Children with allergic and nonallergic rhinitis have a similar risk of asthma

Bo Lund Krogsgaard Chawes, MD, Klaus Bønnelykke, MD, PhD, Eskil Kreiner-Møller, MD, and Hans Bisgaard, MD, DMSc *Copenhagen, Denmark*

Background: Both allergic and nonallergic rhinitis have been associated with increased prevalence of asthma.
Objective: To characterize asthma and intermediary asthma endpoints in young children with allergic and nonallergic rhinitis.
Methods: Thirty-eight 7-year-old children with allergic rhinitis, 67 with nonallergic rhinitis, and 185 without rhinitis from the Copenhagen Prospective Study on Asthma in Childhood birth cohort were compared for prevalence of asthma, eczema, food sensitization, filaggrin null-mutations, total IgE, blood eosinophil count, fractional exhaled nitric oxide (FeNO), lung function, and bronchial responsiveness.
Results: Children with allergic rhinitis compared with asymptomatic controls had increased prevalence of asthma (21% vs 5%; $P = .002$), food sensitization (47% vs 13%; $P < .001$), and eczema (66% vs 43%; $P = .01$) and increased total IgE (155 kU/L vs 41 kU/L; $P < .001$), blood eosinophil count (0.46×10^9/L vs 0.30×10^9/L; $P = .01$), FeNO (15.9 ppb vs 6.6 ppb; $P < .001$), and bronchial hyperresponsiveness (23% vs 9%; $P = .008$). Filaggrin null-mutations were associated with allergic rhinitis (odds ratio, 3.3; 95% CI, 1.3-8.3) but did not modify these associations. Children with nonallergic rhinitis also had increased asthma prevalence (20% vs 5%; $P = .001$) but showed no association with filaggrin null-mutations, eczema, food sensitization, total IgE, blood eosinophil count, FeNO, or bronchial responsiveness.
Conclusion: Asthma is similarly associated with allergic and nonallergic rhinitis, suggesting a link between upper and lower airways beyond allergy associated inflammation. Only children with allergic rhinitis had increased bronchial responsiveness and elevated FeNO, suggesting different endotypes of asthma symptoms in young children with allergic and nonallergic rhinitis. (J Allergy Clin Immunol 2010;126:567-73.)

Key words: *Allergic rhinitis, nonallergic rhinitis, asthma, children, united airways*

Allergic rhinitis is defined by sensitization to inhaled allergens and symptoms such as rhinorrhea, nasal obstruction, nasal itching, and sneezing during exposure to relevant allergens,[1] whereas nonallergic rhinitis is a diagnosis of exclusion characterized by similar symptoms but without allergic sensitization relevant to symptoms and without signs of infection.[2] Studies of adults and adolescents have shown increased prevalence of asthma in subjects with allergic and nonallergic rhinitis.[3,4] We hypothesized that these may represent different endotypes of asthma. This has not been studied previously in young children.

We studied 290 seven-year-old children with allergic rhinitis, nonallergic rhinitis, and asymptomatic controls from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC) birth cohort. We compared prevalence of asthma, eczema, sensitization to food allergens, frequency of filaggrin null-mutations, levels of total IgE, blood eosinophil count, fractional exhaled nitric oxide (FeNO), measures of lung function, and bronchial responsiveness.

The aim of the study was to describe asthma prevalence and intermediary asthma endpoints in children with allergic and nonallergic rhinitis.

METHODS

Design

The COPSAC is a birth cohort study of 411 children born to mothers with asthma, recruited in the region of greater Copenhagen, Denmark.[5-7] The infants were enrolled at 1 month of age and subsequently attended the clinical research unit at 6-month intervals and immediately on onset of any respiratory or skin-related symptom.

Ethics

The study was conducted according to the principles of 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). Informed consent was obtained from both parents at enrollment.[5]

Objective measurements by age 7 years

Baseline lung function was assessed by measurement of specific resistance of airways (sRaw) by whole-body plethysmography.[8,9]

Reversibility of airway resistance was determined as the relative change of sRaw 15 minutes after inhaled β_2-agonist (2 puffs of terbutaline 0.25mg/dose in a pressurized metered-dose inhaler with a spacer).

Bronchial responsiveness was determined as the relative change of sRaw 4 minutes after hyperventilating –18°C cold dry air.[10,11]

Fractional exhaled nitric oxide level was measured by an online technique[12,13] in accordance with recognized guidelines.[14]

Blood samples were analyzed for eosinophil count, total IgE, and specific IgE levels.[15] Sensitization was defined as specific IgE ≥ 0.35 kU/L[15,16]; allergic

From the Copenhagen Prospective Studies on Asthma in Childhood, Health Sciences, University of Copenhagen, and the Danish Pediatric Asthma Center, Copenhagen University Hospital, Gentofte.

Supported by the Lundbeck Foundation, the Pharmacy Foundation of 1991, the Danish Medical Research Council, the Danish Pediatric Asthma Center, the Danish Lung Association, Hans Skoubys og hustru Emma Skoubys Fond, and Oda Pedersens Legat.
Disclosure of potential conflict of interest: K. Bønnelykke is a consultant and paid lecturer for Merck and GlaxoSmithKline. H. Bisgaard is a paid lecturer for AstraZeneca and Merck; is a consultant for Merck and Chiesi; receives research support from the Lunbeck Foundation, the Pharmacy Foundation of 1991, the Augustinus Foundation, the Danish Medical Research Council, and the Danish Pediatric Asthma Center; and has provided legal consultation/expert witness testimony for the EMEA regarding guidelines on pediatric studies for documenting asthma drugs. The rest of the authors have declared that they have no conflict of interest.
Received for publication May 31, 2010; revised June 22, 2010; accepted for publication June 24, 2010.

Reprint requests: Hans Bisgaard, MD, DMSc, Copenhagen Prospective Studies on Asthma in Childhood, Health Sciences, University of Copenhagen, and the Danish Pediatric Asthma Center, Copenhagen University Hospital, Gentofte, Ledreborg Allé 34, 2820 Gentofte, Denmark. E-mail: bisgaard@copsac.com.

0091-6749/$36.00

doi:10.1016/j.jaci.2010.06.026

Abbreviations used
COPSAC: Copenhagen Prospective Study on Asthma in Childhood
FeNO: Fractional exhaled nitric oxide
OR: Odds ratio
sRaw: Specific resistance of airways

sensitization to airborne allergens as any sensitization for cat, dog, horse, birch, timothy grass, mugwort, house dust mites, or molds; and food sensitization as any sensitization for hen's egg, cow's milk, fish, wheat, peanut, soybean, or shrimp.

Nasal eosinophilia was assessed by nasal scrapings and rated by 2 experienced cytologists according to the Meltzer semiquantitative scale[17] as previously detailed.[18]

Clinical diagnoses

Rhinitis was diagnosed by the COPSAC doctors on the basis of parent interviews (not questionnaires) on rhinitis symptoms in the child's seventh year of life. The interview addressed rhinitis symptoms (sneezing, blocked nose, runny nose, and nasal itching/rubbing), nasal steroid trials, limitation of daily activities and sleep disturbance, eye involvement (itching/watery and red eyes), suspected precipitating factors, and time of year with symptoms. According to these interviews, rhinitis was defined by troublesome sneezing or blocked or runny nose severely affecting the well being of the child in periods without common cold or flu.[19] Allergic rhinitis was diagnosed in children with sensitization to aeroallergens clearly related to the symptomatic periods (birch [April-May], grass [May-August], mugwort [July-August], molds [May-October], house dust mites [October-February], and animals [when exposed]). Nonallergic rhinitis was diagnosed in children without sensitization or without symptoms during periods of exposure to such allergens.[18]

In a secondary analysis, we analyzed (1) allergic rhinitis (rhinitis plus any sensitization to aeroallergens irrespective of association with symptoms) and nonallergic rhinitis (rhinitis without any sensitization to aeroallergens), (2) allergic rhinitis and nonallergic rhinitis stratified by presence of nasal eosinophilia, and (3) inflammatory rhinitis (rhinitis plus nasal eosinophilia) and noninflammatory rhinitis (rhinitis without nasal eosinophilia).

Current asthma in the seventh year of life was diagnosed according to international guidelines as previously detailed[7,20] on the basis of respiratory diary cards completed on a daily basis by the parents, symptoms judged by the COPSAC doctors to be typical of asthma (eg, exercise-induced symptoms, prolonged nocturnal cough, recurrent cough outside common cold, symptoms causing wakening at night); need for intermittent rescue use of inhaled β_2-agonist, response to a 3-month trial of inhaled corticosteroids, and relapse when stopping treatment.

Eczema ever in the first 7 years of life was diagnosed by the COPSAC doctors according to predefined morphology and localization at both scheduled and acute visits defined by the Hanifin-Rajka criteria as previously detailed.[21,22]

Genetics

Filaggrin genotyping for 2 independent common null-mutations (*R501X* and *2282del4*) was performed as previously detailed.[23] Children were assigned as having a filaggrin mutation if they carried at least 1 of the mutations.

Statistical analysis

The study group was categorized in 3 groups: allergic rhinitis, nonallergic rhinitis, and a control group (reference group) without persistent rhinitis symptoms. Odds ratios of asthma, eczema, and food sensitization were calculated by logistic regression, whereas associations between rhinitis diagnoses and continuous outcomes (total IgE, blood eosinophil count, FeNO, baseline sRaw, β_2-reversibility, and bronchial responsiveness to cold dry air) were analyzed by generalized linear models expressing results as β-coefficients. Total IgE, blood eosinophil count, and FeNO were log-transformed before analysis.

Results are reported with 95% CIs in brackets; a P value ≤ .05 was considered significant. All analyses were performed with SAS v. 9.2 (SAS Institute, Inc, Cary, NC).

Further details of the Methods are outlined in this article's Online Repository at www.jacionline.org.

RESULTS

Baseline characteristics

Complete follow-up by doctor interview on rhinitis symptoms in the seventh year of life and measurement of specific IgE was available for 290 of the cohort of 411 infants (see this article's Fig E1 in the Online Repository at www.jacionline.org). The study group had increased prevalence of recurrent wheeze in the first 1.5 year of life ($P < .001$) and higher income ($P < .001$) compared with the group without follow-up on these endpoints, whereas there were no differences in eczema, allergic sensitization to aeroallergens, sex, older siblings, or family history of allergic rhinitis (see this article's Table E1 in the Online Repository at www.jacionline.org).

Rhinitis was diagnosed in 105 children (36%) and allergic sensitization to inhaled allergens in 76 children (26%). Allergic rhinitis to aeroallergens was diagnosed in 38 children (13%) and nonallergic rhinitis in 67 children (23%). Five children classified as having nonallergic rhinitis were sensitized to aeroallergens but without symptoms during exposure. The control group without persistent rhinitis symptoms was made up of 185 children (64%).

The overall study group consisted of 142 boys (49%). Prevalence of asthma, food sensitization, eczema, nasal eosinophilia, and filaggrin mutations; levels of total IgE, FeNO, and blood eosinophil count; baseline sRaw, reversibility to β_2-agonist, and bronchial responsiveness to cold dry air are described in Table I.

Associations among asthma, eczema, and allergic and nonallergic rhinitis

The Venn diagrams illustrate the relationships among asthma, eczema, and allergic rhinitis (Fig 1, *A*) and nonallergic rhinitis (Fig 1, *B*). The overlapping areas illustrate that current asthma is equally frequent in children with allergic rhinitis (21%) and nonallergic rhinitis (20%). Accordingly, both allergic rhinitis (OR, 5.0; 95% CI, 1.8-14.0; $P = .002$) and nonallergic rhinitis (OR, 4.6; 95% CI, 1.9-11.4; $P = .001$) were significantly associated with current asthma (Table II). Likewise, asthma was significantly associated with rhinitis symptoms (OR, 4.8; 95% CI, 2.1-10.8; $P < .001$) without evidence of interaction with sensitization to aeroallergens (P value for interaction, 0.87).

The Venn diagrams also show that a history of eczema is a more frequent finding in children with allergic rhinitis than nonallergic rhinitis (66% vs 43%). The OR of eczema was 2.5 (95% CI, 1.2-5.1; $P = .01$) for children with allergic rhinitis and 1.0 (95% CI, 0.6-1.7; $P = .94$) for children with nonallergic rhinitis (Table II).

Allergic versus nonallergic rhinitis

Children with allergic rhinitis compared with nonallergic rhinitis more often had sneezing (79% vs 58%; $P = .03$), nasal rubbing/itching (66% vs 40%; $P = .01$), itchy/watery eyes (66% vs 42%; $P = .02$), and trials of nasal steroid treatments (37% vs 19%; $P = .05$), whereas blocked nose was more prevalent in children with nonallergic rhinitis (76% vs 58%; $P = .02$). Length of the rhinitis history was increased in allergic rhinitis