

Original article

Rhinitis symptoms and IgE sensitization as risk factors for development of later allergic rhinitis in adults

Background: Rhinitis symptoms and IgE-sensitization often mismatch. Asymptomatic sensitization is an established risk factor for later rhinitis, whereas it is not clear whether rhinitis is a risk factor for later development of IgE-sensitization.

Objective: To investigate whether nonallergic rhinitis is a risk factor for later development of IgE-sensitization in adults during an 8-year follow-up period, and whether asymptomatic sensitization is a risk factor for later development of rhinitis.

Methods: In a population-based study of 15–69 years olds in 1990, 734 subjects were re-examined in 1998. On both occasions questionnaires on rhinitis symptoms were completed and serum IgE (against birch, grass, mugwort, cat, dog, and *Dermatophagoides pteronyssinus*) were determined (positive if ≥ 0.35 kU_A/l). Asymptomatic sensitization: positive IgE levels without any rhinitis symptoms. Nonallergic rhinitis: rhinitis symptoms and no sensitization.

Results: Asymptomatic sensitization to pollens, pets, or house dust mite was significantly associated with onset of rhinitis symptoms, also when changing baseline cut-off for sensitization to ≥ 0.1 or ≥ 0.7 kU_A/l. The 8-year incidence of pollen-related rhinitis was 15.1% and 2.6% in subjects sensitized and nonsensitized to pollens, respectively (odds ratio 6.1, 95% CI 2.3–16.0). Persistent or intermittent nonallergic rhinitis was not significantly associated with later sensitization, yet a positive trend for development was observed in nonallergic pollen-related rhinitis.

Conclusion: Asymptomatic sensitization but not nonallergic rhinitis was a significant risk factor for later development of allergic rhinitis.

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The diagnosis of allergic rhinitis is commonly based on a history of rhinitis supported by relevant IgE-sensitization (1). However, mismatch of clinical disease and sensitization often occurs (2, 3). Asymptomatic IgE-sensitization is an established risk factor for the development of intermittent allergic rhinitis to several aeroallergens in children and young adults (reviewed in Ref. 4). The opposite scenario – i.e. that rhinitis not accompanied by IgE-sensitization represents a risk factor for later development of sensitization – has to our best knowledge not been ascertained in adults. Nonallergic rhinitis is common, most often of viral genesis and self-limiting during a few weeks, but up to 50% of subjects with persistent rhinitis is diagnosed as nonallergic and noninfectious (3). This entity covers heterogeneous conditions, yet they have been found to share inflammatory mechanisms with allergic rhinitis (5). It is known that allergic rhinitis and infectious rhinitis interact by several immunological

mechanisms (2, 6, 7), so theoretically nonallergic rhinitis of any aetiology could facilitate IgE-development via nasal inflammation facilitating mucosal allergen-penetration and -presentation to activated T-cells. Furthermore, exclusively local IgE-synthesis in apparently nonallergic rhinitis could represent an initial phase of allergic rhinitis (8–10).

The aim of the present study was to investigate whether nonallergic rhinitis is a risk factor for later development of IgE-sensitization and whether asymptomatic sensitization is a risk factor for later development of rhinitis.

Materials and methods

Participants

A total of 734 adult subjects were examined with a detailed questionnaire and measurement of specific serum-IgE on two occasions eight years apart. The invitational procedure and characteristics of both participants and nonparticipants have previously been described in more detail [baseline study (11);

follow-up study (12)]. Briefly, a total of 1112 subjects participated in the baseline examinations between February 1990 and January 1991. A total of 734 subjects were re-examined between October 1997 and November 1998. The median follow-up duration was 94 months (range: 82–104 months), and a total of 63.9% ($n = 469$) were examined on a date within 2 months (62 days) from the date of examination in the baseline study. The Ethical committee of Copenhagen County approved the study.

Definitions of variables

At both visits, information on health, lifestyle, and socio-economic variables was obtained in a detailed questionnaire completed at home (11). 'Age': participants' age at baseline, categorised into 15–34, 35–49 and 50–69 years. 'Smoking': never, ex-, or current smoker at baseline. 'Atopic predisposition': atopic dermatitis, hay fever or asthma symptoms in parents, siblings or offspring. 'Rhinitis symptoms': definitions presented in Table 1 and 2. 'IgE-sensitization': positive levels of specific IgE in serum (cut-off point: see below) (13). 'Nonallergic rhinitis': rhinitis symptoms without specific IgE against aeroallergens (13).

Measurement of IgE antibodies

Venous blood was taken at both visits, and, in 1999, serum samples were analysed consecutively for specific-IgE to pollens [birch, grass (timothy) and mugwort], dog and cat hair and dander and mite (*Dermatophagoides pteronyssinus*) with the ADVIA Centaur IgE antibody assay system (Bayer Corporation, Tarrytown, NY, USA) (14). The procedure for blood sample handling has previously been described, including confirmation of the stability of IgE (15). General cut-off level for positivity: ≥ 0.35 kU_A/l (class 1), and in additional analyses: > 0.1 kU_A/l ('detectable levels'), and ≥ 0.7 kU_A/l (class 2).

Statistical analysis

Data were analysed using SPSS for Microsoft Windows (release 10.0) with chi-square test or Fisher's exact test and odds ratios with 95% confidence intervals. Odds ratios were adjusted for potential confounders by multivariable logistic regression analysis. Participants reporting rhinitis symptoms (respectively, sensitized to any allergen) at baseline were excluded from prospective analyses when relevant.

Results

Complete data on all variables including IgE-measurements were available for a total of 724 subjects who were included in subsequent analyses. Baseline characteristics, including comparisons of attenders vs nonattenders have been published elsewhere; briefly, no differences were observed in the variables included in the present paper (12). Of the 377 participants (52% of total) who did not report any rhinitis symptoms at baseline, 21% ($n = 81$) were sensitized to at least one allergen (asymptomatic IgE-sensitization). Asymptomatic IgE-sensitization to pollens, animals or house-dust mite was associated with later onset of intermittent and persistent rhinitis symptoms (Table 1). No remission from asymptomatic IgE-sensitization was observed in the study period.

Of the 447 participants (62% of total) who were not sensitized to any allergen at baseline, 35% ($n = 155$) reported rhinitis symptoms. Rhinitis symptoms in non-sensitized subjects were not associated with later onset of sensitization (Table 2). Yet, we observed a trend towards

Table 1. The association between sensitisation (≥ 0.35 kU_A/l) in 1990 and the incidence of rhinitis symptoms from 1990 to 1998 in 377 participants without rhinitis in 1990

		Incidence of rhinitis symptoms from 1990 to 1998			
Sensitization in 1990		(a) Persistent rhinitis symptoms	(b) Rhinitis symptoms to summer pollens	(c) Rhinitis symptoms when near animals	(d) Rhinitis symptoms when cleaning
Specific IgE ≥ 0.35 kU _A /l against	n				
At least one of six allergens: birch, grass, mugwort, cat, dog and/or <i>Der p.</i>					
Yes	82	39.0%	13.4%	11.0%	17.1%
No	295	29.5%	2.7%	2.7%	10.2%
Adjusted odds ratio†		1.4 (0.85–2.4)	4.9 (1.8–13.5)	3.9 (1.4–10.6)	1.8 (0.87–3.6)
Pollens: birch, grass or mugwort					
Yes	73	42.5%	15.1%	12.3%	16.4%
No	304	28.9%	2.6%	2.6%	10.6%
Adjusted odds ratio†		1.7 (1.0–2.9)	6.1 (2.3–16.0)	4.6 (1.7–12.6)*	1.6 (0.78–3.4)
Pets: cat or dog (hair + dander)					
Yes	16	31.3%	12.5%	31.3%	18.8%
No	361	31.6%	4.7%	3.3%	11.4%
Adjusted odds ratio†			0.88 (0.29–2.6)	12.0 (3.4–42.2)	1.7 (0.45–6.3)
House dust mite: <i>Der p.</i>					
Yes	11	54.5%	0%	27.3%	54.5%
No	366	30.9%	5.2%	3.8%	10.4%
Adjusted odds ratio†		2.4 (0.72–8.2)	–	10.4 (2.3–46.7)**	9.2 (2.6–32.2)

Definitions of symptoms (a)–(d): affirmative answer to: 'Have you within the last 12 months had itchy or stuffy nose or sneezing (a) during Summer months *and* during Winter months; (b) when near grass, trees, and flowers, *and* during Summer months *but not* during Winter months; (c) when near horse, dog, cat, rabbit, guinea pig, or hamster; or (d) when cleaning rooms or making beds or when in bed?'

†Adjusted odds ratio (95% confidence interval): adjusted for gender and age by logistic regression analysis (bold: $P < 0.05$).

*OR 3.2 (0.99–10.4) and **OR 2.6 (0.4–17.8); insignificant when adjusted for pet sensitisation.

Table 2. The association between rhinitis symptoms in 1990 and the incidence of IgE sensitization (≥ 0.35 kU_A/l) from 1990 to 1998 in 447 participants without IgE sensitization in 1990

Rhinitis symptoms 1990 Have you, within the last 12 months, had a itchy or stuffy nose or sneezing:		Incidence of IgE sensitisation (IgE ≥ 0.35 kU _A /l) from 1990 to 1998			
		At least one of six allergens*	Pollens: birch, grass or mugwort	Pets: cat, or dog hair + dander	House dust mite: <i>Der p</i>
(a) During summer months <i>and</i> during winter months?					
Yes	152	5.9%	3.9%	1.3%	1.3%
No	295	8.1%	5.1%	1.7%	2.0%
Adjusted odds ratio†		0.96 (0.46–2.0)	0.76 (0.28–2.1)	0.75 (0.14–4.0)	0.80 (0.15–4.2)
(b) When near grass, trees and flowers <i>and</i> during summer months <i>but not</i> during winter months?					
Yes	32	12.5%	12.5%	0%	0%
No	415	7.0%	4.1%	1.7%	1.9%
Adjusted odds ratio		1.1 (0.54–2.3)	3.0 (0.92–9.9)	–	–
(c) When near horse, dog, cat, rabbit, guinea pig or hamster?					
Yes	46	8.7%	6.5%	2.2%	0%
No	401	7.2%	4.5%	1.5%	2.0%
Adjusted odds ratio†		1.1 (0.53–2.3)	1.1 (0.30–4.1)	1.5 (0.17–14.3)	–
(d) When cleaning rooms or making beds or when in bed?*					
Yes	147	6.8%	4.3%	0.9%	1.8%
No	330	7.6%	4.8%	1.8%	1.8%
Adjusted odds ratio†		0.95 (0.45–2.0)	0.71 (0.24–2.0)	0.44 (0.05–3.9)	1.2 (0.21–6.3)

*Birch, grass, mugwort, cat, dog and/or *Der p*.†Adjusted odds ratio (95% confidence interval): adjusted for gender and age by logistic regression analysis (bold: $P < 0.05$).

a positive association between nonallergic rhinitis during summer and onset of IgE-sensitization against pollens (odds ratio 3.0, 95% CI 0.92–9.9). Changing cut-off for IgE positivity to ≥ 0.1 kU_A/l or ≥ 0.7 kU_A/l, or excluding gender, age or atopic predisposition from the regression models did not alter our findings substantially. Neither did restricted inclusion criteria: 'mono'-sensitized subjects (only pollens, pets, and mite, respectively), and nonsensitized subjects without any sensitization (data not shown). Remission of nonallergic rhinitis was frequent, e.g. two of the four reporting pollen rhinitis at baseline did not report pollen rhinitis at follow-up.

Baseline characteristics such as physician-diagnosed hay fever and asthma and IgE sensitization did not differ significantly between participants and nonparticipants to follow up (12). However, we were not able to take into account the possible differences in atopic status at the time of follow-up between participants and nonparticipants.

Discussion

We found that asymptomatic IgE-sensitization but not nonallergic rhinitis was a risk factor for later allergic rhinitis. Asymptomatic IgE-sensitization is generally considered a premorbid state of allergic disease, carrying a high risk for later allergic disease that to the best of our knowledge has not previously been demonstrated in persons more than 35 years old (reviewed in Ref. 4). Nonallergic rhinitis as a risk factor for allergic rhinitis has to our knowledge only been suggested in a few, contradicting paediatric studies on viral respiratory infections

and later atopy (6, 16). Nonallergic rhinitis constitutes at least half of all cases of rhinitis (3), and covers not only the common infectious rhinitis, but also nonallergic noninfectious rhinitis, a heterogeneous group of diseases of diverse pathophysiology (3, 8). The interactions between infectious and allergic rhinitis are complex. In allergic subjects, viral rhinitis exacerbates both allergic inflammation and clinical response to allergen exposure (2, 7). Conversely, reduction of persistent allergic inflammation lowers morbidity of upper respiratory tract infection (17). In children, it has been suggested that RSV-infection creates an enhanced IL-4 response, and that there is a common epithelial susceptibility underlying RSV-infection and atopy (discussed in Ref. 6). There seems to be no evidence of infectious rhinitis being able to induce a pro-allergic inflammation in nonatopic adults (7). In contrast, the interactions between allergic rhinitis and nonallergic noninfectious rhinitis remains to be elucidated (2, 3). The latter covers heterogeneous conditions such as nasal polyposis, sinusitis, and nonallergic rhinitis with eosinophilia syndrome, which present more or less similar symptoms and clinical examination. In nasal secretions, Kramer *et al.* demonstrated elevated inflammatory markers (tryptase and eosinophilic cathionic protein [ECP]) from well-characterised nonallergic rhinitis patients comparable to levels found in patients with allergic rhinitis (5). Furthermore, local IgE-synthesis has been demonstrated in rhinitis patients with (9, 18) and without detectable levels of specific serum IgE (10). Exclusively local IgE-synthesis could explain the positive trend of an increased risk of developing pollen-IgE in nonsensitized subjects with pollen-related rhinitis (Table 2). However, initial allergy to pollens that rarely

induce allergy, which we did not test for, and later development of sensitization to common pollens could also explain this (19, 20).

However, from the present epidemiological study, we conclude that the impact of any of the above mechanisms on later IgE-sensitization seems to be of minor importance in an adult population. This might simply be due to a relatively inert adult immune response, which could also account for our relatively low incidence of rhinitis symptoms in the asymptotically sensitized (e.g. pollens: 15.1%) (21). This incidence is comparable to that found in other epidemiological studies on adults (discussed in Ref. 4). We consider it unlikely that our results were due to poor IgE-detection. We used a validated assay (14) and relevant allergens (11, 19, 22), changed the cut-off point for positivity to the detection limit of the assay (≥ 0.1), and reproduced the high risk inflicted by asymptomatic sensitization. In fact, we used a diagnostic approach similar to everyday clinical life: a history and detection of specific IgE (1, 3, 5). We did not directly assess nonallergic inflammation by, e.g. rhinomanometry, or detection of nitric oxide, IgA, or other inflammatory cells/mediators, as these are not established markers of nonallergic rhinitis (1, 2, 9). It is possible that concomitant skin testing would enhance the diagnostic power of our allergy (1, 22) yet we have previously demonstrated that the repeatability of skin test positivity is significantly lower when not accompanied by specific IgE in serum (< 0.7 kU/l) (23). We find it unlikely that our findings were caused by false-positive cases of rhinitis. Indeed, we assume that self-reported rhinitis symptoms reflect nasal nonallergic mucosal pathology, but we used a validated questionnaire (15), included questions on exposure to ascertain intermittent rhinitis, and as mentioned reproduced the risk of asymptomatic sensitization. After we

terminated our data collection, interesting studies have been published. Inclusion of prevalence of symptoms (24), and detection of tryptase and ECP in nasal secretion by a simple method (5) could probably reduce the unknown number of healthy subjects misinterpreting normal nasal function as discomfort. However, to date there is no consensus on diagnostic criteria for nonallergic noninfectious rhinitis: the distinction to normality remains unclear (1, 2, 8). We did not include asthma symptoms in our statistical model, since rhinitis and asthma are connected diseases, and therefore interdependent as parameters (and the relatively small number of cases did not justify possible analyses of interaction).

In conclusion, we confirmed the allergological paradigm that IgE-development precedes symptoms: asymptomatic sensitization (cut-off ≥ 0.1 , ≥ 0.35 , or ≥ 0.7 kU_A/l) to pollens, pets, or house dust mite was a strong risk factor for later development of allergic rhinitis symptoms. In contrast, persistent or intermittent nonallergic rhinitis symptoms did not imply an increased risk of becoming sensitized, suggesting that nonallergic nasal inflammation is not a major risk factor for IgE-sensitization in adults. The issue needs further clinical investigation including objective measures of symptoms and inflammation.

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References

1. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**:S147–S334.
2. Scadding GK. Non-allergic rhinitis: diagnosis and management. *Curr Opin Allergy Clin Immunol* 2001;**1**:15–20.
3. Fokkens WJ. Thoughts on the pathophysiology of nonallergic rhinitis. *Curr Allergy Asthma Rep* 2002;**2**:203–209.
4. Bodtger U. Prognostic value of asymptomatic skin sensitization to aeroallergens. *Curr Opin Allergy Clin Immunol* 2004;**4**:5–10.
5. Kramer MF, Burow G, Pfrogner E, RASP G. In vitro diagnosis of chronic nasal inflammation. *Clin Exp Allergy* 2004;**34**:1086–1092.
6. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;**171**:137–141.
7. Greiff L, Venge P, Andersson M, Enander I, Linden M, Myint S et al. Effects of rhinovirus-induced common colds on granulocyte activity in allergic rhinitis. *J Infect* 2002;**45**:227–232.
8. Van Rijswijk JB, Blom HM, Fokkens WJ. Idiopathic rhinitis, the ongoing quest. *Allergy* 2005;**60**:1471–1481.
9. Kleinjan A, Vinke JG, Severijnen LW, Fokkens WJ. Local production and detection of (specific) IgE in nasal B-cells and plasma cells of allergic rhinitis patients. *Eur Respir J* 2000;**15**:491–497.
10. Powe DG, Jagger C, Kleinjan A, Carney AS, Jenkins D, Jones NS. 'Entopy': localized mucosal allergic disease in the absence of systemic responses for atopy. *Clin Exp Allergy* 2003;**33**:1374–1379.
11. Nielsen NH, Dirksen A, Madsen F. Can subjects with a positive allergen skin test be selected by a short questionnaire? The Glostrup allergy study, Denmark. *Allergy* 1993;**48**:319–326.
12. Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Smoking and the development of allergic sensitization to aeroallergens in adults: a prospective population-based study. The Copenhagen Allergy Study. *Allergy* 2001;**56**:328–332.

13. Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: report of the nomenclature review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004;**113**: 832–836.
14. Petersen AB, Gudmann P, Milvang-Gronager P, Morkeberg R, Bogestrand S, Linneberg A et al. Performance evaluation of a specific IgE assay developed for the ADVIA centaur immunoassay system. *Clin Biochem* 2004;**37**:882–892.
15. Linneberg A, Nielsen NH, Madsen F, Frolund L, Dirksen A, Jorgensen T. Increasing prevalence of specific IgE to aeroallergens in an adult population: two cross-sectional surveys 8 years apart: the Copenhagen allergy study. *J Allergy Clin Immunol* 2000;**106**:247–252.
16. Henderson J, Hilliard TN, Sherriff A, Stalker D, Shammari NA, Thomas HM. Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol* 2005;**16**:386–392.
17. Ciprandi G, Ricca V, Tosca M, Landi M, Passalacqua G, Canonica GW. Continuous antihistamine treatment controls allergic inflammation and reduces respiratory morbidity in children with mite allergy. *Allergy* 1999;**54**:358–365.
18. Durham SR, Gould HJ, Hamid QA. Local IgE production in nasal allergy. *Int Arch Allergy Immunol* 1997;**113**:128–130.
19. Pollen and spore calendar and counts, Denmark. Danish Meteorological Institute. available at: http://www.dmi.dk/eng/index/research_and_development/pollen-4.htm. (accessed on 3–6-2005).
20. Solomon WR, Platts-Mills TA: Aerobiology and inhalant allergens. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, editors. *Allergy principles and practice*. St. Louis, MO: Mosby-Year Book Inc., 1998:367–403.
21. Wedderburn LR, Patel A, Varsani H, Woo P. The developing human immune system: T-cell receptor repertoire of children and young adults shows a wide discrepancy in the frequency of persistent oligoclonal T-cell expansions. *Immunology* 2001;**102**:301–309.
22. Droste JH, Kerhof M, De Monchy JG, Schouten JP, Rijcken B. Association of skin test reactivity, specific IgE, total IgE, and eosinophils with nasal symptoms in a community-based population study. The Dutch ECRHS group. *J Allergy Clin Immunol* 1996;**97**: 922–932.
23. Bodtger U, Jacobsen CR, Poulsen LK, Malling HJ. Long-term repeatability of the skin prick test is high when supported by history or allergen-sensitivity tests: a prospective clinical study. *Allergy* 2003;**58**:1180–1186.
24. Hansen B, Mygind N. How often do normal persons sneeze and blow the nose? *Rhinology* 2002;**40**:10–12.