

ORIGINAL PAPER

The prognosis of occupational asthma due to detergent enzymes: clinical, immunological and employment outcomes

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Clinical and Experimental Allergy

Summary

Background Little is known about the prognosis of occupational asthma induced by high molecular weight proteins.

Objective Our objective was to measure the clinical, immunological and employment outcomes of individuals with occupational asthma induced by detergent enzymes.

Methods We undertook a workforce-based follow-up study in 35 (78%) of the 45 employees from a single factory with occupational asthma. In each case the diagnosis was supported by evidence of specific sensitization and characteristic changes in peak flow or a positive response to specific bronchial provocation testing.

Results This group had left the factory on average 37 months before study. On review 25 (71%) reported chest symptoms during the last month. Compared with when working at the factory, most (86%) reported that their symptoms had improved. Twenty continued to attend their general practitioner for respiratory symptoms and 19 still used asthma medications. Since leaving the factory 16 (46%) and four (11%) had found full-time or part-time employment, respectively; of these 16 found they were paid less than when they worked at the factory. The remaining 15 subjects had not had any paid employment. All but two had positive skin prick tests to one or more three detergent enzymes. The estimated half-life of serum-specific IgE antibodies was 20 months for protease, and 21 months for cellulase and amylase.

Conclusions Population-based follow-up studies of the prognosis of occupational asthma are rare but probably avoid the bias in clinic-derived surveys. This study demonstrates that 3 years after the avoidance of exposure with detergent enzymes most patients continue to be troubled by, albeit improved, symptoms and experience difficulty in re-employment.

Keywords detergent, enzymes, IgE, occupational asthma

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Introduction

There are few workforce-based cohort studies of the prognosis of occupational asthma [1–5]. Most publications report the outcomes of patients recruited from specialist clinics who are likely to have been referred because of more severe disease and followed-up because of continuing symptoms. Patients identified from compensation and company surveillance schemes may also have important selection and reporting biases. Furthermore, the majority of studies have been of patients whose disease was induced by low molecular weight (LMW) chemicals, particularly isocyanates and western red cedar. Less is known about the prognosis of occupational asthma caused by high molecular weight (HMW) proteins [6–8], a group responsible for around a third of the reported cases of occupational asthma in the UK [9]. These allergens

generally elicit specific IgE responses that can be measured by skin prick test (SPT) or serum RAST.

We have previously described a large outbreak, in a single factory, of occupational asthma attributed to detergent enzymes [10]. Here we present findings of a follow-up study of patients from this factory who left employment there and were no longer exposed to enzymes in their workplaces. We investigated the clinical, immunological and employment consequences of occupational asthma attributable to these HMW allergens.

Methods

We identified every employee at the factory in whom a diagnosis of occupational asthma had been made, during their employment, between 1992 and 2002 and who had

left employment there for at least 4 months. Individuals were identified either by the company's occupational health service or through cross-sectional surveys, performed by our department in 1998 and 2000. These individuals were then formally investigated for occupational asthma. In each case the diagnosis was made through a combination of characteristic history (work-related shortness of breath and/or wheeze), evidence of enzyme-specific IgE sensitization, serial peak flow measurement and/or specific bronchial challenge. The enzyme(s) used in the bronchial challenge were those to which the individual was sensitized and exposed at the factory. Sensitization was assessed to the three enzymes (a protease, an amylase and a cellulase) used at the factory by serum RAST. At diagnosis all had SPTs with these enzymes, considered positive if the weal was ≥ 3 mm over and above control.

Forty-five patients were identified; none had a history of asthma before their diagnosis of occupational asthma. Seven could not be traced and three declined to be re-interviewed. The 10 who were not followed-up were similar in age, sex, atopic status and enzyme RAST level at diagnosis to the 35 patients we re-assessed. Both groups had a similar duration of symptoms at diagnosis but participants had worked at the factory for longer (median 72 months) than those who did not take part (median 57 months).

The 35 (78%) study participants were re-assessed; 29 in April 2002, two in July 2002 and four in February 2003. Each answered a questionnaire enquiring into their employment history after leaving the factory, any continuing detergent enzyme exposure and their current health. Each was asked to compare his or her current lower and upper respiratory symptoms with those when they were still employed at the factory using a point scale: 'completely disappeared', 'much better', 'a little better', 'no different', 'a little worse', 'a lot worse'. Potential determinants of outcome were compared between participants who described their symptoms as either 'completely disappeared', or 'much better' (Group 1) and the remaining individuals (Group 2).

Current chest symptoms were elicited by positive responses to the questions: 'over the last month, has your chest felt tight or your breathing become difficult?' or 'over the last month, has your chest ever sounded wheezing or whistling?'. Similarly current nose/eye symptoms were elicited by positive responses to the questions: 'over the last month, has your nose been blocked, itchy, runny or sneezing?' or 'over the last month, have your eyes been itchy or runny?' Questions on subsequent employment history included those enquiring into reasons for leaving the factory, the nature of any further employment and any impact on income. The durations of employment and symptomatic exposures were acquired through the patient record. Individuals were asked as whether or not they were a current smoker.

At re-assessment, simple spirometry (Vitalograph alpha III, Vitalograph Ltd, Maids Morton, UK) was performed; forced expiratory volume in 1 s and forced vital capacity were recorded with predicted results for age and height. SPT were undertaken to extracts (1 mg/mL) of the three detergent enzymes used in the factory, and to common aeroallergens to assess atopy.

A blood sample was drawn and serum-specific IgE to enzymes was measured by RAST. Briefly enzymes were coupled to 300 mg of activated discs by the method of Ceska *et al.* [11]. We incubated 50 μ L of serum with the antigen-coupled discs in duplicate overnight. Discs were washed and bound allergen was detected by adding 50 μ L ^{125} I anti-IgE (Sweden Diagnostics Ltd, Milton Keynes, UK). After 16 h incubation at room temperature, the discs were washed and radioactivity counted on a γ -scintillation counter (COBRA auto- γ -counter; Canberra Packard, Pangbourne, Berks, UK). Results are expressed as the percentage binding of the total ^{125} I anti-IgE added. The results were considered positive if binding was $\geq 2\%$. Serum-specific IgE levels at diagnosis (during employment) and follow-up were compared within the same assay; the measurements were blinded.

Statistical analysis

Two sample *t*-tests for comparison of means were performed for normally distributed data and Mann-Whitney tests for comparisons of means of non-normally distributed data. We used χ^2 analysis for comparisons of proportions and Cusick's non-parametric test for trend. Decay curves for enzyme-specific IgE were generated using an exponential model $Y_N = Y_0 \exp(k \times t)$, where *t* is the time in months between the patient's last exposed IgE measurement and that taken during the follow-up visit, *Y*₀ is the median level of all last exposed IgEs and *k* is the median decay constant. Using the same exponential decay model it can be shown that the half-life estimate is: $-\ln(2)/k$, where *k* < 0. Decay times were calculated only for those employees who had provided a blood sample at or near the time of leaving the factory; paired samples were assessed using the same assay.

Results

Symptoms

Twenty-five of the 35 (71%) subjects reported chest symptoms during the last month at a median interval of 37 months (range 4–94 months) after leaving the factory. Twenty continued to attend their general practitioner for these symptoms and 19 still used asthma medications. Similarly 26 (74%) subjects had continuing nose and eye symptoms, in nine cases requiring medication.

The subjects were divided according to their reported chest symptoms: Group 1 included the 19 subjects (54%) who reported that their chest symptoms had either 'completely disappeared' ($n = 5$) or were 'much better' ($n = 14$) than when they worked at the factory; Group 2 included the remaining 16 subjects who had symptoms that were 'a little better' ($n = 11$), unchanged ($n = 2$) or worse ($n = 3$). There was no difference in age, sex, atopy or smoking between these groups (Table 1). The median length of time away from the factory for patients in Group 1 was 41 months compared with 34 months for those in Group 2; this difference was not statistically significant. The two groups did not differ in their average duration of employment at the factory or the length of their symptomatic exposure. Thirteen (68%) subjects in Group 1 – compared with seven (44%) in Group 2 – had been in full-time work as leaving the factory, but again this difference was not statistically significant. No significant differences were found when comparing the nose and eye symptom groups.

These findings were essentially unchanged if patients were re-categorized by whether or not they had noticed any symptom improvements (data not shown).

Employment and financial consequences

Thirty-two of the 35 (91%) subjects reported that they left the detergent factory because of their illness; 22 (63%) thought their health had made it subsequently difficult to find alternative employment. Since leaving the factory, 16 (46%) had found full-time and four (11%) part-time employment, respectively. Sixteen of this group reported that they were paid less, in their first subsequent job, than they were in the factory. The remaining 15 subjects had not had any paid employment. There was no association

between the length of time since leaving the factory and being currently in paid employment ($P = 0.8$). The unemployed reported more chest symptoms than their employed counterparts although this difference was not statistically significant (Table 2).

Thirty-four made a claim for Industrial Injuries Benefit, a UK statutory compensation scheme. In 30 instances the claim was successful with an average disability assessment of 21%. Three reported that their claim was denied and one did not yet know its outcome. All 34 had made a claim for compensation from the company; 10 were still awaiting the outcome while one reported that his application had been declined. There were no differences in the persistence of chest symptoms between individuals who had completed a successful claim and those who were still awaiting outcome: of the 23 successful claimants 12 were from Group 1, and of the 10 awaiting outcomes five were from Group 1.

Immunology

At diagnosis all 35 had a positive SPT to one or more enzymes. At follow-up 33 continued to have a positive SPT test. Of the individual enzymes, eight ($n = 29$) subjects lost their SPT response to protease, seven ($n = 22$) to cellulase and two ($n = 33$) to amylase. There was no relationship between the loss of a positive enzyme SPT and age, atopy or duration of time since leaving the factory.

At reassessment, 34 of the 35 still had a positive RAST to one or more enzymes. The persistence of symptoms (by comparison of Groups 1 and 2) at follow-up was not related to the level of specific IgE at either diagnosis ($P = 0.66$, P_{trend}) or follow-up ($P = 0.74$, P_{trend}); nor was there a relationship between symptoms and the number

Table 1. Respiratory symptoms: comparison of determinants of Groups 1 and 2

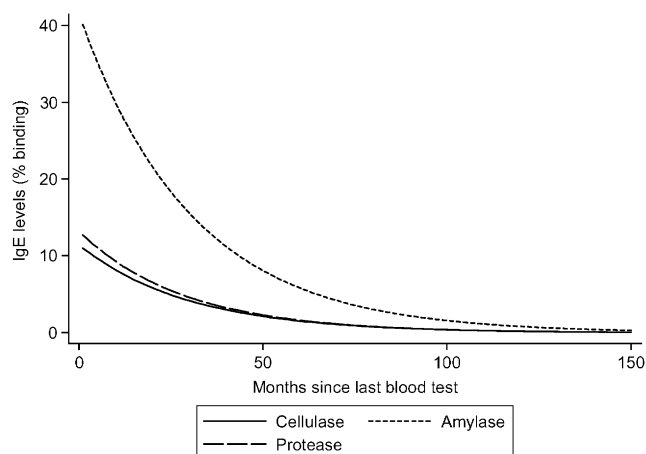
	All	Chest symptoms			Eye/nose symptoms*		
		Group 1 (%)	Group 2 (%)	<i>P</i> value	Group 1 (%)	Group 2 (%)	<i>P</i> value
<i>N</i>	35	19	16		15	19	
Age follow-up mean ($\pm$ SE)	42 ($\pm$ 2)	42 ($\pm$ 2)	41 ($\pm$ 2)	0.71	43 ($\pm$ 2)	41 ($\pm$ 2)	0.75
Age diagnosis mean ($\pm$ SE)	39 ($\pm$ 2)	39 ($\pm$ 2)	38 ($\pm$ 2)	0.78	40 ($\pm$ 2)	38 ($\pm$ 2)	0.65
Male	27	14 (74%)	13 (81%)	0.6	12 (80%)	14 (74%)	0.67
Atopy	18	10 (53%)	8 (50%)	0.88	6 (40%)	11 (58%)	0.3
Smoking	15	6 (32%)	9 (56%)	0.14	5 (33%)	9 (47%)	0.4
Mean FEV ₁ , % predicted	100	102	98	0.4			
Median duration of employment in months (range)	72 (9–369)	75	58	0.91	75	64	0.73
Median duration of symptomatic exposure in months (range)	28 (7–96)	30	28	0.72	31	28	0.96
Median duration since leaving (months)	37 (4–94)	41	34	0.42	41	34	0.21
Employed	20	13 (68%)	7 (44%)	0.14	11 (73%)	8 (42%)	0.07
State benefit	30	16 (84%)	14 (88%)	0.9	13 (87%)	17 (89%)	0.74
Compensation to date	23	12 (63%)	11 (69%)	0.9	11 (73%)	11 (58%)	0.21

*One did not recall eye/nose symptoms while working at the factory.

FEV₁, forced expiratory volume in 1 s.

Table 2. Specific IgE to enzymes measured by RAST (%binding) at leaving exposure and follow-up for estimation of exponential decay curves

Case	Protease		Amylase		Cellulase	
	Left	Follow-up	Left	Follow-up	Left	Follow-up
1	2.9	1.7	41.7	17.5	10.2	4.9
2	6.1	1.4	54	27.3	3	1.6
3	4.5	9.4	1	0.5	66.2	19.6
4	13	11.3	10.7	8.8	11.4	7.5
5	49.4	30.6	41.4	23	62.7	28.2
6	13.3	8	61.9	46.3	12.5	3.8
7	3.2	2.5	2.1	0.6	0.3	0.3
8	15.7	2.7	26.3	5.8	0.3	0.2
9	17.2	3.9	69.3	17.5	45.2	9.6
10	7.8	2.2	5.5	1.2	22.4	6.3
11	55.2	16.3	55.5	17.7	3.4	1.3

**Fig. 1.** Exponential decay curves modelled of detergent enzyme RAST IgE.

of positive enzyme RAST tests ($P=0.32$, P_{trend}) at follow-up.

Eleven subjects (eight from Group 1 and three from Group 2) had provided a blood sample for specific IgE assay either within 3 months before leaving the factory, or up to 1 month afterwards (Table 2). These 11 subjects did not differ in age, sex or atopy from the remaining 24 subjects although they had been employed and had symptomatic exposures for a shorter time. In all but one, the specific IgE levels had decreased at follow-up. There was no difference in the maximum fall in specific IgE levels between Groups 1 and 2. Decay curves for each enzyme are displayed in Fig. 1. The estimated half-lives were 20 months for protease, and 21 months for cellulase and amylase.

Discussion

HMW allergens are a common cause of occupational asthma, but less is known of the prognosis of occupational

asthma caused by them than LMW chemical sensitizers. In this workforce-based cohort study, one of the largest of its kind, 70% of individuals with occupational asthma induced by detergent enzymes continued to report respiratory symptoms after a median interval of 3 years from workplace exposure. Although the majority reported improvement, most required continuing treatment for asthma.

Studies, such as ours, that have recruited workforce populations probably represent a broader spectrum of disease severity than studies that recruit from specialist clinics or compensation schemes. We believe we identified most, if not all, cases of occupational asthma from a single factory within a specified time period and although we were not able to follow them all, our study population (with the exception of duration of employment) was representative of the full cohort. Even if the remaining 10 individuals not seen at follow-up were symptom free, over 50% of the cohort would have reported persistent symptoms.

Comparisons of follow-up studies need to be made with caution as the agent, clinical and physiological measures and other parameters often differ. With this in mind there are, to the best of our knowledge, few examples of other workforce, population-based studies to compare [1–5]. Lozewicz *et al.* [3] reported, in an outcome study of asthma induced by isocyanates, a subset of 12 patients which included all cases of occupational asthma who had worked at a printing factory: all had persistent symptoms despite avoidance from exposure for at least 4 years. Six cases of occupational asthma secondary to tetrachlorophthalic anhydride (which represented all cases from a factory except one who died) were reviewed 12 years after exposure: all had persistent respiratory symptoms and airway hyper-responsiveness, and five were on regular inhaled steroids [1]. In contrast Grammer and Shaughnessy [2] reported that 10 of 11 consecutive individuals with acid anhydride-induced asthma at a single facility

were symptom free at least 1 year after leaving exposure. Among 43 individuals with 'potroom asthma' from an aluminium factory 12 had frequent or persistent symptoms and a further 11 took regular respiratory medication [4].

Few reports on prognosis describe disease induced exclusively by HMW agents. All 56 bakers with occupational asthma, described by Gorski et al. [7], had respiratory symptoms, albeit improved with reduced medication use, 3–4 years after leaving work. In workers with snow crab induced asthma, Hudson et al. [8] reported that 19 out of 31 (61%) remained symptomatic after an average of just over a year's follow-up. Vandenplas et al. [6] reported an improvement in symptom scores after a median interval of 50 months in 16 individuals with latex-induced occupational asthma. Comparisons of asthma caused by LMW and HMW allergens have suggested that recovery from symptoms may be more common with the latter [12, 13]. Nevertheless the proportion of our patients with persistent symptoms are similar to those reported in patients with asthma induced by LMW agents including western red cedar, isocyanates, colophony and acid anhydrides [14–17].

We observed a positive relationship between symptom improvement and duration away from workplace exposure although the difference was not statistically significant. A similar finding has been described by Pirfetti et al. [12] who reported that symptoms were fewer if individuals had been removed from exposure for more than 5 years rather than less. Smoking and atopy were not important in determining outcome in our study, consistent with other reports [14, 18]. Spirometry was not discriminatory and most values were within predicted ranges. We did not find the duration of exposure (or of symptomatic exposure) to be of prognostic value although this has been repeatedly described in follow-up studies of western red cedar [14] and isocyanate [19–21] but not of crab, a HMW allergen [8]. Self-reported symptoms were our primary clinical outcome and are of course subjective, although 76% of those reporting chest symptoms were on asthma medications. Bronchial hyper-responsiveness was not measured, as it was not part of the initial service assessment.

The detection of specific IgE is a sensitive test in detergent enzyme allergy; in our study all patients had measurable specific IgE at diagnosis and all but two at follow-up. Similarly among bakers with occupational asthma, sensitization to flour (assessed by SPT) was found in all but two individuals ($n=54$) up to 4 years after exposure [7]. We found that the magnitude of specific IgE at diagnosis (or follow-up) was not a prognostic feature for respiratory symptoms, a result consistent with findings from western red cedar and snow crab workers [14, 22]. Others however have reported differently. Among workers with acid anhydride asthma those with the highest levels of specific IgE at diagnosis were at the highest risk of persistent asthma [23]. Elsewhere the level of specific IgE

has been associated with a persistence of a specific bronchial challenge response [24]. In contrast in isocyanate-induced asthma Piirila et al. [25] reported that those with specific IgE at diagnosis had fewer symptoms and lower medication use at follow-up than IgE-negative subjects – although these may represent two different diseases. We estimated the half-life of specific IgE to each of the three enzymes to be around 21 months. This compares closely with antibodies to snow crab allergens ($n=9$) where a half-life of 20 months was estimated [22]. With acid anhydrides ($n=6$) the half-life was initially estimated to be 1 year [26], but a later study of the same population found that the half-life increased the more time away from exposure (at 8–8.7 years) [1]. Repeat estimates may be useful in assessing whether a sensitized individual is still exposed to an allergen.

Many of our subjects described problems with re-employment. Fifteen (43%) continued to be unemployed and many ascribed this in part to their disease. Those who were currently unemployed tended to report relatively more persistent symptoms than those who were employed although the difference could have arisen by chance. Interestingly, the persistence of reported symptoms was not related to the status of compensation claims. Of those who found employment the majority (84%) were paid less than they had been at the detergent factory. It is difficult to put these findings into context; temporal, local and national employment conditions vary, and compensation schemes may distort comparisons. In addition, patients may have different capacities to transfer their skills to other jobs. Ideally our study would have included a control group of those who left the factory without occupational asthma. Nevertheless our findings seem to be consistent with other investigations. For example, of those who left their jobs, Venables et al. [17] found that 33% of 79 consecutive outpatients in the UK were unemployed at follow-up. In Canada, Marabini et al. [27] reported that 41% of those with asthma induced by western red cedar were unemployed. Even when new employment has been found, a reduction in income, as found in our study, has been commonly reported [17, 27–29].

Workers who have developed occupational asthma due to detergent enzymes, reviewed on average 3 years after occupational exposure has ceased, continue to report respiratory symptoms. Workforce-based population studies such as this enable a more complete understanding of the prognosis of occupational asthma; and will allow health professionals to better advise their patients of the risks associated with occupational asthma.

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