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Allergy to the cat—from diagnosis to management

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Abstract
Background In allergology practice, efficient counselling of cat owners is often frustrating because the topic of allergen avoidance is mostly a "no-go" and there are only few studies on allergen immunotherapy that prove its efficacy. In the end, what patients are mostly offered in allergy consultations are allergen reduction measures and symptomatic therapy.
Results Sensitisation to the main cat allergen Fel d 1 occurs more frequently in atopic conditions and then represents a risk for allergic rhinitis and asthma. Current guidelines are therefore cautious about the first-time acquisition of a cat in the first months of life in atopic families. However, sensitisation occurs in many cases even without contact with an own cat at home.

Conversely, it has been observed in adult patients that in the case of high Fel d 1 exposure immunological tolerance can also develop through the induction of specific IgG4. The fact that many cat allergic patients keep their animals despite diagnosis is, however, partly due to the psychological phenomenon of coping.
Conclusion In this review, we present current literature and facts that should make everyday life easier for patients, even without giving up the animal. We also review best practices in the management of cat allergy and present new management options and concepts from the development pipeline that our patients are eagerly awaiting.

Keywords Allergy · Pet · Farm effect · IgE · Immunotherapy · Micronutrition

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Introduction

Pets are kept in about one in three households in Germany, including 29% in single-person households, 35% in households with 2 persons, 36% in households with 3 or more persons, but in 67% of households with children [1]. The figures in Austria are very similar [2], but Austrian pets are well distributed between single households and families with children (retrieved from www.statista.com, April 2023). During the coronavirus pandemic, the number of pets increased by about 5%. In Germany, this meant an increase of 1 million pets alone in 2020—the pet supplies segment was thus a big winner of the pandemic [3].

Which animals usually are kept in households is country-specific and probably culture-dependent. Cats as pets are popular in Germany (29%) and Austria (24%), surpassed by e.g. France (41%), Belgium (33%) and Russia (57%). About twice as many women than men tend to keep cats rather than dogs [4].

An impressive number of 15.2 million cats lived in Germany, and 2 million cats in Austria, according to a standardised survey by a market research institute in the survey period 2021 [4]. In contrast, however, dogs take a top position among pets in the international comparison with an average of 33% (up to 66% in Argentina) [5]. Registration of the animals is not obligatory, so a veritable number of unreported cases can be assumed.

Pet owners in the allergology practice

Pets arguably provide carefree quality time in otherwise uncertain times, give a sense of stability and support social interaction. Moreover, there are actually proven health benefits: in a systematic review and meta-analysis of 26 studies, there was a decrease in cardiovascular mortality specifically among cat but not dog owners [6]. Pets are seen as a friend, and increasingly as a family member. This is also evident from the fact that, following a trend from the USA, pet owners are in Europe also mutating from "master and mistress" to parents ("mum and dad") and are also addressed as such by the treating veterinarian. This new phenomenon is also termed "pet parenting" [7]. In fact, did you know that there is a worldwide international "Hug Your Cat Day" on 4th of June? Thus, counselling pet owners requires special empathy in allergy consultations, because allergen avoidance is not enforceable in the vast majority of cases.

In German-speaking countries, according to statistics, among animal allergy sufferers we deal most with cat owners in the allergy consultation, about half of them being women. They consult the allergist because of allergic rhinitis and conjunctivitis, some for urticarial lesions after contact with saliva or claws, or for asthmatic complaints. Cat allergen can also be distributed via urine, but in much smaller quantities [8]. Cat allergy sufferers often report an itchy palate after high exposure to allergens [9].

In general, the numbers of sensitisations to cat among all animal sensitisations are increasing, as reported in various international studies. In the Swedish OLIN study ($n=1657$), the prevalence of sensitisation (SPT) to cats increased from 19.1% to 26.6% between ages 7–8 to 11–12 years [10]. In the Swedish BAMSE birth cohort ($n=4000$, between 4 and 24 years), sensitisation to cats reached 19.6% [11]. The trend is also strongly increasing in Germany [12]: In 13,000 children aged 3–17 years, the prevalence of sensitisation to animals in general climbed from 5.7% in 3–6 year olds to 17.2% in 14–17 year olds. While the course is thus set in childhood, a plateau is probably reached from adolescence onwards, as reported by a Finnish study [13]. Also for adults, cat ownership means a significant risk for subsequent sensitisation [14]. In turn, existing sensitisation is seen in many studies as an increased risk for asthma [15].

What speaks against or for cat ownership

In a meta-analysis of 34 adult cohorts, cat ownership protected against, or at least did neither favour the development of allergic rhinitis nor of asthma [16]. Thus, based on epidemiological studies, keeping cats during and after the first year of life has even been suggested as a strategy against sensitisation [17]. The necessary allergen amounts, time periods, genotype and necessary cofactors have not yet been systematically investigated. Therefore, there are no convincing recommendations for the primary prevention of cat allergy, but secondary prevention in preschool age seems to protect against deterioration of lung function up to asthma [18]. Here, counselling often fails because of the love for the animals.

Patients sensitized to cat who claim that their own cat is tolerated, while others elicit symptoms, are regularly seen in allergology consultations. In most cases, the nasal language and other allergic phenotypes speak more for psychological coping with the unavoidable situation. However, some cat owners despite manifest allergy seem to have actually reached a stage of tolerance during living with the cat. IgG4 immunoglobulins have been discussed for years as a mechanism of tolerance in cat allergy. These are formed during chronic and high antigen exposure and could thus transform an initially unfavourable Th2 immune response into a protective Th2 response [19]. In a study comparing feline asthmatics with or without a cat at home, higher specific IgE levels were detectable when living with the cat; at the same time, higher thresholds for basophil reactivity to allergen were found in the cohort with a cat at home, and this correlated with the presence of Fel d 1-specific IgG4 [20]. Based on the principle that specific IgG4 could positively influence clinical reactivity against cats, new immunotherapeutics are now being considered.

Although only about half as many households have cats in Turkey compared to households in German-speaking countries, a number of recent studies have been carried out there. For example, the prevalence of cat sensitisation was 6% in a cohort of 3033 patients who visited an allergy clinic because of hypersensitivity to cats. These patients suffered more frequently from allergic rhinitis associated with cat contact (29.4%) than from asthma or combined symptoms, while 28% of those sensitised had no symptoms [21].

A larger number (17.3%) of the diagnosed cat allergy sufferers had a cat at home, while 13.4% of patients had contact with a cat but no cat of their own. In another Turkish study, cat sensitisation was evaluated with skin prick tests. Of those who tested positive, 33.9% were cat owners themselves, all of whom preferred to live with the animals, although two-thirds of them actually had rhinitis symptoms [22].

Because more animals, including a disproportionate number of cats, were newly acquired during the

coronavirus pandemic, the rate of patients presenting as sensitised to cats in/after the pandemic (15%) increased significantly compared to prepandemic rates (4.4%) [23].

But who gets sensitised against cats?

Allergen levels are naturally higher in households with cats, with the major allergen Fel d 1 being the most significant biomarker not only for sensitisation (IgE, positive skin prick test, no symptoms) but for the risk of clinically relevant cat allergy and cat asthma. In monosensitisation, Fel d 1 is the only IgE biomarker [24] and can be found in both air and beds [25] (and in the cat litter box [8]). In several birth cohorts, there was a linear dose–response relationship between the amount of allergen in the environment and the risk of sensitisation [26]. The risk particularly affected infants up to 1 year of age. Thereafter, the rate of sensitisation among children in cat families increased by 6% per year less than in families without cats. The prevalence of cat sensitisation was then the same in both groups in adolescence.

Particular advice should be given to families with a parental atopic predisposition of one or both parents, which is transmitted to 30–60% of their children. This also explains why individuals with the same allergen exposure, e.g. in a shared living space, do not all become sensitised. Under the term "gene–environment interaction", in earliest childhood the specific FLG genotype (fillagrin mutations) together with Fel d 1 exposure determines the course of, either cat sensitisation, or whether protection can be built up against it [27]. The situation is more complex with regard to asthma. Here, genetic variations of the ORMDL3 gene on chromosome 17q21 have been correlated with asthma. The genotypes rs7216389 [28] and rs2305480 [29] are high-risk markers associated with Fel d 1 exposure.

The current German guidelines on allergy prevention [30] advise that, in the case of atopic predisposition and a desire for animals, a cat should be acquired later rather than in the critical first months of life.

However, the last word may not yet be spoken. This is announced by some recent studies which show that, depending on the timing of exposure, also protection could be provided: The Copenhagen Prospective Studies on Asthma in Childhood2000 study [28], which investigated animal exposure to cats and dogs, found that high levels of exposure to cat allergens prevented the development of asthma until 12 years of age. The Danish National Birth Cohort Study summarises that cat exposure in early childhood has no, or rather a mild protective effect against atopic eczema, asthma and allergic rhinitis [31].

Cat exposure in pregnancy and early childhood has also recently been associated with a protective effect against food allergies (specifically eggs, wheat and soy) in The Japan Environment and Children's Study [32].

Management of cat allergy: how do I tell the patient?

Tertiary prevention: allergen avoidance with existing sensitisation?

In the delicate diagnostic exploration of cat allergy sufferers, in which the cat is respectfully addressed as a family member, the consequences of continued chronic exposure on a progression of the disease towards respiratory complaints up to asthma should be explained, especially for cat owners with atopic risk.

An essential part of the conversation is to inform the patient that a large proportion of cat allergy sufferers do not need to own a cat themselves in order to suffer from symptoms. Patients should be informed about the high persistence of Fel d 1 allergens on textiles, furniture and generally in homes that have been inhabited by cats. The possibility of indirect exposure via schoolmates or colleagues should also be explained. Likewise, advice should be given on the treatment of bedrooms, textile hygiene, the use of air filtration devices, including all bedrooms, in order to provide respite from allergen exposure at least at night. Keeping animals in all bedrooms should be avoided in affected families. To this end, it should be understood that children's rooms are also bedrooms. It will usually not be possible to also get other rooms cat-free.

In general, the type and amount of exposure to cats has changed. While in the countryside cats still tend to stay outdoors and rarely come into living spaces, in the context of urbanisation we observe the phenomenon of the indoor cat, which is kept hygienically impeccable and, from an allergological point of view, in rooms that are too clean. Therefore, indoor cats are usually a source of much higher allergen load, with a simultaneous lack of dirt exposure, which, according to the hygiene hypothesis, would be better counter-regulated by a stray cat.

Therefore, alternative measures for allergen reduction are called for. These include washing with detergents and mechanical cleaning, especially in combination with tumble dryers [33]. This includes the treatment of all home textiles, including textiles directly contaminated by the cat. Air filtration devices are helpful against indoor cat asthma if they are equipped with HEPA (high-efficiency particulate air) filters [34]. This was also confirmed in a study in an allergen exposure chamber, where relief against immediate type as well as late phase reactions were recorded when air filters were applied [35].

The race to create a hypoallergenic cat that secretes less or no Fel d 1, however, is still undecided [36]. Naked cats or the more sparsely haired werewolf cats, distinguished by hypotrichia [37], still secrete their Fel d 1 via saliva, while possibly the distribution of the allergen via dander might be reduced.

Perhaps the most original approach is to immunise cats against Fel d 1 coupled to virus-like particles to reduce allergen excretion. Clinical studies have shown that by inducing neutralising anti-Fel d 1 autoantibodies in the cat, a significant reduction in symptoms could be achieved in cat owners [38]. This allowed them to devote more time to petting their Fel d 1-vaccinated animals without falling into a sneezing attack.

Symptomatic therapy

Prescriptions for antihistamines or mast cell stabilizers, including cromoglicic acid (nasal spray, eye drops) should be issued in any case; an asthma spray (inhaled betamimetic, for example formoterol, plus corticosteroid) is also recommended in case of wheezing. Advise your cat allergy sufferers to take symptomatic treatment before visiting cat owners if the visits cannot be avoided. For contact urticaria, topical H1 receptor blockers may be useful in addition to antigen abstinence. If respiratory symptoms are present, pulmonary function should be checked and drug therapy should be coordinated with the pulmonologist.

The whole family should be informed about the risk of an allergic reaction and, if necessary, medicines and asthma sprays should be deposited, e.g. with the grandparents who own a cat.

Specific allergen immunotherapy

Is a 3-year course of allergen immunotherapy (AIT) an option for cat allergy sufferers? Some patients specifically request it, but an analysis of systematic reviews by the European Association of Allergy and Clinical Immunology did not result in a clear recommendation [39]. Admittedly, there are hardly any major studies on cat AIT. This may be partly due to the industry's tasks in terms of the therapy allergen ordinance regarding AIT studies for the more common allergens (pollen, mites). Further developments for AIT in animal (hair) allergies, improvements in terms of standardisation and increased safety are currently on hold. A Spanish–Swedish study team reported on the safety of a new feline subcutaneous immunotherapy (SCIT) procedure using rapid updosing by infusion pump, but systemic reactions occurred in 8.1% of the doses administered; during the maintenance phase without a pump, there were still 9.3% systemic reactions [40]. Nevertheless, improvements in allergic symptoms, medication consumption, the asthma control test and quality of life were substantial in cat allergy [40], and lasted at least 6 months.

Other studies have also described a relatively high risk of systemic allergic reactions, particularly with anti-cat SCIT [41].

Sublingual immunotherapy (SLIT) is an option for cat allergy with good results in some cases, as shown in double-blind placebo-controlled trials [42], but there have been no new developments [39].

One may therefore think about improvements. Allergoids are commonly used in Europe to increase the safety of allergens for AIT. Glutaraldehyde and other chemical processes link allergen molecules to larger complexes that can no longer cross-link IgE. This has also been achieved for Fel d 1 and a corresponding allergoid was practically applied [43]. An alternative option would be to make the cat allergen more immunogenic. While most SCIT administrations use aluminium hydroxide as an adjuvant, cytosine–phosphorothioate–guanine oligodeoxynucleotides (CpG-oligonucleotides) could promote a Th1 response counteracting the allergy, associated with the generation of Foxp3hi Treg cells as well as an anti-inflammatory TNF/TNFR2 signalling cascade [44]. This possibility has been supported in animal models [45].

Disappointingly, a change in application to the intralymphatic route (ILAIT) failed to produce therapeutic improvement in cat allergy [46].

In the pipeline: biologics against Fel d 1

Having arrived in the era of biologics, a number of compounds are available for use in severe allergic asthma and rhinitis that have allergen-nonspecific mechanisms of action by targeting IgE or downregulating cytokines. This differs from a new allergen-specific approach using anti-Fel d 1 IgG4 immunoglobulins. On the one hand, the IgG4 blocks the allergen and thereby prevents symptoms. On the other hand, it exploits a mechanism typical for the IgG4 subclass: IgG4 has a better anti-inflammatory effect than other IgG subclasses via FcgRIIb receptors on macrophages and other inflammatory cells [47]. REGN1908-1909 is a cocktail of two monoclonal IgG4 anti-Fel d 1 IgG4 antibodies, which after subcutaneous application not only leads to a lower reaction in the skin prick test [48], but in a double-blind placebo-controlled study prevented both the symptoms of allergic rhinitis [49] and allergic asthma after cat exposure in a standardised exposure chamber [50].

New: dietary management of cat allergy

A special risk for specific sensitisation, including against cats, exists in atopy. But what is the actual cause of atopy? In addition to a genetic predisposition, including the risk alleles described above, environmental factors are increasingly being considered that affect the epigenome, i.e. cause chemical changes in histone proteins and DNA [51]. This can be countered by so-called "green spaces", which contribute to a richness of the (intestinal) microbiota [52].

A recent finding is that nutritional deficiencies support the atopic phenotype [53]. Of particular note among these are iron and zinc deficiency, but also folic acid deficiency. Anaemia has been significantly linked

to the risk of developing atopy and subsequent allergic symptoms in international studies [54–56]. Often it is not a matter of classic anaemia characterized by lower erythrocyte counts, haemoglobin associated with impaired iron parameters in the laboratory test results, but of a so-called "functional iron deficiency", which particularly affects immune cells [57]. Functional iron deficiency is much more difficult to detect in the laboratory, as confirmed by current guidelines [58]. This is not an absolute iron deficiency, but rather an iron utilisation disorder. In the deficiency situation, immune cells tend to retain iron and release less iron. Thus in situations when the so-called "labile iron pool" in macrophages and other regulatory cells is reduced, they cannot fulfil their immunomodulatory role and become pro-inflammatory. In a setting of iron deficiency, the pro-allergic Th2 cells also survive longer than Th1 cells and drive the immune response further towards allergy.

We have found in our own work that functional iron deficiency is a problem in allergic rhinitis, and that it is also associated with a deficiency of iron-producing microbes [59].

The fact that, conversely, allergy can also lead to anaemia [60] reinforces the close causal relationship between a balanced iron balance and the capacity of immune cells to have an immunomodulatory effect.

We concentrated on specifically compensating for this intracellular iron deficiency and thus correcting the natural regulatory function of immune cells [61]. Building on this finding in combination with the well-known farm effect against allergies [62], our own work has led to the development of a holo beta-lactoglobulin (holoBLG) lozenge that showed efficacy as a dietary compound in a double-blind placebo-controlled study in pollen allergy, as well as in an European Centre for Allergy Research Foundation (ECARF) provocation chamber study in house dust mite rhinitis [63]. The clinical efficacy of this dietary approach therefore also produced highly significant clinical improvements.

Since these studies proved the allergen-nonspecific mechanism of the holoBLG lozenge, it was obvious to pursue the question whether an application in cat allergy would be useful.

Therefore, we recently conducted a study in the ECARF exposure chamber on 35 patients with allergic rhinitis to cat allergens. The results of this open-label pilot study showed that 40% improvement in the symptoms specifically associated with allergen provocation could be achieved after only 3 months of supplementation [9]: Allergic ocular symptoms decreased by 33%, the total nasal symptom score (TNSS) decreased by 50%, and itching in general decreased by 50%. In nasal provocation, peak inspiratory nasal flow (PNIF) was improved in the holoBLG-treated patients, and remained negative in 12 of those tested even at

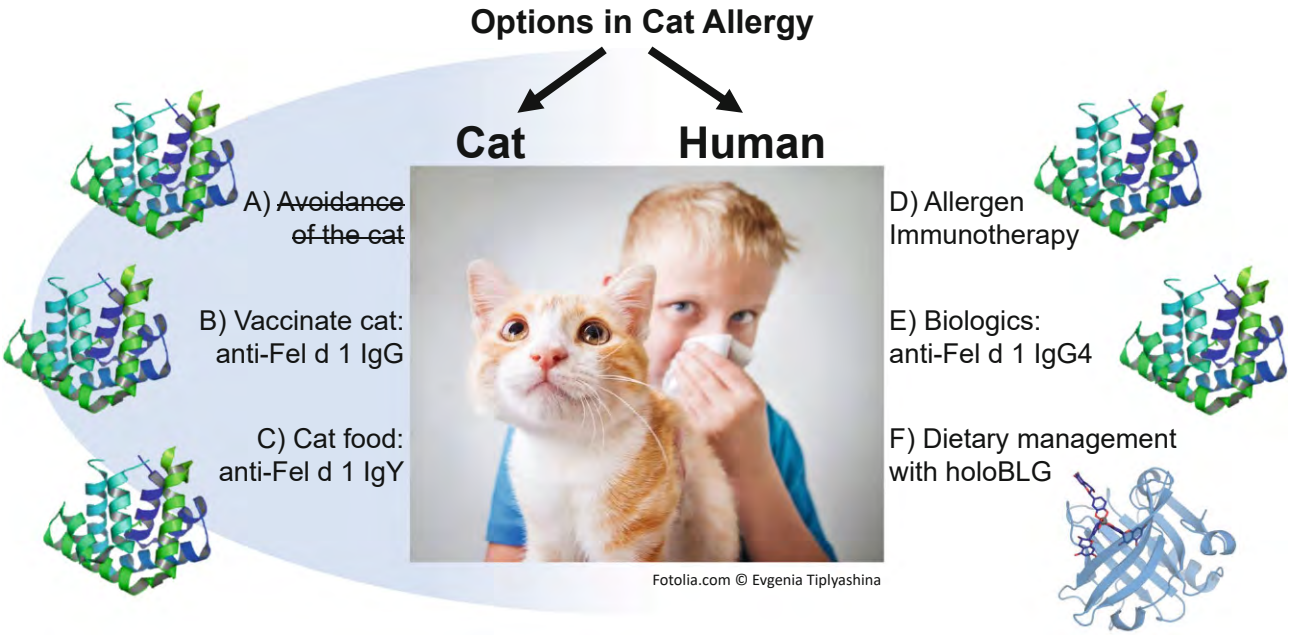

Fig. 1 Decision tree in the allergologic consultation: Specific IgE anti-Fel d 1 and matching clinical symptoms enable the diagnosis of cat allergy. Besides symptomatic therapy, the reduction of allergen exposure is in the foreground. *A* Prescribed allergen abstinence mostly fails due to animal love, *B* in Switzerland, work is being done to develop a protocol for immunising the cat against Fel d 1 in order to induce neutralising, feline anti-Fel d 1 IgG, *C* cat food containing chicken IgY anti-Fel d 1, which reduces the allergen excretion of the pet cat, is already commercially available, *D* allergen immunotherapy applies the specific cat allergen to induce allergen-specific tolerance *E* developments of a human IgG4 anti-Fel d 1 biologic for passive immunotherapy in cat allergy are promising; *A–E* are thus allergen-specific approaches, *F* An entirely allergen-nonspecific approach is dietary management using holoBLG lozenges counteracting cat allergy

the highest allergen dose in the provocation, while 8 reacted only at a higher allergen dose.

Thus, this provocation chamber study indicates that dietary measures can also correct clinically manifest cat allergy. Considering the abundance of non-qualified "food supplements", it seems appropriate to clearly distinguish and emphasise the scientifically sophisticated "dietary management" by means of targeted micronutrition with holoBLG. An overview of the different treatment options for cat allergy is given in Fig. 1.

Synopsis

Allergy to cats particularly affects people with atopic predisposition, and the most significant biomarker is IgE against Fel d 1. Current guidelines advise against acquiring a cat for the first time in early childhood, especially in atopic families. It is unclear how non-cat owners develop clinically significant sensitisation and why some cat owners develop tolerance (often only to their own animal). Although immunological mechanisms are clear and are thought to run via IgG4 induction after high allergen exposure, psychological mechanisms also play a role in coping with cat allergy. However, negation of the allergic disease carries the risk of progression to chronic disease and asthma. Therefore, medical counselling of cat allergy sufferers is particularly delicate. Conversely, the repertoire in the allergological toolbox is limited, resulting mostly in physical allergen reduction recommendations combined with symptomatic treatment. This is due to the fact that the evidence base on the efficacy of allergen immunotherapy is limited and larger studies are needed. For the management of cat allergy, there is therefore currently a high demand for alternative but evidence-based strategies. These include active and passive immunological and micronutritional approaches in the cat or in cat-allergic humans.

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