Published in final edited form as:

Curr Allergy Asthma Rep. 2014 May ; 14(5): 437. doi:10.1007/s11882-014-0437-5.

Relevance of Allergy in Adult Asthma

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Abstract

Recent studies on asthma have demonstrated multiple phenotypes of asthma, based on the clinical characteristics of the disease. With the current interest in personalized medicine, the question arises whether the presence of allergic sensitization has any relevance for these phenotypes and the management of asthma. This review will examine the current knowledge of asthma phenotypes and the impact of atopy on asthma diagnosis and severity in adults. In addition, this review will address whether therapies targeted at the atopic axis help improve asthma outcomes, including lung function indices and exacerbations.

Keywords

Asthma; Allergy; Adult asthma; Atopy; Phenotype; Asthma control; Airway inflammation; One airway hypothesis

Introduction

Asthma is typically considered a disease associated with allergy. However, there are variants such as exercise-induced asthma, late-onset asthma, and some forms of occupational asthma are not typically associated with allergy. Historically, this schism was denoted as extrinsic versus intrinsic asthma; however this is now more commonly considered atopic versus nonatopic asthma. Aside from some differences in the triggers for symptoms of asthma, we are currently recognizing that both atopic and nonatopic forms of asthma appear to share many common inflammatory cascades for its inception and propagation. So, the question arises: is there utility to the assessment of allergy in patients with asthma? This review will address this issue by examining the current knowledge of asthma phenotypes, the impact of atopy on asthma diagnosis and severity in adults, and discuss whether therapies targeted at

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Sameer K. Mathur has served as a consultant for TEVA, has received grant support from the National Institutes of Health, and served as vice president of the Wisconsin Allergy Society and chair of the AAAAI Asthma and Allergic Diseases in the Elderly Committee. Ravi K. Viswanathan declares that he has no conflict of interest.

the atopic axis help improve asthma outcomes, including lung function indices and exacerbations.

Phenotypes of Asthma

One of the earlier reviews describing methodologies for asthma phenotyping proposed many potential categories that could be used for defining distinct phenotypes, which were broadly addressing either clinical features, types of triggers, or airway inflammatory composition.(1) There are several large cohort studies that have identified phenotypes of asthma using clinical information on patients and statistical approaches to allow the data to define the characteristics of each phenotype. In the Severe Asthma Research Program (SARP) cohort, the use of cluster analysis of the clinical data identified 5 clusters or phenotypes of asthma. (2) These included three phenotypes characterized by higher prevalence of atopy and two phenotypes with lower prevalence of atopy. However, it is notable that the atopy prevalence rates in the three high atopy phenotype prevalence rates were 85%, 78% and 83%, while the two low atopy phenotype prevalence rates were 64% and 66%. Although the difference was statistically significant, the magnitude of difference does not suggest that atopy is a predominant or independent determinant of assignment into any of the respective phenotypes. However, the data can also indicate that atopy is a dominant feature of all cluster groups in the SARP cohort.

In The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) cohort, the use of cluster analysis also identified 5 clusters or phenotypes of asthma, both in children and adults.(3) One of the adult phenotypes had the highest prevalence of atopy, 68.9%, while the prevalence rates for atopy in other phenotypes were statistically significantly lower at 56.7%, 47.9%, 51.5% and 67.1%. Two cohorts of asthma patients from Korea were examined by cluster analysis and both identified 4 clusters, including an “early-onset atopic asthma”, which differed from the other clusters with a higher prevalence of atopy, 66.0% and 74.2%.(4) However, the prevalence rates of atopy in the other clusters for one cohort were 34.6%, 49.7%, and 53.6% and for the other cohort, 57.6%, 55.5%, and 47.9%. Latent class analysis of children in the International Study of Asthma and Allergies in Childhood (ISAAC) II Spain cohort identified seven classes or phenotypes of childhood asthma.(5) The prevalence rates for atopy for these phenotypes were 23.7%, 20.6%, 25.4%, 33.7%, 44.8%, 61.2%, and 75.0%.

It is clear from the studies identifying phenotypes of asthma that the prevalence of atopy can vary, but atopy does not seem to be the predominant distinguishing feature for any of the phenotypes derived from the clinical patient characteristics. In fact, there are numerous limitations to the use of these clinical phenotypes, which has led to a movement towards considering asthma “endotypes” which focus on categorization of asthma patients based on pathophysiological mechanisms.(6) With this in mind, the role of atopy would be its contribution along with other factors in promoting specific features of inflammation, such as eosinophilia or elevated Th2 cytokine expression.

Atopy and Asthma Severity

In a study of 102 female asthma patients, there was no association between the presence of positive skin prick tests and asthma severity based on Global Initiative for Asthma (GINA) criteria.(7) However, though not statistically significant, there was a suggestion that serum IgE levels may be greater in those with more severe asthma. Another study of 639 patients with asthma showed no relationship between the presence or absence of positive skin prick tests and asthma symptoms, quality of life, emergency room visits, hospitalizations, lung function or response to treatment.(8) Therefore, the severity of asthma in adults is not necessarily a function of atopy. Atopy can be present, but does not predict a more severe disease course.

While studies in adults seem to show an inconsistent relationship between atopy and asthma severity, the data from studies in the pediatric population are unambiguous. There are several studies in children demonstrating association between atopy and severity of asthma as measured by increased use of controller medications and rescue inhaler.(9, 10) Atopy was identified as a risk factor for hospital admission in children and young adults.(11) Also, in a study of 123 children with asthma, the number and size of positive skin prick tests increased with increasing severity of asthma.(12)

In addition, a very intriguing concept regarding atopy in childhood is that there may be different patterns of acquiring sensitization with respect to the age of sensitization and allergen(s) to which the child is sensitized.(13) When considering four different patterns or phenotypes of atopy, children who are polysensitized early in life exhibited both greater association with a diagnosis of asthma and greater risk of hospitalization for wheezing or asthma (hazard ratio of 9.2).

The difference between children and adults regarding the role of atopy in asthma severity is intriguing. It appears that atopy in childhood can drive the development of asthma and affect the severity of disease. However, in adulthood, once asthma is present, the presence of atopy continues to be a marker and associated with presence of the disease but no longer seems to have any consistent relationship to severity.

Atopy as a Risk Factor for Asthma Diagnosis

There is a significant body of literature in children describing the presence of atopy in early childhood as a risk factor for subsequent development of asthma. Several birth cohort studies have identified the presence of atopy independently and especially with concomitant early viral upper respiratory infections as significant risk factors for subsequent diagnosis of asthma.(14) In a study of 147 children from birth to 10 years of age, there was a relative risk of 17.14 of having asthma at 10 years of age with the presence of atopy also at 10 years of age.(15) In the Childhood Origins of Asthma (COAST) cohort of 259 children, aeroallergen sensitivity at 1 year of age had an odds ratio of 3.6 for a diagnosis of asthma at age 6.(16) In a study of 1034 children, significantly higher prevalence of allergic sensitization was observed in children with persistent wheezing or late-onset wheezing by 10 years of age.(17) In the birth cohort of 2979 children from the Western Australian Pregnancy Cohort Study, there was an odds ratio of 2.3 for a diagnosis of asthma with presence of allergen sensitivity

by skin prick testing.(18) The odds ratio increased to 9.0 for children that were skin test positive and had more than 2 wheezing illnesses. In the ISAAC study, a history of hayfever had an odds ratio of 1.72 for a diagnosis of asthma or wheezing illness.(19) In another birth cohort of 47 children, current atopy had a risk ratio of 3.58 for current wheezing.(20) In a study of interviews from 7225 subjects in a birth cohort, the prior history of hayfever increased the incidence of asthma in the evaluation interval by a factor of 1.7 to 2.0.(21)

There have been several analyses addressing atopy in older adults with asthma. One analysis of the Veterans Administration Normative Aging Study cohort evaluated three markers (total IgE, skin prick test, eosinophilia) of atopy against respiratory diseases and found the strongest association of total IgE for asthma along with skin prick test positivity to be strongly associated with both hay fever and asthma.(22) Based on this analysis, the authors recommend, at a minimum, the evaluation of total IgE and skin prick test in adults with asthma and hay fever symptoms. Similarly, another study also showed a strong relationship between markers of atopy and airway hyper-responsiveness.(23) More recently, data from the National Health and Nutrition Examination Survey (NHANES) showed that the rate of allergic sensitization did not differ significantly (75.4% vs 65.2%) between younger (age: 20–40) asthmatics and older asthmatics (age>55) and concluded that allergic sensitization in older asthmatics may be more common than what was initially thought.(24)

Improving Asthma Control

Although the role of atopy in the diagnosis or severity of asthma in adults is not clear, there is a classic example of allergen effect on asthma with the relocation of dust mite allergic asthma patients to Davos (Switzerland) where dust mite allergen is not present.(25) Similar benefit was observed for patients transitioning to alternate high altitudes or allergen-free environments.(26–28) Thus, in extreme conditions of allergen avoidance, there is significant improvement in asthma control. However, in a Cochrane review of house dust mite control measures using physical and chemical methods, data from 55 trials were examined with the net conclusion that there was no statistically significant difference in asthma control, including no changes in morning peak expiratory flow rates, numbers of patients improved, symptom scores, or medication use.(29)

Another approach to managing allergic sensitivity is the use of immunotherapy to induce tolerance. In a Cochrane review of 88 trials examining the use of immunotherapy and effect on asthma, the meta-analysis indicated that allergen-specific subcutaneous immunotherapy (SCIT) can significantly reduce asthma symptoms and medication requirements.(30) However, SCIT is contraindicated in patients with unstable asthma as it poses a significant mortality risk in this population. Another method for immunotherapy that is considered much safer is the use of sublingual immunotherapy (SLIT), which is available in Europe and was recently recommended for approval by an FDA advisory committee for two products in the USA. A meta-analysis of 13 sublingual immunotherapy trials, mostly performed in children, demonstrated evidence for improvement in asthma symptoms.(31) However, asthma was typically mild and it was commented that the majority of sublingual immunotherapy trials had some risk of bias and that future higher quality studies will be essential to better address efficacy and optimal dosing. There is great interest in pursuing

these studies since SLIT appears to be safer and associated with fewer systemic reactions in patients with allergic rhinitis or asthma.

Airway Inflammation in Atopic and Nonatopic Asthma

It is often thought that the allergic airway inflammation of asthma, characteristically consisting of eosinophils and Th2 cytokine expression, are triggered by sensitivity to allergens. In fact, there are several studies suggesting that features of airway inflammation are directly related to disease severity; for example, airway eosinophilia is associated with an increased frequency and severity of asthma exacerbations. In a study of adult asthmatics comparing standard of care with using airway eosinophilia to direct adjustment of inhaled corticosteroid doses, it was found that management based on airway eosinophilia provided superior control.(32) Furthermore, an experimental therapeutic approach using mepolizumab, a neutralizing monoclonal antibody to IL-5 to deplete eosinophils, has been shown to reduce asthma exacerbations in adults with eosinophilic or steroid-dependent asthma.(33, 34) IL-4 and IL-13 are two other prototypical Th2 cytokines associated with airway inflammation in asthma. Two recent experimental studies, one employing lebrikizumab (anti IL-13 monoclonal antibody) and another using dupilumab (anti IL-4 and IL-13 monoclonal antibody) exploited this knowledge and demonstrated an improvement in lung function in adult asthma subjects.(35, 36) Although airway eosinophilia and expression of Th2 (IL-4, IL-5) cytokines are typically associated with allergic inflammation, such prototypical markers and cell types are also found in the bronchial mucosa of nonatopic asthmatics.(37, 38) Therefore, there is cause to reconsider the relationship between allergy and the airway inflammation observed in asthma.

Omalizumab has been shown to be effective in the treatment of severe allergic asthma.(39) The mechanism for the improvement is thought to be related to suppression of allergic inflammation with sequestration of IgE molecules as well as a downregulation of FCεR1. (40) Interestingly, a recent study on the use of omalizumab in a nonatopic population also demonstrated efficacy with an improvement in FEV1 over 16 weeks and a trend toward reduced exacerbations.(41) This clinical observation suggests that mechanisms considered central to allergic inflammatory responses are also activated in the absence of atopy.

One Airway Hypothesis

Although it is tempting to think of asthma as a disorder restricted to the lung, there is now recognition that the entire respiratory tract is linked, a concept that is described as the “one airway hypothesis”.(42) It is well recognized clinically and supported by numerous studies that nasal and sinus disease can impact asthma control. Therefore, in atopic individuals, the comorbidity of allergic rhinitis can influence asthma control. Furthermore, therapies directed at allergic rhinitis may have indirect benefits that may not have been completely recognized and evaluated in the studies focused on asthma.

Conclusions

The presence of allergic sensitivity is a clear risk factor in childhood for development of asthma, especially in the setting of concomitant viral respiratory infections. There are also

suggestions that the extent of allergic sensitivity may correspond to severity of asthma in children. However, in adults, there appears to be an inconsistent relationship between allergen sensitization and asthma severity. Although clinical phenotypes of adult asthma exhibit some differences in the prevalence of atopy, the presence of atopy is not the predominant independent factor defining any clinical phenotype. It should also be acknowledged that atopy, while perhaps not a defining factor for any clinical phenotype, is still an important feature of all the asthma clusters.

In extreme cases of complete allergen avoidance, there is clear improvement in asthma control. As a result, there are recommendations for environmental allergen avoidance including dust mites, cockroach, pet dander, and molds.(43, 44) However, the data are not clear as to whether more practical avoidance measures are sufficient to achieve improvement in asthma control and risk of exacerbations. Furthermore, other allergen specific therapy such as SCIT can be effective, but also carries significant risk in asthma patients that are not well controlled. SLIT may be a safer alternative that offers reasonable efficacy; however, there is relative paucity of data with regard to its dosing and duration. In summary, the presence of allergic sensitivity is a risk factor for the development of asthma and contributes to disease activity; however, at present, aside from omalizumab, there are not safe and effective therapies to counteract the specific contribution of allergy. Nonetheless, it is beneficial to address the atopic contribution to respiratory disease with a more global approach employing anti-inflammatory medications such as intranasal or inhaled corticosteroids. More importantly, it is critical to continue to devote our efforts to developing targeted therapies directed at the various inflammatory and cytokine pathways that promote the inception and propagation of both atopic and nonatopic asthma in adults.

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