema and wheeze in the first 18 months of life and higher income compared with the drop-out group, whereas there were no significant differences regarding gender, siblings and family history of allergic rhinitis (univariate tests, data available on request). Study profile is illustrated in Fig. 2.

Rhinitis was diagnosed in 83 children (33%) and allergic sensitisation against inhaled allergens in 66 children (26%). Allergic rhinitis could be defined in 23 children (9%) and nonallergic rhinitis in 60 children

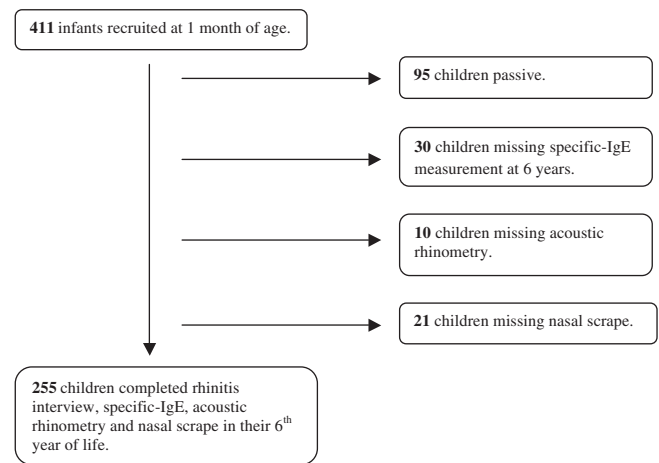


Figure 2. Study profile.

(24%); 34 children (13%) had asymptomatic sensitisation. The control group without rhinitis diagnosis or allergic sensitisation consisted of 138 children (54%).

Within the allergic rhinitis group, 52% were sensitised against birch; timothy grass 78%, mugwort 17%, house dust mites 35%, moulds 26%, cat 35%, dog 35% and horse 22%. Thirty percentages were sensitised to one inhaled allergen; 17% to two; 22% to three; 4% to four; 9% to five; 9% to six and 9% to seven inhaled allergens.

Nasal eosinophilia was found in 18 children; five controls, six allergic rhinitis subjects and seven nonallergic rhinitis subjects. Interobserver variation of the two cytologists was 0.9; intraobserver variations were 0.95 and 0.93 respectively.

End-point associations

Figure 3 illustrates the associations between allergic rhinitis, nonallergic rhinitis, nasal eosinophilia and baseline nasal airway patency, decongested nasal airway patency as well as nasal responsiveness in a multivariate graphical model adjusted for gender, height and nasal steroid usage. Decongested nasal airway patency was significantly associated with allergic rhinitis diagnosis ($P = 0.004$) but not with nonallergic rhinitis ($P = 0.29$). Neither baseline nasal airway patency nor nasal responsiveness was directly associated to allergic or nonallergic rhinitis.

Figure 4 shows that 52% (12/23) of the allergic rhinitis subjects and 23% (14/60) of the nonallergic rhinitis subjects had decongested nasal airway patency below the 1st quartile of the healthy controls. This suggests that subjects with allergic rhinitis have reduced decongested nasal airway patency, i.e. irreversible nasal airway obstruction, whilst nonallergic rhinitis subjects have decongested nasal airway patency largely similar to healthy controls.

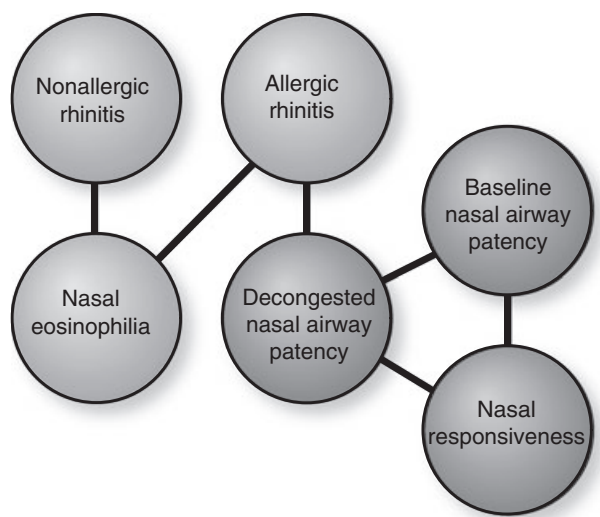


Figure 3. Graphical model; modified Markov graph. Relationship between allergic rhinitis, nonallergic rhinitis, nasal eosinophilia, baseline nasal airway patency, decongested nasal airway patency and nasal responsiveness. The model investigates all potential associations between all variables (nodes) in the model. Significant associations between variables are presented as lines; no line between two nodes indicates a nonsignificant relationship. The model is corrected for gender, height and nasal steroid usage.

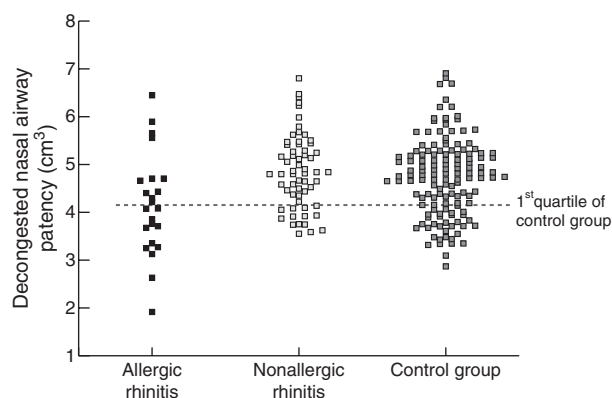


Figure 4. Decongested nasal airway patency in the study group. The first quartile of the healthy controls is shown as a dashed horizontal line. The control group is defined by no rhinitis symptoms and no allergic sensitisation.

Nasal eosinophilia was directly and significantly associated with both allergic rhinitis ($P = 0.000$) and nonallergic rhinitis ($P = 0.014$) (Fig. 3). Nasal eosinophilia was found in 26% (6/23) of subjects with allergic rhinitis and 12% (7/60) of subjects with nonallergic rhinitis compared to 4% (5/138) in subjects with neither, suggesting the association between allergic rhinitis and nasal eosinophilia was stronger than the association between nonallergic rhinitis and nasal eosinophilia.

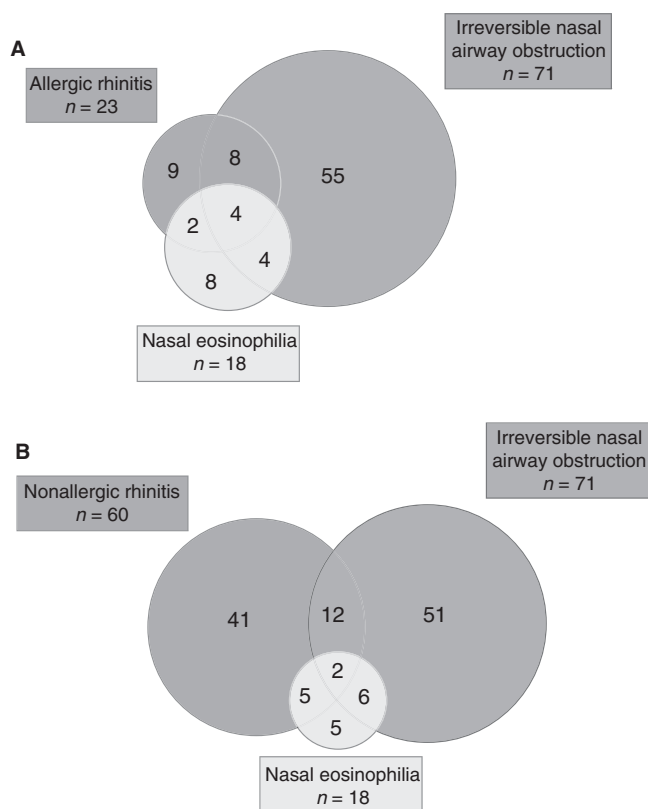


Figure 5. Relationships between rhinitis diagnosis, nasal eosinophilia and irreversible nasal airway obstruction. Irreversible nasal airway obstruction is defined as decongested nasal airway patency below the 1st quartile of the healthy controls.

Associations between rhinitis diagnosis and abnormal nasal findings

The Venn diagrams illustrate the relationship between nasal eosinophilia, irreversible nasal airway obstruction and allergic rhinitis (Fig. 5A) and nonallergic rhinitis (Fig. 5B). The overlapping and nonoverlapping areas between rhinitis diagnosis and abnormal nasal findings describe sensitivity and specificity of the objective measures. The figures illustrate that irreversible nasal airway obstruction is more closely associated (greater overlap) with allergic rhinitis than with nonallergic rhinitis. Still, 39% (9/23) of subjects with allergic rhinitis presented neither nasal eosinophilia nor irreversible nasal airway obstruction as compared to 68% (41/60) of subjects with nonallergic rhinitis. Conversely, 28% (5/18) of subjects with nasal eosinophilia and 63% (45/71) of subjects with irreversible nasal airway obstruction had neither allergic nor nonallergic rhinitis.

Discussion

Principal findings

This is the first objective assessment of allergic and nonallergic rhinitis in young children. Nasal mucosal

eosinophilic inflammation was more closely associated with allergic than with nonallergic rhinitis in children of 6 years suggesting a stronger association between allergic rhinitis and upper airway inflammation.

Irreversible nasal airway obstruction was strongly associated with allergic rhinitis in 6-year-old children, whilst there was no association to nonallergic rhinitis. This suggests that structural remodeling of the nasal mucosa is part of allergic but not nonallergic rhinitis in children at 6 years of age.

Strength and limitations of the study

The major strength of this study is the standardized objective assessments. Nasal mucosal eosinophilia was evaluated from strict criteria with high agreement among the two cytologists. Nasal airway patency was assessed objectively by acoustic rhinometry before and after decongestion from topical α -agonist.

It is also a major strength that diagnosis was made solely by the doctors at the COPSAC clinical research unit based on parent interviews and not on questionnaires. The diagnosis was in principle based on the traditional definition of 'a significant problem with sneezing, blocked or runny nose in the past 12 months in periods without accompanying cold or flu' (5), but the clinical interviews by trained doctors at the single research unit allowed in-depth validation of the history. Furthermore, 77% of mothers in this high-risk cohort had a diagnosis of allergic rhinitis which improves symptom recognition. Additionally, allergic sensitisation was evaluated as relevant *vs* irrelevant based on congruence between exposure and symptoms.

We found a 9% prevalence of allergic rhinitis in our high-risk population (all mothers have an asthma history). Misclassification of rhinitis in children is common (23, 26); it is probably underdiagnosed in clinical practice, whereas questionnaire based surveys may overreport the prevalence (8, 23). A recent study reported allergic rhinitis diagnosed by their general practitioner in 5.3% of 5-year-old children compared to 10% when diagnosis was based on sensitisation and parent interviews in a research clinic (26). Another unselected cohort reported 15% of 7-year-old children were diagnosed with allergic rhinitis based on questionnaire and specific-IgE against birch and grass (27).

The external validity of the study is limited from the setting of a high-risk cohort and the acoustic rhinometry reference values in the control group might differ from the background population. Furthermore, the study group displayed more eczema and wheeze compared with the drop-out group and possibly an increased risk of eosinophilic inflammation and abnormal nasal airway patency.

The internal validity however, is not affected by the high-risk nature and the associations between rhinitis symptoms, allergic sensitisation, nasal eosinophilia and nasal airway patency are probably unaffected from the increased risk of atopy in the cohort.

Meaning of the study

Allergic rhinitis was significantly associated with nasal mucosal eosinophilia, which has been related to sustained nasal obstruction in allergic rhinitis subjects (28) and may lead to structural remodeling with thickening of the reticular basement membrane; a phenomenon that may exist to a greater extent than previously thought in allergic rhinitis subjects (29).

Allergic rhinitis was also significantly associated with irreversible nasal airway obstruction suggesting chronic inflammation and structural remodeling of the nasal mucosa in children at the age of 6 years. In agreement with this, a recent study in adults with allergic rhinitis showed that increased duration of allergic rhinitis is associated with an impaired response to nasal decongestion (30).

Chronic inflammation and structural remodeling of the upper airways might be part of a generalized remodeling of the airways including lower airways (31). Loss of the protective functions of the nose is the simplest mechanistic explanation while absorption of inflammatory mediators (e.g. IL-5 and eotaxin) from sites of inflammation into the systemic circulation has been shown to result in release of eosinophils from the bone marrow, prolonged blood eosinophilia, and thereby possibly systemic propagation of the disease from the nose to the lung (32).

Nonallergic rhinitis exhibited no change in the nasal airway patency, but some nasal mucosal eosinophilia albeit less than children with allergic rhinitis. This association may reflect local nasal IgE production in a fraction of nonsensitized rhinitis subjects, who over time will turn allergic (33) or eosinophilic inflammation triggered by other mechanisms than allergy.

The objective measures of nasal mucosal eosinophilia and nasal airway patency provide an important insight into the pathology associated with allergic and nonallergic rhinitis. However, they are not sensitive as 39% of children with allergic rhinitis presented neither nasal eosinophilia nor abnormal decongested nasal airway patency. This could be explained by short duration of allergic rhinitis as increased duration of allergic rhinitis is associated with an impaired response to nasal decongestion (30). Likewise, 68% of children with nonallergic rhinitis presented neither nasal eosinophilia nor abnormal decongested nasal airway patency suggesting that chronic inflammation and structural remodeling is not part of nonallergic rhinitis. A complementary and possible reason for the poor sensitivity of the methods is the issue of misclassification.

The low number of allergic rhinitis children with eosinophilic inflammation (26%) stresses that nasal eosinophilia is not useful in clinical practice with children at age 6. Chronic inflammation and structural remodeling of the nasal mucosa in allergic rhinitis children might have important implications for rhinitis management

in terms of pharmacological treatment and allergen avoidance. Allergic rhinitis in young children is presumably undertreated and future studies should address whether early intervention controls disease propagation.

Conclusion

Allergic rhinitis and nonallergic rhinitis are of different pathologies as suggested from their different associations to irreversible nasal airway obstruction and eosinophilic inflammation. Children with allergic rhinitis by age 6 are characterized by nasal mucosal eosinophilia and irreversible nasal airway obstruction suggesting chronic inflammation and structural remodeling of the nasal mucosa, contrasting nonallergic rhinitis with less indication of chronic inflammation.

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Supporting information

Additional supporting information may be found in the online version of this article.

Supporting methods. Selection of nasal airway patency end-points.

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Objective Assessments of Allergic and Non-Allergic Rhinitis in Young Children

Bo Lund Krogsgaard Chawes, MD; Eskil Kreiner-Møller, Med Stud.; Hans Bisgaard, MD, DMSci.

On-line Repository

Selection of nasal airway patency end-points

The SRE 2100 continuous wide-band acoustic rhinometer provided cross-sectional area against distance curves before and after decongestion from topical α -agonist for each child. Minimum cross-sectional area 0-2.2 cm into the nasal cavity (internal isthmus) (MCA1) and 2.2-5.4 cm into the nasal cavity (anterior part of the inferior turbinate) (MCA2) were given. A recent study showed that nasal resistance correlated better with changes in volume compared to cross-sectional areas (1). Therefore, nasal volume 1-4 cm into the nasal cavity was calculated by integration of cross-sectional area against distance curves as suggested by previous studies (1-3).

Selection of nasal airway patency end-points was based on coefficients of variation of the change in acoustic rhinometry variables after decongestion. Coefficients for the nasal airway variables (MCA1, MCA2, nasal volume 1-4 cm) were calculated as:

$$\frac{\text{standard deviation difference}}{\text{Mean difference (variable after decongestion – variable before decongestion)}}$$

Nasal volume 1-4 cm into the nasal cavity yielded the lowest coefficient of variation, i.e. improved signal to noise ratio, which is in agreement with a previous study (1).

Assessment of nasal airway patency by volume is thus more informative for rhinitis phenotyping than assessments of cross-sectional areas and nasal volume 1-4 cm into the nasal cavity was therefore chosen as nasal airway patency end-point for further analysis.

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