

Letters

ALLERGIC CONJUNCTIVITIS IN ASTHMATIC CHILDREN: AS COMMON AS UNDERREPORTED

Allergens can directly affect the eye's surface and promote the development of local allergic inflammatory disorders. Epidemiologic studies have demonstrated that more than 75% of patients with allergic rhinitis and 20% of patients with asthma have ocular symptoms, such as itching, tearing, and redness.¹⁻³ Contrary to settled epidemiology of allergic rhinoconjunctivitis, there are few data on the occurrence of allergic conjunctivitis in childhood. The aim of this study was to assess the reported frequency of allergic conjunctivitis in asthmatic children attending a tertiary specialty outpatient clinic.

We performed a cross-sectional study using clinical data obtained from a standardized allergy workup form that includes oriented questions on common allergic diseases. At the initial visit parents were asked about their children's symptoms of allergic skin and respiratory conditions and we reviewed the patients' systems. An asthma diagnosis was considered for recurrent wheezers with 3 or more episodes, according to the Global Initiative for Asthma. Asthmatic patients seen at their first visit to the pediatric allergy unit, from January 2001 to January 2006, were selected for analysis. Diagnosis of allergic conjunctivitis was based on the presence of 1 or more ocular symptoms (itching, tearing, and redness). Allergic sensitization was assessed by skin prick tests with glycerinated allergenic extracts (IPI-ASAC, São Paulo, Brazil) of *Dermatophagoides pteronyssinus*, *Blomia tropicalis*, *Blattella germanica*, *Lolium perenne*, and dog and cat danders. This panel consists of common sensitizing aeroallergens to our population based on regional prevalence.⁴ A test result was considered positive if the wheal cross-diameter was 3 mm or greater. Data entered in MS-Excel and categorical variables were analyzed with the nonparametric χ^2 test. Sensitivity, specificity, odds ratios, and 95% confidence intervals were also obtained using the statistical software Statistica, version 9.1 (StatSoft Inc, Tulsa, Oklahoma). The institutional review board approved this protocol.

A total of 1549 asthmatic children (59% male; mean [SD] age, 4.3 [3.5] years) provided complete medical record information. A physician diagnosis of conjunctivitis was registered in 245 medical records (15.8%), but 681 (43.9%) had at least 1 ocular symptom that suggested ocular allergy. A higher number of children had repor-

ted individual symptoms as itching (596 [38.4%]), tearing (308 [19.9%]), redness (388 [25%]), and combined symptoms, such as itching plus redness (335 [21.6%]) and itching plus tearing (257 [16.6%]). Nevertheless, a diagnosis of allergic conjunctivitis was not reported by the attending physician.

Although the report of ocular symptoms by patients is not parallel to physician report of allergic conjunctivitis, there was a greater odds ratio to conjunctivitis report when ocular itching was registered. Itchy eyes had the highest sensitivity, and the specificity was an association of itching plus tearing (Table).

Children with allergic conjunctivitis were sensitized to the house dust mites *D pteronyssinus* (71.4%) and *B tropicalis* (70.9%), followed by *B germanica* (30.6%), *L perenne* (19.1%), and dog (20.6%) and cat dander (16.7%).

Worldwide, data on the epidemiology of allergic conjunctivitis are scarce. In the United States ocular allergy is estimated to occur in 15% to 20% of the general population.³ Response to a written questionnaire followed by a subsequent interview of 396 Swedish schoolchildren aged 12 to 13 years estimated a cumulative prevalence of allergic conjunctivitis in 19.1% and showed an association with allergic rhinitis in 92%.⁵

The association of allergic nasal and ocular symptoms (rhinoconjunctivitis) is common. Gradman and Wolthers⁶ reported that 97% of children with allergic conjunctivitis had allergic rhinitis and 42% of allergic rhinitis patients had allergic conjunctivitis.

In this population of asthmatic children, allergic rhinitis was more frequently seen than allergic conjunctivitis, but a high number of children with ocular symptoms was not reported or did not have the diagnosis reported, even in a tertiary pediatric allergy clinic. The study has several limitations. It was retrospective, it was conducted on an asthmatic population in a specialty center, and the chief complaint of patients for most visits was not allergic conjunctivitis. In addition, results could be different if the observation was in a pediatric population seen in a primary care setting. We assume a hypothesis of allergic conjunctivitis based on symptoms; however, tearing and redness, although specific, were less sensitive and would not necessarily indicate allergic conjunctivitis. The diagnosis of allergic conjunctivitis was reported 20-fold more often when patients presented with at least 1 or both ocular symptoms, and itching had higher sensitivity and other symptoms had more specificity. From a pathophysiologic point of view, allergic conjunctivitis may be part of the "one airway, one disease" concept.⁷

In conclusion, itchy eyes remain an important symptom to be properly evaluated for the diagnosis of allergic conjunctivitis. The

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Table. Diagnostic Probability of Reported Allergic Conjunctivitis in 681 Asthmatic Children With Ocular Symptoms

Ocular symptoms	Reported conjunctivitis diagnosis, %	Odds ratio (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	P value
Itching	37.9	20.2 (13.4–30.4)	89 (85.1–92.8)	71.4 (69–73.9)	<.001
Redness	46.9	13.4 (9.8–18.2)	71.7 (66.1–77.2)	84.1 (82.1–86.1)	<.001
Tearing	43.8	7.4 (5.5–9.9)	53.1 (47–59.3)	86.6 (84.8–88.5)	<.001
Tearing and redness	51	14.2 (10.4–9.4)	67.3 (61.6–73.1)	87.3 (85.5–89.1)	<.001
Itching and tearing	49.2	9.0 (6.6–12.2)	50 (43.9–56.1)	90 (88.3–91.6)	<.001

Abbreviation: CI, confidence interval.

frequency of allergic conjunctivitis in asthmatic children is high but underreported. In today's world of potential micromanagement of health care utilization, it is incumbent on the practicing physician to clearly delineate, report, and treat all relevant problems.

HERBERTO JOSÉ CHONG NETO, MD, PhD
NELSON AUGUSTO ROSÁRIO, MD, PhD
GABRIELE LIMA CARDOSO WESTPHAL, MD
CARLOS ANTÔNIO RIEDI, MD, PhD
HEVERTTON LUIZ BOZZO SILVA SANTOS, MD

Pediatric Allergy Division
Federal University of Paraná
Curitiba, Paraná, Brazil
h.chong@uol.com.br

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EXHALED NITRIC OXIDE IN YOUNG, SYMPTOMATIC PATIENTS WITH ATOPIC ASTHMA RECEIVING NEBULIZED BUDESONIDE THERAPY

Exhaled nitric oxide (eNO) is a noninvasive marker of airway inflammation and is elevated in young patients with asthma.¹ In asthmatic patients, eNO has been shown to decrease with anti-inflammatory medication, such as oral or inhaled steroids.² There are no published studies on the effect of nebulized steroids on eNO in exclusively young asthmatic children with active symptoms. We studied the effect of nebulized budesonide inhalation suspension (BIS) once daily on eNO levels in 4- to 6-year-old children with physician-diagnosed mild-moderate asthma. Few studies have examined the timing of onset of the anti-inflammatory effect of steroids on eNO.³ Therefore, we measured eNO early in the treatment course after 72 hours.

Although measuring eNO in 4-year-olds has been approved with the NIOX analyzer (Aerocrine, Solna, Sweden), it can be difficult to attain and reproduce in children younger than 7 years. We measured eNO using NIOX but with a specific maneuver that would attain acceptable NO plateau levels by the American Thoracic Society guidelines.^{4,5}

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We performed a prospective, open-label study design with BIS (0.5 mg/2 mL) once daily for 2 weeks. After written consent, a 1-week run-in with twice daily diary scoring was started to document compliance and asthma symptoms with eNO. A 2-week active treatment period was started with nebulized BIS (with ProNeb Ultra with face mask) followed by a 2-week washout period. In addition, after 3 days during active treatment with BIS, a study visit was performed to measure early effects of BIS on eNO. Three reproducible eNO measurements were collected at each visit. Exhalation time and pressure for the eNO measurements were adapted for this age group to have attainable respiratory maneuvers.⁶ The eNO measurements had acceptable plateaus with the 6-second exhalation time selected, which is dependent on age and height.^{5,7} The pressure selected (+5–10 mm Hg) was maintained to close the velum during eNO measurements to avoid upper airway contamination. Measurements of spirometry (Koko, Louisville, Colorado) and peak flow (Respironics, Cedar Grove, New Jersey) with collection of daily asthma symptom scores (total symptom score 4) and rescue medication use were obtained at each visit. Asthma symptoms collected were cough, nighttime awakenings, exercise tolerance, and shortness of breath.

Sixteen patients were enrolled in the study (mean age, 5 years; 12 males; 14 white, 1 African American, and 1 Asian) with a mean asthma duration of 3.5 years, and all were atopic as measured by skin test sensitivity to perennial allergens. Inclusion criteria required that all children have an asthma diagnosis of at least 1 year and elevated baseline eNO levels greater than 15 ppb. No systemic steroid use was allowed during or 60 days before the study. No other asthma medication that would influence eNO levels was allowed during or 30 days before initiation, including nasal, ocular, topical, or inhaled steroids, leukotriene modifiers, or cromolyn. Rescue medication of short-acting bronchodilator agents was allowed during the study. Patients with signs or symptoms of upper or lower airways infection by report or examination were excluded.

At baseline, mean eNO level was 27 ± 11 ppb, and after 2 weeks of BIS it reduced to 14 ± 5 ppb ($P < .005$). After 3 days of BIS, mean eNO reduced to 17 ± 8 ppb ($P < .005$) (Figure 1). Changes in spirometry and peak flow measurements mirrored the improvement in eNO with BIS treatment. Mean forced expiratory volume in 1 second (FEV₁) improved from $85\% \pm 14\%$ to $96\% \pm 12\%$ ($P < .005$) after 2 weeks. Mean FEV₁ improved after 3 days to $92\% \pm 12\%$ ($P < .05$). Mean peak flow improved from 143 ± 40 L/min to 163 ± 41 L/min ($P < .05$), and peak expiratory flow was also significantly improved. After a washout period, mean eNO increased back to 26 ± 11 ppb ($P < .005$) but FEV₁ and peak flow did not worsen after the washout period. Changes of the ratio of FEV₁ to forced vital capacity and total symptom score 4 were not statistically significant.

We have shown that the anti-inflammatory effect of nebulized BIS can be monitored by eNO in young children using NIOX in a reproducible manner. In our study of 4- to 6-year-olds with persistent asthma symptoms, eNO was decreased significantly within 72 hours and continued further with 2 weeks of BIS despite no significant improvement in diary scores, thus revealing the importance of using objective measures in asthma therapy.⁸ Limitations were that this was a small proof-of-concept study performed outside allergy season.

Although there was improvement in eNO and spirometry parameters during BIS therapy, after the washout there was a return to baseline levels only with eNO. This suggests the inflammatory process mirrored by eNO is more labile than the bronchoconstriction