Allergy to laboratory animals: an epidemiological study

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Abstract

A large cross sectional survey was carried out using a self administered questionnaire to examine the prevalence of laboratory animal allergy (LAA) and the factors associated with its development. Out of 5641 workers who were exposed to animals at 137 laboratory animal facilities in Japan, 23.1% had one or more allergic symptoms related to laboratory animals. The commonest symptom was rhinitis. About 70% of LAA subjects developed symptoms during their first three years of exposure. Atopy (past and family history), the number of animal species handled, and the time spent in handling correlated significantly with the development of LAA as did some types of job. A close relation between nasal symptoms and exposure to rabbits and between skin symptoms and exposure to rats were found. LAA subjects developed symptoms most quickly to rabbits.

Laboratory animal allergy (LAA) is receiving increased attention and it is now believed that many persons suffer from allergic symptoms related to laboratory animals. Laboratory animal allergy has been recognised as a health problem for those who work with laboratory animals in Japan but there are few epidemiological surveys of LAA with large numbers of subjects.

Many studies on LAA have been carried out in the United Kingdom and the United States.¹⁻⁸ The prevalence of LAA has been rated at between 11 and 30%.⁹ From the viewpoint of prevention, three basic factors associated with the development of LAA have been considered.^{4,9-11} These are the predisposition

of the subject, the allergenicity of the substances derived from animals, and the nature and intensity of exposure.

We carried out a large scale survey among 5641 animal handlers in 137 laboratory animal facilities to clarify the size of the problem of LAA in Japan, and to consider the various factors involved in the development of LAA.

Subjects and methods

A self administered questionnaire was designed by us and contained questions on sex, age, history and family history of allergic diseases, smoking and pet owning history, duration of working with laboratory animals, job titles, job contents, frequency of contact with animals, species, time spent handling animals, and use of protective equipment. Questions dealing with symptoms asked about experience of nasal, eye, respiratory, and skin symptoms and the association between symptoms and laboratory animals. Further, the subjects with symptoms were specifically asked about the time to first symptoms, the relation between the symptoms and animals, species and time of exposure to animals related to symptoms, and about the effectiveness of protective equipment etc. When subjects reported some symptoms, they were systematically questioned about further symptoms.

The questionnaire was sent to 164 laboratory animal facilities in Japan and handed to 8765 handlers including researchers, assistants, and husbandry personnel. Replies were received from 137 facilities (84%). Of these, 76 were medical schools, 57 were research institutes, and four were breeders. Out of 8765 subjects, 5641 replied (64.4%). All of them had been exposed to laboratory animals and so they were named the exposed group. This group was divided into two sub groups, LAA and non-LAA. In studying the correlation between the development of LAA and predisposing factors, 252 employees without occupational exposure to laboratory animals were selected from our medical school as a control group. The exposed and control groups were young (mean age 33.2 (SD 11.6) and 33.4 (SD 10.5) years respectively) and contained more men than women (man: woman 2.7 and 1.03 respectively).

In this study, animal handlers were defined as the

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Table 1 Prevalence of LAA in 137 institutes

Type of facility	No of subjects	No of LAA subjects (%)
Medical schools	2806	616 (22.0)
Research institutes	2697	660 (24.5)
Breeders	138	28 (20.3)
Total	5641	1304 (23.1)

users or staff of a facility who were exposed to laboratory animals, or the substances derived from them, or both. The LAA subjects were defined as workers who had allergic symptoms related to laboratory animals—namely, sneezing, rhinitis, conjunctivitis, wheezing or cough, asthma, and urticaria. The following markers of atopy were assessed in all subjects: (1) past history of allergic rhinitis, conjunctivitis, asthma, and urticaria to pollen, house dust, food and unknown allergens; (2) family history of the same symptoms.

The results were computed and analysed with the SPSS computer program package. The χ^2 test was used to detect significance of association. The level of significance accepted was $p < 0.05$.

Results

THE OCCURRENCE OF LAA IN JAPAN

Out of 5641 subjects, 1304 (23.1%) had one or more allergic symptoms related to laboratory animals (table 1). No significant difference in the prevalence of LAA was found between the three types of facilities.

Figure 1 shows that LAA subjects had various combinations of nasal, respiratory, and skin symptoms (nasal symptoms are combined with eye symptoms in this figure); 43.6% of LAA subjects had two or more symptoms. The proportion of LAA subjects suffering from nasal or eye symptoms alone (39.7%) was largest followed by the combination of nasal or eye and skin symptoms (19.3%), nasal or eye, skin,

Figure 1 Combinations of symptoms in LAA subjects (%).

Figure 2 Distribution of duration of exposure to laboratory animals.

and respiratory symptoms (11.6%) and nasal or eye and respiratory symptoms (11.1%). Of all LAA subjects, 81.7% had nasal or eye symptoms and most of them complained of rhinitis; 45.6% had skin symptoms and 16.0% of them complained of contact urticaria; 27.9% had respiratory symptoms and 33.2% of them complained of asthma. No subjects had asthma without other symptoms.

Figure 2 shows the distribution of the duration of exposure to laboratory animals in LAA and non-LAA subjects at the time of the survey. The LAA subjects had a significantly shorter time in exposure than non-LAA subjects ($p < 0.01$).

Figure 3 shows the distribution of latency and the period from first exposure to first manifestation of LAA symptoms in LAA subjects. About 70% of LAA subjects reported the occurrence of first symptoms during their first three years of exposure, 33% of them in the first year. The proportion of the subjects who reported the occurrence of the symptoms during the first year of exposure was highest among those with respiratory symptoms.

About 61% of the subjects in this survey handled two or more species of animal. Table 2 shows the number of persons handling different species and the prevalence of LAA by different species. Rats and mice were used most frequently (62.4% and 57.5% respectively). The subjects handling guinea pigs had the highest prevalence of LAA (31.0%), then cats (30.1%), rabbits (29.7%), and mice (26.1%).

We surveyed the effectiveness of protective equipment, such as masks, gloves, and glasses in the prevention of LAA (table 3). Some 46% of those with nasal symptoms reported that the use of protective equipment helped to reduce symptoms. Skin (44.6%), respiratory (44.8%), and eye symptoms (31.0%) were less well prevented and 36.5 to 56.4% of subjects with LAA symptoms also reported protective equipment to be “not available” or “not regularly available”.

Figure 3 Distribution of latency by different symptoms.

FACTORS RELATED TO THE DEVELOPMENT OF LAA
Atopy, exposure density, and animal species were examined as the factors related to the development of LAA.

Of all LAA subjects, 59.2% had a history of allergy whereas 30.4% of the non-LAA subjects and 30.7% of the control subjects had such a history (table 4). The differences were significant. A similar tendency was also found for family history, although the frequencies were lower than those of history in all groups.

As the indices of exposure density, we chose job category, the frequency of handling animals, and the number of animal species handled. Job category was defined by selecting from four categories (table 5). Several subjects selected two or more job categories. The prevalence of LAA was similar in researchers, experimental assistants, and animal husbandry personnel. Staff in charge of cleaning and washing

Table 3 Effectiveness of protective equipment for preventing LAA symptoms

	Nasal (n = 1022)	Eye (n = 564)	Respiratory (n = 364)	Skin (n = 595)
Available (%)	46.7	31.0	44.8	44.2
Not available (%)	10.3	10.3	7.4	13.6
Not regularly (%)	37.6	46.1	29.1	34.3
Unknown (%)	5.5	12.6	18.7	7.9

implements had a significantly lower prevalence than experiment assistants ($p < 0.05$). No significant difference existed, however, in the proportion of each job category when the LAA group was compared in total with the non-LAA group. Table 6 shows job content in LAA and non-LAA subjects. More LAA subjects engaged in animal experiments, breeding, and quarantine duties than non-LAA subjects.

According to the frequency of handling animals, the exposed group was divided into two sub-groups: daily exposure group (five or more days per week) and non-daily exposure group. The prevalence of LAA in the daily exposure group (26.9%) was significantly higher than in the non-daily exposure group (19.5%)

Table 2 The prevalence of LAA symptoms in handlers by different animal species

Species	No of handlers (%)	Prevalence of LAA
Mouse**	3246 (57.5)	26.1
Rat**	3518 (62.4)	24.9
Guinea pig**	1482 (26.3)	31.0
Rabbit**	2198 (39.0)	29.7
Hamster	589 (10.4)	25.5
Dog*	1580 (28.0)	24.9
Cat**	579 (10.3)	30.1
Monkey	692 (12.3)	23.6
Others	446 (7.9)	24.2

*Significant between handlers and non-handlers of the species ($p < 0.05$).

**Significant between handlers and non-handlers of the species ($p < 0.01$).

Table 4 Frequency of own history and family history of allergy in control and exposed groups

History of allergy	Control group (%) (n = 251)	Exposed groups	
		Non-LAA subjects (n = 4337)	LAA subjects (n = 1304)
Own history	30.7	30.4	59.2***
Family history	28.7	22.9	39.5***

**Significantly different from the control group ($p < 0.01$).

†Significantly different from the non-LAA group ($p < 0.01$).

Table 5 Job categories in LAA and non-LAA subjects

Job categories	No of subjects†	LAA subjects (%) (n = 1304)	Non-LAA subjects (%) (n = 4302)	Prevalence of LAA (%)
Researchers	3236	57.9	57.2	23.3
Experimental assistants	1100	21.2	19.0	25.1*
Animal husbandry	1130	20.8	19.8	24.0
Personnel carrying out cleaning and washing	380	5.6	7.1	19.2

*Significantly different from cleaning and washing personnel ($p < 0.05$).

†Some subjects had two or more job categories.

(table 7). Also, the frequency of history in the daily exposure group (56.5%) was significantly lower than in the non-daily exposure group (62.9%; $p < 0.05$). Similar differences were also found for family history.

The prevalence of LAA rose as the number of handled species increased from one to five (table 8).

To estimate the correlation between symptoms and animal species, we examined the differences in the proportion of LAA subjects citing each species as a percentage of LAA subjects who actually handled the species (fig 4). Rabbits were cited by 60.5% of the LAA subjects with nasal symptoms who handled them and by 51.9% of those with respiratory symptoms who handled them. Figure 4 shows equivalent data for other animal species.

Figure 5 shows the distribution of latency of symptoms by different animal species (data on eye symptoms not shown). Information on the latent period was obtained from LAA subjects who knew the animal species relevant to their symptoms. No significant difference was found in the mean latent periods between individual species for any symptoms. The proportion of LAA subjects who developed symptoms during the year of first exposure to the species was the highest in those citing rabbits for all symptoms.

Discussion

The present study was the first large scale survey of the prevalence of LAA in Japan. Prevalence was 23.1% and corresponds to the range reported in the United Kingdom and the United States.^{1-8 12 13} This

prevalence, however, may be underestimated. People who had developed LAA had significantly shorter duration of exposure than the non-LAA group (fig 2). This is evidence that some animal handlers who had become aware of their LAA symptoms had removed themselves from exposure. Of those who did not participate in our survey some apparently did not submit a questionnaire because of concern about admitting to having LAA symptoms.

Of course, questionnaires have a number of limitations and in this case the questionnaire was administered to the subjects without medical interview or immunological investigations. Therefore, primarily irritant symptoms may be, in part, included in LAA symptoms in this survey.

On this point, after the present survey, Hanada (one of the members of our project group on the LAA study)¹⁴ showed findings that partly supported the reliability of our questionnaire survey. He carried out skin tests to guinea pig extracts in 38 subjects who had been listed as guinea pig handlers according to the questionnaire survey and included five LAA subjects citing guinea pig. All five LAA subjects reacted to urine, saliva, and epithelium and four reacted to serum. Twelve per cent of 33 subjects without LAA symptoms reacted to urine. These findings suggest that the specificity of our questionnaire survey was good, at least for the guinea pig.

We found that the most common LAA symptom was rhinitis. Only 12.9% of the subjects with respiratory symptoms did not have rhinitis. These findings indicate that the development of respiratory symptoms is likely to follow that of nasal or eye symptoms and further suggests that allergens from animals sensitise mostly by way of the respiratory tract.

Concerning the latent period of LAA, most LAA subjects (70%) developed symptoms during their

Table 6 Job content in LAA and non-LAA subjects

Job content†	LAA subjects (n = 1304)	Non-LAA subjects (n = 4337)
Animal experimentation	82.4**	74.3
Breeding	48.0**	43.9
Quarantining	9.4*	7.4
Washing and sterilising	17.3	16.3
Cleaning rooms‡	10.5	9.9
Others	11.3	12.6

*Significantly different from non-LAA group ($p < 0.05$).

**Significantly different from non-LAA group ($p < 0.01$).

†Some subjects selected two or more job contents.

‡Rooms except animal rooms.

Table 7 Prevalence of LAA by frequency of animals handling

Frequency of exposure	No of subjects	Prevalence of LAA
Non-daily	2852	19.5
Daily	2789	26.9**

**Significant at $p < 0.01$.

Table 8 Number of animal species handled in LAA and non-LAA subjects

No of animal species handled	LAA subjects (%) (n = 1304)	Non-LAA subjects (%) (n = 4302)	Prevalence of LAA (%)
1**	25.9	37.3	17.8
2	24.1	25.9	22.5
3**	17.6	13.3	29.3
4**	12.6	9.7	29.0
5**	9.1	5.3	35.2
6	5.6	3.9	31.2
7	2.5	2.7	22.7
8	2.6	2.0	29.0

**Significantly different between both groups by numbers of species handled ($p < 0.01$).

first three years of exposure; this confirms the findings reported by other investigators,^{5,6} and suggests that persons who do not become allergic to laboratory animals during three years are unlikely to develop LAA after this. Possibly it also supports the suggestion that short periods of high exposure are more important than the equivalent dose accumulated by lower exposure over a longer time.¹⁵

Preventing the ingress of animal allergens would be a primary preventive measure. In the present survey, the number of LAA subjects who reported the availability of protective equipment for LAA symptoms was less than half of those with nasal or respiratory symptoms. These findings suggest that personal protective equipment is unlikely ever to prevent completely the manifestation of LAA. Other methods to decrease allergens in the air are required. Recently, our co-workers have developed a one way airflow type ventilation system.¹⁶ This system draws air contaminated with allergens from the work area to the back of the racks and cages and thus away from human contact. They showed that this system could suppress the diffusion of airborne allergens toward

the work area of animal rooms and reduced symptoms in those with LAA.

The relation between the development of LAA and atopy has been studied by several researchers. Asthma resulting from LAA has been reported to associate with atopy as defined by skin tests with common antigens.^{4-8, 17, 18} In the present study, a significant correlation between the development of LAA and atopy, defined by personal history or family history of allergy, was found. The finding that atopic persons are more likely to have LAA symptoms than non-atopic persons supports the findings of some other authors.^{5, 11-13}

In studying the relation between the development of LAA and the density of exposure, several researchers^{2, 5, 11} have failed to find a correlation and have suggested the operation of self selection bias as the reason for the failure. In their work, the density of exposure has been based on job category. In the present study, the prevalence of LAA in the staff responsible for cleaning and washing was significantly lower than that in experimental assistants. Most of them appeared to be indirectly or more lightly exposed to animals. No significant association between job categories and the development of LAA was found, however. It seems that job categories are not well enough categorised in Japan to find any effect, especially in medical schools. We tried to use the actual content of work as an index of the density of exposure and found a significant correlation between the development of LAA and some jobs. Animal experimentation, breeding, and quarantining, we assumed to have relatively heavy exposure. Even so no differences could be found for the prevalence of LAA between these job categories.

Taking the frequency of handling (days a week) as another index of the density of exposure, we found a significant correlation between the development of LAA and the density of exposure. The finding that the prevalence of LAA in daily exposed subjects was significantly higher than in the non-daily exposed we suggest is strong evidence of a dose-effect relation. On the other hand, for LAA subjects, the frequency of atopy in the non-daily exposure group was significantly higher than in the daily exposure group. This finding is probably evidence of self selection. A significant relation between the development of LAA and the number of animal species handled was also found. Handling a larger number of species may result in an increase in "dose" and may also increase the chance to meet animal species to which the handler is likely to become allergic.

Previous studies of LAA^{2, 4, 19} have shown that rats and mice were the main causal species. In the present study, most subjects handled two or more species and mice and rats are widely used in facilities in Japan, but the prevalence of LAA indicated that guinea pigs and rabbits were also important causal species.

Figure 4 Relations between LAA symptoms and causal species.

Figure 5 Distribution of latency by different species.

We considered that it would be profitable for the prevention of LAA to know the detailed symptoms caused by different species and the allergenicity of those species. Comparing the proportion of LAA subjects citing each species as a percentage of those who actually handled the species we estimated the relation between symptoms and species. We consider that characteristic relations between symptoms and species can be seen (fig 5). Associations between exposure to rabbits and nasal symptoms and between exposure to rats and skin symptoms have been shown in previous reports.^{20,21} Their relations may reflect the nature of antigens and exposure forms in different species.

The proportion of LAA subjects who developed symptoms during the year of the first exposure to a species was highest in those citing rabbits for all symptoms. These findings may imply a higher concentration of airborne allergens²² or the high allergenicity of allergens derived from rabbits, although primary irritancy cannot be excluded.

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