

# Progression from nasal polyps to adult-onset asthma: a different process from atopic march?\*

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**Rhinology Online, Vol 1:** 22-29, 2018  
<http://doi.org/10.4193/RHINOL/18.006>

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**\*Received for publication:**

January 25, 2018

**Accepted:** March 9, 2018

## Abstract

Nasal polyps and comorbid asthma (NPcA) is a severe clinical entity, which is often treated as a united airway disease. Asthma is frequently associated with allergic rhinitis and nasal polyps and the natural course of asthma has long been explored. The “atopic march” has been proposed for decades to explain the progression of the united airway diseases. The atopic march principally relates to the development of childhood asthma from atopic conditions. In contrast, adult-onset asthma, which is often non-atopic and more severe, has been shown to be highly associated with nasal polyps. Recently, asthma onset pattern and its association with upper airway diseases have gained increasing attention, which is partly due to the different phenotypes of asthma with respect to comorbidity, disease severity, and treatment responses. Despite extensive research over the past years, the progression of asthma from upper airway diseases remain incompletely defined. This review compares the natural course of childhood and adult-onset asthma and highlights the distinct progression of NPcA. Additionally, risk factors, mechanisms and potential targets of NPcA are also summarized. Advancements in understanding the natural course and pathogenic mechanisms of NPcA may guide the effective therapeutic strategies or possibly curb the progression of NPcA.

**Key words:** nasal polyps, adult-onset asthma, childhood asthma, natural course, risk factor

## Introduction

Nasal polyps and comorbid asthma (NPcA) is a severe upper and lower airway disease characterized by high nasal polyp recurrence rates and corticosteroid dependence<sup>(1,2)</sup>. There is growing evidence that supports the disease entity of NPcA from the perspective of the prevalence, phenotype and disease course<sup>(3-6)</sup>. Indeed, approximately 20% to 60% of patients with nasal polyps have asthma<sup>(7-9)</sup> and approximately 7% to 25.4% of patients with asthma have nasal polyps<sup>(10)</sup>. What’s more, about 19.30% to 38.64% patients with adult-onset asthma have nasal polyps<sup>(11-13)</sup>. This indicates a high association between adult-onset asthma and nasal polyps.

Recent studies show that the comorbidity of nasal polyps significantly influences the remission and persistence of adult-onset asthma<sup>(13)</sup>, characterizes by severe or difficult-to-treat asthma<sup>(14,15)</sup>, and highly associates with increased asthma hospitali-

zation<sup>(16)</sup>. Similarly, chronic rhinosinusitis (CRS) patients with late-onset asthma have more frequent nasal polyps and late-onset asthma might be a predictor of more severe disease in CRS<sup>(17)</sup>. Furthermore, a study by Lin et al. showed that increasing severity of asthma was associated with a greater prevalence of nasal polyps and radiological severity of CRS<sup>(18)</sup>. While multiple studies have explored the association between CRS and asthma, there is not enough information about the natural course of NPcA. It is imperative to explore the natural course, risk factors, and mechanism of NPcA. This review describes the differences in the natural history of childhood asthma and adult-onset asthma and highlights the distinct progression of NPcA. Advances in the pathogenesis of the NPcA are also summarized.

## Different roles for the atopic march in the progression of childhood versus adult-onset asthma

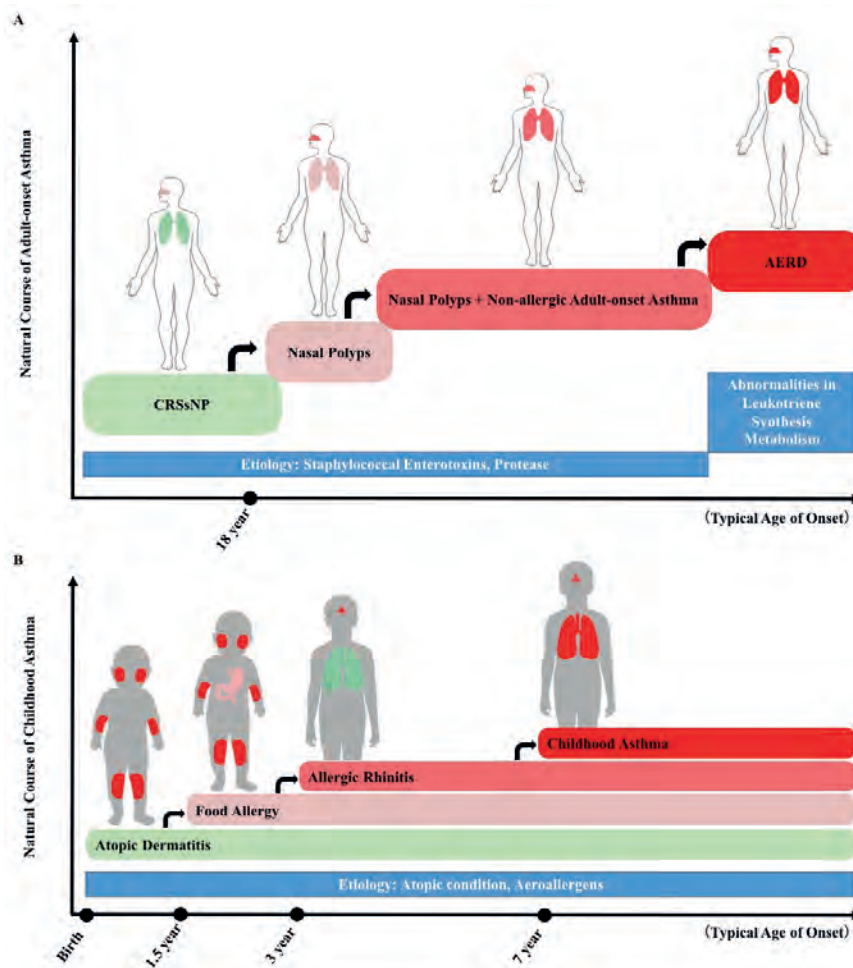


Figure 1. A hypothetical diagram for two different marches of united airway diseases. (A) The natural course of non-allergic adult-onset asthma which starts from chronic rhinosinusitis without nasal polyps. Etiology factors include *Staphylococcus aureus*, proteases, and abnormalities in leukotriene synthesis metabolism. (B) The natural course of childhood asthma which involved in the atopic march. Etiology factors include atopic condition and aeroallergens.

The concept of the atopic march (Figure 1) has been well acknowledged and a series of risk factors for the development of childhood asthma have been identified including atopic dermatitis, frequent wheezing during the first years, allergic rhinitis, peripheral blood eosinophilia of 4% or greater, and allergic sensitization to aeroallergens<sup>(19-21)</sup>. Childhood asthma is typically associated with other atopic conditions, such as allergic rhinitis and atopic dermatitis and the amounts of total and specific IgE are higher in childhood asthma than in adult-onset asthma<sup>(22,23)</sup>. Epidemiological data show that up to 80% of patients with asthma suffer from allergic rhinitis<sup>(24)</sup> and approximately 15% to 38% of patients with allergic rhinitis have asthma<sup>(25)</sup>. Furthermore, allergic rhinitis often precedes asthma<sup>(26,27)</sup>. Recently, a study by Tran et al. showed it is a combination of atopic dermatitis and allergic sensitization, not atopic dermatitis alone, is associated with an increased risk of asthma at age 3<sup>(28)</sup>. Thus, the development of childhood asthma is highly associated with allergy<sup>(22)</sup>. In contrast, adult-onset asthma is often non-atopic<sup>(29,30)</sup>, espe-

cially in severe adult-onset asthma<sup>(12)</sup>. A 14-year longitudinal study which aimed to identify risk factors of adult-onset asthma concluded that neither pre-existing atopy nor new atopy was associated with adult-onset asthma<sup>(31)</sup>. A recent study shows that atopy is negatively correlated with age of asthma onset in elderly patients<sup>(32)</sup>. Additionally, a longitudinal study concluded that the development of adult-onset asthma in rhinitis is independent of allergy<sup>(33)</sup>. Furthermore, adult-onset asthma is often associated with specific triggers such as occupational agents<sup>(34)</sup>, aspirin intake<sup>(35)</sup>, cigarette smoke<sup>(31)</sup>, and respiratory tract infection<sup>(36)</sup>. However, there was also opposite evidence that atopic symptoms and the family history of atopy were associated with the incidence of adult-onset asthma<sup>(37)</sup>. It seems that the progression of adult-onset asthma does not fit well with the principle of atopic march or allergic united airway disease<sup>(38-40)</sup> and may represent a unique subtype of diseases entitled non-allergic united airway diseases.

### From allergic airway diseases to non-allergic airway diseases: focus on the severity

The link between upper and lower airways has long been studied for about two decades since the proposition of united airway disease<sup>(41)</sup> with a main focus on the allergic rhinitis and asthma<sup>(42-44)</sup>. When atopic march firstly progresses into the upper airway<sup>(45,46)</sup>, the rest of the march is commonly discussed in allergic united airway disease<sup>(38,40,47)</sup>, which is mainly linked to the progression of childhood asthma from allergic rhinitis<sup>(48-50)</sup>. The concept of atopic march can explain the progression of allergic united airway diseases, but it does not apply to the non-allergic united airway diseases, for example, adult-onset asthma with nasal polyps. Furthermore, the risk factors, development, and prognosis of adult-onset are proved to be different from childhood asthma<sup>(29-31,51)</sup>.

Although comorbidity of allergy or atopy significantly influences the airway disease course, it seems that inhaled allergens are fewer contributors to the pathogenesis and disease severity of adult-onset asthma<sup>(11,12,29)</sup>. Our understanding of united airway disease has expanded and non-allergic airway disease (e.g. adult-onset asthma and nasal polyps) has gained more attention for its more severity<sup>(1,12,52)</sup>. A new concept about the progression of adult-onset asthma should therefore be proposed.

### Role of chronic rhinosinusitis in the development of adult-onset asthma

There are large amounts of evidence that support the high association between CRS and asthma with respect to prevalence<sup>(53-56)</sup> and disease severity<sup>(13,18,57-59)</sup>, but the exact role of CRS in the development of adult-onset asthma are not well validated. A recent study by Hirsch et al. shows that chronic rhinosinusitis without nasal polyps (CRSsNP) is a significant risk factor for the comorbidity of asthma in the future 5 years<sup>(60)</sup>. Similarly, a population-based longitudinal study concluded that about one in 13 individuals with CRS would be subsequently diagnosed with adult-onset asthma during the subsequent 12 years<sup>(61)</sup>. In addition, a population-based epidemiological survey showed that CRS in the absence of nasal allergies was positively associated with late-onset asthma (onset age of asthma  $\geq 16$  years) and negatively associated with childhood asthma<sup>(3)</sup>, which further supports the unique role of CRS without atopy in the progression of adult-onset asthma. Furthermore, the risk of adult-onset asthma was higher in non-atopic patients with rhinitis than atopic counterparts<sup>(62)</sup>. In addition, there are also other risk factors for adult-onset asthma such as smoking, snoring, airway hyperresponsiveness<sup>(63)</sup> and concomitant atopic manifestations, and female<sup>(64-67)</sup>. It can be inferred that CRS without atopy is a significant risk factor for the progression of adult-onset asthma.

### Development of nasal polyps and comorbid asthma: epidemiology and disease course

Clinically, CRS can be divided into chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP)<sup>(68)</sup>. It has been proposed that all types of CRS have the potential to develop NPs when given enough time and insult<sup>(69)</sup> and CRSwNP is a result of more prolonged and severe inflammation<sup>(70,71)</sup>. The mean age of NPs onset is 42 years and the typical age of diagnosis ranging from 40 to 60 years<sup>(68,72)</sup>. From the perspective of the natural course, nasal polyps and comorbid asthma might be an end product of CRS<sup>(73)</sup> and possibly the most severe type of the united airway diseases<sup>(74)</sup>.

Similar to the development of childhood asthma from allergic rhinitis, nasal polyps and asthma do not occur simultaneously. During the natural evolution of this disease entity, a clinical history of nasal polyps usually precedes asthma, and up to 45% patients with NPs will develop adult-onset asthma<sup>(3,75)</sup>. Indeed, more than 60% of undiagnosed asthmatic patients with NPs have some level of lower airway involvement<sup>(76,77)</sup>, especially in patients with eosinophilic subtypes of nasal polyps<sup>(78,79)</sup>. After evaluation of bronchial hyperresponsiveness (BHR) in adult patients with NPs, approximately 28% to 40% patients with NPs had newly diagnosed asthma<sup>(77,80-83)</sup>, indicating that asthma might coexist as a subclinical disease in NPs.

Patients with aspirin exacerbated respiratory disease (AERD) is a distinct phenotype of NPCA, which is usually defined as Samter's triad or nonsteroidal anti-inflammatory drug exacerbated respiratory disease<sup>(84,85)</sup>. Three cardinal features of AERD include CRSwNP, asthma, and hypersensitivity to cyclooxygenase-1 (COX-1) inhibitors. The underlying pathogenic mechanism appears to be related to abnormalities in leukotriene synthesis metabolism and eosinophil levels<sup>(86)</sup> and excessive amounts of Cysteinyl leukotrienes is generated with a reflection of urinary leukotriene E4 concentrations<sup>(87)</sup>. In general, AERD develops quite suddenly in adulthood and the mean age of NPs onset in patients with AERD is 34 years<sup>(88)</sup>. The clinical course of patients with AERD differs greatly to NPCA patients without sensitive to COX-1 inhibitors<sup>(1)</sup>. It has been proposed that AERD might be the end stage of the march: from CRS, NPs, adult-onset asthma, and finally AERD<sup>(73)</sup>. This is based on the cross-sectional studies which show that the risk of future of AERD is high in patients with eosinophilic NPs and comorbid asthma<sup>(89,90)</sup>. Future longitudinal studies are needed to verify this speculation. Aspirin desensitization provides therapeutic benefits to patients with nasal polyps in AERD<sup>(91-93)</sup> and plasma 15-Hydroxyeicosatetraenoic acid is identified as a predictor of the outcome<sup>(94)</sup>. What's more, the causes of AERD are yet to be determined, and the contributions of potential epigenetic or environmental factors to disease pathogenesis are largely unknown<sup>(95)</sup>. Therefore, further research is needed to explore the mechanism of AERD and the potential targets for prevention of the AERD.

### Risk factors for nasal polyps and comorbid asthma

There is a wide consensus that allergen immunotherapy is the only treatment that alters the course of allergic diseases by preventing the development of asthma and has a long-term efficacy after termination of the treatment<sup>(96,97)</sup>. However, the pathogenesis of adult-onset asthma is different from childhood asthma. Although several previous studies showed the benefit of endoscopic sinus surgery for the control of asthma in patients with NPCA<sup>(2, 98,99)</sup>, whether early surgery for NPs is an effective treatment to prevent the progression of adult-onset asthma needs further studies. Now, it still lacks a strategy to prevent the progression of adult-onset asthma. Identification of risk factors that promote the formation of NPCA may provide a foundation from which to understand the pathogenesis of NPCA and ultimately to develop primary prevention intervention strategies.

It was shown that NPCA was a unique phenotype different from NPs or asthma<sup>(1,5)</sup>. A series of risk factors, such as asymptomatic BHR, IL-9, IL-5, *Staphylococcus aureus* enterotoxin (SE)-specific IgE, atopy, sex, allergic rhinitis, and aspirin sensitivity exert different influences on the formation and natural courses of NPCA<sup>(82,82,100,101)</sup>. A recent study reported a certain endotype of patients with NPCA characterized by the presence of SE-specific IgE and high levels of IL-5 and IgE<sup>(5)</sup>. Our recent study based on cluster analysis of disease history shows that patients with NPCA exhibit three clinical phenotypes with distinct natural courses<sup>(102)</sup>. Furthermore, the disease duration, the age of nasal symptoms onset, age at subsequent asthma diagnosis, and history of family asthma are different among three clusters, which possibly points out the heterogeneity among patients with NPCA.

### Mechanism of nasal polyps and comorbid asthma and potential targets

Previous studies showed that total IgE was a biomarker for eosinophilic NPCA<sup>(6)</sup> and a human anti-IgE mAb demonstrated clinical efficacy in the treatment of NPCA, which supported the functionality of local IgE formation in the airways of patients with NPCA<sup>(103,104)</sup>. Additionally, the presence of IL-5 proteins and IgE antibodies to staphylococcal enterotoxins in NPs was associated with comorbid asthma suggesting a causal role of staphylococcal enterotoxins in chronic upper and lower airways disease. It has been shown that staphylococcal enterotoxins played a crucial role in the pathogenesis of adult-onset asthma<sup>(105-107)</sup>. Furthermore, *Staphylococcus aureus*, the local superantigens in the airway, was treated as a strong link between upper and lower airway diseases and asthma comorbidity could be the consequence of local superantigen-induced inflammation in nasal cavity<sup>(108-110)</sup>. However, whether intervention targeting *Staphylococcus aureus* in the early stage of NPCA patients is an effective way to prevent the progression of adult-onset asthma is still unknown.

Periostin has been proposed as a biomarker for the Th2-skewed immune responses in asthmatic patients<sup>(111)</sup>. Periostin is an extracellular matrix and a matricellular protein facilitating tissue remodeling and it is produced primarily by fibroblasts in response to IL-4 and IL-13<sup>(112,113)</sup>. Elevated serum levels of periostin are highly associated with asthma exacerbations<sup>(114,115)</sup> and the presence of late-onset eosinophilic asthma<sup>(116)</sup>. Furthermore, serum periostin has been identified as a biomarker for comorbid nasal polyps in patients with asthma<sup>(117,118)</sup>. There is also more and more evidence supporting the role of periostin in patients with AERD. Recent studies suggest that periostin levels are elevated in tissues from patients with CRSwNP compared with CRSsNP and controls, especially in those with aspirin sensitivity<sup>(119,120)</sup>. In addition, serum periostin levels are significantly elevated in AERD patients<sup>(115)</sup>, especially in those with severe chronic rhinosinusitis<sup>(121)</sup>. It can be inferred that periostin plays a crucial role in the pathogenesis of NPCA patients with or without aspirin sensitivity. A recent study by Brook et al. showed that inhibition of periostin expression in patients with NPCA significantly delayed the time to revision sinus surgery by >2 years<sup>(122)</sup>. Based on these findings, great attention has been paid to periostin as a biomarker or a target to develop therapeutic agents against eosinophilic inflammation in patients with NPCA<sup>(123)</sup>.

The mechanism of Th2-type inflammation in CRSwNP or asthma has recently been advanced<sup>(124,125)</sup>. The understanding of mechanisms underlying eosinophilic airway diseases has changed from a paradigm in which allergen-driven Th2 lymphocytes are the primary drivers to one in which production of cytokines by a deregulated epithelium is the primary driver for eosinophilic inflammation<sup>(126,127)</sup>. A large series of both environmental and endogenous stimuli can activate the epithelial cell and elicit the release of pro-Th2 cell chemokines and cytokines<sup>(124)</sup>. Protease activity is a common feature of many insults<sup>(128-130)</sup>. External stimuli such as the allergen, fungus, *Staphylococcus aureus* and microbiome disturbance have proved to be significant contributing factors both in asthma<sup>(105,131)</sup> and CRSwNP<sup>(132,133)</sup> pathophysiology. Furthermore, epithelial barrier dysfunction caused by external stimuli has been implicated in driving Th2-biased airway<sup>(124,134)</sup>. Proteases play an important role in initiating and maintaining of eosinophilic airway inflammation<sup>(135)</sup> and an imbalance between proteases and endogenous protease inhibitors was treated as a crucial contributor in the mechanism of eosinophilic airway diseases<sup>(136)</sup>. The role of protease activation of inflammation has long been recognized and discussed in allergic respiratory diseases<sup>(137)</sup>. However, it is not clear whether airway proteases are potential targets in controlling the systematic inflammation of patients with NPCA.

### Conclusions and future directions

Both childhood asthma and adult-onset asthma have distinct natural courses and the non-atopic factors are often involved in

the progression of adult-onset asthma. United airway diseases can be divided into allergic and non-allergic united airway subtypes which represent two different marches and development directions. The final stage of the non-allergic united airway diseases is often a more severe disease entity such as NPCa and AERD. Furthermore, the development of adult-onset asthma is highly associated with CRS, especially nasal polyps. Risk factors, such as asymptomatic BHR, IL-9, IL-5, *Staphylococcus aureus* enterotoxin (SE)-specific IgE, atopy, sex, allergic rhinitis, and aspirin sensitivity contribute to the formation of NPCa. Chronic local stimuli mainly from microbiome, such as *Staphylococcus aureus* proteases and their products may be critical in promoting the progression of non-allergic airway diseases. The primary prevention to inhibit NPCa or AERD development should focus on the local microbiome. Longitudinal epidemiological cohort studies are needed to verify these two marches and further preventive measures might be designed to curb the development of marches.

## Acknowledgments

**Funding Sources:** This study was supported by the International Science & Technology Cooperation Program of China (2015DFA30160); the Natural Science Foundation of China (81670903); Beijing Key Laboratory of upper airway dysfunction related cardiovascular diseases (BZ0377); Beijing Municipal Administration of Hospitals (DFL20150602); Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (ZYLX201605)

## Authorship contribution

All authors have contributed to the preparation and reviewing the final version of the manuscript.

## Conflict of interest

The authors declare that they have no conflict of interest.

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