Current perspectives

Allergy to furry animals: New insights, diagnostic approaches, and challenges

Jon R. Konradsen, MD, PhD,[a,b,c] Takao Fujisawa, MD, PhD,[d] Marianne van Hage, MD, PhD,[e] Gunilla Hedlin, MD, PhD,[a,b,c] Christiane Hilger, PhD,[f] Jörg Kleine-Tebbe, MD,[g] Elizabeth C. Matsui, MD, MHS,[h] Graham Roberts, DM, MRCPCH,[i,j,k] Eva Rönmark, PhD,[l] and Tom Platts-Mills, MD, PhD[m] *Stockholm, Sweden, Mie, Japan, Luxembourg, Luxembourg, Berlin, Germany, Baltimore, Md, Isle of Wight and Southampton, United Kingdom, Umeå, Sweden, and Charlottesville, Va*

The prevalence of allergy to furry animals has been increasing, and allergy to cats, dogs, or both is considered a major risk factor for the development of asthma and rhinitis. An important step forward in the diagnosis of allergy to furry animals has been made with the introduction of molecular-based allergy diagnostics. A workshop on furry animals was convened to provide an up-to-date assessment of our understanding of (1) the exposure and immune response to the major mammalian allergens, (2) the relationship of these responses (particularly those to specific proteins or components) to symptoms, and (3) the relevance of these specific antibody responses to current or future investigation of patients presenting with allergic diseases. In this review research results discussed at the workshop are presented, including the effect of concomitant exposures from other allergens or microorganisms, the significance of the community prevalence of furry animals, molecular-based allergy diagnostics, and a detailed discussion of cat and dog components. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

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Allergy to furry animals, cats and dogs in particular, has been recognized for many years and is considered to be a major risk factor for the development of asthma and rhinitis.[1] The prevalence of allergy to furry animals[2] and the prevalence of allergic airway disease[3] have been increasing. Exposure to allergens from these animals is ubiquitous, and the clinician should evaluate all patients with allergic airway disease for sensitization to animal dander.[4] Allergic sensitization to several mammalian animals is prevalent, which might reflect cosensitization or cross-reactivity.[5] In some countries sensitization to furry animals is associated with more severe allergic disease,[6] which poses extended diagnostic and therapeutic challenges.

An important step forward in the diagnosis of allergy to furry animals has been made with the introduction of molecular-based allergy diagnostics,[7,8] which offer new opportunities for improved characterization. One example of novel insights gained by this approach is the differentiation of reactions to meat from patients with pork-cat syndrome.[9-11] Patients with this syndrome sensitized to albumins from animal dander report symptoms after the consumption of pork because of the cross-reactivity of albumins from different species.

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DEFINITIONS

Allergic sensitization was defined as the presence of specific IgE antibodies to an allergen. *Allergy* was defined as the occurrence of reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by nonallergic persons and mediated by specific immunologic mechanisms (antibody or cell mediated). A *component* was defined as a molecule (ie, protein or glycoprotein) derived from a given allergen source that is identified by IgE antibodies. *Cross-reactivity* was defined

From [a]the Department of Women's and Children's Health and [b]the Centre for Allergy Research, Karolinska Institutet; [c]Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm; [d]the Institute for Clinical Research, Mie National Hospital; [e]the Clinical Immunology and Allergy Unit, Department of Medicine, Karolinska Institutet and University Hospital, Stockholm; [f]the Laboratory of Immunogenetics and Allergology, CRP-Santé, Luxembourg; [g]the Allergy & Asthma Center Westend, Outpatient Clinic and Research Unit, Berlin; [h]the Division of Pediatric Allergy/Immunology, Johns Hopkins School of Medicine, Baltimore; [i]the David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight; [j]Human Development and Health and Clinical and Experimental Sciences Academic Units, University of Southampton Faculty of Medicine, Southampton; [k]the NIHR Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton; [l]the Department of Public Health and Clinical Medicine, Occupational and Environmental Medicine, Umeå University; [m]the Asthma and Allergic Diseases Center, University of Virginia, Charlottesville.

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Corresponding author: Jon R. Konradsen, MD, PhD, Astrid Lindgren Children's Hospital, q2:04, Karolinska University Hospital, SE-17176 Stockholm, Sweden. E-mail: jon.konradsen@karolinska.se.

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Abbreviation used
Alpha-gal: Galactose-α-1,3-galactose

as the process of IgE antibodies originally developed against a given allergen binding homologous molecules originating from a different allergen source.

ALLERGEN SOURCES

Given that most persons in Western societies spend more than 90% of their lives in indoor environments, it is not surprising that indoor allergens play an important role in allergic sensitization and symptoms. In addition to residential environments, exposure to furry animal allergens can occur in schools and occupational and/or leisure environments (eg, animal facilities, stables, pet shops, and farms). The allergen quantities derived from these sources might be clinically significant at the site where the animal is kept or at another site because of passive transfer (Table I). The primary source of cat and dog allergens is thought to be dander coming off the skin,[4,12] whereas for mice and rats, urine is thought to be a more important source.[13,14]

CAT ALLERGEN EXPOSURE AND ALLERGIC SENSITIZATION

For many years, it was assumed that living in a house with a cat increased the risk of allergy. However, in 1999, Hesselmar et al[15] reported that children who lived in a house with a cat were less likely to be sensitized to cat allergens. This observation has had a major effect and has been confirmed in many, but certainly not all, subsequent studies.[1,16-19] A systematic review of recently published articles from birth cohorts and cross-sectional and case-control studies of the association between cat exposure and allergic diseases suggests that early-life cat exposure is likely to protect against allergic disease.[20] A recent meta-analysis of pooled results from 11 prospective European birth cohorts concluded that there is no clear evidence for a protective or "harmful" effect of cat ownership on sensitization to animal dander.[21] These reviews confirm 2 observations: that the very high levels of cat allergens present in a house with a cat do not increase the risk of sensitization and that a large proportion of subjects who become sensitized to cat allergens do not live in a house with a cat. Furthermore, in the review of birth cohorts, the results were similar among children of parents without allergies compared with those among children of parents with allergies, indicating that selection bias did not have a major effect on the results of these studies. However, the issue of selection bias could be more complex; families with the most severe allergy could avoid owning pets, whereas families with mild allergy could be more highly represented among those who have cats at home. If this is the case, the apparent protective effect of cat ownership could be explained in part by the fact that the families with the most severe allergic constitution do not have pets at home.

CLINICAL EFFECTS OF ALLERGEN EXPOSURE IN THE SENSITIZED SUBJECT

Several studies have found a strong relationship between allergen exposure in sensitized subjects and allergic airway disease.[22] For instance, cat-sensitized children exposed to cat allergen have increased bronchial hyperreactivity compared with nonexposed children.[23] The lung function of dog-sensitized 3-year-old children who are exposed to dog allergens is reduced compared with that of sensitized children without exposure and exposed children without sensitization.[24] Sensitization to furry animals has been associated with increased bronchial hyperresponsiveness in adolescents.[25] In a population-based study IgE antibodies to 103 allergen molecules were assessed by microarray, and subjects with IgE antibodies to allergen components from furry animals had increased asthma prevalence, higher fraction of exhaled nitric oxide levels, and increased bronchial hyperresponsiveness.[26] Furthermore, a follow-up of children with asthma clearly showed that the probability of remission from age 7 years to age 19 years was significantly reduced if the child had been sensitized to furry animals at age 7 years.[27] In addition, exposure to allergens from small furry animals, such as hamsters or mice, has also been associated with symptoms of asthma in sensitized subjects.[28,29]

FREQUENCIES OF ALLERGIC SENSITIZATION

In the United States and Europe the prevalence of sensitization to furry animals has increased over the past decades.[2,30,31] Age- and sex-adjusted data from a pan-European study published in 2009 found that 26% and 27% of adults were sensitized to cats and dogs (by using skin prick tests), respectively,[32] which could be compared with data from 1992 showing that the frequency of sensitization to cat (by using skin prick tests) was 8.8%.[33] In the United States the frequencies of cat and dog sensitization in subjects aged 6 years and older are 12.1% and 11.8%, respectively.[34] A population-based study from Germany (n = 17,641; age, 3-17 years) reported sensitization to dogs of 11.6% and 7.6% and to cats of 9.6% and 6.6% in boys and girls, respectively.[35] The prevalence of sensitization is modified by the age of the subject, with increasing prevalence throughout childhood[36-38] culminating in peak prevalence during adolescence.[39] However, it should be emphasized that estimates of the prevalence of sensitization are based on skin tests or *in vitro* assays with extracts. If the extract's constituents or the strength of the extract changes over time, this could lead to an apparent change in prevalence.

DETERMINANTS FOR ALLERGIC SENSITIZATION

A number of determinants for allergic sensitization to furry animals in the exposed subject have been identified, including factors not directly related to the pet. In particular, the genetic constitution of the exposed subject,[40,41] the environmental setting,[42,43] and other environmental exposures, including concomitant exposure to other allergen sources[1,44] and microorganisms,[45,46] have been shown to be important in this connection.[47-49] Additionally, several determinants directly related to the animal have proved to be of importance, such as the biological activity of the allergen[50] and the timing,[51,52] variability,[13] and intensity[16,53,54] of the allergen exposure. Of particular interest is that there seems to be a tolerance effect with increasing levels of exposure, which could be caused by a modification of the T_H2 response[16] or induced by concomitant exposures.