Progression of self-reported symptoms in laboratory animal allergy

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Background: Laboratory animal allergy is a common illness among workers exposed to laboratory animals and can progress to symptoms of asthma.
Objectives: This study evaluates the continuum of disease from allergy symptoms to asthma symptoms in a dynamic cohort of workers exposed to animals in a pharmaceutical company.
Methods: Data arose from annual questionnaires administered to workers in a surveillance program established to monitor exposure to animals and the development of allergy. The life-table method was used to compare asthma-free survival between workers with and without symptoms of allergy. A Cox proportional hazards model was used to examine the effects of covariates on the development of asthma.
Results: A total of 603 workers contributed 2527.4 person-years to the study over the 12.3-year period. The probabilities of experiencing asthma symptoms by the 11th year of follow-up were 0.367 for workers with allergy symptoms and 0.052 for those without allergy symptoms. The hazard ratio for asthma symptoms when comparing workers with and without allergy symptoms was 7.39 (95% CI, 3.29-16.60) after adjustment for sex and family history of allergy. Female subjects developed asthma at a rate 3.4 times that of male subjects.
Conclusions: This study supports the hypothesis that laboratory animal allergy symptoms are a major risk factor for the development of asthma. It also suggests a heightened risk of asthma for women who work with laboratory animals, a finding that has not been previously reported. (J Allergy Clin Immunol 2005;116:127-32.)

Key words: *Asthma, laboratory animal allergy, symptom progression, incidence, animal workers, occupational asthma*

Abbreviations used
HR: Hazard ratio
LAA: Laboratory animal allergy

Laboratory animal allergy (LAA) is a common but significant illness among persons who work with laboratory animals, with prevalence estimates ranging from 11% to 44% among exposed workers.[1] The most common manifestations of LAA are allergic rhinitis and allergic conjunctivitis, which are characterized by nasal congestion, runny nose, sneezing, and watery and itchy eyes. Almost all workers with LAA exhibit at least one of these symptoms, and most workers exhibit a combination of symptoms.[2]

A possible corollary of LAA is the development of occupational asthma, a more serious disorder of the lower respiratory system that might result in life-threatening episodes. It has been estimated that approximately 20% to 30% of workers with LAA have asthmatic symptoms, such as coughing, wheezing, or shortness of breath.[3,4] Although estimates vary, the overall prevalence of self-reported asthma among exposed workers is generally reported to be between 9% and 12%.[2,5-7]

Some studies have suggested that there is a progression of symptoms in LAA, from milder symptoms of rhinitis to more serious symptoms of asthma.[2,8] Others have suggested that there are 2 distinct syndromes associated with LAA, a regional form characterized by the presence of rhinitis alone and a progressive form characterized by rhinitis progressing to asthma.[9] The latter syndrome has been linked to the presence of atopy.

Most information about the natural history of LAA and LAA-related asthma comes from cross-sectional studies in which the temporal relationship between exposures and the development and progression of symptoms is difficult to ascertain. The few prospective studies that have addressed issues related to LAA symptomatology have not directly addressed the question of the continuum of disease from rhinitis to asthma. Although these studies have contributed to the understanding of the symptom constellations among workers with LAA, they have been relatively short in duration or have obtained information from pre-exposure and post-exposure questionnaires.

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In this study we examined the relationship between LAA-related symptoms of the eyes, nose, and skin and the development of asthma symptoms in workers exposed to laboratory animals. We also considered the effects of exposure-related variables on these relationships. Elucidation of these issues might contribute to asthma and allergy prevention practices in institutions that house and use laboratory animals.

METHODS

All workers with potential exposure to laboratory animals at GlaxoSmithKline, Research Triangle Park, North Carolina, were enrolled in an LAA medical surveillance program since January 1, 1991. Medical surveillance included baseline and annual examinations by a company physician, with completion of a questionnaire about exposures and symptoms. The medical examination included a complete physical examination plus clarification of any LAA-related problems noted on the questionnaire.

This population comprises a heterogeneous group of at-risk workers, including scientists, veterinarians, physicians, animal technicians, housekeeping personnel, biologists, toxicologists, laboratory technicians and technologists, computer programmers, and safety personnel. The population has been described in more detail previously.[10]

The data for this study were obtained from questionnaires completed by workers at annual visits to the GlaxoSmithKline health clinics during the period from January 1, 1991, through April 30, 2003. On the questionnaires, workers reported information about personal and family history of allergic disorders, smoking history, pet ownership, and general demographic information, including age, race, and education. They also reported information about work-related exposures to animals, including prior exposure to animals before completing the initial questionnaire, average weekly (hours per week) work in the animal rooms, and average weekly exposure to specific laboratory animals and job tasks. Workers were exposed to a variety of laboratory animals, including dogs, cats, mice, rats, rabbits, hamsters, and guinea pigs. The questionnaire included questions about symptoms from exposures to specific animals, use of personal protective equipment, and job location and title. (The questionnaire has been made available elsewhere.[1])

LAA symptoms were defined as self-reported symptoms from working with laboratory animals or their cages. Nonasthma symptoms of LAA included sneezing spells, runny or stuffy nose, watery or itchy eyes, skin rashes, or hives. Asthma symptoms included coughing spells, wheezing, or shortness of breath. Progression of symptoms was defined as a change from nonasthma to asthma symptoms.

All workers who completed at least 2 questionnaires and did not report asthma symptoms at initial examination were included in the analysis. In descriptive analyses the Student t test was used to examine differences in means between groups, and the χ^2 test was used to test proportions.

The life-table method was used to compare differences in asthma-free survival between workers with and without LAA symptoms. Workers who developed LAA during the study period contributed follow-up time to both groups if their initial symptoms did not include asthma symptoms. A Cox proportional hazards model was used to examine the effects of both fixed and time-dependent covariates on the development of asthma in each group of workers. Independent fixed variables included sex, race, family history of allergy, years in this particular job at baseline, and years of previous work with animals. Independent variables that could change with each questionnaire included pet ownership, smoking status, number of laboratory animals to which a worker was exposed, number of specific tasks a worker performed, and average hours per week spent in the animal room. In addition to the total number of animals and tasks, association with each animal and task was assessed in the model. Age, an inherent time-dependent characteristic, was also evaluated.

A backward elimination strategy was used in the modeling procedure, with all variables of interest entered into the full model. Likelihood ratio tests (P cutoff value of .05) and comparison of stratum-specific hazard ratios (HRs) were used to determine inclusion of interaction terms. In assessment of confounders, variables were retained in the model if their exclusion resulted in a greater than 10% change in the coefficient of the main exposure variable (presence of nonasthma symptoms). Results were reported as HRs, and precision was reported as 95% CIs. Statistical analyses were conducted with PC SAS software v.8.2 (SAS Institute, Cary, NC).

RESULTS

During the period from January 1, 1991, through April 30, 2003, 792 workers were enrolled in the surveillance program. Of these, 603 (76%) workers completed at least 2 questionnaires and contributed 2527.4 person-years to the study. The majority of workers were white (77.3%), male (57.5%), and nonsmokers (91%). The average age at entry was 36.4 years (range, 18-63 years), and the average period of prior work with laboratory animals was 5.2 years (range, 0-35 years). One hundred eighty-nine workers were enrolled in the surveillance program but did not have a follow-up questionnaire: 90 of them left the program before the end of the study and were lost to follow-up, and the rest entered in later years and had not completed a follow-up questionnaire by the end of the study.

At baseline examination, 108 workers reported the presence of at least one symptom from exposure to laboratory animals (ie, prevalent cases). Over the study period, LAA developed in 47 workers (ie, incident cases). The distributions of symptoms reported by the 2 groups on the first and last questionnaires are shown in Fig 1. At initial report, the distributions of symptoms were similar for prevalent and incident cases, except for the proportion of workers reporting skin symptoms only ($P = .02$). Few workers experienced asthma symptoms alone (difference between groups, $P = .47$), and by the end of follow-up, all workers with asthma symptoms had symptoms of the eyes or nose. On the last questionnaires, there were significant differences between the 2 groups in the reporting of nasal-eye symptoms ($P = .01$) and in the joint distribution of nasal-eye and skin symptoms ($P = .01$). The greatest increase in symptoms occurred among workers with LAA at entry, especially in the joint distribution of all symptoms (212% increase). By the end of follow-up, 35% of the workers with LAA at entry reported asthma symptoms (73% increase from initial questionnaire) compared with 22.4% of the workers who began the study without LAA but developed it during follow-up (11.7% increase from the first report).

Among the nasal-eye symptoms, the most common was runny or stuffy nose, with 77% of initially symptomatic

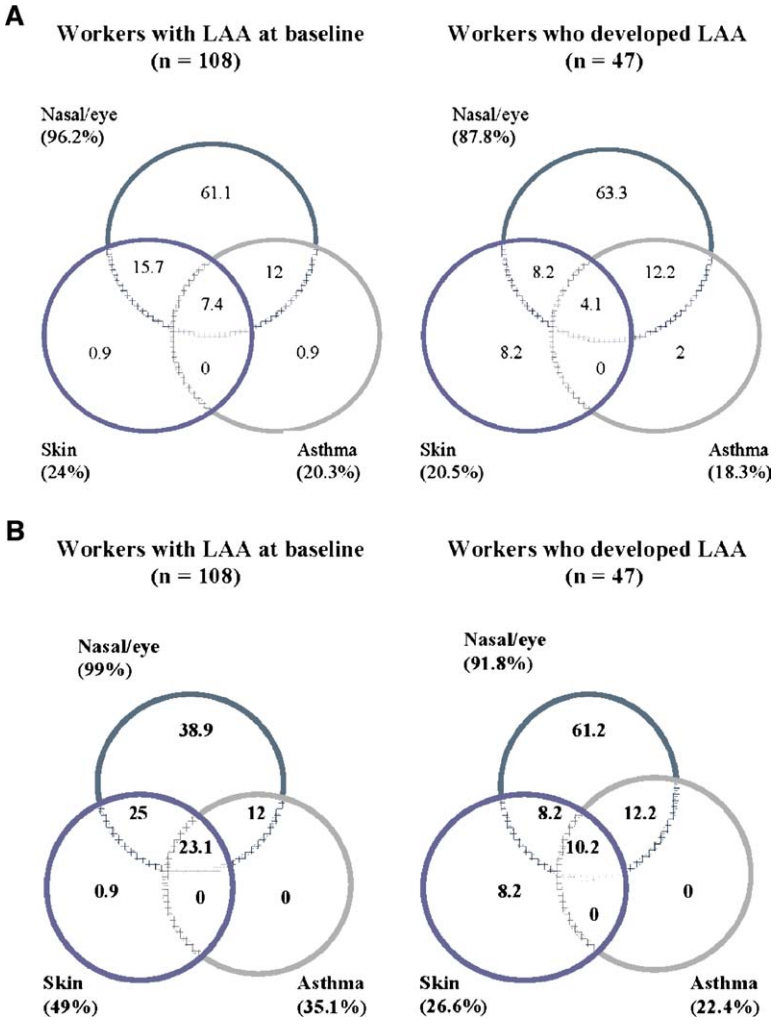

FIG 1. A, Symptom distributions of workers on initial questionnaires (workers with LAA at baseline) or at first report of symptoms (workers who developed LAA during the study). **B**, Symptom distributions of workers on final questionnaires.

and 70.2% of initially asymptomatic workers reporting it on their first questionnaires (Table I). Wheezing was the most common asthma symptom, reported by 76.1% of the workers with prevalent LAA and 55.5% of those with incident LAA.

After exclusion of workers with asthma at entry (n = 22), there were 86 workers with nonasthma symptoms and 496 symptom-free workers for survival analysis. Workers contributed 2414 person-years of observation.

The group of workers who began the study with LAA symptoms had a higher proportion of female sex than the symptom-free group, performed more work tasks at entry into the study, and had significantly more allergy indicators (Table II). The survival experiences of the 2 groups were significantly different (log-rank test of equality over strata, $P < .01$; Fig 2). The probability that workers with rhinitis, conjunctivitis, or skin symptoms would have asthma symptoms by the third year was 0.121, compared with 0.015 for symptom-free workers. The probabilities for the development of asthma symptoms by the 11th year of follow-up were 0.367 and 0.052 for symptomatic and asymptomatic workers, respectively.

The incidence rates of asthma for initially symptomatic and initially asymptomatic workers were 4.04 and 0.43 per 100 person-years, respectively. Sixteen workers in the LAA group and 11 workers in the LAA-free group had asthma symptoms over the 12-year period. Two workers in the latter group had allergy symptoms first and then asthma symptoms 1.5 and 6.0 years later. Nineteen workers had allergy and contributed follow-up time to both groups. The remaining workers who had LAA did not contribute time to the study after allergy development because the allergy was reported on their last questionnaire.

Results of fitting the Cox proportional hazards model are shown in Table III. The crude HR for development of LAA-related asthma, comparing initially symptomatic with initially asymptomatic workers, was 9.39 (95% CI, 4.21-20.93), which was reduced after adjusting for sex and

TABLE I. Percentage of symptomatic workers reporting specific symptoms on initial and final questionnaires

	Workers with LAA symptoms at the beginning of the study		Workers in whom LLA developed during the study	
	Initial	Final	Initial	Final
Runny-stuffy nose	77	89.6	70.2	72.9
Itchy-watery eyes	67.7	82	70.2	78.3
Sneezing	66.6	75.3	62.1	64.8
Coughing	42.8	52.4	44.4	44.4
Wheezing	76.1	80.9	55.5	66.6
Shortness of breath	38	66.6	22.2	22.2

family history. When family history of allergy was included as a modifier of the relationship between allergy symptoms and asthma, the HR for symptomatic workers with a family history of allergy was approximately 3 times that for workers without a family history of allergy. The HR for female subjects was more than 3 times that for male subjects. Other variables, including race, years in this particular job at baseline, years of previous work with animals, pet ownership, smoking status, number of laboratory animals to which a worker was exposed, number of specific tasks a worker performed, average hours per week spent in the animal room, and age, did not substantially change the results of the model.

DISCUSSION

To address the hypothesis of symptom progression in workers with LAA, we examined the relationship between the presence of allergy symptoms and the development of LAA-related asthma symptoms among a dynamic cohort of laboratory animal workers followed for 12.3 years. We found a substantial difference in rates of asthma incidence between workers who had allergy symptoms at the beginning of follow-up (4.04 per 100 person-years) relative to those who did not (0.43 per 100 person-years). The crude HR when comparing these groups was 9.39 (95% CI, 4.21-20.93), which was reduced to 7.39 (95% CI, 3.29-16.60) after adjustment for sex and family history of allergy and asthma. This suggests that the progression of allergy symptoms to asthma is a major risk for workers who have LAA and continue to be exposed to animals. Family history was evaluated as a modifier of the effects of LAA-related allergy symptoms, but the CIs were wide. Sex appeared to confound the relationship between the presence of LAA-allergy symptoms and the development of LAA-asthma, with female subjects having higher rates of asthma (HR, 3.39; 95% CI, 1.43-8.07).

Development of asthma in the presence of allergy symptoms appeared to be unrelated to race, age, number of years employed at entry into the study, pet ownership, smoking, and a number of measures of exposure to laboratory animals. The resulting higher rates of asthma

TABLE II. Baseline characteristics of initially symptomatic and initially asymptomatic workers compared in survival analysis

Characteristic	Initially symptomatic (n = 86)	Initially asymptomatic (n = 496)	*P* value*
Mean age, y (range)	36.4 (18-63)	36.2 (24-55)	.83
Female sex	52.9%	41.1%	.04
Mean years employed at job before baseline; median	4.5 (0-20); 2.4	4.0 (0-22.8); 1.5	.38
Mean follow-up, y (range of follow-up, y)	4.3 (0.67-12)	4.2 (0.4-12)	.74
Average h/wk in animal room (SD)	9.9 (12.3)	10.7 (13.3)	.59
Mean no. of work tasks performed (SD)	3.7 (2.7)	3.0 (2.8)	.03
Physician-diagnosed allergy	48.8%	32.1%	<.01
Hay fever	40.7%	21.6%	<.01
History of asthma	12.8%	9.5%	.34
History of allergy shots	19.8%	8.9%	<.01
Smoking	3.5%	10.9%	.03

*Student *t* test for means; χ^2 test for proportions.

incidence among workers with LAA symptoms lends strength to the hypothesis that among all workers exposed to laboratory animals, workers with LAA symptoms have a higher risk of asthma development than those who do not have LAA.

Comparison of the symptom distributions between workers who began the study with LAA and those in whom it developed during follow-up also supports the hypothesis of symptom progression and highlights the advantage of observing exposed workers over longer periods of time. The initial symptom distribution for workers who began the study with LAA is similar to the final symptom distribution for workers who developed it during follow-up. Because workers in the latter group have had symptoms for a shorter period of time, it is not unreasonable to infer that these workers will have symptom distributions similar to those for the group of workers who began the study with symptoms. This finding might raise a question about the hypothesis that there are 2 forms of LAA, one characterized by rhinitis alone and the other characterized by a progression of symptoms and the presence of atopy.[9] It might be that a complete progression of symptoms has not been observed because the observation periods of other studies have been relatively short and any progression that has been observed is similar to the limited progression seen among the workers who developed LAA during follow-up in this study. On the other hand, we also observed that the rate of asthma for workers with a family history of allergy and asthma was 3 times the rate for workers without a family history of allergy and asthma. If

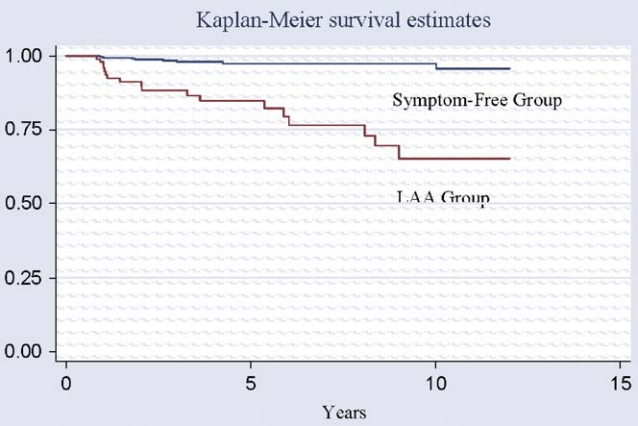

FIG 2. Survival curves comparing development of asthma between workers with and without LAA symptoms.

family history is a marker for atopy, then the findings might lend support to the hypothesis that atopy modifies the effects of rhinitis in the progression of symptoms.

Both occupational and nonoccupational studies have found rhinitis to be common among persons with asthma, but it is not known whether rhinitis is a risk factor for asthma development or an early manifestation of the same disorder.[11] Nonoccupational studies have found that increased levels of IgE are related to both rhinitis and asthma, although it is not clear why some persons have one disorder without the other.[11] Workers in this study with asthma symptoms alone developed other symptoms over the study period. Skin symptoms were more common than asthma symptoms in this population, and they either occurred alone or with rhinitis or rhinitis-asthma combination, although never with asthma symptoms alone.

A reduction in the incidence of asthma with cessation of exposure would suggest that rhinitis is a precursor to asthma and that asthma could be prevented. The effectiveness of personal protective equipment in preventing asthma was assessed in this analysis (not shown), but the reported use of gloves, gowns, masks, or shoe covers was high among all worker groups. Issues related to compliance or of timing of exposures relative to the use of equipment might hinder the assessment of this type of preventive practice. For example, workers might feel pressured to report the use of company-mandated equipment, or workers might begin wearing equipment after the onset of symptoms.

A sex difference in asthma prevalence has been reported in nonoccupational studies, but studies of LAA have not addressed it as a risk factor for asthma. Studies have reported a higher prevalence of asthma in prepubertal boys relative to girls, most likely because of the relatively smaller airway of male subjects at that age.[12] At puberty, however, the airway differences are reversed, and the prevalence of asthma in female subjects increases in comparison with male subjects. It is possible that female hormonal cycles also contribute to the increased prevalence among women.[12] The finding in this study supports the current understanding of sex differences in asthma and highlights the importance of informing female workers of their increased risk of asthma development from working with animals.

TABLE III. Results of fitting Cox proportional hazards model for the development of asthma, comparing workers who began the study with LAA symptoms with those who did not have symptoms

Variables	HR	95% CI
Allergy symptoms*	9.39	4.21-20.93
Allergy symptoms†	7.39	3.29-16.60
Family history of allergy	2.27	1.03-4.99
Female sex	3.39	1.43-8.07
No LAA-related allergy symptoms (no family history of allergy or asthma)‡	Reference	
LAA-related allergy symptoms (no family history of allergy or asthma)	5.12	1.47-17.78
LAA-related allergy symptoms (family history of allergy or asthma)	14.74	5.22-41.61
Family history of allergy or asthma (no LAA-related allergy symptoms)	1.52	0.41-5.66
Female sex	3.45	1.45-8.21

*Univariate model.
†Model without interaction term for family history of allergy.
‡Model with interaction term for family history of allergy as a modifier of the relationship between allergy symptoms and the development of asthma.

Family history of allergy was the only indicator of atopy used in this study because self-reported allergy and physician-diagnosed allergy were functionally correlated with the exposure (ie, the existence of LAA symptoms). Atopy has been recognized as a risk factor for LAA[2,13-17] and for asthma,[9] although some studies have found this relationship only among workers with low levels of exposure.[18]

This study represents the longest prospective observation period of a dynamic cohort of workers exposed

to laboratory animals. Valuable information about possible symptom progression has been derived from cross-sectional studies and pre-exposure and postexposure studies, and the present study suggests quantitative measures for describing the rates of disease progression from rhinitis to asthma among exposed workers. The findings are strengthened by the systematic method in which these workers have been followed through surveillance by the same medical staff over a period of approximately 12 years. Although workers were supposed to have annual clinic visits, more than 50% of the population had some missing questionnaires. The mean percentage of missing person-time for cases was lower than for noncases, and only 2 workers had an interval of more than 1 year between questionnaires before reporting asthma symptoms. Because these workers were only missing one person-year of information before reporting asthma symptoms, it is unlikely the missing information greatly influenced the results of the study.

Self-reported exposures and allergy symptoms are almost always subject to information bias. Symptomatic workers might be reluctant to report symptoms if they believe their employment will be affected or if they are unsure that their symptoms are related to animal exposure. In this study differential bias might be present if symptomatic workers are more likely than asymptomatic workers to report onset of asthma symptoms, which would lead to an overestimate of the effects of existing allergy symptoms. However, workers received an annual medical examination at the same time they completed their questionnaires, and it is unlikely that asthma symptoms were not noticed by the medical examiner. Tests of respiratory function have been used in other studies to assess the effects of exposure on the respiratory system, and similar tests would have strengthened this study.

The healthy worker survival effect is a concern in occupational studies, especially when relationships between exposures and health outcomes are being examined. The healthy worker effect could influence this study if exposed workers who had asthma symptoms left work without reporting them. Nevertheless, the asthma-free survival experience among workers with existing LAA symptoms answered the question of whether symptoms progress to asthma, even if the healthy worker survival effect had been in force in this population.

These findings reinforce the need for safety and prevention education for workers exposed to laboratory animals. The important finding is that workers who have seemingly minor symptoms from working with animals might be on a path to asthma, which can result in significant personal and medical costs. In particular, this study has brought to light the increased risk of asthma to women who work with animals, which has not been addressed previously.

It remains to be seen whether cessation of exposure, either through stringent protective equipment and engineering controls or through change in work, will stop the continuum of disease. This question will need to be addressed with more focused attention to the use of protective equipment and the effectiveness of engineering controls.

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