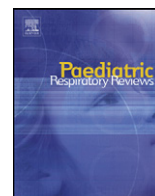




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Clinical Usefulness

Atopy is important in the management of asthma

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SUMMARY

Allergic diseases are a public health problem in industrialized countries due to the increasing number of allergies related to Western lifestyle. The multiplicity of organs affected by allergy (skin (atopic dermatitis), airway epithelium (respiratory allergy), and digestive tract (food allergy)) worsens the prognosis of each of the allergic diseases and specially asthma. The importance of allergy in management of asthma is also underlined by the risk of fatal or near fatal acute asthma attacks due to multiple allergic sensitizations. Preliminary studies suggest that specific treatment of allergy could change the asthma course.

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INTRODUCTION

Allergic diseases are a public health problem in industrialized countries due to the increasing number of allergies related to Western lifestyle. The increased frequency of allergic diseases is partly explained by the “hygiene hypothesis”. This hypothesis is based on the emergence of an inverse relationship of prevalence of infectious diseases on the one hand and allergic diseases and autoimmune conditions on the other over the last 30 years. The immunological explanation has come from studies in the urban farmer.¹ Being exposed at a young age to endotoxins in inhaled air (from the bacterial wall of farm (or domestic) animals, or in the air of daycare facilities) could “protect” the child from the occurrence of allergy.

The multiplicity of organs affected by allergy (skin (eczema), airway epithelium (respiratory allergy), digestive tract (food allergy)) worsens the prognosis of each of the allergic diseases and especially asthma. Therefore, in this paper we discuss: (1) The “Atopic March” (2) Which allergic sensitizations are responsible for fatal or near fatal acute asthma attacks, (3) How the association of concomitant atopic dermatitis or food allergy and asthma results in severe asthma phenotypes and (4) Finally how specific allergy treatment could change the asthma course.

The Atopic March (Progression of atopic dermatitis and food allergy to respiratory allergy)

Early expression of allergy is a predisposition of a phenotype of persistence of severe asthma during childhood² showed that

early and multiple allergen sensitizations in infants is related to severe asthma during childhood defined as (i) persistent asthma at the age of 8 years (ii) a history of hospitalizations for asthma exacerbations, (iii) poor respiratory function. In the same manner, our group showed^{3,4} how a major atopic disease in early childhood (association of atopic dermatitis, multiple allergic sensitization and parental asthma) predisposes a child to the persistence of asthma throughout childhood. Similarly, Lowe *et al.*⁵ showed that severe atopic dermatitis beginning before 6 months of age is a high-risk phenotype for the development of asthma, especially in boys. In the same manner, in a cohort of children at risk of developing food allergy followed prospectively, children with multiple severe food allergies were found to be at a higher risk of developing asthma⁶. Finally, the MAS cohort⁸ showed that a first manifestation of allergic rhinitis in preschool children⁷ is a good predictor for developing asthma between the ages of 5 and 13 years.

Allergic sensitizations to inhaled allergens are responsible for fatal or near fatal acute asthma attacks

Numerous studies have shown that allergic asthma conveys a risk of serious acute exacerbations and is difficult to control. Moreover, the exacerbation rates in children with severe asthma are high, and may differ from those described in the adult population.⁹ Patients with allergic asthma have large fluctuations in their lung function (which is usually normal between attacks) that are responsible for life-threatening attacks. This phenotype of severe asthma is significantly associated with a polymorphism of IL-4 (the cytokine involved in the IgE response)¹⁰. The relationships between allergy and severe acute exacerbations are linked to direct exposure to an allergen to which the patient is sensitized. This has been well described for outdoor allergens such as mould (associated or not with pollen) and multiple allergic sensitizations.¹¹ In the same manner, the relationship between multiple

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allergic sensitizations and asthma severity was observed in a study of a cohort of 400 children from seven to 18 years. A high score of positive skin tests to aeroallergens was found to be associated with an increased risk of hospitalization, corticosteroid use and impaired lung function.¹²

The association of concomitant atopic dermatitis or food allergy and asthma exposed to severe asthma phenotypes

Patients with atopic dermatitis associated with sensitization to food allergens, and in particular filaggrin mutations (a protein of the epithelial barrier), are characterized by more severe asthma with impaired lung function at puberty.¹³ Moreover, the existence of food allergy exacerbates asthma severity and increases the risk of hospitalization in the intensive care unit for severe acute asthma. In 72 asthmatic children, Voegel *et al.*¹⁴ observed that food allergy was 7.4 times more frequent in the group of children who had experienced a severe acute asthma attack requiring the use of emergency services compared with children treated as outpatients. Recently, Erbas *et al.*¹⁵ have shown that a linear increase in asthma emergency department presentations correlated with an increased concentration of ambient grain of grass pollen independent of any impact of thunderstorm-associated asthma ($p < 0.001$). This underscores the role of seasonal grass pollen on severe exacerbations. Moreover, the relationship between food allergy and pollen is a well known feature due to cross reactivity of plant and food allergens.¹⁶ In this case severe exacerbations could be due to food allergy.¹⁷

We have recently found further evidence to support the findings of these studies by identifying¹⁸ an inflammatory phenotype of severe asthma with multiple allergies to inhaled allergens and food allergens, with eosinophilic and basophilic inflammation, who were at risk of severe acute attacks compared to a mild asthma phenotype in children aged 6 to 12 years (Figure 1).

In the same manner, in 551 young children with active asthma we identified,^{19,20} a severe asthma phenotype characterized by infants with recurrent wheezing and many features of atopy (atopic dermatitis in 75% of cases, Phadiatop[®] infant positive in 90% of cases) (Figure 2; Cluster 3). They were compared to a group of viral induced recurrent wheezers with mild asthma controlled with low doses of inhaled corticosteroids (Cluster 1) and a group of recurrent wheezers with “non-atopic” disease and often uncontrolled despite high doses of inhaled corticosteroids (Cluster 2). These phenotypes were reproduced by Herr *et al.*²¹ who described an atopic severe wheezing phenotype and non-atopic severe

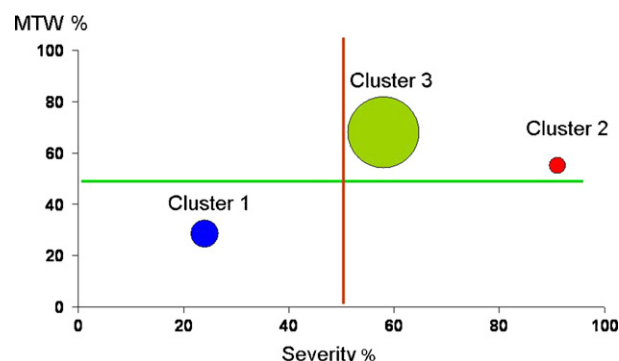


Figure 2. Three phenotypes of infant asthma according to severity, atopy and triggers MTW (Multiple trigger wheeze), Severity (severity according to the GINA).¹⁹

wheezing phenotype (very close to our severe phenotypes *Atopic MTW* and *NAUW* respectively) in a birth cohort reviewed at 18 months of age.

Specific treatment of allergy can modify the asthma course

Specific treatments for respiratory allergy act by reducing asthma exacerbations and limiting degradation of lung function and tissue remodelling. Thus, control of the environment, but more especially active specific immunotherapy and perhaps passive immunotherapy (e.g. omalizumab), could have a disease-modifying effect.

Control of the environment

Meta-analyses on the efficacy of dust mite covers do not show that environmental control is effective against asthma exacerbations or allergic rhinitis.²² However, most studies have been conducted in heterogeneous populations in terms of asthma severity and also in terms of the definition of allergy. They have included multi-sensitized patients at different stages of asthma (mixing adults and children) and even patients who were not necessarily allergic. Conversely, a study of a population of children with moderate asthma sensitized against house dust mites concluded in favour of the efficacy of dust mite covers (against placebo) on asthma exacerbations.^{23,24}

Specific immunotherapy

Specific immunotherapy is a treatment that has been used for more than a century and the efficacy of allergen immunotherapy in the treatment of asthma²⁵ or of allergic rhinitis^{26,27} has been demonstrated by numerous meta-analyses. Moreover, immunotherapy could have a disease-modifying effect, with the ability to modify the natural history of the disease as the shift from allergic rhinitis to asthma^{28–31} or by reducing the risk of new allergenic sensitizations. Lastly, immunotherapy may play a role in preventing asthma progression, by allowing the doses of inhaled corticosteroid required to obtain control of asthma to be reduced.³² The first indication for immunotherapy in asthmatic children is for patients with respiratory allergy with moderate severity but controlled with conservative treatment. However, because of side effects, this treatment has not been adopted by all countries. Furthermore, it has been positioned as a second line treatment option after the more conventional treatments.³³ However, the European Academy of Allergology and Clinical Immunology recommends that specific immunotherapy should be introduced at early stages of allergic disease to avoid irreversible tissue remodeling.³⁴

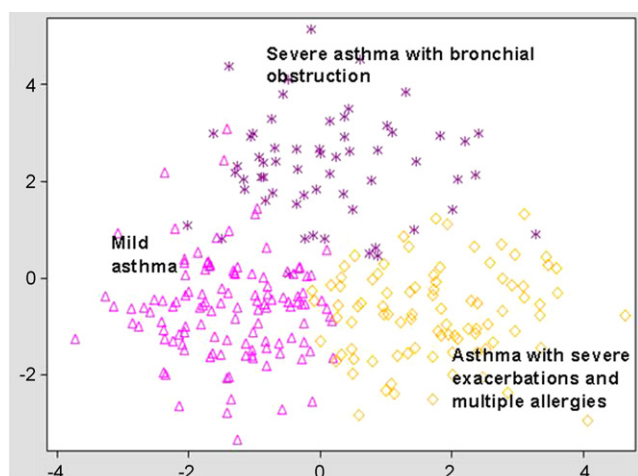


Figure 1. Three phenotypes of asthma in children aged from 6 to 12 years of age.¹⁸

Omalizumab

Omalizumab is an anti-IgE antibody that blocks an early step in the allergic cascade. A meta-analysis has demonstrated its efficacy in the management of severe uncontrolled asthma despite adapted treatments with allergic sensitization to perennial allergens. This treatment is effective, mainly on asthma exacerbations, which supports the link between allergy and exacerbations. Furthermore, an observational study has shown that after stopping prolonged treatment with omalizumab, asthma control can persist as a residual effect indicating a potential modifying effect on the natural history of asthma.³⁷ Omalizumab might thus reduce airway remodelling in the longer term. A potential mechanism involves the reduction of free IgE levels following the anti-IgE therapy that could lead to reduction in high affinity receptor for IgE (Fc RI) expression on mast cells, basophils and dendritic cells.^{35,36}

CONCLUSION

IgE diseases associated with asthma are related to a more severe asthma phenotype, especially in terms of acute exacerbations¹² but also more rapid decline in lung function into adult life.³⁸ Specific allergy treatments should thus be considered to treat allergic asthma.

DISCLOSURE OF POTENTIAL CONFLICT OF INTEREST

J Just is on the advisory board for Novartis, ALK and Merck; is a speaker for AstraZeneca, Novartis, ALK, Merck and Shering-Plough; and has received grants from Novartis and Shering-Plough.

TEACHING POINTS

- 1) The atopic march (transition of atopic dermatitis and food allergy to respiratory allergy) is a special phenotype
- 2) Multiple allergic sensitizations to inhaled allergens are responsible for fatal or near fatal acute asthma attacks
- 3) The concomitant association of asthma and atopic dermatitis or food allergy exposes to severe asthma phenotypes
- 4) Specific treatment of allergy can modify the asthma course

Three best single answer multiple choice questions

- 1) The atopic march
 - a. does not exist
 - b. is severe allergic phenotype
 - c. is frequent
 - d. is a fortuitous association of allergic diseases

Answer “B” is correct. and answers A, C, D were not: Children with multiple severe food allergies or severe atopic dermatitis (beginning before 6 months of age) were found to be at a higher risk of developing asthma. The association of atopic dermatitis, multiple allergic sensitizations and parental asthma predisposes a child to the persistence of asthma throughout childhood.

- 2) Multiple allergic sensitizations to inhaled allergens are correlated to risk of severe asthma exacerbations
 - a. This sentence is true, only in case of multiple food sensitisations
 - b. This sentence is true, particularly in cases of early onset of multiple sensitisations
 - c. This sentence is true, only with indoor allergens
 - d. Multiple allergic sensitizations and risk of asthma exacerbations are not related

Answer “B” is correct. and answers A, C, D were not. The relationship between multiple allergic sensitizations and asthma

severity was observed in numerous studies. Effectively, a high score of positive skin tests to aeroallergens was found to be associated with an increased risk of hospitalization, or with a frequent use of corticosteroid and consequently an earlier risk of lung function decline.

- 3) The association of concomitant atopic dermatitis or food allergy with asthma
 - a. is a fortuitous association of allergic diseases without any consequence
 - b. predisposes to severe asthma phenotypes
 - c. is always a not dangerous association of allergic diseases

Answer “B” is correct. and answers A, C, were not. Patients with atopic dermatitis associated with sensitization to food allergens and in particular flaggrin mutations (a protein of the epithelial barrier) are characterized by more severe asthma with impaired lung function at puberty. The existence of food allergy exacerbates asthma severity and increases the risk of hospitalization in the intensive care unit for severe acute asthma.

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