

Original article

Differences between allergic and nonallergic rhinitis in a large sample of adolescents and adults

Background: The aim of this study was to describe differences between allergic rhinitis (AR) and nonallergic rhinitis (NAR) in a large community-based sample of Danish adolescents and adults.

Methods: A total of 1186 subjects, 14–44 years of age, who in a screening questionnaire had reported a history of airway symptoms suggestive of asthma and/or allergy, or who were taking any medication for these conditions were clinically examined. All participants were interviewed about respiratory symptoms and furthermore skin test reactivity, lung function and airway responsiveness were measured using standard techniques.

Results: A total of 77% of the subjects with rhinitis had AR, whereas 23% had NAR. Subjects with NAR were more likely to be females, OR = 2.05 (1.31–3.20), $P = 0.002$, to have persistent symptoms within the last 4 weeks, OR = 1.88 (1.23–2.89), $P = 0.003$, and to have recurring headaches, OR = 1.94, (1.12–3.37), $P = 0.019$. On the other hand, subjects with NAR were less likely to have airway hyperresponsiveness, OR = 0.40, (0.24–0.66), $P < 0.001$, food allergy, OR = 0.40, (0.19–0.36), $P = 0.009$ and to have been treated with antihistamines in the last 4 weeks, OR = 0.22, (0.13–0.38), $P < 0.001$ compared with subjects with AR. Subjects with AR were symptomatically worse within their season in terms of sneezing ($P < 0.001$) and itchy eyes ($P < 0.001$), compared to subjects with NAR, whereas nasal congestion and rhinorrhea were equally frequent in the two groups ($P = 0.901$ and $P = 0.278$, respectively).

Conclusions: The proportion of subjects with NAR in an adolescent and adult population with rhinitis is around one-fourth. Women have NAR twice as often as men. In general, subjects with NAR have more persistent but equally severe symptoms compared to subjects with AR. However, subjects with AR have more sneezing and itchy eyes within their particular season of allergy compared to subjects with NAR.

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Rhinitis is a common condition, which affects 20–40% of the western population and the incidence is rising (1, 2). Patients with persistent rhinitis often suffer from low work productivity, low concentration skills, and have more days lost through illness than the general population (3). This poses an expense for the community with accelerating demands for medical treatment and therapy (4, 5).

Rhinitis may be divided into two groups, those with concurrent allergy (allergic rhinitis, AR) and those without allergy but who still suffer from nasal symptoms (nonallergic rhinitis, NAR). The former is defined by symptoms of runny or stuffy nose, or sneezing accompanied by raised levels of allergen-specific IgE or a positive reaction to a skin prick test (SPT) (6). Allergic rhinitis is often subdivided into seasonal or perennial

rhinitis according to the frequency and persistence of symptoms (7).

Nonallergic rhinitis is a less well-defined condition, which in some studies has been indicated to be less severe than AR (8). Nonallergic rhinitis can be subdivided into several groups, with vasomotor rhinitis and rhinitis with eosinophilic syndrome as the larger ones (9). As the precise cause for either of these is not known both groups should belong to the idiopathic rhinitis group. There is no laboratory test to confirm that a patient suffers from NAR, and therefore NAR often is a diagnosis of exclusion (3, 4). Although AR and NAR may have different characteristics they may also share several common features (10). However, only a few previous studies have addressed the differences and similarities between AR and NAR in a clinical setting (8). We aimed

to describe clinical and demographic differences and similarities between AR and NAR in a large community-based sample of adolescents and adults.

Methods

Study population

A short questionnaire adopted from American College of Allergy, Asthma and Immunology (ACAAI) on respiratory health and use of medication was mailed to a random sample of 10 877 subjects, between 14 and 44 years of age, who lived in urban Copenhagen, Denmark (3). After one reminder a total of 5849 (54%) questionnaires were returned and among these, subjects who reported any symptoms suggestive of asthma or allergy, or who were taking any medication for these conditions were invited to take part in a clinical examination. A total of 1186 subjects participated in the clinical examination. Their lung function, airway responsiveness and skin test reactivity were measured and a respiratory physician performed a questionnaire based interview. All participants gave their written informed consent and the Scientific Ethics Committee of Copenhagen approved the study.

Clinical questionnaire-based interview

A physician diagnosed rhinitis and asthma based on a clinical interview. Rhinitis was identified by the presence of considerable episodes of rhinorrhea, nasal congestion and/or attacks of sneezing apart from periods with colds. Furthermore, itchy episodes in the nose and/or eyes were also recorded. Allergic rhinitis was defined as a history of any of these symptoms concomitantly with a positive SPT, whereas NAR was defined by the same set of symptoms but with a negative SPT. Subjects with AR were divided into two groups depending on whether they were skin prick tested within their season of allergy or not. Season of allergy was defined as April and May for those with birch pollen allergy, May, June, July and August for those allergic to grass and July and August in case of mugwort allergy.

The severity of rhinitis was classified according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines resulting in four different categories; (i) mild intermittent, (ii) severe intermittent, (iii) mild persistent and (iv) severe persistent (6). Intermittent symptoms were defined as the presence of symptoms <4 days a week or <4 weeks per year, whereas persistent symptoms were defined as symptoms more frequently than this. Mild symptoms were defined by the absence of sleep disturbance, impairment of daily activities and/or sports, impairment of school or work and/or troublesome symptoms, whereas severe symptoms included any of these impairments.

In the clinical interview a physician diagnosed asthma as recurrent episodes of wheezing, shortness of breath, chest tightness and/or cough at rest, following exertion and/or subsequent to allergenic or unspecific stimuli apart from periods with respiratory tract infections. Concurrent disorders; sinusitis, depression, food allergy and recurring headaches were reported by the study subjects in a separate questionnaire. These recordings were verified by the clinical interview.

Airway responsiveness test

A spirometry was performed and airway responsiveness to inhaled methacholine was measured in accordance with the method of Yan et al. (11). The dose producing a 20% fall in forced expiratory volume in one second (FEV₁) (PD20) was estimated, and the dose-

response slope (DRS) calculated as the decline in FEV₁ divided by the highest dose of methacholine given. Logarithmically transformed DRS values were used for the analysis. Airway hyperresponsiveness (AHR) was defined as a PD20 below 3.9 µmol.

SPT

Skin prick tests were performed using standard dilutions of 10 common aeroallergens. The allergens used were birch, grass, mugwort, horse, dog, cat, house dust mite (HDM) (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), and mould (*Altaria iridis* and *Cladosporium herbarium*) with positive and negative references being histamine 10 mg/ml in 50% glycerol and glycerol 50%, respectively. The concentrations of allergens were 10 HEP (Soluprick SQ® system, ALK Abelló, Denmark). Reactions were read after 15 min (12). The reaction to each of the allergens was regarded as positive if the mean wheal diameter was at least 3 mm. A positive test result (atopy) was defined as a positive reaction to at least one of the allergens. The participants were requested to discontinue medications that contained antihistamine at least 3 days before skin testing.

Statistical analysis

The data were analysed with the statistical package spss (14.0; SPSS Inc, Chicago, IL, USA). Frequencies were calculated for the entire group and differences were assessed by chi-squared tests for categorical data and by *t*-tests for normally distributed data. Logistic regression analysis with backward elimination was performed with rhinitis (NAR vs AR) as the dependent variable. Factors that resulted in *P*-values <0.05 in the descriptive analysis were included as independent variables in the model. A *P*-value < 0.05 was considered to be statistically significant.

Results

Of the 1186 subjects who participated in the clinical examination, 686 (58%) were women and 500 (42%) men. The mean age was 29.2 years. A total of 696 had rhinitis diagnosed by the clinical interview and of those 659 also had a SPT performed. The general characteristics of these subjects are shown in Table 1. We found that 77% of the population with rhinitis had AR, whereas 23% had NAR. The mean number of sensitizations among subjects with AR was 3.12. In total 22.3% were monosensitized.

A total of 67% of the subjects with NAR had had persistent symptoms within the last 4 weeks compared with 48% of the subjects with AR (*P* < 0.001), whereas the fraction of subjects with severe symptoms was the same in the two groups (31% vs 27%, *P* = 0.26). Women had NAR twice as often as men and moreover, NAR was characterized by more frequent episodes of sinusitis and recurring headaches. Conversely, subjects with AR had more severe airway responsiveness, used antihistamines more often, and were more likely to have concomitant asthma and food allergy. These results were subsequently analysed with logistic regression retaining only significant covariates in the model (Table 2).

Differences between allergic and nonallergic rhinitis

Table 1. Characteristics of allergic and nonallergic rhinitis in a sample of adolescents and adults

Variable	Allergic rhinitis (n = 506)	Nonallergic rhinitis (n = 153)	P-value
Demographics			
Sex (female)	51.6%	69.3%	<0.001
Age (mean)	29.4	28.8	0.501
BMI (mean)	24.8	24.8	0.896
Smoking (mean packyears)	2.9	3.3	0.519
Symptoms within the last 4 weeks			
Persistent symptoms	48.2%	67.3%	<0.001
Severe symptoms	26.7%	31.4%	0.260
Objective tests			
AHR	34.9%	19.9%	0.001
LogDRS (mean)	0.36	0.18	0.001
FEV ₁ of predicted	94.5%	94.0%	0.734
FVC of predicted	97.9%	95.5%	0.060
FEV ₁ /FVC	83.2%	83.9%	0.338
Medication*			
Antihistamines	43.7%	13.7%	<0.001
Nasal steroids	11.1%	13.1%	0.502
Nasal cromoglicate	3.0%	2.0%	0.489
Any medication	46.8%	24.8%	<0.001
Concurrent disorders			
Asthma	51.2%	38.6%	0.006
Food allergy	17.0%	8.1%	0.004
Depression	3.1%	5.4%	0.218
Recurring headaches	11.0%	25.5%	<0.001
Recurring sinusitis	7.1%	14.8%	0.006

BMI, body mass index; AHR, airway hyperresponsiveness; LogDRS, logarithm of dose-response slope; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity.

*Medication taken within the last 4 weeks.

Table 2. Factors that significantly distinguishes subjects with allergic rhinitis from subjects with nonallergic rhinitis

Variable	Odds ratio	95% CI	P-value
Sex (female)	2.05	(1.31–3.20)	0.002
Persistent symptoms*	1.88	(1.23–2.89)	0.003
Antihistamines†	0.22	(0.13–0.38)	<0.001
Airway hyperresponsiveness	0.40	(0.24–0.66)	<0.001
Food allergy	0.40	(0.19–0.36)	0.009
Recurring headaches	1.94	(1.12–3.37)	0.019

Allergic rhinitis is reference category in logistic regression analysis. Odds ratios above 1 are in favour of nonallergic rhinitis and odds ratios below 1 are in favour of allergic rhinitis.

*Persistent symptoms within the last 4 weeks.

†Use of antihistamines within the last 4 weeks.

Classification of rhinitis according to the ARIA criteria is shown in Table 3. Subjects with NAR were mainly classified as mild persistent (41%), whereas allergic subjects were classified mainly as severe persistent (38% of those within season) and mild intermittent (50% of those being out of season). Comparing subjects with NAR to subjects with AR, who were within their season, showed that both persistence (67% vs 70%, $P = 0.560$)

Table 3. Percentage of subjects with symptoms of rhinitis according to the ARIA classification

	Allergic rhinitis			Nonallergic rhinitis (n = 153)	All (n = 659)
	Within season (n = 125)	Out of season (n = 381)	Total (n = 506)		
ARIA					
Mild intermittent	28.0	50.1	44.7	27.5	40.7
Severe intermittent	1.6	8.9	7.1	5.2	6.7
Mild persistent	32.8	27.3	28.7	41.2	31.6
Severe persistent	37.6	13.6	19.6	26.1	21.1
Total					
Severe	39.2	22.6	26.7	31.4	27.8
Persistent	70.4	40.9	48.2	67.3	52.7
Symptoms*					
Rhinorrhea	46.3	20.2	26.7	39.2	29.5
Nasal congestion	39.3	17.9	23.2	41.2	27.3
Sneezing	56.1	23.8	31.8	24.3	30.1
Itchy eyes	45.1	14.4	21.9	20.4	21.6
Reduced sense of smell	18.7	8.1	10.7	13.8	11.4

*Percentage of subjects with persistent symptoms within the last 4 weeks.

and severity (31% vs 39%, $P = 0.153$) were the same in the two groups. However, when considering specific symptoms both sneezing (24% vs 57%, $P < 0.001$) and itchy eyes (20% vs 45%, $P < 0.001$) were more prominent in subjects with AR, whereas both groups suffered from the same degree of nasal congestion (41% vs 39%, $P = 0.901$), rhinorrhea (39% vs 46%, $P = 0.278$) and reduced sense of smell (14% vs 19%, $P = 0.192$).

Discussion

Three main conclusions can be drawn from this study: (i) the proportion of subjects with NAR in an adolescent and adult population with rhinitis is around one-fourth; (ii) women have NAR twice as often as men; (iii) generally, subjects with NAR have more persistent but equally severe symptoms compared to subjects with AR. However, subjects with AR have more sneezing and itchy eyes within their particular season of allergy compared to subjects with NAR. Furthermore, our study showed that subjects with AR more often suffer from asthma, have more severe airway responsiveness, more food allergy and use more antihistamines, whereas patients with NAR suffer more frequently from recurring headaches and sinusitis.

Prevalence of AR and NAR

We found that 77% of the population with rhinitis had AR, whereas 23% had NAR. In line with this the European Community Respiratory Health Survey (EC-RHS) reported a frequency of 25% of NAR (13). Also, the National (USA) Rhinitis Classification Task Force

(NRCTF) collected data in 1999 from 15 allergists' clinics; they found that 23% had NAR (14, 15). And finally, in a Belgian survey 24% of patients with rhinitis were categorized as AR (8). From these findings we may assume that the distribution of NAR and AR in the western world approximately is 1 : 4.

Our study showed that more women had NAR than AR. This was also the case in the NRCTF where 71% of patients with NAR were women compared with 51% of the allergic patients (14). Also, Leynaert et al. (13) found as a part of the ECRHS that there was a higher prevalence of rhinitis among women than among men. On the contrary Olsson et al. (16) found no significant difference in gender distribution in their survey from Sweden, based on self-reported rhinitis. The wide age range in their study (19–80 years) may partly explain this (16).

Clinical characteristics

We found that NAR was characterized mainly by nasal congestion and rhinorrhea while AR patients had more sneezing and itchy eyes. This is in accordance with Togias (17) and Lindberg & Malm (18) who found nasal blockage and rhinorrhea to be the most prominent features in NAR patients. Our data showed that two-thirds of the subjects with NAR suffer from persistent symptoms, and furthermore that severe symptoms were equally frequent in NAR patients compared with AR patients who were within their particular season of allergy. This indicates quite a serious condition, and contradicts what Bachert et al. (8) found in a questionnaire-based survey in Belgium, which reported that the AR patient has both more persistent and more severe symptoms than the NAR patient. However they may have missed some nonallergic patients, especially those classified as mild persistent because those patients may not have recognized their symptoms as relevant when filling out the questionnaires.

According to our results co-morbidities also differed in the two groups. Subjects with NAR suffered more from recurring headaches and sinusitis while AR had more asthma, food allergy and AHR. This is in concordance with the Belgian survey (8) and Leynaert et al. (13) who also found that atopic subjects had more asthma and AHR. However, we found a considerable number of subjects with asthma and food allergy among subjects with NAR. This suggests an allergic diathesis underlying NAR maybe explained by the fact that we only tested for the 10 most common allergens and therefore perhaps overlooked allergic subjects within the NAR group.

The presence of recurrent sinusitis in patients with NAR could partly explain why they also tend to suffer from recurring headaches. However, recurring headaches are subjectively and therefore quite diffusely defined. It is reasonable to assume that having nasal obstruction all year round could be causing recurring headaches (19), however, this association will need further investigation

considering the relation between headaches and rhinitis symptoms and also the effect on the quality of life in the NAR patient (20).

Limitations

Firstly, the overall response rate in the screening phase of the present study was quite low (54%) and it may therefore not be possible to generalize the data to the population as a whole. However, our focus was the rhinitis population and not an epidemiological study of the prevalence of AR and NAR in the general population. Results are therefore consistent with the prevalence of AR and NAR in the general population with rhinitis. Secondly, subjects who only suffered from mild and intermittent symptoms may not recognize their condition as treatable, which could influence the patients' motivation for participating in the study. This may also apply to subjects who had symptoms all year around and who therefore may take their symptoms as a condition of life rather than a disease that requires treatment. This group is likely to include individuals with NAR and therefore both subjects with NAR and mild intermittent AR may be underrepresented.

Another aspect to consider is the fact that we separated AR and NAR patients only by the presence or absence of a positive SPT. Measuring specific and total IgE could have strengthened this separation, still the SPT seems to be a good measure for the serum IgE levels (21). It is obvious that a positive SPT indicates atopy, but a negative one does not automatically preclude that allergic mechanisms account – at least partly – for the occurrence of symptoms. That is, a patient may have been sensitized earlier in life, but atopy is no longer detectable by SPT, yet respiratory symptoms and AHR remains (22). Secondly it has been shown that some patients, diagnosed as NAR after a negative SPT, have localized production of IgE in the nasal mucosa, and therefore have a local allergic reaction, which is independent of systemic atopy and therefore undetectable by SPT (23, 24). Hence, although we categorized rhinitis into AR and NAR by the outcome of the SPT the two different subforms may still share common aetiological and pathophysiological characteristics. Thirdly, it will always be possible to investigate participants in a study even more thoroughly, and in our case an inspection of the nasal cavity would have given us information about the presence of nasal polyposis and deviations of the nasal septum. These are conditions, which would explain some of the symptoms characteristic of NAR.

Conclusions and perspectives

This large cross-sectional study shows that NAR is a prevalent condition, which is characterized both by severe

and persistent symptoms, most prominently rhinorrhea and nasal congestion. The majority of patients with NAR are women, and they have a tendency to suffer from recurring headaches and recurrent sinusitis as well. Subjects with AR show more seasonal variability with regard to severity of symptoms. Within periods where allergen exposure is excessive, patients with AR are symptomatically worse than patients with NAR. In particular, sneezing and itchy eyes are predominant symptoms. Subjects with AR have more coexisting asthma, AHR and food allergy, which indicates a closer pathophysiological resemblance between these conditions

and AR compared with NAR. These results underline several clinical and demographic differences between patients with AR and NAR and emphasize the need for diagnosis and medical treatment, not least of subjects with NAR. Future research needs would include closer investigation of subjects with NAR. In particular, more attention should be paid to accurately distinguish between different subtypes of NAR in relation to treatment, mucosal characteristics and anatomical variations, i.e. nasal septum deviations, nasal polyps and local IgE production towards common allergens.

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