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Gender and Atopy Influences on the Natural History of Rhinitis

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Abstract

Purpose of Review—Rhinitis is a common condition associated with significant under-recognized morbidity and impaired quality of life. The natural history of rhinitis is poorly characterized. Better understanding of its natural history and associated risk factors would improve the ability to effectively manage rhinitis in clinical practice. This review focuses on current research findings on the natural history of rhinitis and how that is influenced by atopy and gender.

Recent Findings—Recent work from the Isle of Wight Birth Cohort Study has demonstrated that the prevalence of atopic rhinitis increases steadily in the first 18-years of life in both sexes. However, non-atopic rhinitis behaves differently during adolescence. Its prevalence decreases in boys but continues to increase in girls resulting in a female predominance after puberty. Numerous recent studies have proposed potential roles for sex and adipose related hormonal changes in influencing the course of allergic disease. Further research is needed to establish mechanisms that could underlie such findings.

Summary—Rhinitis becomes increasingly common through childhood, with prevalence during adolescence being mediated by differential effects of gender and atopy. Mechanisms to explain these findings await elucidation.

Keywords

Atopy; Gender; Prevalence; Rhinitis; Transitions

INTRODUCTION

Rhinitis has emerged as a common childhood/adolescent condition, associated with substantial morbidity, at the start of the 21st Century [1, 2]. Similar significant prevalence of other allergic states including asthma [3], food allergy [4] and eczema [5], has been reported. Comorbidity of rhinitis with asthma is now well recognized [6] and rhinitis is accepted as a significant risk factor for the development of asthma [7–9]. Similarly, treatment of rhinitis may reduce some indices of asthma morbidity like healthcare utilization

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[10]. It has been previously suggested that allergic comorbidity follows an “allergic march” with characteristic evolution of allergic disease from one state to another through childhood [11]. The original view of this allergic march suggested that rhinitis was a later allergic manifestation appearing during adolescence, though recent perspectives suggest a more complex pattern of multiple allergic disease trajectories in relation to the allergic march [12]. Very few studies have longitudinally studied the natural history of rhinitis [13, 14]. The dynamics of changing rhinitis prevalence from childhood to adulthood and factors influencing those changes have not been convincingly determined. For asthma, a “gender switch” from male predominance in childhood to female predominance after puberty has again been recently demonstrated [15]. In parallel, rhinitis has been shown to have male predominance in the prepubertal phase [16] though it is unclear whether a similar postpubertal change in gender predominance also pertains. Rhinitis is conventionally regarded as an allergic disease. However, the role of atopy in the natural history of rhinitis certainly merits further consideration. It is now recognized [13, 17, 18] that evidence of allergic sensitization may be absent in a proportion of people with rhinitis and that different mechanisms may influence atopic and non-atopic rhinitis [19]. Recently published findings from the Isle of Wight Birth Cohort Study described longitudinal assessment of the natural history of rhinitis during the first 18-years of life, with particular reference to the influence of gender and atopy [14]. This unselected whole population birth cohort (n= 1456) was established on the Isle of Wight, United Kingdom, in 1989 with the aim of prospectively studying the natural history of allergy and asthma. The study population was then assessed at the ages of 1-,2-,4-,10- and 18-years, with 90% of the original cohort reviewed at 18-years. Rhinitis prevalence steadily increased during childhood to affect more than a third of the population at 18-years. Atopic rhinitis became increasingly common during adolescence, with male predominance and no evidence of a “gender switch” in prevalence. Non-atopic rhinitis showed a female predominance at 18-years as girls “grew into” while boys “grew out of” that state during adolescence. These findings suggest that differential pubertal-related factors may influence the development of both atopic (in boys) and non-atopic (in girls) rhinitis. In this paper we first review recent findings on the nature of rhinitis, before further examining and discussing findings from the Isle of Wight Birth Cohort on the influence of atopy and gender on rhinitis.

The Changing Prevalence of Rhinitis from Birth to Adulthood

Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC) recently documented considerable geographical variation in rhinitis prevalence with higher levels in more affluent nations [1]. It also noted substantial average global prevalence of rhinoconjunctivitis at 6-to7-years (8.5%) and 13-to-14-years (14.6%). Such figures additionally suggest that the prevalence of rhinitis rises through childhood. However, in a recent cross-sectional analysis of the PATCH study in Taiwan [20] there was relatively little difference in current rhinitis prevalence (~40%) between groups simultaneously surveyed across the 4 – to 18-year period. Given a cross-sectional design, those findings probably reflect time-related differences within a population rather than a true reflection of disease natural history as it evolves in the same group of subjects from childhood to adulthood. Few longitudinal studies have prospectively assessed the changing prevalence of rhinitis through childhood and adolescence. Most of these report a considerable rise in rhinitis prevalence with time. Keil et al [13] recently showed in the German multicentre allergy study (MAS) birth cohort that the 12 month prevalence of allergic rhinitis quadrupled from 6% at 3-years to 24% at 13-years in children with non-allergic parents and tripled from 13% to 44% in the same time period for children with at least one allergic parent. In the Isle of Wight Birth Cohort it was found that rhinitis prevalence increased 7-fold from 5.4% at 4-years to 35.8% at 18-years [14].

Changes in Gender Prevalence for Rhinitis with Time

Recent studies have demonstrated a change in gender prevalence for allergic disorders like asthma [15], food allergy [21] and eczema [22] from early childhood through adolescence and into adulthood. Thus while male predominance for such diseases may be seen in early childhood this changes to female predominance by early adulthood. There is very limited data for rhinitis in this regard. Cross-sectional analysis of the Manchester Asthma and Allergy Study (MAAS) found no significant gender difference in rhinoconjunctivitis prevalence at 5-years [18]. Similarly, the Taiwanese PATCH study [20] found no significant gender difference in rhinitis prevalence in the preschool era. In this study male dominance was observed between 6 and 11-years, though by adolescence this difference disappeared. This indicates a shift in gender prevalence of rhinitis with age. The German MAS analysis [13] identified no variation in allergic rhinitis prevalence by gender in those with non-allergic parents between the ages of 3 and 13-years. However, in children of allergic parents there was a consistent male predominance for allergic rhinitis between 3 and 13 years of age. This could indicate a role for atopy in influencing male expression of allergic rhinitis. In the Isle of Wight Birth Cohort recent findings showed male predominance for rhinitis at age 1-or 2-years but no significant gender differences in prevalence during the remainder of the first 18-years of life [14]. Further characterization of rhinitis in infancy in that study demonstrated a predominantly non-atopic state presumably associated with viral upper respiratory tract infection.

Associations of Atopy with Rhinitis

Rhinitis is conventionally regarded as an allergic disorder. However recent studies have highlighted that rhinitis may be both atopic and non-atopic. In the Isle of Wight Birth Cohort [17] during the 1st decade of life, 31.4% of never atopic subjects said yes to “ever had rhinitis”, though only 0.5% had suffered persistent rhinitis. The transient nature of rhinitis in never atopic participants may indicate a viral aetiology for many such cases. Marinho et al [18] found that 46.6% of 5-year olds with rhinitis in the MAAS were non-atopic on skin testing, which is similar to the Isle of Wight cohort, where 45% of children with rhinitis at age 4 years were found to be non-atopic. Further follow-up of the Isle of Wight Cohort to 18-years demonstrated that the proportion of non-atopic rhinitis was lower (30.2%) by that age [14]. As discussed below those findings reflect different incident and remission patterns of atopic and non-atopic rhinitis in the transition through adolescence. Significant heritable influences for the role of atopy in rhinitis were demonstrated in the German MAS study by Keil et al [13] who showed that 13.9% of 13-year old rhinitis sufferers with allergic parents were non-atopic compared to 35.5% of those with non-allergic parents.

Gender differential effects of atopy on rhinitis; 18-year follow-up of the Isle of Wight Birth Cohort

The combined influence of gender and atopy on rhinitis in childhood and adolescence has gained little attention in the literature to date. Recent findings from the 18-year follow-up of the Isle of Wight Birth Cohort [14] sought to assess the gender-specific differences in atopic and non-atopic rhinitis during the first two decades, hypothesizing a gender reversal in rhinitis prevalence associated with adolescence. Atopic rhinitis significantly increased in prevalence from 3.4% at 4-years to 27.3% at 18-years, with significant male predominance at both 4- (4.7% v 2.1%; $p=0.02$) and 18-years (31.1% v 24.0%; $p=0.02$). Non-atopic-rhinitis also substantially increased in prevalence through childhood with significant female predominance at 18-years (16.6% v 6.6%; $p<0.001$). The different dynamic for atopic/non-atopic rhinitis in males and females is illustrated in Figure 1.

Analysis of changes in disease prevalence in this paper used positive and negative transitions rather than incidence and remission since these measures were more informative

in a dynamic cohort where individual longitudinal participation might vary. Positive transition was defined as a change in the individual status from rhinitis-free to rhinitis, independent of whether that was the first occurrence. Calculations of atopic and non-atopic rhinitis positive and negative transitions were based on rhinitis status during two consecutive investigations and skin prick test information for the second examination. Negative transition of rhinitis between follow-ups was defined as the individual change in rhinitis status from “disease” to “disease-free”. Calculations of negative transition for atopic and non-atopic rhinitis followed similar rules as for positive transition. Positive transition for atopic rhinitis rose steadily between study periods and was significantly greater in males during the 1-or-2- to 4-year (5.6% v 2.0%; $p=0.009$) and the 10- to 18-year (24.3% v 16.3%; $p=0.01$) periods. Non-atopic-rhinitis positive transition also rose significantly from the 1-or-2- to 4-year period to the 4- to 10-year period ($p<0.001$) but then fell significantly during the 10- to 18-year period ($p=0.038$). There was significantly greater female (15.7% v 6.9%; $p<0.001$) positive transition of non-atopic-rhinitis from 10- to 18-years. Negative transition of rhinitis was considerable greater in the 1-or-2- to 4-year time period in comparison to subsequent study periods. There were no significant gender differences in negative transition of overall rhinitis and non-atopic rhinitis at any stage during the study. However, there was significantly greater male negative transition of atopic rhinitis ($p=0.01$) in the 10- to 18-year study period.

In summary, these recent findings suggest differential gender effects on the increasing prevalence of both atopic and non-atopic rhinitis in adolescence. Atopic rhinitis becomes increasingly common as children grow into adolescents, with stronger associations to male gender, and no evidence of a gender switch in prevalence. Non-atopic rhinitis shows a female predominance at 18-years as females “grow into” it while boys grow out of non-atopic rhinitis.

Exploring These Adolescent Phenomena

A growing body of work supports the concept of a change in gender predominance from male to female for allergic disorders like asthma [15], eczema [22] and food allergy [21] with the transition from childhood to adulthood. There is minimal literature on rhinitis in this regard. However, while not detecting evidence of such patterns for overall or atopic rhinitis, recent findings from the Isle of Wight Cohort study identified this to be the case for non-atopic rhinitis [14]. Attention naturally focuses therefore on adolescence as a key period of influence for conditions like rhinitis, asthma, food allergy and eczema. Currently there is little information and no exploratory model on how genetic polymorphisms can account for sex-specific changes in atopic and non-atopic rhinitis. Future studies will bring to light whether epigenetic markers acquired in the prenatal period or during adolescent transition can explain the dynamic development of rhinitis in the first two decades of life. Adolescent factors that are potentially important with regard to rhinitis remain to be clarified and are open to speculation. Given the common comorbidity of asthma and rhinitis it is plausible that similar factors that influence asthma might be relevant to the changing dynamics of upper airway disease (rhinitis) prevalence during adolescence too. In this section we draw on findings relating to asthma to explain the recent findings from the Isle of Wight Cohort study surrounding rhinitis. In that context, both sex hormonal and obesity influences have gained attention for asthma.

Sex hormonal influences—Recent findings [14] of significantly greater male development of atopic rhinitis but greater female development of non-atopic rhinitis during adolescence find parallels with those for adolescent asthma [23] in the Dunedin cohort. Several studies have also found greater female incidence of lower airway disease during adolescence [23–25] which when characterized was predominantly non-atopic [23,24].

Early menarche was shown to carry a 2-fold increased risk of early-adult onset asthma in a recent Canadian study [26] which was also consistent with prior work reported by Salam et al [27] from the Children's Health Study in California. Early menarche could be taken as a surrogate marker for more prolonged exposure to significant female sex hormone levels suggesting that they may be important to such associations. By contrast, Vink et al [15] recently failed to identify influence of pubertal stages on asthma prevalence. This apparent discrepancy in findings may be accounted for by the period of follow-up in those different studies. Follow up in the Vink study was to 16-years which may not have allowed sufficient time for pubertal related factors to accrue since not all subjects may have completed puberty by age 16. Conversely Salam [27] studied subjects until 28-years of age and Al-Sahab [26] until 21-years of age allowing completion of puberty in all subjects in those studies.

While adolescent female physiological changes appeared to predispose towards non-atopic rhinitis development in the Isle of Wight study, it is worth considering whether male physiological changes during puberty could also serve a protective role against development of non-atopic rhinitis. Conversely adolescent boys appeared to be more predisposed to developing atopic rhinitis. This may again parallel changes previously seen for wheeze/asthma development [23] or persistence [25] during adolescence in boys where atopy has emerged as a significant risk factor. So could male related pubertal factors protect against development of non-atopic rhinitis but predispose to, or perpetuate, a risk of developing atopic rhinitis? Gender differential effects of atopic status on airways disease development remain largely unexplored in the literature. The complexity of such relationships are illustrated by recent demonstration of enhanced T-helper(TH)2 lymphocyte stimulation in female atopic asthmatics [28] which may contribute to gender-mediated differences in allergic diseases. The Isle of Wight study highlights the need to consider the distinction between atopic and non-atopic status when assessing the influence of risk factors in development of airways disease during adolescence.

Obesity—It is widely acknowledged that the increasing prevalence of asthma/allergy in recent years has been accompanied by an increasing prevalence of obesity [29]. Associations between obesity and asthma have been demonstrated in several populations across childhood and adolescence while associations between obesity and rhinitis have gained little scrutiny. Relationships between asthma and obesity that take into account gender and atopy have been inconsistent in their findings. Increased asthma risk with obesity was recently reported for 3-year olds regardless of gender [30]. Overweight adolescents (especially boys) have been shown to have increased risk of current wheeze and atopy [31] in one recent study while another showed that obese female adolescent asthmatics suffered poorer asthma control [32]. Female sex hormone levels have been linked to increased fat mass [33], a relationship that might be exacerbated by an altered adolescent hormonal environment. Female predisposition to development of both non-atopic upper and lower airways disease could partly reflect the complex interaction of sex hormonal and fat-related hormonal (such as leptin or adiponectin) changes associated with physiological changes during puberty in females. Exploration of such relationships with allergic disease remains rudimentary at present.

Fat related hormones, adipokines, could be important in these relationships. Recent evidence supporting roles for adipokines have associated high leptin and low adiponectin with risk of exercise-induced bronchospasm in prepubertal children [34], and high adiponectin with better asthma control in adolescent males [32]. However another recent study found no association between either leptin or adiponectin and asthma in adults [35]. Findings in relation to rhinitis and adipokines are sparse but suggest potential associations. Hsueh et al [36] recently demonstrated association between leptin and rhinitis while Ciprandi et al [37] showed an association between leptin and seasonal allergic rhinitis symptoms. How

adipokines influence airway disease is a matter for future exploration. Associations between leukotriene mediated inflammation in asthma and obesity have recently been shown which may be modified by adipokine balance [38]. Relationships between leptin, eosinophil chemotaxis and intracellular signaling have also been shown [39] further defining potential pathophysiological pathways.

Conclusion

Recent work confirms changes in prevalence of rhinitis during adolescence that appears to be influenced by the impact of atopy and gender. Therefore it is important to consider atopic status when assessing factors of relevance for the development of allergic disease such as rhinitis. Consistent evidence about underlying mechanisms is lacking and needs to be a focus for future work. Such work could considerably enhance our understanding of common conditions like rhinitis.

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Key Messages

1. Prevalence of rhinitis increases throughout childhood (from 1 to 18 years).
2. Gender and atopy are two major factors influencing the natural history of rhinitis.
3. Atopic rhinitis increases in both sexes.
4. In boys, non-atopic rhinitis decreases in prevalence during adolescence after an initial increase during childhood.
5. In girls, non-atopic rhinitis increases consistently from 4 to 18 years, resulting in a female dominance of this condition at 18 years.

Figure 1. Changes in Atopic and Non-atopic Rhinitis Prevalence for Boys and Girls over the First 18-years of Life

Figures indicate rhinitis prevalence (percentage with 95% confidence intervals) at each assessment for boys and girls, stratified by atopic status. *Previously published* [14].