



Cat Allergy as a Source Intensification of Atopic Dermatitis in Adult Patients

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Abstract

Atopic dermatitis (AD) is characterized by exacerbations and remissions of eczematous skin, underlain by impaired skin barrier and aberrant Th2-type and Th-22 cytokine production. A number of allergens, in particular contact with fur animals, may aggravate the disease. This study seeks to define the influence of having a regular contact with a pet cat at

home on the severity of symptoms and signs of AD. We addressed the issue using the SCORing Atopic Dermatitis (SCORAD) and visual analog (VAS) scores to assess the intensity of pruritus and by measuring the blood content of specific IgE and IL-4, IL-13, and IL-22 cytokines. The study group consisted of 47 adult patients suffering from AD since childhood, 18 of whom declared having regular contact with a cat and the remaining 29 who denied it. There also was a control group consisted of 16 healthy volunteers with no AD signs. The SCORAD and VAS scores were significantly higher in patients in contact with a cat than in those without it (median SCORAD 61.0 vs. 50.4 and VAS 9.0 vs. 4.0 points, respectively). The sIgE of a majority of patients (94.4%) in contact with a cat was in Class V–VI, compared with just a few patients (3.4%) with no such contact, having sIgE in the same classes ($p < 0.001$). Significant correlations were revealed between SCORAD and VAS scores and the class level of serum sIgE value. In addition, IL-22 was a single elevated cytokine, only in the patients in contact with a cat, and it correlated with pruritus severity. The results of the study underline the need to beware of the cat fur allergen, and they stress forethought and caution in acquiring and keeping a pet cat by patients suffering from AD.

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Keywords

Allergy · Animal fur allergen · Atopic dermatitis · Inflammation · Interleukins · Pet cat · Skin pruritus

1 Introduction

Atopic dermatitis (AD) is a chronic inflammatory dermatosis characterized by inefficiency of the skin barrier, immunological disturbance, and dysbiosis of the saprophytic microbial flora at skin surface (Gavrilova 2018; Jaworek and Wojas-Pelc 2017). Clinically, the disorder manifests as intensive pruritus, an essential diagnostic element, which is accompanied by erythematous papules, bullae, and lichenous lesions. Skin lesions have a chronic and recurrent course, and their location depends on the patient's age. AD is considered as one of the most common skin disorders which affects about 20% of the population in the developed countries, with the number of patients in the developing countries continuously increasing as well (Weidinger and Novak 2016). According to the Polish Society of Allergology, there is approximately 1.5–2.5 million of patients with AD in Poland (Kruszewski 2012).

AD is a disease that has been known for hundreds of years, but it was distinguished as a separate medical condition not until the second half of the nineteenth century, with the pioneer works of Ernest Henri Besnier on infantile atopic dermatitis, reputed for the characterization of pruritus as the primary symptom of AD: “le premier symptome et le symptome premier” (Weyers 2013). AD, along with bronchial asthma, allergic rhinitis, conjunctivitis, and food allergy, belongs to a group of atopic disorders. Skin disease is often the first symptom of systemic atopy (Sampson et al. 2018; Weidinger and Novak 2016). Although AD is rather associated with the pediatric population as 60% of AD cases show up in the first year of life, the number of adult patients is on the rise, making the old notion of AD abating with the maturation process

outdated (Leung and Guttman-Yassky 2014). Among numerous AD phenotypes, a division into extrinsic (eAD) and intrinsic (iAD) or atopiform dermatitis is widely accepted. The pathogenesis of AD consists of genetic, epigenetic, environmental, and immunological interactions, with the overlapping defect of the epidermal barrier (Nowicki et al. 2015). Classification criteria consist of the level of specific IgE (sIgE) in relation to food and airborne allergens. In eAD, particularly, Th2 lymphocyte-dependent production of cytokines (interleukins IL-4, IL-5, IL-13, and IL-31), Th17 lymphocyte-dependent (IL-17), and Th22 lymphocyte-dependent (IL-22) are considered the predominant immunological reaction (Rożalski et al. 2016). In a chronic phase of AD, Th1 lymphocytes are also involved (IL-2, IL-12, and interferon-gamma) (Gavrilova 2018; Nomura et al. 2018; Werfel et al. 2016; Mirshafiey et al. 2015).

Among the factors leading to AD exacerbations, contact with the animal fur comes to the forefront, which has been confirmed by recent studies and formulated in the expert guidelines concerning the allergen exposure withdrawal (Oncham et al. 2018; Wollenberg et al. 2018). To this end, the pet cats seem to be the most frequent sensitizers and to a much greater extent than other animals. Therefore, this study seeks to define the influence of having a pet cat at home on the severity of AD symptoms. We addressed the issue using the SCORing Atopic Dermatitis (SCORAD) and visual analog (VAS) scales of pruritus severity in connection with the serum content cat sIgE. In addition, we measured the serum IL-4, IL-13, and IL-22 cytokines, modifiers of allergic inflammation.

2 Methods

2.1 Patients and Skin Lesion Assessment

The study group included 47 adult patients with AD (F/M 30/17, median age 35 years, range 19–74 years). There were 34 (72.3%) persons

Table 1 Structure of atopic dermatitis (AD) patient group ($n = 47$) and control group of healthy subjects ($n = 16$) with regard to contact with cat allergens

	Patient with AD		Control group
	Cat – yes	Cat – no	Cat – no
<i>n</i>	18	29	16

with mild/moderate and 13 (27.7%) persons severe AD. The control group consisted of 16 healthy volunteers (F/M 8/8, median age 29 years, range 24–67 years). Regular contact with a cat at home was defined as at least 5 days per week for 4 h a day. Structure of the study groups with regard to contact with cat allergens is shown in Table 1. In the AD group, 18 patients reported having regular contact. The remaining 29 patients denied it. The diagnosis of AD was based on the diagnostic criteria of Hanifin and Rajka (1980). The severity of skin lesions in AD was assessed using the SCORAD criteria as follows: mild <25 points, moderate AD 25–50 points, and severe >50 points (Oranje et al. 2007). Each patient carried out a self-assessment of pruritus on a VAS scale during the 24 h preceding the study as follows: no pruritus 0 points, mild pruritus 1–3 points, moderate pruritus 4–6 points, intense pruritus 7–8 points, and extremely intense pruritus 9–10 points (Schoch et al. 2017). Exclusion criteria were a lack of consent, age under 18 years, active unrelated inflammatory disorders, and a systemic anti-inflammatory therapy during the 12 months preceding the study. The patients reported the onset of skin lesions in the early childhood between the fourth month and first year of life.

2.2 Blood Biochemical Indices

Blood samples were taken from an ulnar venipuncture in a volume of 10 ml between 7:00 am and 9:00 am. They were left for 2 h at room temperature for a clot to form, centrifuged at 3,500 RPM for 10 min, and frozen at -80°C until use. Cat sIgE (e1) was measured using a UniCAP 100 fluoro-enzymatic immunoassay (FEIA) (ImmunoCAP-System; Phadia AB,

Sweden), according to manufacturer’s instructions. The IgE classes were stratified as follows: Class I 0.35–0.69 IU/ml, Class II 0.70–3.49 IU/ml, Class III 3.50–17.49 IU/ml, Class IV 17.50–49.90 IU/ml, Class V 50.00–100.00 IU/ml, and Class VI >100.00 IU/ml. The cytokines IL-4, IL-13, and IL-22 were measured using an ELISA assay (R&D System, Minneapolis, MN). The detection level was set at ≥ 0.35 IU/ml for IgE and > 0.35 pg/ml for both sIgE and cytokines.

2.3 Statistical Elaboration

Quantitative data were expressed as medians and interquartile ranges (IQR). Differences between two groups were evaluated with the Mann-Whitney U test. For more than two groups, the Kruskal-Wallis test, followed by multiple comparison post hoc tests, was used. The strength of a relationship between quantitative data was assessed with the Spearman rank correlation coefficient. Significance of differences was assumed at the level of $\alpha \geq 0.05$. The analysis was performed using a commercial Statistica v13 package (StatSoft; Tulsa, OK).

3 Results

SCORAD score was significantly higher in the 18 patients having regular contact with a cat than that in the patients with no such contact: median 61.0, min–max 37.4–80.4, and IQR 71.3–54.1 points vs. median 50.4, min–max 10.6–75.2, and IQR 61.4–24.4 points, respectively ($p = 0.003$) (Fig. 1). Likewise, median VAS score was 9, min–max 7–10, and IQR 10–8 in the patients having regular contact with a cat vs. median 4, min–max 2–8, and IQR 6–4 points in those with no such contact ($p < 0.001$) (Fig. 2).

3.1 Specific Blood IgE

The patients with severe AD were significantly more often categorized into higher sIgE classes

Fig. 1 Skin lesions severity in atopic dermatitis (AD) patients who declared contact with a cat (Yes) and those who did not (No), according to the SCORing Atopic Dermatitis (SCORAD) score

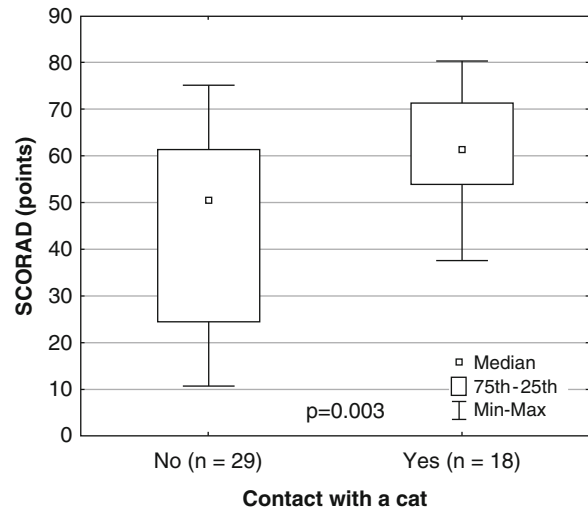
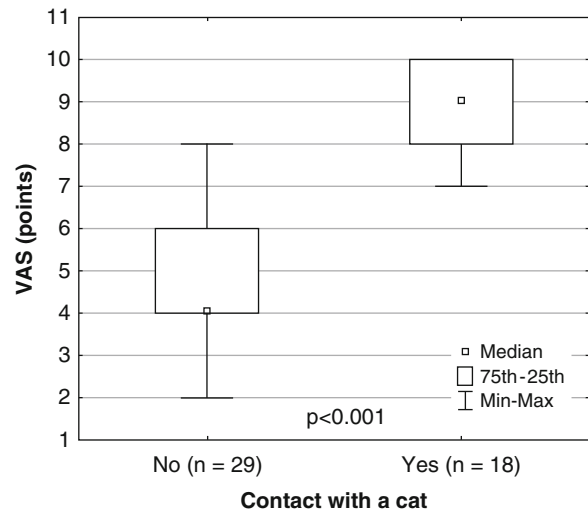


Fig. 2 Skin lesions severity in atopic dermatitis (AD) patients who declared contact with a cat (Yes) and those who did not (No), according to the visual-analog scale (VAS) score

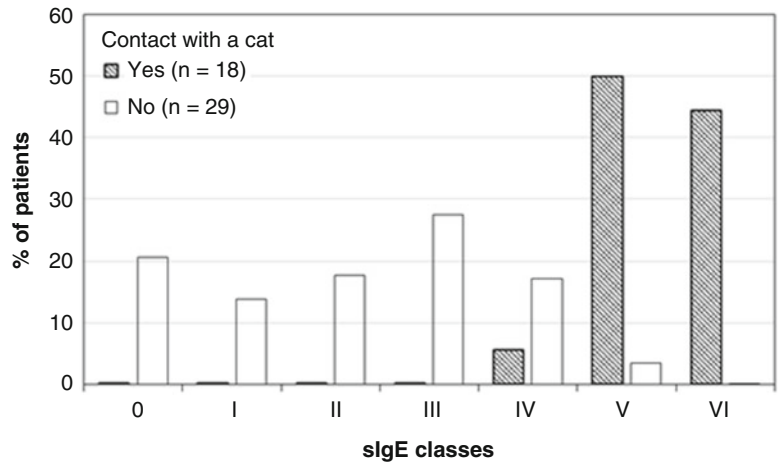


(67.7% had Class IV–VI) than the patients with mild/moderate AD (15.4% of patients had Class IV–VI) ($p < 0.001$). Among the patients who declared having regular contact with a cat (Yes), 94.4% had sIgE in the class level V–VI, which was a significantly more numerous group of patients than those without such contact (No) of whom 3.4% had sIgE in the same class level V–VI ($p < 0.001$) (Fig. 3). Further, significant correlations were revealed between pruritus

intensity in AD patients, assessed on both SCORAD and VAS scales, and sIgE class level ($\rho = 0.47, p = 0.003$ and $\rho = 0.89, p < 0.001$, respectively).

The control subjects were free of AD, had neither pruritic symptoms nor elevated blood sIgE levels, and thus were not included in the above presented elaboration of results concerning the AD patients who either declared or denied regular contact with a cat.

Fig. 3 Distribution of atopic dermatitis (AD) patients, who declared (Yes) or did not declare (No) contact with a cat, by sIgE classes



3.2 Blood IL-4, IL-13, and IL-22 Content

Concerning the cytokine content, IL-22 was the only one distinctly elevated in AD patients who declared regular contact with a cat. Its level was threefold greater than that in AD patients with a lack of such contact and about sixfold greater than that in the healthy subjects ($p < 0.001$). The content of IL-4 and IL-13 failed to differ appreciably among the three groups (Table 2). The analysis of a relationship between the intensity of skin lesions and IL-22 serum content across the three groups, i.e., severe AD in 34 patients vs. mild/moderate AD in 13 patients vs. healthy 16 subjects, shows that IL-22 was significantly higher in the severe AD (median 236.6 pg/ml, min–max 35.4–445.1 pg/ml) than that in mild/moderate AD (median 66.8 pg/ml, min–max 0–195.9 pg/ml), followed by that in healthy

subjects (median 48.3 pg/ml, min–max 0–80.4 pg/ml) ($p < 0.001$).

IL-22 was a single cytokine that correlated with pruritus severity assessed on both SCORAD ($\rho = 0.52$, $p < 0.001$) and VAS scales ($\rho = 0.60$, $p < 0.001$).

4 Discussion

The significance of allergens as factors exacerbating AD is commonly accepted (Gavrilova 2018; Weidinger and Novak 2016; Werfel et al. 2016; Langan and Williams 2006). Fur animals, particularly cats, are most frequent house pets all over the world, raising concern for their role in the development of allergy. A substantial increase in sIgE we noticed in this study is consistent with other reports on the subject matter (Rożalski et al. 2016; Dhar et al. 2005). Elevated sIgG content also predisposed to intense skin

Table 2 Cytokine blood content in AD patients with and without contact with a cat and in control healthy subjects (pg/ml)

	Patients with AD				Control group		<i>p</i>
	Cat – yes		Cat – no		Cat – no		
	Median	Min–max	Median	Min–max	Median	Min–max	
IL-4	5.0	2.6–7.6	5.1	1.3–11.3	4.5	0.1–10.5	0.430
IL-13	55.2	49.8–257.9	55.2	36.3–82.2	57.9	39.0–74.1	0.860
IL-22	299.9	0.0–445.1	98.7	0.0–320.2	48.3	0.0–80.4	<0.001

lesions. Laboratory indicators of cat allergy were present in 41 out of the 47 patients investigated and were associated with the severity of pruritus, assessed on VAS. However, our patients had mostly severe AD, which ruled out the execution of skin prick tests. These findings are in line with those obtained by Mittermann et al. (2016) who have found the cat's hair the most frequent antigen raising the allergic response in a population of 179 adult patients with moderate/severe AD. Allergic reactions are often manifest in the adult population in response to environmental exposures to house pets. Oncham et al. (2018) have reported positive results of skin prick tests for cat and dog in 13% and 10% out of the 49 adult AD patients, respectively. In a Hungarian study in 34 adult AD patients, skin prick and patch tests with cat allergens, and also cat sIgE in blood serum, were positive in some of the patients. Further, in four patients of that study, exacerbation of skin lesions occurred after exposure to cats (Pónyai et al. 2008). Likewise, Will et al. (2017) have reported an unusually high level of IgE in 41 out of the 54 patients, 10 of whom were allergic to cats, with 6 of the 10 with severe AD and with 4 of the 6 who used sleeping with their beloved pets. The authors recommended lifestyle changes, consisting of withdrawal of allergen exposure, which resulted in a significant health improvement in some of the patients.

An increase in the incidence of animal allergies is ubiquitous (Asher et al. 2006). Notably, AD patients, particularly of eAD type, are predisposed to develop hypersensitivity to environmental allergens (Nomura et al. 2018; Knaysi et al. 2017). The issue of whether early contact with an animal in childhood has a protective influence on the occurrence of allergic condition in adulthood still remains unanswered (Chan and Leung 2018). A particularly interesting study concerning this issue is reported by Bisgaard et al. (2008) who have shown an interaction between a defunct gene encoding filaggrin and the development of eczema during early childhood environmental exposure, which specifically concerns cat allergens. Hon et al. (2007) have investigated

119 children, confirming the presence of allergic responses to a cat in 40 (34%) of them, using skin prick tests. Of note, only did three children declare regular contact with the animal.

In this study we also investigated the blood level of the cytokines IL-4, IL-13, and IL-22. The interleukins IL-4 and IL-13 are produced by antigen- or mitogen-induced Th2 lymphocytes, NK cells, eosinophils, innate lymphomatoid cells, mast cells, and basophils. The genes encoding for IL-4 and IL-13 are located on chromosome 5 (5q31), and the structure of both cytokines is similar. IL-4 is responsible for the class switching of antibodies produced by plasmocytes, to IgE class in case of allergy. It "recalibrates" the immune system activity to the Th2-dependent pathway, and its activation also weakens the expression of genes for filaggrin, loricrin, and involucrin which are indicators of terminal epidermal differentiation (Brandt and Sivaprasad 2011; Kim et al. 2008). IL-13's function resembles that of IL-4; receptors for both cytokines also have the same subunit. IL-13 stimulates skin inflammation, leading to fibrosis and dermis vascularization. It stimulates migration of TCD4 lymphocytes, mast cells, eosinophils, and macrophages to the dermis layer (Oh et al. 2011). Both IL-4 and IL-13 inhibit production of the antimicrobial peptides β -defensins and cathelicidins in the skin, which leads to more frequent bacterial and viral skin infections in the course of AD (Brunner et al. 2017; Chieosilapatham et al. 2017). The finding above outlined connecting IL-4 and IL-5 with inflammatory skin reactions have all been reported in adult patients with severe chronic AD (Gavrilova 2018; Nomura et al. 2018). There is a paucity of information on both cytokines concerning AD in the adult population. In this study we failed to notice any association between IL-4 or IL-13 content and clinical parameters in adults suffering from AD.

IL-22 is a cytokine which belongs to the IL-10 family and is produced mainly by T-helper 22 (Th22) lymphocytes, Th17, TCD 8 (Tc22), $\gamma\delta$ lymphocytes, and others. Trifari et al. (2009)

have described a new lymphocytes population with surface receptors for CCR4, CCR6, and CCR10 chemokines, which suggests relevance to the immune system of the skin. Th22 lymphocytes produce IL-22, IL-13, tumor necrosis factor- α , and fibroblast growth factor. Lymphocytes express aryl hydrocarbon receptor (AHR) transcription factors (Nomura et al. 2018; Mirshafiey et al. 2015). The AHR ligands, such as dioxin and polycyclic aromatic hydrocarbons, promote conversion of naive TCD4+ into Th22 lymphocytes. Stimulation of naive TCD4+ by dendritic cells also promotes the development of Th22 lymphocytes. Of note, IL-22 receptors are not situated on any immune system cells but only in tissues such as the skin, kidneys, pancreas, liver, or bowels; thus they belong to tissue cytokines. IL-22 is associated with the non-specific, innate immune processes, particularly against bacteria and viruses, such as stimulation of S100 family proteins, platelet-derived growth factor A, and CXCL5 chemokines. In the skin, IL-22 stimulates keratinocyte proliferation (epidermis hyperplasia) and inhibits their terminal differentiation (Fujita 2013). Wolk et al. (2006) have shown in vitro that stimulation of keratinocytes by IL-22 induces the antimicrobial β -defensins by way of STAT3. It appears that Th22 lymphocyte performance is primarily related to the structural integrity of epidermis due to the induction of keratinocyte proliferation and migration. In case of inflammation, Th22 lymphocytes support release of cytokines and chemokines by keratinocytes (Mirshafiey et al. 2015).

Despite a consensus on the dominant role of the Th2-dependent cytokine pathway in AD, attention is also directed toward Th17-, Th1-, and especially Th22-dependent immune responses (Nomura et al. 2018; Wollenberg et al. 2018). Nograles et al. (2009) have described increased expression of IL-22 in CD4 and CD8 lymphocytes in peripheral blood in a range of skin lesions. The majority of IL-22 producing cells in skin lesions belong to the Th22 lymphocyte line, and the number of Tc22 lymphocytes in the skin associates with AD severity. There are reports showing that IL-22 content increases in

both blood and skin in AD patients (Kanda and Watanabe 2012). In the blood, it associates with TARC (CCL 17), an indicator of AD severity, which in relation to CCR4 receptor expression on Th22 lymphocytes underlines the leading role of IL-22 in the pathogenesis of AD (Thijs et al. 2015; Hayashida et al. 2011). The findings of the present study showing that AD severity, assessed by SCORAD score, correlated with IL-22 blood content are in line with the role of IL-22 in AD above outlined. It should be emphasized that expression of proteins which are essential for maintaining the epidermal structure, such as filaggrin, loricrin, and involucrin, decreases in the presence of IL-22 (Brunner et al. 2016; Fujita 2013; Gutowska-Owsiak et al. 2011). It is possible that in AD patients, especially in the eAD group, high IL-22 content potentiates the defect of the epidermis barrier and, therefore, eases the exposure to allergens, which is clinically manifest by the elevated sIgE and the intensification of pruritus.

In conclusion, this study points to a key pathogenetic role of IL-22 in atopic dermatitis, particularly in the exacerbation of inflammatory skin lesions. Thus, this cytokine may become a potential target of future monoclonal therapy in atopic dermatitis. In fact, fezakinumab, a human monoclonal antibody against IL-22, is currently tested as novel treatment for atopic dermatitis, a disease otherwise highly refractory to therapy (Vakharia and Silverberg 2018).

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol received approval of the Bioethics Committee of the Medical College of the Jagiellonian University in Cracow, Poland.

Informed Consent Written informed consent was obtained from all individual participants included in the study.

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