

Review Article

Asthma Phenotypes: Nonallergic (Intrinsic) Asthma

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The definition of nonallergic asthma includes that subset of subjects with asthma and with whom allergic sensitization cannot be demonstrated. These individuals should have negative skin prick test or *in vitro* specific-IgE test to a panel of seasonal and perennial allergens. Nonallergic asthma occurs in 10% to 33% of individuals with asthma and has a later onset than allergic asthma, with a female predominance. Nonallergic asthma appears to be more severe than allergic asthma in many cases and may be less responsive to standard therapy. Although many of the immunopathologic features of nonallergic asthma are similar to those observed with allergic asthma, some differences have been described, including a higher expression of RANTES in mucosa and bronchoalveolar lavage fluid, as well as a higher GM-CSF receptor alpha expression. Unbiased statistical methods, such as cluster analysis and latent class analysis, indicate that the lack of atopy is not the most important defining factor in assigning an individual to many specific phenotypes but rather is more important in some phenotypes than others, and appears to modulate the clinical expression of the disease. Despite an appreciation of this clinical entity for many years, many of its clinical implications remain unclear. © 2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;■:■-■)

Key words: nonallergic asthma; intrinsic asthma; nonatopic asthma; asthma phenotypes

Although a category of asthma termed “intrinsic” was described more than 50 years ago,¹ whether this entity has distinct clinical and immunopathologic features²⁻⁴ or should be

abandoned as an entity (chronicle of an announced death: the end of intrinsic asthma)⁵ continues to be debated. The generally accepted definition of nonallergic asthma includes asthma of a subject with whom allergic sensitization cannot be identified (by skin prick or *in vitro* specific-IgE tests) to a panel of local allergens, and, at a minimum, a panel of perennial allergens; serum total IgE levels are typically normal or low.^{6,7}

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

A number of reviews compared and contrasted clinical and immunopathologic features of allergic and nonallergic asthma.^{3,4,6,7} Nonallergic asthma is said to occur in 10% to 33% of individuals with asthma and has a later onset than allergic asthma, with a female predominance. Nonallergic asthma appears to be more severe than allergic asthma in many cases and may be less responsive to standard therapy.^{4,8} A lack of personal or family history of allergy is common, and seasonal or exposure-related triggers are absent. A multivariate analysis reported a history of nasal polypectomy, female sex, FEV₁ < 80% predicted, and greater age to be positively associated with nonallergic asthma, whereas a history of hay fever, seasonal exacerbations, and longer asthma duration were associated with a decreased risk of nonallergic asthma.⁴ Mothers of children with nonatopic asthma report the presence of phlegm, wheezing, and a physician diagnosis of asthma, and have increased bronchial hyper-responsiveness in comparison with mothers of children with atopic asthma.⁹

COMORBIDITIES

Comorbidities commonly associated with nonallergic asthma include nasal polyposis, rhinosinusitis, and gastroesophageal reflux disease.^{3,4,6-8} Aspirin exacerbated respiratory disease (AERD) (eg, severe asthma, associated with chronic rhinosinusitis with nasal polyps, and sensitivity to aspirin and other nonsteroidal anti-inflammatory agents) can either be considered a specific type of nonallergic asthma or a separate phenotype of asthma, as discussed in an accompanying article in this issue.^{6,10} However, atopy (positive skin prick tests) has been reported to be present in 52% of subjects with AERD and ranged from 47% to 65% of subjects in the 4 classes of these subjects identified by latent class analysis.¹⁰

BIOMARKERS

Many of the immunopathologic features of nonallergic asthma are similar to those observed in allergic asthma.^{3,4,6,7} In the bronchial mucosa, they include a similar expression of Th2 cytokines as allergic asthma (with a possible exception of lower IL-4 levels), similar local IgE synthesis, a similar number of FCεR1⁺ cells, and a similar or higher number of eosinophils in the mucosa. Individuals with nonallergic asthma have a higher

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Abbreviation used

AERD-Aspirin exacerbated respiratory disease

expression of RANTES in mucosa and bronchoalveolar lavage fluid as well as a higher GM-CSF receptor alpha expression.¹¹⁻¹³ In blood, individuals with nonallergic asthma show an eosinophilia similar to individuals with allergic asthma, with lower IL-4 production from peripheral blood leukocytes and decreased B cells that express CD23, the low affinity IgE receptor, with increased CD4⁺ lymphocytes that express the cytotoxic molecule perforin and increased CD68⁺, GM-CSF receptor alpha⁺ macrophages (reviewed by Novak and Bieber⁷).

RELATIONSHIP TO STATISTICALLY DEFINED PHENOTYPES

In an effort to empirically differentiate clinically different phenotypes of subjects with asthma, unbiased methods, such as cluster analysis or latent class analysis, have been performed with asthma populations of both adults^{14,15} and children.¹⁶⁻¹⁸ The percentages that were atopic in the adult clusters in the cohorts studied by Haldar et al¹⁴ and Moore et al¹⁵ were 52% to 95% and 64% to 85%, respectively. In children, the percentage of atopy ranged from 9% to 70% in the Spycher cohort¹⁶ and from 5% to 90% when tested as infants in the cohort in the study by Just et al,¹⁸ and the median numbers of positive skin prick tests that were positive ranged from 1 to 4 (of a total of 12) in the cohort in the study by Fitzpatrick et al.¹⁷

Adult cohorts with the highest number of individuals without atopy were women who were obese and without eosinophilia (cluster 2, 46% [Haldar et al¹⁴]) and older women who were obese and with a high body mass index (cluster 3, 36% [Moore et al¹⁵]). Both the cohorts in Haldar et al¹⁴ and Moore et al¹⁵ with low numbers of individuals with atopy were characterized by subjects with more-severe disease, unlike the nonatopic cohort D of Siroux et al,¹⁹ 89% of whom had an IgE level of <100 IU/mL, which were described as having inactive-to-mild untreated nonallergic asthma.

Children without atopy and with persistent wheeze numbered 91% in phenotype D in cohort in the study by Spycher et al¹⁶ and 95% in the nonatopic uncontrolled wheeze cluster 2 of the study by Siroux et al.¹⁹ Children with the least number of positive skin prick tests (median, 1) in cluster 1 of the cohort in the study by Fitzpatrick et al¹⁷ had late-onset symptomatic asthma with normal lung function. All 3 of the childhood cohorts with the highest number of individuals without atopy had more-severe disease, as defined by persistent wheeze or symptomatic disease, than other statistically defined groups.

Cluster analysis also has been performed of data of children and adults with difficult-to-control asthma.²⁰ In children, cluster 3 was characterized by a relative lack of atopy (ie, no subjects with allergic rhinitis). With adults, the most common cluster (approximately 35% of subjects [cluster 1]) included white women most likely to have adult onset disease without AERD and who had lower total IgE levels. Finally, adult clusters distinguished by nonwhite race and AERD manifested poorer quality of life than others. From these observations, it can be concluded that the lack of atopy plays a complex role in modulating the effect of a variety of factors in the expression of an asthma phenotype. The fact that a majority of subjects

assigned to a specific phenotype remained in the same phenotype over a 10-year observation period (54%-88%)²¹ suggests that, although the pattern of disease expression can change over time, in most individuals, it remains stable.

DEFINITION

The definition of nonallergic asthma includes that subset of subjects with asthma with whom allergic sensitization cannot be demonstrated. These individuals should have negative skin prick test or *in vitro* specific-IgE test to a panel of seasonal and perennial allergens, including local pollens (grass, tree, weed), molds (*Alternaria*, *Aspergillus*, *Cladosporium*), house dust mites (*Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*), cockroach, cat, and dog. A minimum panel of allergens would include perennial allergens (molds [*Alternaria*, *Aspergillus*, *Cladosporium*], house dust mite [*D farinae*, *D pteronyssinus*], cockroach, cat, and dog), without local pollens. Serum total IgE levels should be normal or low.

RECOMMENDATIONS FOR INFORMATION TO BE OBTAINED TO DETERMINE PHENOTYPES (RELATED TO NONALLERGIC ASTHMA)

Tests of allergic sensitization must be performed, and these tests (skin prick test or *in vitro* specific-IgE test) must be negative, as described. It also is recommended that a series of defining questions be posed:

1. Have you had allergy tests in the past that were positive? (no, yes, not sure)
2. At what age did your asthma start? (childhood, <12 years old; adolescence, 12-18 years old; or adulthood, >18 years old)
3. Does your asthma gets worse during a certain season or after exposure to something in the environment? (never, rarely, sometimes, most of the time, always)

Finally, as suggested in other sections of this document, information concerning comorbidities (rhinosinusitis, nasal polypsis, gastroesophageal reflux disease), and sensitivities (to aspirin and other nonsteroidal inflammatory drugs) should also be obtained.

RESEARCH QUESTIONS AND FUTURE DIRECTIONS

A number of evolving issues and questions have arisen when considering nonallergic asthma. Among the most common questions are the following:

- Are there different inflammatory and immune mechanisms operating in nonallergic versus allergic asthma?
- To what extent are comorbidities more important in nonallergic versus allergic asthma (eg, gastroesophageal reflux disease, rhinosinusitis)?
- Is nonallergic asthma a less reversible form of asthma than allergic asthma?
- Do individuals with nonallergic asthma respond differently to controller medications than those with allergic asthma?
- What is the role of IgE in nonallergic asthma?
- Does anti-IgE therapy have a role in the management of nonallergic asthma?
- Is the prognosis worse for nonallergic asthma than for allergic asthma?

- Can further refinement of cluster and latent class analysis provide additional insight into the pathogenesis and natural history of nonallergic asthma?

CONCLUSION

The concept of intrinsic or nonallergic asthma has been discussed for decades. Although clinical experience certainly supports such an entity, both the immunopathology and unbiased methods, such as cluster analysis or latent class analysis, do not identify this characteristic as a separate phenotypic entity. Rather, the lack of atopy appears to be a factor that modulates the expression of asthma to a different extent in phenotypes identified by other criteria. Additional information from genomic, proteomic, and metabolomics analyses might provide further insight into the role that the lack of atopy plays in the expression of asthma in patients with different asthma phenotypes.

REFERENCES

1. Rackemann FM. Intrinsic asthma. *J Allergy* 1940;11:147-62.
2. Kroegel C, Jager L, Walker C. Is there a place for intrinsic asthma as a distinct immunological entity? *Eur Respir J* 1997;10:513-5.
3. Humbert M, Menz G, Ying S, Corrigan CJ, Robinson DS, Durham SR, et al. The immunopathology of extrinsic (atopic) and intrinsic (non-atopic) asthma: more similarities than differences. *Immunol Today* 1999;20:528-33.
4. Romanet-Manent S, Charpin D, Magnan A, Lanteaume A, Verloet D. EGEA Cooperative Group. Allergic vs nonallergic asthma: what makes the difference? *Allergy* 2002;57:607-13.
5. Molina C. Chronicle of an announced death: the end of intrinsic asthma [in French with English abstract]. *Bull Acad Natl Med* 1990;174:799-804.
6. Virchow JC Jr. Intrinsic asthma. In: Busse WW, Holgate ST, editors. *Asthma and Rhinitis*. 2nd ed. Oxford: Blackwell Science; 2000. p. 1355-78.
7. Novak N, Bieber T. Allergic and nonallergic forms of atopic diseases. *J Allergy Clin Immunol* 2003;112:252-62.
8. Kanani AS, Broder I, Greene JM, Tarlo SM. Correlation between nasal symptoms and asthma severity in patients with atopic and nonatopic asthma. *Ann Allergy Asthma Immunol* 2005;94:341-7.
9. Ozdemir C, Ceyhan BB, Yazi D, Eifan AO, Yesil O, Bahceciler NN, et al. Non-atopic asthma in children is related to maternal bronchial hyperreactivity. *Pediatr Allergy Immunol* 2008;19:248-54.
10. Bochenek G, Kuschill-Dziurda J, Szafraniec K, Plutecka H, Szczeklik A, Nizankowska-Mogilnicka E. Certain subphenotypes of aspirin-exacerbated respiratory disease distinguished by latent class analysis. *J Allergy Clin Immunol* 2014;133:98-103.
11. Humbert M, Ying S, Corrigan C, Menz G, Barkans J, Pfister R, et al. Bronchial mucosal expression of the genes encoding chemokines RANTES and MCP-3 in symptomatic atopic and nonatopic asthmatics: relationship to the eosinophil-active cytokines interleukin (IL)-5, granulocyte macrophage-colony-stimulating factor, and IL-3. *Am J Respir Cell Mol Biol* 1997;16:1-8.
12. Ying S, Meng Q, Zeibecoglou K, Robinson DS, Macfarlane A, Humbert M, et al. Eosinophil chemotactic chemokines (eotaxin, eotaxin-2, RANTES, monocyte chemoattractant protein-3 (MCP-3), and MCP-4), and C-C chemokine receptor 3 expression in bronchial biopsies from atopic and nonatopic (intrinsic) asthmatics. *J Immunol* 1999;163:6321-9.
13. Kotsimbos AT, Humbert M, Minshall E, Durham S, Pfister R, Menz G, et al. Upregulation of alpha GM-CSF-receptor in nonatopic asthma but not in atopic asthma. *J Allergy Clin Immunol* 1997;99:666-72.
14. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.
15. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315-23.
16. Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehl CE. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. *Eur Respir J* 2008;31:974-81.
17. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol* 2011;127:382-9.
18. Just J, Gouvis-Echraghi R, Couderc R, Guillemot-Lambert N, Saint-Pierre P. Novel severe wheezy young children phenotypes: boys atopic multiple-trigger and girls nonatopic uncontrolled wheeze. *J Allergy Clin Immunol* 2012;130:103-10.
19. Siroux V, Basagana X, Boudier A, Pin I, Garcia-Aymerich J, Vesin A, et al. Identifying adult asthma phenotypes using a cluster approach. *Eur Respir J* 2011;38:310-7.
20. Schatz M, Hsu J-WY, Zeiger RS, Chen W, Dorenbaum A, Chipps BE, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2014;133:1549-56.
21. Boudier A, Curjuric I, Basagana X, Hazgui H, Anto AM, Bousquet J, et al. Ten-year follow-up of cluster-based asthma phenotypes in adults. *Am J Respir Crit Care Med* 2013;188:550-60.