Original Article

HOW HAY FEVER IMPACTS KIDS AND ADOLESCENTS - AN EPIDEMIOLOGICAL STUDY

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Abstract

Objectives: To comprehend the different phenotypes of upper airway inflammation from childhood up to adolescence through epidemiologic data from pediatric population.
Methodology: A birth cohort was used with 4090 children who had been followed from birth up to the 16 years of age. Questionnaires and clinical follow-ups were used for this purpose.
Results: AR is common at 4 years of age (5.5%) and prevalence increased to 15% at 8 years. 88% of the 4-year-old kids showing AR had disease up to 9 years. In contrast to this, among the 8% with NAR at 4 years of age, 75% had no rhinitis symptoms at 8 years of age. It was also discovered that co-morbidity along with asthma and eczema was common for AR and NAR both.
Conclusion: Both AR and NAR are common in children. They are associated with asthma and eczema and affected by parental allergy-related diseases. The prevalence of CRS in adolescence appears to be less but for those affected, the symptoms are troubling.

Keywords: Allergic Rhinitis, Non allergic rhinitis, infectious rhinitis, questionnaire, cohort.

INTRODUCTION

Rhinitis is characterized by rhinorrhea, sneezing, nasal blockage and or itching of the nose.[1,2] It has three main groups- infectious rhinitis, allergic rhinitis (AR), and non-allergic rhinitis (NAR) and they all may overlap. The most common type is infectious rhinitis, i.e. (Viral), a common cold. The commonest type of non-infectious rhinitis is AR. Here, the inflammation is caused by an IgE-mediated reaction after contact of an allergen (IgE).[3] When AR is complicated by ocular symptoms, it's called allergic rhinoconjunctivits. When not caused by infection/allergy, the entity is called non-allergic rhinitis (NAR) or non-allergic non-infectious rhinitis (NINA).[2-4] When the cause is unknown, it can be called idiopathic rhinitis (previously vasomotor rhinitis). When the inflammation extends to the paranasal sinuses, it's called Rhinosinusitis, characterized by nasal congestion/blockage, nasal discharge, facial pressure, pain and loss of smell.[5]

In the 19th century John Bostock noticed that a number of patients reported symptoms related to nose, eyes or even chest recurring at the same season of the year.[6,7] It was termed as 'hay fever' since the symptoms correlated to the hay season. Later, Blackley discovered that pollen grains from hay could cause the above symptoms.[8,9]

The characteristic symptoms of allergic rhinitis were first defined by Hansel in 1929: sneezing, nasal obstruction, and mucous discharge.[10] 90% of patients also have ocular symptoms of redness, itching or watery eyes, called allergic rhinoconjunctivitis.[11] AR has been considered as an ordinary disease but evidence now shows that it causes a reduced quality of life and reduced productivity at work/school.[12-14]

The process by which a human produces specific IgE-antibodies is called sensitization. Why certain individuals become sensitized and others not is still not fully comprehended. A family history of allergic disease in combination with lifestyle factors may be responsible. An established risk factor for allergic rhinitis is a positive family history for the allergic disease. However, not all individuals sensitized to an airborne allergen have clinical symptoms of allergy.[15,16]

Rhinitis has also been shown to be an independent risk factor for asthma in both children and adults.[17] Moreover, allergic rhinitis is associated with poor asthma control and an increased risk of asthma hospitalization.[18,19]

On the other hand, there are no specific diagnostic criteria for NAR. The diagnostics rely instead on symptoms of rhinitis in the absence of infection and sensitization. Among children, data on NAR is scarce because so far, the focus for rhinitis research in children has been on allergic rhinitis. Similarly, rhinosinusitis is also a poorly defined clinical entity.[5]

The main aim of this study was to contribute towards the epidemiologic data from a pediatric general population on rhinitis and rhinosinusitis extending from childhood towards adolescence.

MATERIALS AND METHODS

A cohort was planned to study environmental risk or protective factors associated with allergic diseases. Children born between 2001 and 2018 were identified. 10,000 children were born during this period. Exclusion criteria were families who planned to move within a year, children with very severe chronic diseases or a sibling already included in the cohort. 4090 children were included in the cohort, with an average age of inclusion of 2 month. At this time, the families filled questionnaires regarding background characteristics such as living conditions, number of people/pets in the household, smoking and parental allergy related diseases (Table 1).

Table 1. Questionnaire at different time intervals

Baseline:	Parental questionnaire Q0	N= 4090
1 year:	Parental questionnaire Q1	N=3930
2 years:	Parental questionnaire Q2	N=3850
4 years:	Parental questionnaire Q4 and blood sample	N=3730
8 years	Parental questionnaire (Q8) and blood sample	N=3420
12-14 years	Parental and child questionnaire Q12	N=3360
16 years	Parental and child questionnaire and blood samples	N=3180

The cohort has been followed up with questionnaires at 1, 2, 4, 8, 12 and 16 years of age. At 4, 8 and 16 years everyone who had completed the questionnaire was asked for a clinical follow up for IgE-testing. Blood samples were obtained from 2600 children at 4 years, 2490 children at 8 years and 2560 children at 16 years. The number of children with blood samples from all 3 time points was 1700. Of this, 800 were randomly selected for IgE-testing.

Four studies were designed. For Study I, 2026 children with completed questionnaires and results from blood tests at both 4 and 8 years of age were included. For Study II we included 2400 children who had complete answers for maternal and paternal hay fever, asthma and eczema at baseline as well as result from blood tests and complete answers for the rhinitis questions at the 8 year follow up. For Study III we used the subgroup of children who were tested for IgE reactivity with microarray and who had complete answers in the parental questionnaires of rhinitis symptoms after exposure to birch pollen at 4, 8 and 16 years of age. Study IV is based on 3120 children who answered the questions regarding chronic rhinosinusitis at the 16-year-follow-up. Everyone who fulfilled the EP3OS criteria for chronic rhinosinusitis was confirmed or rejected by an interview. The median time between questionnaire and interview was 16 months. Twenty nine children fulfilled the CRS symptom criteria and had ongoing symptoms and were invited for clinical examination. Twenty two children were examined. Twenty one children still fulfilled the symptom criteria for CRS after the clinical examination.

Background characteristics, collected at baseline, helped compare the study populations with the original cohort to interpret the results and selection bias. These background characteristics were demographic data as well as potential risk factors for allergic disease.

In Study II we analysed different aspects of parental allergy related diseases in the aspect of risk of developing allergic or non-allergic rhinitis at 8 years of age (Table 2).

Table 2: Definitions of exposure variables used in Study II

Variable	Definition
Maternal Hay fever	Mother said “yes” to the question: “Do you have or previously had allergic rhinitis (hay fever)?” at time of Q0.
Maternal asthma	Mother said “yes” to the question: “Do you have or previously had asthma?” at time of Q0.
Maternal eczema	Mother said “yes” to the question: “Do you have or previously had eczema?”
Paternal hay Fever	Father said “yes” to the question: “Do you have or previously had allergic rhinitis (hay fever)?” at time of Q0.
Paternal eczema	Father said “yes” to the question: “Do you have, or previously had eczema?”

Hay fever only	Mother and/or father said "yes" to the question of hay fever as mentioned above. Those with positive answers to asthma/eczema were kept excluded.
Asthma only	Mother and/or farther said "yes" to the question of asthma as mentioned above. Those with positive answers to hay fever/eczema were kept excluded.
Eczema only	Mother and/or farther said "yes" to the question of eczema as mentioned above. Those with positive answers to hay fever/asthma were kept excluded.
Any allergic disease	Mother and/or father said "yes" to any of hay fever, asthma or eczema.
No Heredity	Reference category: both parents were needed to have answered "no" to hay fever, asthma and eczema.

Gender, socioeconomic status, maternal smoking, furred animals in the home, older siblings, early fish intake, birth month, mothers age, breast feeding, home dampness are the variables analysed for potential confounding factors (Table 3).

Table 3- Variables analysed for potential confounding factors

VARIABLES	DEFINITIONS
Parental allergy	Mother and/or father with a diagnosis of asthma and/or medication for the same.
Parental Hay Fever	Mother and/or father with allergic rhinitis symptoms during Q0
Low socioeconomic status	Blue collar worker
Young mother	Mother age <25 at the time of birth
Exclusive breast feed	For at least 4 months
Furried animals	Pets at the time of Q0
Mother smoking	During pregnancy or later at home

Classification of severity of allergic rhinitis was used in Study III. Severity was classified according to the ARIA document as mild: no impact on daily activities or sleep, moderate/severe: impact on daily activities and/or sleep.[3]

In Study IV we measured the health-related quality of life among adolescents with CRS. We used the generic instrument EQ-5D VAS which is a visual analogue scale from 0-100 where the respondent indicates his or her current state of health. We also used the disease-specific instrument Sino Nasal Outcome Test 22 (SNOT-22) consisting of 22 parameters on symptoms and disease-related quality of life which the respondent scores from 0 to 5. The total score can take a value between 0=no symptoms to 110=maximum symptoms.

In Study IV 20 of the 28 adolescents who fulfilled the symptom criteria of CRS underwent examination with nasal endoscopy. Endoscopic signs of CRS like nasal polyps, mucopurulent secretion or oedema/mucosal obstruction were considered. Also, we wanted an objective measure of the odour threshold on the 23 adolescents who attended the clinical follow up. So, the validated test "sniffin' sticks" was used.[20]

The chi square test of independence was used in Study I-IV to examine associations between two variables. Fisher's exact test was used when the number in any group was 5 or less. A p-value <0.50 was considered to be statistically significant.

RESULTS

In Study I, we used sensitization to an inhalant allergen to calculate allergic and non-allergic symptoms. When combining rhinitis symptoms with sensitization to an inhalant allergen we found a prevalence of allergic rhinitis at 4 years of 5.5% that increased to 14% at 8 years. The prevalence of non-allergic rhinitis symptoms decreased from 8% to 6% during the same period.

In Study III we examined reported symptoms of allergic rhinitis to pollen. The prevalence at 4 years of age was low, 2.6% but increased up to 8 years (10.7%) and 16 years (17%).

In Study IV we estimated the prevalence of CRS (according to the EPOS criteria), to be 1.6% which accounted for only a very small part of the total prevalence of upper airway symptoms at 16 years. After clinical examination the prevalence of CRS was only 0.3-0.9%. The true prevalence was estimated to be more than 0.4% but lower than 1.6%.

Table 4- Prevalence of sensitization and reported symptoms of rhinitis at 4 and 8 years-

	4 years (n)	4 years (%)	8 years(n)	8 years (%)
Sensitization	330	16	520	25
Symptom to allergen	80	5	300	16
AR	106	10	282	13

NAR	90	8	128	6

Parental allergic disease increased the risk of AR as well as NAR developing in the child at 8 years of age. If the parents had hay fever or if both parents were allergic, it led to an increase in risk of AR. An increased risk of NAR was also seen if one parent showed evidence of two or more allergy-related diseases. No difference was found in risk between the maternal/paternal heredity patterns.
The prevalence of symptoms of AR to pollen increased from 3.5% at 4 years to 12.6% at 8 years and 18.8% at 16 years. Bet v 1-specific IgE was the most prevalent specific IgE against allergen molecules (PR-10).
The prevalence of CRS at 16 years of age was estimated to be between 0.5% and 2.5%. Adolescents who had CRS more often reported symptoms of AR and asthma. Such individuals had poorer health-related quality of life than those without CRS.

Table 5- Proportions of 8-year-old kid's AR and NAR for 6 clusters in the cluster analysis.

CLUSTERS	AR (%)	NAR(%)
CLUSTER 1	40	6
CLUSTER 2	20	10
CLUSTER 3	15	7
CLUSTER 4	17	10
CLUSTER 5	9	6
CLUSTER 6	10	5

DISCUSSION

In Study I, it was noticed that the prevalence of rhinitis symptoms increased with increasing age and this was due to the rise in prevalence of AR. This was also seen in Study III for pollen allergy. In spite of the total increase of rhinitis symptoms, NAR symptoms decreased slightly from 4 to 8 years. Consequently, the proportion of NAR among children with rhinitis was higher at 4 years (62%) than at 8 years (30%). Among adults the proportion of NAR among rhinitis patients is estimated to be between 25%-50%.[4]
75% of kids with NAR in our study at 4 years remitted up to 8 years of age. One possible explanation for the higher prevalence at preschool age could be that at this age, children have an enlarged adenoid with symptoms mimicking rhinitis. The adenoid reaches its maximum size around 5-6 years of age and normally decreases in size during school age, which parallels the finding of remitting cases from 4 to 8 years. Therefore, it cannot be excluded that non-allergic, non-infectious rhinitis exists and is common in preschool age.
It is most likely that there are several causes for children to present with non-allergic rhinitis symptoms. This needs to be further investigated.
In Study I, it was found that AR was associated with both asthma and eczema in kids of 4 and 8 years of age. NAR symptoms were associated with not only asthma, but also eczema indicating a non IgE-mediated association between these diseases.
A family history of allergy is an important risk factor for AR.[3] However, to make better clinical assessments and to better understand the genetic basis of atopy, further investigations of the hereditary patterns of allergic diseases are required.
The finding that parental hay fever, but not asthma or eczema, was associated with AR at 8 years, indicates that genes specific for rhinitis may play an important part. But, on the other hand, the co-morbidity between asthma, eczema and hay fever among the parents of the studied kids was associated with an even higher risk of AR, hence suggesting that shared genetic factors can also influence disease development.
The strength of this study is that it's based on data from a prospective, population-based cohort with a large number of participants and a high response rate from baseline over the years. The possibility of using a blood test for determining allergic sensitization enabled us to distinguish between AR and NAR symptoms. This is an advantage not always available in large population-based studies. Also, in Study IV, we interviewed every case who fulfilled the criteria of chronic rhinosinusitis according to the questionnaire and we did not only rely on the questionnaire answers for the estimation of prevalence. The potential weaknesses are mostly of the type that may occur in observational studies.

CONCLUSION

The results clearly show that symptoms of upper airway inflammation are common in childhood and adolescence. Allergic rhinitis, nonallergic rhinitis and chronic rhinosinusitis show similarities, but also differences. This points to the importance of distinguishing these entities from a clinical perspective and in research as well.
We concluded that there seem to be different prognoses for 4 years old with allergic and non-allergic rhinitis, up to 8 years of age. Children with AR are more likely to show persistent disease than children with NAR, who

seem to remit. Sensitization to inhaled allergens at an early age (4 years) leads the development of AR, whereas symptoms of rhinitis do not. Both AR and NAR are associated with asthma and eczema.
Parental allergy-related disease may be an important risk factor for NAR and AR. The risk is comparable for maternal- and paternal allergy. There seem, however, to be different hereditary patterns for AR and NAR. Parental hay fever (with pollen allergy) seems to be the dominating hereditary risk factor for AR, while for NAR one parent with several diseases seems to be the most important risk factor.
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