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Sensitisation to occupational allergens in bakers' asthma and rhinitis: a case – referent study

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Abstract Objectives: To study the importance of sensitisation to occupational allergens for the occurrence of asthma and rhinitis in bakers. **Methods:** This is a nested clinical case–referent study of bakers based on a cohort of Swedish former bakery students. Cases were asthmatic ($n=25$) or rhinitic bakers ($n=20$). Randomly selected bakers ($n=44$) were referents. All subjects underwent skin prick tests (SPTs) with common allergens, flours, fungal α -amylase and the storage mite *L. destructor*. Indices of airway inflammation were assessed in serum and the nose. **Results:** Seven of the asthmatics and eight of the rhinitics reported onset of disease during bakery work. Flour SPTs were positive in 43% of the asthmatics or rhinitics vs 16% of referents. The corresponding figures for α -amylase were 29%, 25%, and 7%. The odds ratio, adjusted for atopy, for an SPT positive to flour or α -amylase for asthmatics with onset during bakery work was 5.8 (95% confidence interval 1.1–32), and 2.6 (0.4–16) for the corresponding rhinitics. The positive predictive value of sensitisation to flour or α -amylase in relation to a clinical diagnosis of asthma or rhinitis was 71%. Sensitisation to *L. destructor*

was rare. The indices of airway inflammation were similar in cases and in referents. **Conclusions:** Bakers' asthma is associated with sensitisation to flour and/or α -amylase, atopy taken into account. A similar association was suggested in bakers' rhinitis. Indices of airway inflammation were of low predictive value for detecting bakers' asthma or rhinitis in this study.

Keywords Bakers · Sensitisation · Asthma · Rhinitis

Introduction

Asthma and rhinitis among bakers are regarded as some of the most common occupational respiratory diseases. Occupational asthma is reported to affect 2%–5 %, and rhinitis 3%–21% of bakers, as reviewed by Houba et al. [10]. It is assumed that a substantial proportion of the respiratory morbidity is caused by IgE-mediated sensitisation to flour proteins or fungal α -amylase [2, 13, 15]. Cross-sectional studies have revealed that 5%–28% of bakers are sensitised to flours and 2%–16% to fungal α -amylase [10]. However, not all bakers reporting respiratory symptoms are sensitised to occupational allergens. Houba [9] reported that only about one-third of bakers with work-related respiratory symptoms were sensitised to bakery allergens. It is not clear whether this is due to non-allergic mechanisms or because of methodological shortcomings of cross-sectional studies.

We have previously reported the findings from a retrospective cohort questionnaire study in bakers, showing approximately doubled risks for asthma in men and for rhinitis in bakers of both genders [5, 7]. The objective of this clinical case–referent study was to evaluate the importance of sensitisation to occupational sensitisers for asthma and rhinitis in bakers. The study is based on the previously reported questionnaire study [5, 7].

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Methods

Subjects

Cases and referents were selected from a cohort comprising persons who had completed the bakery programme of a trade school from 1961 to 1989 as previously reported [7]. In a mailed questionnaire 2,226 persons answered (response rate 76%) and 1,644 reported working as a baker after graduating. For practical reasons the study base was restricted to persons living in Gothenburg and Stockholm ($n = 717$). All asthmatics ($n = 31$), a random sample of rhinitics ($n = 25$) and a random sample of all questionnaire responders (referents, $n = 50$) were invited to participate. Hence, cases could also be selected as referents, as they represented the study base rather than "healthy" persons [14].

Asthma in the questionnaire study was defined as having asthma diagnosed by a doctor. Rhinitis was defined as having a blocked or runny nose and/or attacks of sneezes without having a cold or hay fever.

Five of the asthmatics, four rhinitics and six referents abstained from participating. Thus, there were 26 asthmatics, 21 rhinitics, and 44 referents participating.

Clinical examinations

Skin prick tests (SPTs) were performed with a standard battery of common allergens including pollens, house-dust mites, moulds, cat and dog dander; and positive and negative controls. SPTs were also carried out with a bakery series with the storage mite *L. destructor* (1,000 NU/ml, Diephuis, The Netherlands), flour of wheat, rye and barley, and hops (1:2 w/v); two fungal α -amylase (10 mg/ml) products (Novo Industries, Bagsvaerd, and Grindsted Products, Braband, Denmark); flours of commercial soy and malt, and malted wheat and rye (1:20 w/v), diluted in 0.9% saline with 50% glycerol and 0.5% phenol. A wheal reaction greater or equal to one-quarter of the positive control was regarded as positive [1]. Atopy was defined as an SPT positive to at least one common allergen and sensitisation to flour as an SPT positive to at least one flour extract.

Whole blood was analysed for eosinophil cationic protein (ECP) according to the manufacturer's instructions (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden).

All 25 asthmatic bakers (one baker with self-reported asthma was excluded because asthma was clinically unlikely) and 22 randomly selected referents underwent spirometry with a Vitalograph, which was calibrated regularly. Three technically acceptable trials (maximum variation 5%) were performed, and the largest value for the vital capacity (VC) and the forced expiratory volume in one second (FEV₁) was compared with predicted values [3]. A methacholine challenge test (MCT) was performed according to Thorn et al. [16].

All 20 rhinitic bakers and 15 randomly selected referents had nasal examinations performed (one referent was excluded due to an upper airway infection). Nasal peak expiratory flow (nasal PEF), nasal mucociliary clearance function, and nasal lavage (NAL) were performed [6]. The NAL fluid was analysed for ECP, myeloperoxidase (MPO) and hyaluronic acid (HA) according to the manufacturer's instructions (Pharmacia & Upjohn Diagnostics, Uppsala, Sweden).

Clinical definitions of asthma and rhinitis

All participants were interviewed by a structured questionnaire by one of the authors (J.B. or M.A.). Clinical asthma was defined according to criteria modified after Hopp et al. [8]. *Definite asthma* included (1) occasions of shortness of breath or wheeze and (2) normal breathing in-between and (3) a physician's diagnosis of asthma or having been hospitalised with asthma. *Probable asthma* included (1) and (2). *Possible asthma* included (1) or cough with wheeze together with (3) or medication because of asthma, or

shortness of breath, wheeze or cough when exposed to cold air, exertion, pollen, furred pets or dust at home or at work.

Clinical *definite rhinitis* included (1) a blocked or runny nose or attacks of sneezes without having a cold but (2) elicited by exposure to pollen, furred pets or dust at home or at work, (3) having seen a doctor and (4) received medication because of the nasal symptoms. *Probable rhinitis* included (1) and (2). *Possible rhinitis* included (1).

In the analysis of sensitisation asthmatics and rhinitics with a definite, probable or a possible clinical diagnosis were included. All referents were included, as they should reflect the occurrence of the determinants in the study base, i.e. among all bakers.

Statistical analyses

Comparisons of proportions were performed with the chi-square test, and comparisons of continuous variables with Students *t*-test. Variables without a normal distribution were transformed logarithmically. Odds ratios (ORs) were calculated by Mantel-Haenszel procedures with test-based 95% confidence intervals (95% CI) [11, 12].

Results

Clinical vs questionnaire diagnosis

One each of the asthmatics and rhinitics, according to the questionnaire, did not fulfil the clinical criteria of asthma or rhinitis, respectively. The referents, as a random sample of all bakers, contained one baker included among the selected asthmatics and two bakers also included among the selected rhinitics. There were four cases of clinical asthma and 27 cases of clinical rhinitis in the referents.

The asthmatics had a significantly lower mean FEV₁ than the referents (91% vs 101% of predicted, $P = 0.0018$) but no significant difference in VC (94% vs 97%, $P = 0.42$). A significantly higher proportion of the asthmatics had a positive MCT (18 out of 25), compared with the referents (5/22, $P = 0.001$).

Markers of airway inflammation, and nasal examination

Serum concentrations of ECP were generally low, and the means were similar in all groups (Table 1). There

Table 1 Age, ECP in serum (geometric mean), and prevalence of SPTs positive to common or bakery allergens. The asthmatics and rhinitics with onset during bakery work are in separate columns ("as baker")

Characteristic	Asthma		Rhinitis		Referents $n = 44$
	All $n = 25$	As baker $n = 7$	All $n = 20$	As baker $n = 8$	
Age (mean)	31	36	32	35	33
ECP ($\mu\text{g/l}$)	7.7	6.7	6.8	7.1	7.4
Sensitisation % (n)					
SPT					
Common allergens	64 (16)	71 (5)	79 (11)	71 (5)	32 (14)
Any flour	40 (10)	43 (3)	30 (6)	43 (3)	16 (7)
Amylase	24 (6)	29 (2)	10 (2)	25 (2)	7 (3)

Table 2 Prevalence of SPTs positive to any flour, and α -amylase, in relation to atopy in bakers with a clinical diagnosis of asthma or rhinitis, and in referents

Category	Number	Any flour		Amylase	
		%	(n)	%	(n)
Atopics					
Asthma	16	50	(8)	38	(6)
Rhinitis	14	43	(6)	14	(2)
Referents	14	21	(3)	0	(0)
Non-atopics					
Asthma	9	22	(2)	0	(0)
Rhinitis	6	0	(0)	0	(0)
Referents	30	13	(4)	10	(3)

were no differences in nasal PEF, the mucociliary function or concentrations of MPO, ECP and HA between rhinitics and referents (data not shown).

Sensitisation

Atopy or sensitisation to flour or α -amylase was more common among persons with asthma or rhinitis than among referents (Table 1). An SPT positive to *L. Destructor* was rare and similarly distributed among asthmatics, rhinitics and referents ($n=2$, $n=2$ and $n=4$, respectively).

Approximately half of the atopic bakers with asthma or rhinitis were SPT positive to flour, twice as many as among the atopic referents (Table 2). Seven of the asthmatics and eight of the rhinitics reported onset of disease during bakery work (Table 1). In the case-referent analysis, the crude OR for sensitisation to flour or α -amylase was 7.0 (95% CI 1.5–34) among the asthmatics with onset during bakery work and 3.2 (0.6–16) among the eight rhinitics. The corresponding ORs adjusted for atopy were 5.8 (1.1–32) and 2.6 (0.4–16).

Discussion

It is indicated that the asthma questionnaire diagnosis had a relatively high predictive value in this group of bakers. Only 1/26 asthmatics, according to the questionnaire, was clinically unlikely to have that diagnosis. Differences in spirometry and bronchial hyper-reactivity between asthmatics and referents also supported the clinical and questionnaire diagnoses. Torén et al. reviewed the validity of questionnaires to diagnose asthma [17]. The sensitivity varied between 48%–100%, but the specificity was high, especially for the question on “physician-diagnosed asthma” (specificity $\geq 99\%$). Since we examined only a small sample of referents, the sensitivity of our study was only 32% and the specificity 99.8%, after we had corrected for the sampling fractions.

The clinical diagnosis of rhinitis strongly depends on the history, and the occurrence may vary over time. The

clinical examinations in this study did not improve the diagnostic accuracy.

The number of examined persons was low, making the estimates less precise. Few bakers were lost to follow-up (12%–16%), and the loss probably does not influence the results considerably. Both sensitisation and symptoms of asthma or rhinitis may vary over time, and an examination at the time of diagnosis would have been preferable.

Our results, however, based on rather small material, indicate that sensitisation to flour or α -amylase is an important mechanism in bakers’ asthma. There was a similar tendency among the rhinitics with onset during bakery work. Flour was a more common sensitiser than α -amylase – all bakers but one sensitised to α -amylase were also sensitised to flour. Our sensitisation rates of 16% to flour and 7% to α -amylase are similar to those found in cross-sectional studies [10]. The relation between sensitisation rates of flour and α -amylase may differ between studies because of differences in exposure. Sensitisation to *L. Destructor* seemed to be of very little or no clinical importance in Swedish bakers. Other studies have also indicated that storage mites are not to be regarded as occupational allergens in bakers [10].

The positive predictive value (PPV) of sensitisation to flour or α -amylase in relation to a clinical diagnosis of asthma or rhinitis was estimated in the referents, as a random sample of all bakers. Seven bakers were sensitised to flour or α -amylase, five had either clinical asthma or rhinitis. The PPV was thus 71% (5/7). (One of the two without a clinical diagnosis had not worked as a baker for 17 years, and past symptoms might have been forgotten. The other was sensitised only to soy flour.)

ECP in serum or inflammatory markers in NAL seems to be of low sensitivity in detecting asthma and rhinitis in bakers. Neither seems to contribute to diagnosis. The result of the nasal examinations was similar in cases and in referents, indicating that those tests have low predictive value for diagnosing rhinitis.

In conclusion, sensitisation to an occupational allergen, especially flour, is an important, but not the only, mechanism in bakers’ asthma. There was a suggestion for a similar importance in bakers’ rhinitis. Sensitisation to *L. Destructor* seemed to be of very little or no clinical importance in Swedish bakers. The indices of airway inflammation seemed to be of low predictive value in detecting bakers’ asthma or rhinitis in this study.

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