RBSO Revista Brasileira de Saúde Ocupacional
ISSN: 2317-6369 (online)
http://dx.doi.org/10.1590/2317-6369000036718

Assorted Topics/
Short Communication

Prolonged exposure to laboratory animals is associated with increasing asthma cases

Exposição prolongada a animais de laboratório está associada ao aumento de casos de asma

Christian S. Simoneti[a]
https://orcid.org/0000-0001-6140-1981

Tiago S. B. Nocera[a]
https://orcid.org/0000-0003-1928-1634

Elcio O. Vianna[a]
https://orcid.org/0000-0003-1902-6326

[a] Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Clínica Médica. Ribeirão Preto, SP, Brasil.

Contato:
Elcio O. Vianna
E-mail:
evianna@fmrp.usp.br

The authors declare no conflict of interests.

This study was funded by Fapesp Process 2010/50212-6. Tiago Nocera received scientific scholarship from PIBIC-USP, and Elcio Vianna received productivity scholarship from CNPq 311851/2018-5 during the development of this study.

The authors declare that this study was not presented at scientific events and that it was not based on dissertation or thesis.

Abstract

Objective: to describe the follow-up evaluation of sensitized workers who prolonged their occupational exposure to laboratory animals. *Methods:* after a follow-up period of approximately 7 years, we contacted all individuals with occupational allergic sensitization detected in a previous study. A questionnaire was employed to assess present occupational status, relationship between allergy and decision on quitting job or exposure, and to assess asthma, wheezing, rhinitis, skin symptoms, and nocturnal dyspnea. *Results:* of the 74 individuals with occupational sensitization, 45 volunteers completed the questionnaire at the second evaluation and 37 were still exposed. By comparing the data from the first evaluation with data from the current evaluation, we observed an increase in asthma frequency. In the first evaluation, among all sensitized subjects (n=74), 27.0% answered yes to both questions "*Do you have or have you ever had asthma?*" and "*Was the asthma diagnosed by a doctor?*" In the second evaluation, 7 years later, among the 37 subjects who were still exposed, 51.3% answered yes to these questions (OR: 2.80; 95%CI: 1.23-6.38; p=0.013). There was no change in the frequency of positive responses to the other questions. *Conclusion:* data demonstrate increasing frequency of asthma among workers with occupational sensitization who prolong exposure to laboratory animal.

Keywords: asthma; diagnosis; occupational allergies; work; occupational health.

Resumo

Objetivo*: descrever o resultado do acompanhamento de trabalhadores sensibilizados a animais de laboratório que prolongaram sua exposição.* Métodos*: após um período de aproximadamente 7 anos, entramos em contato com todos os indivíduos com sensibilização alérgica ocupacional detectada em estudo anterior. Um questionário foi aplicado para situação ocupacional atual, relação entre alergia e a decisão de deixar o trabalho ou exposição e para asma, sibilância, rinite, sintomas cutâneos e dispneia noturna.* Resultados*: dos 74 indivíduos com sensibilização ocupacional, 45 responderam ao questionário na segunda avaliação e 37 ainda estavam expostos. Ao comparar os dados da primeira avaliação com os da avaliação atual, observou-se um aumento na frequência de asma. Na primeira avaliação, entre todos os sensibilizados (n = 74), 27,0% responderam sim a ambas as questões* "Você tem ou já teve asma?" *e* "A asma foi diagnosticada por um médico?"*. Na segunda avaliação, 7 anos depois, dos 37 sujeitos que ainda estavam expostos, 51,3% responderam sim a essas questões (OR: 2,80; IC95%: 1,23-6,38; p = 0,013). Não houve mudança na frequência de respostas positivas às outras perguntas.* Conclusão*: os dados demonstram aumento da frequência de asma entre trabalhadores com sensibilização ocupacional que prolongam a exposição a animais de laboratório.*

Palavras-chave: asma; diagnóstico; alergias ocupacionais; trabalho; saúde do trabalhador.

Recebido: Oct 24, 2018
Revisado: May 05, 2019
Aprovado: May 06, 2019

Introduction

Workers exposed to laboratory animals frequently develop allergic symptoms, a condition known as laboratory animal allergy (LAA)[1], characterized by urticaria, conjunctivitis, rhinitis and asthma[2]. Prevalence of LAA may range from 11 to 44%, wherein this large variation in prevalence is due to the different criteria for defining LAA, with definitions based on reports of symptoms or laboratory tests[3,4]. In any case, LAA is a significant occupational health problem[5].

LAA is caused by an immunological hypersensitivity reaction to high-molecular-weight antigens that are present in laboratory animals' urine, dander and saliva[6]. The major antigens eliminated by rats capable of generating allergic reactions are Rat n 1A and Rat n 1B, which are variant antigens of alpha 2 globulins; and, the major mouse antigen is a pre-albumin called Mus m1[7]. Both Rat n1 and Mus m1 are produced in the liver, under control of androgenic hormones. Rat n1 is released in larger amounts by adult male rats. Similarly, adult male mice release up to 4 times more Mus m1 allergen than female mouse[8].

In the workplace, contact with antigens eliminated by these animals occurs during routine activities such as contact with body fluids during cleaning cages, animal feeding, and transportation, collecting tissues, surgery, inoculation and sacrifices. In addition, these antigens can be found suspended in the air or deposited on any surface[9]. All these characteristics make animal rooms and research laboratories work environments that lead to the development of allergic reactions to laboratory animals[10,11].

Allergic sensitization to laboratory animals is associated with an increased risk of skin symptoms, nocturnal dyspnea, rhinitis, wheezing, bronchial hyperresponsiveness and asthma, compared to allergic sensitization to common allergens[12]. Occupational sensitization, as an important risk factor for LAA, draws much attention, since the prevalence of sensitization to laboratory animals ranges from 16 to 25%[13,14].

Many of the individuals who become sensitized to laboratory animals prolong their exposure to animals due to a need to maintain employment or to complete their research activities.

In a previous evaluation (2010-2012), we described the prevalence of laboratory animal sensitization. For this article, we re-evaluated subjects who were found to be sensitized. The aim of this follow-up study was to assess and report the risk for allergic symptoms associated with prolonged exposure. We also aimed to describe how the previous allergic animal sensitization affected the subjects' decision to quit laboratory animal exposure.

Methods

This is a prospective study evaluating technicians, students and researchers working in animal laboratories. For the first evaluation carried out from 2010 to 2012, 453 subjects were enrolled. One hundred and fifty-two were employees and 301 students of two Brazilian universities, University of São Paulo (USP) in Ribeirão Preto and State University of Campinas (Unicamp) in Campinas.

Among these 453 subjects, 74 volunteers (16.3%) were found to be sensitized to at least one laboratory animal[12]. Sensitization was defined by positive skin prick test to one or more of the following allergens: rat, mouse, rabbit, hamster, or guinea pig.

For this analysis all 74 individuals with animal sensitization were contacted by phone, email, social network and by search in the workplace. A questionnaire was employed to assess evolution, present occupational status, relationship between allergy and decisions on quitting or not that job or exposure.

To assess symptoms, we used questions from the European Community Respiratory Health Survey questionnaire, a self-applicable questionnaire translated into Portuguese, adapted to the Brazilian lexicon, and validated[15]. The study and consent form were reviewed and approved by the Ethics Committee of the Medical School of Ribeirão Preto, USP-RP (protocol number 4674/2015). An informed consent form was obtained from all subjects after reading and discussing the protocol individually. Volunteers had a good cultural background and were able to understand the informed consent form concerning the risks of occupational exposure to laboratory animals.

Statistical analysis

Univariate analysis (Chi-squared test) was performed to compare frequency of outcomes between the first and second evaluations.

Results

Of the 74 individuals with occupational sensitization, 45 volunteers completed the questionnaire, 37 of them were still exposed to laboratory animals up to the date of this study. We lost follow-up data of 29 subjects because 10 refused to answer our questionnaire, even in its reduced format, which was designed for non-compliers, and 19 were not found. The mean follow-up period was 7 years (5.0 – 7.5 years). When comparing the data from both rounds, an increase in asthma frequency was observed, from 27.0% to 51.3% (OR: 2.80; 95%CI: 1.23-6.38; p=0.013), with 7 new cases of asthma. There was no change in the frequency of wheezing, rhinitis, skin symptoms and nocturnal dyspnea (**Table 1**).

Table 1 Comparison of the frequency of outcomes

Outcomes	*2nd versus 1st evaluation*	*OR*	*95%CI*		*p*
Asthma	51.3% vs 27.0%	2.80	1.23	6.38	0.013
Wheezing	40.5% vs 45.9%	0.74	0.33	1.68	0.467
Rhinitis	86.4% vs 90.5%	0.72	0.19	2.72	0.623
Nocturnal dyspnea	37.8% vs 24.3%	1.86	0.79	4.36	0.150
Skin symptoms	48.6% vs 51.3%	0.95	0.42	2.13	0.896

OR: odds ratio; CI: confidence interval; 1st evaluation n = 74; 2nd evaluation n = 37.

To check if the 45 subjects were representative of the whole group, comparisons were carried out regarding characteristics that were different from the outcome variables. The results showed that sex, age, institution (USP x Unicamp) and type of affiliation (researchers, students, or technicians) were not different when comparing the current study group with the previous study group. A similar comparison was made between the 37 subjects who were still exposed and the whole group of 74 subjects, and no difference was detected.

Among the 37 subjects with prolonged exposure, 3 reported willing to give up being exposed to laboratory animals because of the clinical information provided during the first analysis. Regarding the results of the bronchial responsiveness assessments performed during the first evaluation, 16 cases out of these 37 subjects with prolonged exposure had been positive. We have not detected a clear or consistent outcome associated with a positive test. Among those 3 subjects willing to stop being exposed, one had positive bronchial challenge test, i.e., bronchial hyperresponsiveness.

Among those 8 subjects who quit their animal-related activities, two had bronchial hyperresponsiveness, but reported that reasons to quit were not associated to these findings, symptoms or other tests results. All subjects had normal spirometry, and therefore normal FEV1.

Among the 7 new cases of asthma, 6 individuals did not present bronchial hyperresponsiveness during the first evaluation and developed asthma throughout the follow-up, and 2 cases with bronchial hyperresponsiveness in the first evaluation were not considered asthmatic at that time because they had no symptoms.

Discussion

The prevalence of asthma in this study is very high. Among adult Brazilians, the prevalence of medical diagnosis of asthma is 7.0%[16]. In a study published in 2017, where we analyzed the prevalence of outcomes among individuals with common sensitization and occupational sensitization, we showed that prevalence of asthma among individuals with common sensitization was 9.8%, and the prevalence of asthma in the occupational sensitization group was 27.0%[12]. Now, in the current evaluation of the individuals with occupational sensitization, the prevalence of medical diagnosis of asthma was 51.3%, more than 7 times the general prevalence of asthma among adults.

Previous studies[17,18] have already presented the deleterious effects of continued exposure to the occupational allergen to which the individual is sensitized. Palmberg et al[17] observed that in the 12th month of exposure, individuals who became sensitized to laboratory animals reported more nasal and ophthalmologic symptoms compared with non-sensitized individuals. In addition, those authors[17] observed in the 24th month of exposure that individuals with animal sensitization presented lower FEV1 compared to non-sensitized individuals. Portengen et al.[18] investigated the relation between sensitization and changes in lung function in sensitized and non-sensitized laboratory animal workers. According to multiple regression analysis, sensitization was associated with excess declines in FEV_1 of 83 ml/year ($p<0.05$), in FVC of 148 ml/year ($p<0.01$), and in FEF25-75% of 7 ml/s/year ($p=0.9$) in laboratory animal workers who were sensitized and continually exposed compared to continually exposed, but non-sensitized workers. The authors did not describe spirometric values or reductions per group.

With respect to bronchial reactivity, Renstron et al.[19] showed that at the end of the follow-up period (median of 18 months), there was a difference in reactivity among workers with occupational sensitization, where the mean methacholine dose for a 20% drop in FEV_1 was 0.30, whereas in the non-sensitized group the mean methacholine dose required for a 20% drop in FEV_1 was 1.97.

The data published in previous studies corroborate our findings of the present study, where prolonged exposure to the sensitizing agent

poses a risk to workers' health, i.e., development of symptoms, changes in lung function and increased bronchial reactivity. This study adds data on the increase in the number of asthmatics, even though a limited number of individuals participated in the second round. Interestingly, we only see an increase in cases of asthma, which is the most severe outcome resulting from exposure to laboratory animals. This fact leads us to believe that asthma is a final route of allergic reactions caused by exposure to laboratory animals.

One issue that draws attention in the present analysis is the apparent lack of importance given by the volunteers to occupational sensitization. In the first phase (7 years ago), each result obtained by these studies was forwarded to the volunteers individually in a written report, and quickly sent. Moreover, a summary of the results was sent to the board of directors of every facility without subjects' identification. This study served to raise awareness of allergy risks in each institution. Positive cases for any diagnosis (rhinitis and/or asthma) and sensitization were referred for outpatient care at the respective university hospital.

Of the 8 volunteers who gave up being exposed to laboratory animals, none did it due to occupational sensitization, and among the 37 volunteers who continued being exposed, only 3 thought to leave the exposure due to occupational sensitization. This characteristic is perhaps due to the lack of knowledge of these individuals concerning allergies to laboratory animals. This could be evidenced in the first evaluation of the study before clinical diagnoses, when only 25.1% of workers exposed to laboratory animals reported receiving verbal guidance or having read anything about the risks of animal exposure inducing allergic reactions[13]. All subjects received the results of the first evaluation, including the information on positive skin prick test to animal allergens.

Providing information and training for safe practices regarding exposure to laboratory animals is of utmost importance, as shown by Larese et al.[14] after a prevention program where some of its elements consisting in education and training, in establishing good working practices to reduce exposure to laboratory animals, use of respiratory protection equipment, SPT with occupational allergens and medical evaluation. After these practices there was a reduction in the prevalence of sensitization to laboratory animals, from 25.6% between 2001 and 2004 to 8.2% between 2013 and 2016[14].

In conclusion, data from this study show the risks of prolonged exposure to laboratory animals. We believe that this group of workers should be submitted to SPT with occupational allergens periodically. In case of occupational sensitization, workers should be warned about the risk of remaining exposed to animals. In addition, we believe that prevention programs would be very useful as they could highlight the risks of exposure to laboratory animals and reduce the frequency of sensitization to laboratory animals.

Authors' contributions

The authors contributed equally to the study design, data analyses and interpretation, and manuscript drafting. All authors critically reviewed the final version and take full responsibility for the study and this article.

References

1. Wolfle TL, Bush RK. The science and pervasiveness of laboratory animal allergy. ILAR J. 2001;42(1):1-3.
2. Hunskaar S, Fosse RT. Allergy to laboratory mice and rats: a review of the pathophysiology, epidemiology and clinical aspects. Lab Anim. 1990;24(4):358-74.
3. Acton D, McCauley L. Laboratory animal allergy: an occupational hazard. AAOHN J. 2007;55(6):241-4.
4. Bush RK, Stave GM. Laboratory animal allergy: an update. ILAR J. 2003;44(1):28-51.
5. Jeal H, Jones M. Allergy to rodents: an update. Clin Exp Allergy. 2010;40(11):1593-601.
6. Corradi M, Ferdenzi E, Mutti A. The characteristics, treatment and prevention of laboratory animal allergy. Lab Anim. 2012;42(1):26-33.
7. Wood RA. Laboratory animal allergens. ILAR J. 2001;42(1):12-6.
8. Jones M. Laboratory animal allergy in the modern era. Curr Allergy Asthma Rep. 2015;15(12):73.
9. Harries MG, Cromwell O. Occupational asthma caused by allergy to pigs' urine. Br Med J. 1982;284(6319):867.
10. Bush RK, Wood RA, Eggleston PA. Laboratory animal allergy. J Allergy Clin Immunol. 1998;102(1):99-112.

11. Taylor AN, Longbottom JL, Pepys J. Respiratory allergy to urine proteins of rats and mice. Lancet. 1977;2(8043):847-9.

12. Simoneti CS, Ferraz E, Menezes MB, Bagatin E, Arruda LK, Vianna EO. Allergic sensitization to laboratory animals is more associated with asthma, rhinitis, and skin symptoms than sensitization to common allergens. Clin Exp Allergy. 2017;47(11):1436-44.

13. Ferraz E, Arruda LKP, Bagatin E, Martinez EZ, Cetlin AA, Simoneti CS, et al. Laboratory animals and respiratory allergies: the prevalence of allergies among laboratory animal workers and the need for prophylaxis. Clinics. 2013;68(6)750-9.

14. Larese FF, Drusian A, Mauro M, Negro C. Laboratory animal allergy reduction from 2001 to 2016: an intervention study. Respir Med. 2018;136:71-6.

15. Ribeiro M, Angelini L, Robles-Ribeiro PG, Stelmach R, Santos UP, Terra-Filho M. Validation of the Brazilian-Portuguese version of the European Community Respiratory Health Survey in asthma patients. J Asthma. 2007;44(5):371-5.

16. Vianna EO, García CA, Bettiol H, Barbieri MA, Rona RJ. Asthma definitions, relative validity and impact on known risk factors in young Brazilians. Allergy. 2007;62(10):1146-51.

17. Palmberg L, Sundblad B, Lindberg A, Kupczyk M, Sahlander K, Larsson K. Long term effect and allergic sensitization in newly employed workers in laboratory animal facilities. Respir Med. 2015;109(9):1164-73.

18. Portengen L, Hollander A, Doekes G, Meer G, Heederik D. Lung function decline in laboratory animal workers: the role of sensitization and exposure. Occup Environ Med. 2003;60(11):870-5.

19. Renstrom A, Malmberg P, Larsson K, Larsson PH, Sundblad BM. Allergic sensitization is associated with increased bronchial responsiveness: a prospective study of allergy to laboratory animals. Eur Respir J. 1995;8(9):1514-9.