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Clinical signs and diagnosis of feline atopic syndrome: detailed guidelines for a correct diagnosis

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Background – Feline atopic syndrome (FAS) describes a spectrum of hypersensitivity disorders characterised by highly diverse clinical presentations including skin, gastrointestinal and respiratory systems. Among these disorders is feline atopic skin syndrome (FASS), in which hypersensitivity is typically associated with environmental allergens, although food allergy may coexist. Involvement of other organ systems (e.g. asthma) also may occur. Because of its highly heterogeneous clinical presentation, diagnosis of FASS can be challenging.

Objectives – A subgroup of the International Committee on Allergic Diseases of Animals was tasked to summarise the most current information on the clinical presentations of FASS and to develop diagnostic guidelines.

Methods and materials – Online citation databases and abstracts from international meetings were searched for publications related to feline allergic conditions. These were combined with expert opinion where necessary.

Results – A total of 107 publications relevant to this review were identified. Compilation of these data enabled development of a detailed description of the clinical features of FASS and development of guidelines focusing on systematic elimination of other skin conditions with similar clinical characteristics. As allergen tests are frequently used by dermatologists to support a clinical diagnosis of FASS, a brief review of these methodologies was also performed.

Conclusions and clinical importance – In a similar way to atopic dermatitis in dogs, FASS is a clinical diagnosis based on the presence of compatible clinical signs and exclusion of other diseases with similar clinical features. Elimination or exclusion of fleas/flea allergy, other parasites, infections and food allergy is mandatory before reaching a diagnosis of FASS.

Introduction

The term "feline atopic syndrome" (FAS) encompasses a variety of allergic diseases in cats. These disorders include allergic dermatitis, asthma/respiratory diseases and gastrointestinal diseases that may be associated with a hypersensitivity to environmental allergens and foods, and which may coexist with flea allergy dermatitis. Unlike dogs, cats may demonstrate a pleomorphic clinical response when sensitised to any of these items. In addition, there has been some lack of consensus regarding the role of immunoglobulin (Ig)E in the development of hypersensitivity to environmental allergens (formerly atopic dermatitis), whereas the role of this antibody is more evident in other species (e.g. dogs and people). Because of these difficulties, there has been some hesitancy to use the term "atopic dermatitis" when describing cats demonstrating hypersensitivity to environmental allergens. Different alternative terminologies have been proposed, including "nonflea, nonfood-induced feline

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hypersensitivity dermatitis".[1,2] In this series of manuscripts, we propose that this latter nomenclature be changed to "feline atopic skin syndrome" (FASS).

The first manuscript of this series describes the most updated information on the pathogenesis of FAS and the reasons behind the proposed new nomenclature. The primary aim of the current manuscript is to summarise the clinical presentations associated with FASS. This work will focus on cutaneous and noncutaneous manifestations of FASS. However, as many of the conditions that comprise FAS may be tightly and inextricably linked with FASS, some discussion will be devoted to them as well (Table 1).

A secondary aim of this manuscript is to provide information to guide the practitioner towards a correct diagnosis of FASS. This diagnosis may be challenging because of the striking similarities in clinical presentation among feline allergic and nonallergic dermatoses. Thus, we describe a logical diagnostic pathway based upon the evaluation of the patient for the presence of clinical signs consistent with FASS and exclusion of other skin conditions resembling FASS. Finally, similar to published guidelines for canine atopic dermatitis,[3] a subgroup of the International Committee on Allergic Diseases of Animals (ICADA) reviewed the most up-to-date information on diagnostics to help confirm a clinical presumptive diagnosis of FASS.

Methods and materials

A literature search for studies on feline allergies published between 1950 and 2020 was conducted using Pubmed (pubmed.gov), Web of Science (Thomson Reuters), CAB Abstracts (EBSCOhost Research Databases) and CAB Abstracts Archive (EBSCOhost Research Databases) databases. Restrictions (date or language) were not enforced for the manuscript search. Published abstracts from annual meetings of the European Society of Veterinary Dermatology/European College of Veterinary Dermatology, American Academy of Veterinary Dermatology/ American College of Veterinary Dermatology and World Congresses of Veterinary Dermatology between 1995 and 2016 were included. Finally, expert options were reported where necessary to supplement the literature search. A total of 107 manuscripts were selected and summarised below.

Clinical characteristics of FASS

Clinical appearance

By contrast with species such as people and dogs (in which atopic dermatitis typically is associated with a limited range and distribution of clinical signs), the cutaneous lesions of FASS are far more variable in appearance and less predictable in distribution. As is seen in other forms of feline skin disease, the majority of cats with FASS typically present with one or more "cutaneous reaction patterns". These patterns include miliary dermatitis (MD), self-inflicted alopecia/hypotrichosis (SIAH), head and neck pruritus (HNP) and eosinophilic granuloma complex (EGC). Either alone or in combination, and after excluding other possible causes, these patterns are consistent with a diagnosis of FASS.

In its simplest form, MD presents as several small (typically ~ 1–2 mm) papules, generally surrounded by crusts (Figure 1). These lesions may be distributed over relatively small portions of the body or may be present in a more generalised fashion. This condition is usually pruritic and, as a result, excoriations, erosions and varying degrees of hair loss often are superimposed on MD. In some cases, MD may be present without a history of pruritus. Some of these cats may truly be nonpruritic, yet it is likely that many of them may simply not be observed to be pruritic by the owners. Regardless, patients with "nonpruritic" MD may appear clinically normal from a distance, with the presence of lesions becoming obvious only upon handling the cat and close inspection of the skin.[4]

Table 1. Algorithm showing the clinical signs associated with feline atopic syndrome

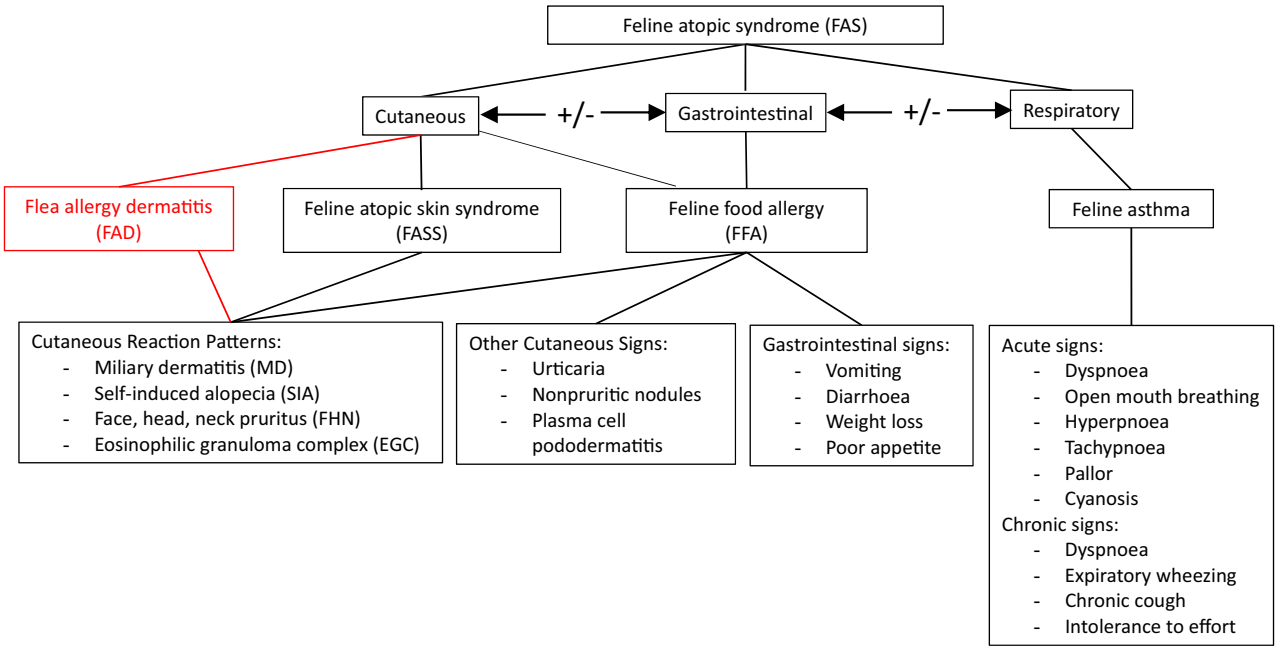

Figure 1. Classic clinical pictures of cats affected by feline atopic skin syndrome (FASS).
Miliary dermatitis; note the small, crusted papules on the neck. Diffuse self-induced alopecia affecting the thighs and flanks of a cat with FASS.

Figure 2. Classic clinical pictures of cats affected by feline atopic skin syndrome (FASS).
Diffuse self-induced alopecia affecting the thighs and flanks of a cat with FASS.

In SIAH, the pruritic cat removes its hairs either by repetitively licking, biting or pulling at the fur, occasionally accompanied by scratching (Figure 2). This behaviour often results in the swallowing of excessive hair and the formation of hairballs, which may cause vomiting. It may be helpful to ask the owners of affected cats whether they have noticed the patient vomiting, or if they have noticed excessive hair being passed in the faeces. These activities may be mistaken for normal grooming by the client and so are not reported. Alternatively, the cat may perform these activities in seclusion. In these cases, the client may believe that the cat is losing hair spontaneously. In other cases, the exuberant overgrooming may be noted, yet misinterpreted by the client or the veterinarian as an aberrant response to some stressful condition rather than a manifestation of pruritus. Although some cats may remove their own hair under real or perceived stressful conditions ("psychogenic alopecia"), primary behaviour-based overgrooming appears to be uncommon in cats. In one study of 21 cats referred for evaluation of psychogenic alopecia, a primary behavioural or psychogenic cause was demonstrated only in two cats.[5] By contrast, 16 of the cats were found to be suffering from pruritic dermatitis alone, with the remaining three cats

Figure 3. Classic clinical pictures of cats affected by feline atopic skin syndrome (FASS).
Severe erythema, alopecia, crusts and excoriation in a case of FASS with face, head and neck pruritus.

Figure 4. Classic clinical pictures of cats affected by feline atopic skin syndrome (FASS).
Severe ulceration of the upper lip in a cat affected by indolent ulcer.

Figure 5. Classic clinical pictures of cats affected by feline atopic skin syndrome (FASS).
White papules affecting the hard palate in a cat affected by oral granuloma.

afflicted by pruritic disease with a superimposed behavioural component.[5]

The third reaction pattern (HNP) is characterised by (often intense) pruritus of the face, head and neck. Patients may claw or scratch frantically at the areas, resulting in varying degrees of excoriation, erosion and ulceration (Figure 3). Blepharitis may be observed, with or without associated corneal ulceration. The pruritus associated with this pattern may be particularly severe and difficult to manage, often requiring physical intervention (in the form of bandages or protective collars) to minimise self-trauma.

The fourth reaction pattern is EGC. This "complex" consists of a loosely grouped (and often confusingly named) set of clinical syndromes.[6] The first is indolent ulcer, also known as "rodent ulcer". This condition typically affects the upper lip, at or immediately adjacent to the mucocutaneous junction (Figure 4). Lesions initially start as focal ulceration on the lip margin. Unilateral disease is more common than bilateral disease, at least in the beginning. As the condition progresses, the lip can become ulcerated and fibrotic, resulting in the deformation of the entire rostral portion of the lip up to (and occasionally past) the planum nasale. This syndrome is typically not pruritic unless complicated by bacterial infections.

The second syndrome is eosinophilic granuloma, also called "linear granuloma". Lesions can appear in a variety of locations, each with its own phenotype. Lesions on the rear legs typically appear as linear areas of dermal thickening on the caudal aspect of the thigh and may extend distally past the stifle fold onto the caudal crus. Erosion or ulceration is common. This syndrome also may present as proliferative lesions in the mouth, especially on the tongue or hard palate (Figure 5), or as poorly defined chin swelling ("fat chin"). These lesions may or may not be pruritic.

The third clinical syndrome is eosinophilic plaque. These lesions are most frequent on the ventral abdomen and medial thighs, yet may appear in other locations (Figure 6). These are characterised by raised, frequently eroded or ulcerated areas. Individual lesions range in shape from circular, to oval, to serpiginous. They often are associated with intense pruritus, with self-inflicted damage resulting in a self-perpetuating positive feedback cycle of inflammation. These lesions often are complicated by secondary bacterial infections.

Although any of these reaction patterns may be seen with FASS, some patterns appear to be seen more frequently than others. A review of 10 manuscripts describing 263 cats diagnosed exclusively with FASS suggests the following overall prevalence rates: 31.2% with MD; 60.1% with SIAH; 43.0% with HNP; and 25.9% with one or more forms of EGC. The number of cats demonstrating multiple syndromes was not always specifically stated, yet 37.7% of cats were reported as having at least two syndromes.[1,7–15]

Nonetheless, there is considerable variability in the prevalence values for each of these patterns between the individual manuscripts (Table 2). This is particularly true for MD and HNP, with SIAH being somewhat less variable and EGC the least variable of all. Some of this variability may be related to the small number of cases in some studies. A second reason may be related to differences in pattern characterisation between observers. For example, although one observer might characterise a cat as having MD localised to the neck, another observer might describe that same cat as having HNP. By contrast, there is far less variability in the reported prevalence of EGC, which tends to be distinct in appearance.

Few articles provide specifics regarding the distribution of lesions in cats with FASS. Frequently involved areas appear to include the face, head, neck and pinnae, the ventral abdomen, the legs (especially the medial aspects) and the dorsum.[1,9,12,15,16] Less common areas of involvement include the lateral thorax/flanks, perineum, axillae and lumbosacral area.[1,9,16] "Lesionless" alopecia and generalised or multifocal involvement occasionally are reported.[9,11,12,16] By contrast with dogs, paw involvement appears to be uncommonly involved in FASS.[1,9,15,16]

Otitis is a frequent clinical presentation in dogs with atopic dermatitis.[3] In cats, the presence of otitis, with or without secondary infectious, has been reported in 20.9% (48 of 230) of patients with FASS.[1,9–12,15,17]

Finally, there also are "atypical" clinical signs that have been attributed (tentatively or definitively) with FASS. These include pododermatitis (with or without plasma cell involvement)[18,19] and alesional pruritus.[20] In some cases, these signs have been reported as the only manifestation of FASS, whereas in others they accompany more "typical" manifestations of FASS.

Age of onset

Determination of the average age of onset of FASS is somewhat complicated by the fact that many studies either provide only the age at presentation or a range of ages. In many cases, cats have been adopted as adults, and thus the information is not known. Furthermore, approximate ages of onset may have been "back-calculated" by subtracting the estimated duration of disease from the current age. Regardless, the age at which cats first demonstrate signs of FASS appears to vary widely, ranging from cats as young as six months to cats as old

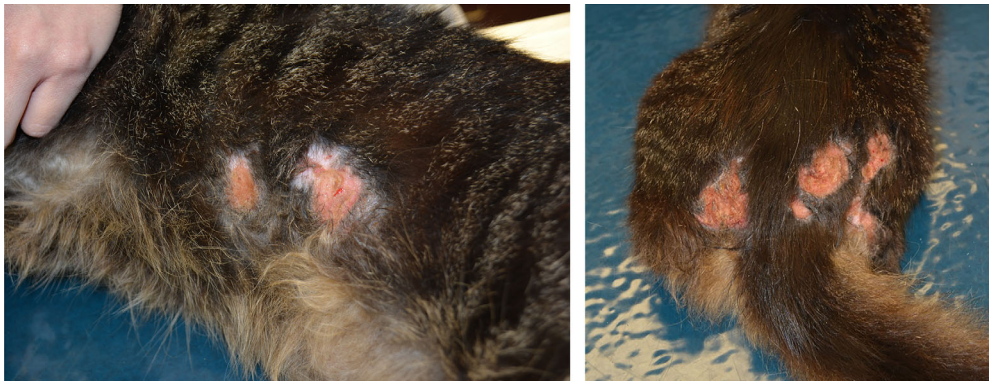

Figure 6. Classic clinical pictures of cats affected by feline atopic skin syndrome (FASS).
Multiple eroded dermal plaques in the flank and rump on a cat affected by FASS.

Table 2. Prevalence of the different clinical manifestation of feline atopic skin syndrome (FASS) reported in selected references

Reference	Number of cats with FASS	MD (%)	SIAH (%)	FHNP (%)	EGC (%)
Moriello[12,*]	3	0 (0.0)	3 (100.0)	3 (100)	0 (0.0)
Saridomichelakis[11,*]	10	6 (60.0)	5 (50.0)	1 (10.0)	2 (20.0)
Carlott[9*]	10	6 (60.0)	6 (60.0)	8 (80.0)	2 (20.0)
Schleifer[13,*]	10	6 (60.0)	0 (0.0)	5 (50.0)	2 (20.0)
McDougal[8]	13	4 (30.8)	6 (46.2)	0 (0.0)	3 (23.1)
Reedy[7]	15	7 (46.7)	7 (46.7)	0 (0.0)	1 (6.7)
Ravens[15,*,†]	29	6 (20.7)	21 (72.4)	23 (79.3)	10 (34.5)
Diesel[14,*]	31	6 (19.4)	24 (77.4)	17 (54.8)	3 (9.7)
Hobi[1,*]	100	18 (18.0)	57 (57.0)	56 (56)	26 (26.0)
Halliwell[10,*,†]	42	23 (54.8)	29 (69.1)	0 (0.0)	19 (45.2)
Total (%)	263 (100)	82 (31.2)	158 (60.1)	113 (43.0)	68 (25.9)

Values in each column represent the number of cats demonstrating that reaction pattern in the corresponding study, while the numbers in parentheses represent the percentage of cats displaying that pattern. Many cats demonstrated more than one reaction pattern; thus, the sums often exceed the total number of cats in the study. Likewise, the sums of the percentages of cats demonstrating specific reaction patterns frequently exceed 100%.

MD, miliary dermatitis; FHNP, face, head and neck pruritus; SIAH, self-induced alopecia; EGC, eosinophilic granuloma complex.

*Individual cats had a combination of clinical presentations.

†Number excludes cats with concurrent flea or food allergy.

as 15 years.[1,8,9,11,12,14–16] However, the majority of reports suggest that most cases have a relatively young age of onset, with reported means ranging from 0.5 to 4.8 years.[1,8,11,12,14,15] This pattern is similar to that described in two large-scale retrospective studies. In one of these studies, the median age of onset was two years, with 62% of patients first experiencing signs before three years of age and only 22% developing disease after seven years of age.[15] In the second study, the mean age of onset was three years, with 72% first showing signs before three years and only 12% developing disease after six years of age.[1] These results contrast with those from an older report in which five of 10 cats first developed signs at seven years or older.[9]

Sex predilection

In general, FASS appears to be reported more frequently in female than male cats. Of the 226 cats with confirmed FASS (as a sole diagnosis) reported in the literature reviewed for this study, females represented 58.4% (132 of 226) while males represented only 41.6% (94 of 226).[1,7–9,11–14] These figures must be viewed with some skepticism, as many of these manuscripts were relatively small case reports and were not compared to the clinical population as a whole. There are only two large reports in which sex specifics were provided for cats diagnosed with FASS (as a sole diagnosis).[1,15] However, the sex ratios in these studies were similar to those reported above (59.7% female: 40.3% male).

Three studies evaluated the sex proportions of cats with FASS in which flea and/or food allergy was either present as a concurrent problem in some or all of the cats, or in which it could not be ruled out in all cases owing to owner compliance issues.[15–16,21] Of these 267 cats, females and males accounted for 58.4% (156 of 267) and 41.6% (111 of 267), respectively.

Seasonality

It must be noted that there is some degree of uncertainty inherent in the determination of whether or not a patient demonstrates seasonal or nonseasonal disease, as this determination often is based upon client assessment. Although astute owners may be able to distinguish between complete remission and partial remission, or between partial remission and no improvement, not all clients are capable of making these observations.

The presence or absence of seasonality was reported for 141 cats diagnosed with FASS, of which 75.2% (106

of 141) demonstrated nonseasonal disease.[1,8,9,11,12,17] Two of these cats had initially presented with seasonal disease, and developed nonseasonal signs over time.[17] Of the 35 cats with seasonal disease, further specifics were available for seven. Of these seven cats, one demonstrated signs in spring, one in spring and summer, two in late summer to early autumn, one in both spring and autumn, one in winter and one demonstrated signs corresponding to its oestrus cycle.[11,12]

Two additional studies evaluated populations of cats with FASS including cats with concurrent flea and/or food allergy.[15,16] In these 238 cats, 70.2% (167 of 238) demonstrated nonseasonal signs, while 29.8% (71 of 238) of cats demonstrated seasonal signs. In the nonseasonally affected cats, 9.6% (16 of 167) had always demonstrated nonseasonal signs, 72.5% (121 of 167) had nonseasonal signs with seasonal exacerbations, 6% (10 of 167) progressed from seasonal to nonseasonal signs, and 12% (20 of 167) had intermittent or waxing and waning exacerbations. Of seasonally affected cats, 25.4% (18 of 71) demonstrated signs during the spring, 39.4% (28 of 71) during the summer, 33.8% (24 of 71) during the autumn and 46.5% (33 of 71) during the winter.[16] Many of these cats demonstrated clinical signs during two or three seasons (primarily summer and autumn).

Breed predisposition and heritability

By contrast with dogs, in which varying degrees of breed predisposition, heritability and/or predisposing genetic polymorphisms have been demonstrated, relatively little is known of the contribution of heritability to feline allergic diseases. One possible reason for this is the relatively small number of purebred cats in relation to domestic mixed-breed cats (domestic short hair and domestic long hair cats). In addition, the large breeding populations of stray cats in many areas makes any attempt at discerning specific lineages extremely difficult. Finally, although many dog breeds often have very distinctive appearances, many breeds of cat (and their crosses) are difficult to distinguish by the untrained eye.

Nonetheless, there is some evidence that there may be a heritable component to the development of allergic dermatitis in cats. The Abyssinian breed was disproportionately affected by FASS in two large retrospective evaluations of allergic cats.[15,16] Abyssinians (along with cats of the Somali and Ocicat breeds) were over-represented in cats demonstrating "skin allergy" (Odds Ratio of 2.1 for all three breeds) in a large retrospective study of >8,000 Finnish cats.[22] In another retrospective study of 502 cats with allergic and nonallergic dermatitis, Abyssinians were found exclusively in the "nonflea hypersensitive dermatitis" group.[1] However, the clinical relevance of this finding is difficult to determine, as this breed represented only a small portion of the cats evaluated (10 cats total). Abyssinians and Abyssinian crosses frequently appear in smaller studies as well, although their prevalence typically has not been compared to the general hospital population in most of these studies.[7,13,23,24]

There have been a small number of case reports describing familial dermatitis of allergic origin. One case report described three littermates that developed varying degrees of pruritus and self-inflicted alopecia of the head and neck starting at approximately six months of age.[12] By one year of age, the signs had expanded to include biting at the legs and furious licking of the abdomen. Skin scrapings, faecal flotation, otoscopic examination, ear cytological evaluation and examination of surface debris failed to demonstrate parasites or infectious causes of pruritus. The cats' pruritus also failed to respond to a flea control trial, ivermectin therapy or an elimination diet trial. Intradermal testing was performed, and the cats were started on immunotherapy based on the results. Two of the cats had an excellent response and were asymptomatic for most of the year, while the signs of the third cat were considerably improved. Interestingly, the dam of these kittens was noted to develop crusting of the head and neck as well as ventral abdominal alopecia during the autumn. Unfortunately, a workup was not permitted in this cat. Another report mentioned that five of 16 cats with atopic dermatitis had first-degree relatives (siblings or parents) affected in a similar way, yet further specifics were not provided.[17]

Two further reports describe cats with lesions and/or clinical signs consistent with allergic dermatitis, for which specific diagnoses were not made. One described three closely related Abyssinians which developed intensely pruritic, crusting dermatitis, rhinitis, conjunctivitis, peripheral eosinophilia and elevated total serum IgE levels.[25] However, it is unclear whether the affected cats all lived in the same household at the time of the development of disease (between 12 and 18 months of age). Furthermore, there is no mention of the methods used to rule out flea allergy, food allergy or nonallergic causes of dermatitis. The second manuscript described seven Norwegian forest cats that developed indolent ulcers and/or linear granulomas.[26] None of these cats were pruritic. All cats had the same father and were born to either the same cat, or to her daughter. Detailed information was not provided for all cats, and the age of onset was reported to be between five and 15 months, with some lesions possibly present as early as one week of age. None of these cats lived in the same household. Unfortunately, as no attempt was made to identify any associated allergic or nonallergic diseases, definitive attribution of these lesions to FASS (or any other allergic disease) cannot be made.

Noncutaneous clinical signs associated with FASS

The true frequency in which cats with FASS develop extracutaneous clinical signs is unknown. In most reports with a dermatological bias, no mention is made of noncutaneous signs at all, which may be because they were not present or simply were not recorded for inclusion in the paper. Alternately, concurrent noncutaneous signs may be masked by anti-inflammatory therapy directed towards the skin disease.

Specifics regarding the presence of noncutaneous signs were provided in seven manuscripts.[1,9–12,15,17] One of these included some cats with concurrent flea (11 of 45) and/or food allergy (six of 45), both of which were presumably in remission when the diagnosis was made.[15] Of the 230 cats described in these seven manuscripts, 8.3% (19 of 230) of the cats reportedly had some form of respiratory disease, of which five had sneezing, three had asthma and 11 had nonspecified respiratory

signs.[1,10,11,15] Conjunctivitis was reported in 4.8% (11 of 230) of the cats and nonspecified digestive signs in 3.9% (nine of 230).[1,11,15] Overall, there were 39 instances of noncutaneous signs reported; however, several of these cats had more than one condition (e.g. rhinitis and conjunctivitis). Because these manuscripts include only a minority of the reported cases of FASS, it is unclear whether these values may be generalised to the atopic feline population as a whole.

Association of FASS with flea and food allergy. In many case series focusing on cats with FASS, cases with concurrent flea or food allergy have been specifically excluded for the purpose of clarity. For this reason, the relatively small number of manuscripts in which this information has been provided limits estimation of the frequency with which other allergic skin diseases appear concurrently with FASS. Together, these manuscripts describe 321 cats with FASS, of which 74 cats had concurrent flea allergy, food allergy or both.[14,15,22,23,26] If all of the cats are examined as a group, flea allergy was present in association with FASS in 16.5% (53 of 321) of cats reported in these studies. Concurrent food allergy was seen in 5.9% (19 of 321) of the patients and 0.6% (two of 321) of the patients were affected by all three disorders. These figures should be interpreted with some degree of caution, as the focus of these particular manuscripts was on FASS, and some cases with food- or flea-related issues may have been missed, or excluded based upon individual differences in diagnostic criteria. Alternately, cats with flea allergy started on aggressive flea control in the autumn or winter may be mistakenly characterised as having seasonal allergic dermatitis consistent with FASS.

However, these figures may be somewhat misleading, as there was great variability in the prevalence of concurrent flea allergy and food allergy between manuscripts. Specifically, FASS cats with concurrent flea allergy represented 100%, 48.5%, 33.3%, 24.4% and 0% of the cases reported in their corresponding studies.[15,16,23,24,27] The reason for this extreme variability is uncertain. However, review of another report from one of these authors covering the same time period suggests that feline flea allergy may simply represent an unusual diagnosis (3.7% of 1,497 cases) at that institution.[28] This particular institution is located in the upper northeastern portion of the United States, suggesting that the low reported prevalence of flea allergy may be more reflective of a relatively low flea population overall (geographical location) rather than a decreased relative frequency of flea allergy.

Other possible reasons for the variation in the reported frequency of flea allergy include the more recent availability of more user-friendly and effective flea control products, as well as individual differences in the criteria required to diagnose flea allergy. For example, one investigator might diagnose flea allergy solely based upon the clinical response to insecticidal therapy, while others might require the concurrent presence of positive serology or intradermal test results or response to live flea challenge. Finally, the possibility cannot be excluded that the diagnosis of flea allergy may have been missed in some cases as a consequence of confounding variables such as (unreported) poor owner compliance.

By contrast with flea allergy, the presence of food allergy was less variable, with 13.3%, 6.1% and 4.6% of cats affected in three studies, and 0% affected in both of the final two studies.[15,16,23,24,27]

Other diseases in the FAS spectrum

Feline food allergy

Because of the striking clinical similarities between FASS and food allergy, it is essential to perform a strict food trial to identify and/or rule out a diagnosis of food allergy in cats before starting diagnostics for FASS. As in dogs, a strict food trial (only the prescribed diet and water) should be followed using either a novel limited ingredient (commercial or home cooked diet) or a hydrolysed diet.[28,29] During the trial, anti-inflammatory medications may be allowed in the initial stages to ameliorate the clinical signs and improve the quality of life for pets and their owners. In some circumstances a second diet trial may be required to confidently rule out food allergy.

A review of the literature (1982–2014) revealed 243 cats diagnosed with food allergy. Concurrent FASS was reported in 2.4% (24 of 243) of cats and FAD in 0.002% (two of 243) of them, with only one cat having both FASS and FAD. However, it should be noted that there will be bias in these figures as the majority of publications were selecting for cats with confirmed food allergy.

In 10 studies,[30–39] the age of onset of clinical signs was detailed and of these 95 cats, 27% (26 of 95) developed clinical signs before the age of 12 months. The age range of disease onset was three months to 13 years with mean calculations between 3.4 and 4.9 years. A median range of onset was not possible to determine from the published data. Domestic short hair cats were the predominant breed, although purebred cats also were reported in small numbers. In one study, Siamese cats were computed to be at increased risk (RR 5.0) compared with the hospital population.[40] The female:male ratio (where reported) was 1.4:1.[30–40]

Table 3. Offending allergens reported in cats with adverse food reactions in selected published studies

	Number of cats	Lamb (%)	Poultry (%)	Fish (%)	Beef (%)	Dairy (%)	Egg (%)	Commercial food (%)
Leistra[35]	19	6 (31.6)	13 (68.4)					
Guaguere[34]	10			2 (20)	4 (40)	3 (30)	1 (10)	
Denis[33]	9	9 (100)						
White[31]	8			6 (75)		2 (25)		
Vogelnest[39]	14		1 (7.2)	2 (14.3)	1 (7.2)			10 (71.4)
Total (%)	60 (100)	15 (25)	14 (23.3)	10 (16.7)	5 (8.3)	5 (8.3)	1 (1.7)	10 (16.7)

Reports of clinical signs are varied, making conclusions about "typical" presenting clinical signs difficult. The data from nine studies involving 153 cats with food allergy either reported specific reaction patterns (e.g. MD, HNP, SIAH, EGC), or allowed extrapolation to one or more of these patterns.[1,14,30,31,34,36–39,41] Head and neck pruritus was reported in 42% (65 of 153), SIAH in 52% (80 of 153), MD in 31% (47 of 153) and EGC in 18% (28 of 153) of the cats. Pruritus was invariably present. Other reported cutaneous signs included urticaria,[35] nonpruritic cutaneous nodules[32] and plasma cell pododermatitis.[42] Involvement of the ears was frequently reported, yet differentiation between the pinna and ear canal was unclear. Extracutaneous signs were reported in five studies; gastrointestinal signs (e.g. flatulence, vomiting and diarrhoea) affected 18% (15 of 83) of the cats,[31,33,34,39,43] conjunctivitis was present in 12% (nine of 75),[1,31] respiratory signs in 11% (seven of 61) and hyperactivity in one cat.[35] A favourable response to antipruritic doses of oral or topical (one cat) glucocorticoids was reported in 85% (23 of 27) of cases,[37,39] whilst no response to injectable glucocorticoids was seen in another study.[41]

In these studies, the diagnosis of food allergy was achieved by conducting a hypoallergenic diet trial using a limited antigen or novel protein diet selected on the basis of the cat's previous dietary history. The duration of the diet trial varied from one to 13 weeks, which was generally determined by the time to resolution of clinical signs without the concurrent use of anti-inflammatory medications. In one study, although not ideal, no challenge was performed as the cats' clinical signs resolved completely[41] and in a second only 59% (10 of 17) of the cats were challenged for the same reason.[31] Because no challenge was performed to confirm the diagnosis of food allergy, the assumption that the nonchallenged cats were indeed food-sensitive must be interpreted with caution. The time to clinical relapse after dietary challenge was reported in three studies[35,37,39] and ranged from 15 min to 18 days. In 60 cases the offending allergens were reported and these are tabulated in Table 3.

Feline asthma

Asthma is a common lower airway inflammatory condition in cats with significant morbidity and occasional mortality. From a clinical and pathogenetic point of view, feline asthma is remarkably similar to human asthma, thus justifying the use of the cat as an animal model. As in people, affected cats show a spontaneous and natural hyperexcitability of the airways resulting in reversible bronchoconstriction.[44] Feline asthma is driven by a type-1 hypersensitivity response to aeroallergens, characterised by a T helper 2 cell-dominated cytokine profile [interleukin (IL)-5, IL-4, IL-6 and IL-13].[40,44–47]

Affected cats exhibit bronchial hyper-reactivity associated with lower airway inflammation causing dyspnoea with expiratory wheezing, chronic cough and exercise intolerance. The clinical signs observed during an asthma attack result from multiple factors which may include reversible spontaneous bronchoconstriction (airway smooth muscle constriction), oedema of the bronchial mucosa, excessive mucus production and chronic airway remodelling. Generally, cats with asthma are affected by a chronic inflammation of the airways whether or not they have clinical signs. Such inflammation is dominated by eosinophils, which represent the main effector cells of this inflammatory process. They infiltrate the submucosa and the resulting damage may lead to epithelial desquamation.[45,48,49] The asthmatic cat may present with an acute onset of expiratory dyspnoea with respiratory distress, open-mouth breathing, hyperpnoea, tachypnoea, pallor, cyanosis and collapse. The clinical signs are usually reversible with combined administration of glucocorticoids, a bronchodilator and oxygen. In some cases, a chronic cough may be the only clinical sign observed. Auscultation reveals wheezes and expiratory cracklings. The thorax may be hyper-resonant due to chronic pulmonary overinflation. Auscultation between episodes of bronchoconstriction may be completely normal. It should be remembered that coughing in the cat may resemble vomiting, because many cats will terminate a paroxysm of coughing with a retch, mimicking hacking up hairballs. Exercise intolerance in younger or more active cats often is noted.[40,45,47–49]

Diagnosis of feline asthma

As for FASS, there is no specific test for routine diagnosis of asthma in cats. Owing to lack of availability of the instrument and technical difficulties, spirometry and total

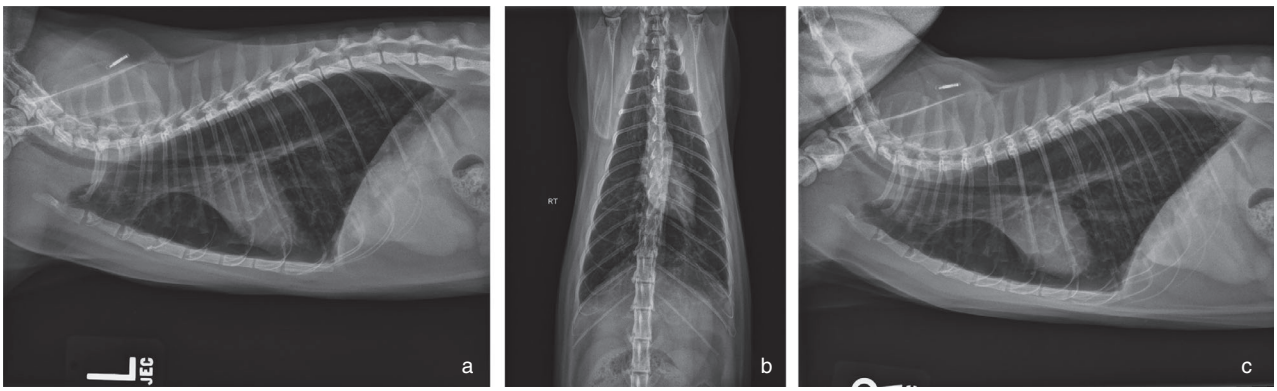

Figure 7. Thoracic radiograph of a cat with asthma.
In the three projections [left (a), sternal (b) and right (c) recumbency] is evident the soft tissue opacity characterised by air bronchograms and border effacement of the pulmonary vasculature (pulmonary hyperinflation).

body plethysmography are rarely performed for the diagnosis and monitoring of feline asthma.[49] Diagnosis is based on history, clinical signs, thoracic imaging (Figure 7), bronchoalveolar lavage (BAL) sampling and cytological examination.[46,49–51] Ruling out other diseases that mimic clinicopathological features of asthma, including chronic bronchitis, respiratory parasites, heart disease, pneumothorax, fluid effusions, tumours, foreign bodies, bacterial or viral infections, is essential.

Thoracic imaging (X-ray or computed tomography)
Radiographs commonly demonstrate a bronchial pattern with thickening of the bronchial walls due to the presence of peribronchial infiltrates, in a pattern suggestive of "doughnuts" or "rails". Pulmonary hyperinflation often is seen, causing flattening of the diaphragm. Local atelectasis also is described, most often involving collapse of the right middle lobe. The presence of air in the stomach and digestive tract may be associated with aerophagia that accompanies dyspnoea. However, some asthmatic cats may have normal thoracic radiographs. Computed tomography (CT) can be used for evaluating asthmatic cats as a complement to radiographs. The use of a Plexiglas cylinder allows acquisition of images with light or no sedation. Although CT is useful to differentiate asthmatic cats from healthy cats, it does not discriminate asthma from other lower-airway diseases.

Airway sampling
Cytological examination of the BAL is the key for differential diagnosis from chronic bronchitis. Whilst neutrophils are the markers of chronic bronchial inflammation, asthma is characterised by eosinophilic inflammation. In healthy cats eosinphilis comprise in 6–7% (up to 18%) of the total BAL cell population. Bronchial eosinophilia is defined as the eosinophil count exceeding 17–20%.[49–53] When undertaking glucocorticoid therapy, administration should be stopped for 48 h before performing the respiratory endoscopic examination and fluid collection. Although bacteriological cultures are recommended to rule out infectious diseases in asthmatic cats, they are most often negative. Feline asthma is rarely complicated by a bacterial infection.

Additional diagnostic tests
Other useful diagnostic tests to confirm feline asthma and rule out other differentials may be necessary. These include a complete blood cell count (peripheral eosinophilia is an inconsistent finding in asthmatic cats), faecal examination (faecal flotation and Baermann technique to search for *Aelurostrongylus abstrusus* and *Eucoleus aerophilus*) and heartworm testing (to rule out dirofilariosis due to *Dirofilaria immitis*).

Specific differential diagnoses to consider and eliminate to ensure a correct diagnosis of FASS

Because of the incredible variability in the clinical presentation of FASS, many differential diagnoses should be considered when approaching a cat with potential FASS (Table 4). Many other cutaneous and noncutaneous diseases also may present with encrusted papules, alopecia, head/neck pruritus and cutaneous eroded plaques.

Ectoparasitoses

In addition to fleas, cats also may harbour other ectoparasites that can cause pruritus and/or dermatitis, and these parasites must be identified or ruled out before embarking upon a workup for allergic skin disease. These include lice, *Demodex* mites (especially *D. gatoi*), *Notoedres*, *Cheyletiella*, *Otodectes*, Trombiculid mites (chiggers; *Neotrombicula/Eutrombicula*, and *Walbachia*) and *Lynxacarus*.[54–61] Although all of these mites can affect almost any area of the body, some tend to favour particular body areas, which may assist the practitioner in formulating a list of differential diagnoses. *Notoedres*, *Otodectes* and Trombiculid mites tend to be associated with clinical signs localised on the face, head and ears/pinnae.[55,58,61–65] *Cheyletiella* and *Lynxacarus* are more likely to affect the dorsum and (in the case of *Lynxacarus*) perineum, caudolateral thighs and tail base.[54,59,65]

Diagnostic tests which may prove useful in identifying these mites include superficial skin scrapings (*D. gatoi, Notoedres, Cheyletiella*, ectopic *Otodectes* and trombiculid mites), deep skin scrapings (*D. cati*), direct examination of epilated hairs (*D. gatoi, Lynxacarus*, and the as-yet-unnamed third species of feline *Demodex* mite), collection and examination of surface debris (*Cheyletiella* and ectopic *Otodectes*), acetate tape impressions of affected skin (*Notoedres*, *D. gatoi*, ectopic *Otodectes*, *Cheyletiella* and trombiculid mites), ear swabbings or collection of material using Volkmann curettes (*Otodectes* and *D. cati*), and direct examination of the affected area using a magnifying lens or otoscope (*Otodectes*, Trombiculid mites and *Cheyletiella*).[55,57,61,64–67] Faecal examination is occasionally useful for identification of mites.[55,57,67,68–70] Because many of these mites are contagious to other cats, sampling in-contact animals (which if asymptomatic may be less prone to dislodging/ingesting the mites on their own) may be useful.[57] Finally, for mites that are very difficult to find (especially *D. gatoi*), symptomatic therapy and post-treatment observation may be required.

Flea allergy dermatitis

One of the most important differentials for FASS is flea allergy dermatitis (FAD). The prevalence of fleas (and associated allergies) varies between different geographical areas. For example, fleas tend to flourish in hot, humid climates, and do less well in arid areas or at high altitudes.[71] The most common flea parasitising cats worldwide is *Ctenocephalides felis* subsp. *felis*, although other flea genera also may be present in some areas.[71,72]

The true prevalence of flea infestation and FAD is difficult to ascertain in cats, as many cases are identified and treated at the general practitioner level. Indeed, in one large single-centre retrospective study of 1,407 cats with dermatological disease, flea infestation was identified in only 7.0% (99 of 1,407) of the total feline dermatology case population, and FAD was identified in only 4.9% (70 of 1,407) of the cats.[16] By contrast, FAD was identified in 29% of 502 cats in a large multicentre retrospective study.[1] Part of the variability may be related to

Table 4. Major differential diagnoses for feline atopic skin syndrome

Reaction pattern	Main differential
Miliary dermatitis	Fleas
	Flea allergy dermatitis
	Food allergy
	Dermatophytosis
	Bacterial folliculitis
	Otodectes cynotis
	Cheyletiella spp.
	Pemphigus foliaceus
	Drug eruption
Self-induced alopecia	Fleas
	Flea allergy dermatitis
	Food allergy
	Demodex gatoi
	Dermatophytosis
	Malassezia dermatitis
	Psychogenic alopecia
	Feline lower urinary tract disease
Head and neck pruritus	Fleas
	Flea allergy dermatitis
	Food allergy
	Demodex gatoi
	Notoedres cati
	Otodectes cynotis
	Dermatophytosis
	Superficial and deep bacterial infection
	Malassezia dermatitis
	Viral diseases (herpesvirus, papillomavirus, calicivirus, poxvirus, feline leukaemia virus)
	Skin neoplasia (cutaneous lymphoma, mast cell tumour, squamous cell carcinoma)
	Adverse reaction to spot-on medication
	Drug reaction (e.g. methimazole)
	Pemphigus foliaceus
	Primary hypoparathyroidism
Eosinophilic granuloma complex (indolent ulcer, eosinophilic plaques, linear granuloma, oral granuloma)	Fleas
	Flea allergy dermatitis
	Food allergy
	Mycobacteriosis
	Nocardiosis
	Fungal disease (sporothricosis)
	Viral diseases
	Skin neoplasia (cutaneous lymphoma, mast cell tumour, squamous cell carcinoma)
	Deep bacterial infection
	Sterile granulomatous skin diseases (e.g. xanthomatosis)

geographical differences in flea distribution. The single-centre study area referenced above[16] is located in the upper northeastern United States, where long, harsh winters may limit flea numbers. By contrast, the cases evaluated in the multicentre study[1] came from a wide variety of geographical locations including France, Germany, Switzerland, southeastern United States, Belgium, Sweden, Estonia and the UK. Many of these areas have a temperate or even subtropical climate, in which fleas might be expected to flourish.

Clinical criteria have not yet been developed specifically for the diagnosis of FAD in cats. By contrast with dogs, in which the signs of flea allergy tend to be very distinctive, FAD in cats may manifest in any of the four major clinical reaction patterns: MD, SIAH, FHDP and EGC.[1,73] Cats also may demonstrate generalised, localised or focal pruritus, with or without associated excoriation and other signs of self-trauma. Flea allergy also may present in association with other forms of allergic dermatitis.[23,24,27] For these reasons, identification and elimination of FAD represents a critical step in the workup of any cat suspected of having FASS.

Historically, several methods have been proposed for confirming the diagnosis of FAD, including intradermal injection with either whole-body flea extract or extract of flea salivary antigens; serological testing to identify IgE specific for either fleas or flea saliva; evaluation of basophil activation after challenge with flea extracts; and live flea challenge exposures.[74–77] Of these, live flea challenge most closely mimics the clinical scenario and thus would be expected to be the most "specific" method of supporting a diagnosis of FAD. However, this method

Table 5. Clinical diagnostic criteria to reach a diagnosis of feline atopic skin syndrome

Diagnostic Criteria for NFHD	Diagnostic criteria for NFHD if flea hypersensitivity has been excluded
Presence of at least two body sites affected	Presence of pruritus at onset
Presence of at least two of the four clinical patterns: • Symmetrical alopecia • Miliary dermatitis • Eosinophilic dermatitis • Head and neck erosions/ulcerations	Presence of at least two of the following classical clinical reaction patterns: • Symmetrical alopecia • Miliary dermatitis • Eosinophilic dermatitis • Head and neck erosions / ulcerations
Presence of symmetrical alopecia	Presence of at least two sites affected
Presence of any lesion on the lips	Presence of miliary dermatitis as a dominant pattern
Presence of erosions or ulcerations on the chin or neck	Presence of eosinophilic dermatitis or symmetrical alopecia or erosions / ulcerations on the head, face, lips, ears or neck
Absence of lesions on the rump	Presence of nonsymmetrical alopecia on the rump, tail or hindlimbs
Absence of nonsymmetrical alopecia on the rump or tail	Presence of symmetrical alopecia on the abdomen
Absence of nodules or tumours	Absence of erosions/ulcerations on the forelimbs
	Absence of lesions on the sternum or axilla
	Absence of nodules or tumours
Fulfilment of five of the eight criteria gives a sensitivity of 75% and a specificity of 76% for the diagnosis of NFHD	Fulfilment of six of these 10 criteria gives a sensitivity of 90% and a specificity of 83% for the diagnosis of NFHD

NFHD, nonflea hypersensitivity dermatitis.

requires some skill and infrastructure to be performed successfully, and a live flea challenge would not be practical or ethical in clinical practice.

Although these methodologies may still be of use to convince the client in "flea denial", the recent availability of effective and easily administered flea control agents has rendered most of these procedures obsolete, except perhaps for research purposes. As a result, the diagnosis of FAD is now often made by the institution of total flea control for a period of nine to 12 weeks. Aggressive flea control typically involves the use of multiple agents simultaneously to target both adult and juvenile life stages. This may be accomplished by the addition of an insect growth regulator (typically a juvenile hormone analogue or chitin synthesis inhibitor) to an adulticidal product. Alternatively, some adulticidal products have effects on multiple life stages on their own or may kill quickly enough that the flea dies before eggs can be laid.

Effective flea control programmes also should incorporate some degree of environmental flea control. Both indoor and outdoor environments may be treated with insect growth regulators (particularly pyriproxifen, which is stable in ultraviolet light) to decrease the viability of any immature fleas in the environment. Frequent vacuuming may help to remove flea eggs and some larvae.

Common causes of "flea control failure" include failure to treat all in-contact animals (including dogs and small mammals); allowing the patient (or other animals in the household) to roam freely during the treatment trial; washing the patient after the application of some forms of topical flea control products; and failure to address potential other sources of fleas (e.g. continual "seeding" of flea eggs into areas such as sheds and crawl spaces by infested wildlife).

The complete resolution of signs generally supports a diagnosis of FAD as a sole entity, although the acaricidal effects of some of the newer flea control agents (e.g. isoxazolines) complicates this interpretation somehow. Partial resolution suggests the presence of one (or more) concurrent causes of pruritus/dermatitis. A complete failure to respond suggests that either the cat is not flea-allergic, or that there is a significant flaw in the flea control regimen.

Staphylococcal infection and *Malassezia* overgrowth

Staphylococcal and *Malassezia* overgrowth/infection is very common in allergic cats. They generally present with signs varying from erythema to pustules to seborrhoea. Because of the clinical similarity between such infections and some clinical presentations of FASS (head and neck pruritus, eosinophilic plaques, erythema and scaling), it is important to rule out such infections in order to have a better picture of the severity of the allergic disease.

The prevalence of superficial pyoderma, secondary to allergies, caused by staphylococci is relatively unknown in cats. However, in a retrospective study 22 of 45 (48.9%) cats harboured staphylococcal organisms on the skin surface.[15] That study[15] confirmed that when present, the infections are generally caused by coagulase-positive and coagulase-negative *Staphylococcus* spp. Among others, *S. pseudintermedius* and *S. aureus* are the species most often isolated from healthy cats and cats with skin lesions.[78] Studies in atopic people and dogs have shown an increased adherence and colonisation of *Staphylococcus* on corneocytes;[79–82] however, it is not known whether this is the case in cats with FASS.

Only three studies[15,83,84] have been published evaluating feline *Malassezia* overgrowth/infection. In one study of 18 allergic cats, *Malassezia* spp. overgrowth was diagnosed cytologically on most of the cats on more than one cutaneous site: facial skin (61.1%; 11 of 18), ventral neck (33.3%; six of 18), abdomen (33.3%; six of 18), ear canal (22.2%; four of 18), chin (11.1%; two of 18), ear pinnae (11.1%; two of 18), interdigital (5.6%; one of 18) and claw-fold skin (5%; one of 18).[83] This study was followed by a second one[84] comparing the aural microflora of

healthy, allergic and systemically ill cats. This showed a significantly higher count of *Malassezia* organisms and bacteria in the ears of allergic and systemically ill cats as compared with healthy cats. In addition, allergic cats had a significantly higher number of bacteria, not yeast when compared to systemically ill cats. Finally, a much lower prevalence (three of 45 cats; 6.7%) of *Malassezia* dermatitis was reported in a retrospective study on 45 cats with FASS.[15]

Because of the high variability (6.7–61.1%) in the prevalence of yeast (and potentially bacterial) overgrowth/infections in allergic cats, the performance of otic and skin cytological evaluation is mandatory in cats with FASS to identify the presence of such infections. As in other species, the cytological findings have to be correlated with the clinical picture and history. When such infections are present, they may contribute to pruritus. It is advisable to treat the infected cat with topical and/or systemic antimicrobials before a workup for allergic skin disease to better assess the true severity of the FASS. In addition, the assessment of skin infections is essential to ensure a better management of FASS and optimise the response to anti-inflammatory/antipruritic medications.

Diagnosis of FASS

Because of the great variability in clinical appearance of FASS, attempts have been made to provide a set or sets of criteria to guide the practitioner in making a clinical diagnosis of FASS as have been described for canine atopic dermatitis.[85–87] However, to date, no equivalent set of criteria has yet been devised for the cat. A large retrospective analysis was unable to demonstrate any clear difference between the clinical appearance of cats with FASS and cats with food allergy, with the exception of a significantly higher prevalence of seborrhoea in cats with FASS.[1,85] Although facial involvement was more consistently observed in cats with food allergy, this difference was not statistically significant.

Although no criteria have yet been developed to distinguish FASS from feline food allergy, two criteria sets have been developed to help distinguish between cats with nonflea-induced hypersensitivity dermatitis (NFHD; most commonly FASS, food allergy or both) from dermatitis owing to other causes, including flea allergy and infectious causes of pruritus (Table 5).[85] The first set of criteria is intended to help distinguish cases of NFHD from all other common causes of pruritus or dermatitis. The presence of at least five of the provided criteria is moderately sensitive and specific for NFHD. The second set of criteria is to be used if flea allergy has been ruled out. In this case, the presence of at least six of the criteria is both highly sensitive and moderately to highly specific for NFHD. Neither set of criteria is intended to substitute for a thorough search for infectious, parasitic or other forms of pruritus. However, complete exclusion of some differentials (e.g. *D. gatoi*) may be difficult to achieve. Thus, the use of the clinical criteria can help confirming a diagnosis of FASS. Indeed, if other diseases are excluded and the patient fits one or both sets of criteria, the diagnosis of food allergy or FASS is very likely. In this case, the practitioner may feel reasonably reassured that proceeding with one or more dietary elimination trial(s) to distinguish the two disorders is appropriate.

Allergen testing and FASS

Allergen testing should only be performed once the diagnosis of FASS has been reached by ruling out other disorders. Allergen tests are not diagnostic. Rather, they support a clinical diagnosis of FASS and are used to indicate which allergens may be triggering the disease and should be selected for allergen-specific immunotherapy (ASIT) if this is the preferred treatment.[88] ASIT in cats can be based on either intradermal testing (IDT) or allergen-specific IgE serology (ASIS) testing. Unfortunately, very few studies have critically evaluated IDT and ASIS in cats, and although the former is the preferred method used by clinicians, ASIS is the most commonly used technique by practitioners. This is not only because the cost associated with storage of allergens makes IDT impractical for the general practitioner, but also because IDT results are more difficult to interpret in cats as compared with other species (dog and horse).

Apart from the technical differences between the two tests, it is worth remembering that an IDT detects the presence of allergen-specific IgE bound to cutaneous mast cells, whereas ASIS assesses the presence of circulating allergen-specific IgE. As in dogs, neither IDT nor ASIS are standardised methodologies and both false positive and false negative reactions may be common.[13,14] It has been shown that in dogs the incidence of false negative intradermal reactions is approximately 10–30%;[89–90] such high percentages could derive from testing atopic-like dogs or testing at less appropriate times of the year (e.g. too far away from the peak season or in the peak season)[3] yet such data are not available for cats. Likewise, it is not known whether cross-reactivity between related allergens [e.g. house dust mites (HDM) and storage mites] occurs in cats. Positive reactions must ultimately be interpreted alongside the history and clinical signs. For these reasons, the interpretation of allergen testing can be challenging and a consultation with or a referral to a clinician is recommended.

Intradermal testing

As in dogs and people, the decision of which allergens to test is based on geographical location and data on the prevalence of allergens in the immediate environment of the patient. The assistance of local referral clinicians, veterinary and medical schools, allergy laboratories, textbooks, local human allergists or weather bureaus as well, in the USA, of the National Allergy Bureau (https://www.aaaai.org/global/nab-pollen-counts?ipb=1) may be helpful.

As in dogs, IDT is still considered the "gold standard" in feline allergy medicine; IDT gives immediate results and is thought to be biologically relevant, yet lacks standardisation. In addition, IDT is considered difficult to perform and to interpret in cats as a consequence of the weak reactions often observed in this species for which there are a number of possible causes. One possibility is the increased stress levels that cats show during a veterinary visit. Stress induces a rise in serum cortisol, which may interfere with the reactivity of the test. To reduce

stress and false negative responses, cats should be quickly sedated for IDT. Other possibilities may include low levels of reactive IgE or use of the wrong allergen concentrations. Use of the correct allergen concentration is essential, although the same allergen concentrations used in dogs generally have been used for cats. However, a few feline studies have shown that for ≤15 allergens (grass, weed and tree pollens), the concentrations currently used for dogs would be suboptimal, partially explaining the low reactivity in cats.[91–93] Likewise, using healthy cats, the optimal concentration of histamine was determined to be 1:50,000 w/v instead of 1:10,000 w/v or 1:100,000 w/v used in dogs.[3,92]

Because cats typically demonstrate weak (transient, small) reactions to IDT, the use of intravenously injected dye solutions (Evans blue and fluorescein) has been suggested.[91,94] Fluorescein dye administered intravenously at 5 mg/kg, before or immediately after the IDT, enhances and clarifies the results at 15–20 min post-IDT,[91,94] and reactions can be visualised with the aid of Wood's lamp examination.

As in dogs, intradermal injections are commonly performed on the lateral thorax, after the hair is gently clipped and the injection sites are marked. A volume of 0.05–0.1 mL is injected intradermally and the reactions evaluated after 15–20 min (by Wood's lamp examination if fluorescein is used). The reactions (diameter, turgidity, erythema and size of the wheal or simply diameter of the fluorescence) are compared to those of the positive (histamine phosphate) and negative (allergen diluent) controls. Conventionally, as in dogs, the histamine reaction is graded as 4 and the saline as 0. Subjective reactions with a score of ≥ 2 are considered positive. If intravenous dye solutions are used, positive reactions will show as blue or fluorescent. In that case, the diameter of the positive reaction is considered to be more important than the intensity.[91,94]

Percutaneous prick testing

An alternative to the IDT is the percutaneous prick test (PPT). This technique is substantially different from the IDT; in the IDT, the allergens are injected intradermally, whereas in the PPT the allergens are put on the skin surface, the skin is subsequently punctured using a specific tool or a needle and the allergen is passively absorbed. This method is associated with very low risk of adverse reactions.[95] The PPT is widely used in human allergology to test for allergic rhinitis, eczema, asthma and food allergy.[96,97]

In small animal dermatology, very few studies have assessed the usefulness of PPT in dogs[98,99] and cats[93,100] with environmental allergies. In dogs, the first study[99] comparing IDT and PPT showed that IDT was much easier to interpret than PPT, and thus for more than two decades the PPT was abandoned. New tools have been patented to administer the allergens in a more consistent and standardised fashion, and the PPT has been rediscovered first in cats[93,100] and subsequently in dogs.[98] In particular, reliable controls (6 mg/mL glycerinated histamine and 50% glycerosaline solution) have been identified in cats.[100]

In dogs and cats, PPT is administered using allergens at a dilution of 1:20 w/v (i.e. undiluted).[93,98] Once the patient is sedated, the lateral thorax is clipped and the sites for the "pricks" are marked. Then, a drop (0.05 mL) of the allergen (or control) is applied and introduced into the skin via the prick device. In cats, two devices have been tested, the Duotip-test (Lincoln Diagnostics Inc.; Decatur, IL, USA) and the Greer Pick (Greer Laboratories; Lenoir, NC, USA).[100] These devices have prongs at their end (two for the DuoTip and six for the Greer Pick) that are used to prick the skin surface. The skin reactions are read at 15–20 min. A scoring scale similar to that used for the IDT is used for the PPT. Generally, intravenous dyes are not necessary for the PPT. In a comparative study, the Greer Pick gave greater reactions than did the Duo-Tip.[100]

ASIS testing

Allergen-specific IgE serology testing is used widely in general practice because it offers many advantages over the IDT. In particular, ASIS may not require sedation (reducing the patient risk), is less traumatic (no repeated injections), more convenient (no clipping, less time consuming) and less prone to drug interference with test results (e.g. concurrent anti-inflammatory/antipruritic therapy). However, ASIS only measures circulating allergen-specific IgE and does not take into account cutaneous histaminergic and nonhistaminergic pathways. Test reliability also may be an issue, as positive reactions have been shown in nonallergic healthy cats and specific pathogen-free cats.[17,101] Unfortunately, overall, few studies have been published on the use of ASIS in cats.[13,14,17,101]

Most techniques use a solid phase anti-IgE enzyme-linked immunosorbent assay (ELISA) to evaluate the amount of circulating allergen-specific IgE. Detection may be performed using either monoclonal (more often) or polyclonal antibodies. As in dogs, one of the assays commercially available utilises a unique recombinant fragment of the extracellular portion of the human high-affinity IgE receptor alpha-subunit (FcεRIα).

An alternative or complement to the ELISA assay is offered by a rapid in-clinic immunodot assay (Allercept E-screen 2nd generation, Heska Corp.; Ft Collins, CO, USA).[14] The E-screen assay has been designed for use as screening test to enable the clinician to decide whether running a full allergen test (either ASIS or IDT) is appropriate. The assay simultaneously tests for three groups of allergens (a mixture of individual tree allergens, grass/weed allergens and indoor allergens) as well as a control spot (purified IgE). The Allercept E-screen assay was tested and validated comparing it to a classic ASIS panel in one recent study[14] in which the authors tested 62 feline serum samples (31 from healthy and 31 from atopic cats). In addition, 49 of 62 (18 healthy, 31 atopic) samples also were tested with a full panel ELISA assay and the results compared. The overall agreement between the two assays was 88% with a strong agreement between the two assays when individual allergen groups were compared. However, there was no difference in the number of positive reactions in the healthy and atopic cats using either assay (E-screen: 61.3% versus 51.6%;

ELISA: 66.7% versus 64.5%).[14] Although a strong correlation was seen between the two assays, it is important to remember that the E-screen only tests for groups of allergens and does not allow the identification of the individual offending allergens.

Another study[102], using 179 pruritic cats (FASS, food allergy, flea allergy, undetermined hypersensitivity dermatitis and nonallergic pruritic cats) and 20 healthy cats, showed a positive correlation between levels of allergen-specific IgE and age, outdoor life style, absence of deworming and absence of flea control measures. The same study[102] reaffirmed the unreliable nature of serology testing in making a diagnosis of FASS because no difference was seen among the different groups of pruritic cats.

A study using an experimental model of feline asthma with known sensitising allergens compared IDT with ASIS offered by two commercial laboratories.[103] The detection of allergen-specific IgE using a liquid phase enzymoimmunometric assay showed unreliable results. However, although the FcεRIα-based ELISA test had good specificity, it had lower sensitivity than IDT. This suggests that IDT might be a better screening test yet either can be used to guide selection of allergens for ASIT. It is important to remember that the accuracy of these tests is unknown and response to treatment (ASIT) may be the best measure with which to evaluate their accuracy.

Allergens implicated in FASS

By contrast with dogs, in which multiple studies have identified HDM as the most common allergen involved in AD, few studies describing the relative frequencies of allergen reactivity have been published on cats.[14,15,104] One Australian study[15] of 45 cats diagnosed with FASS showed that strong (≥3) IDT reactions were evident in 63.3% of tested cats (19 of 30 cats). Amongst the reactors, pollens (grass, weed and/or tree) and insects (flea, mosquito, ant, moth, horsefly and housefly) were the most common in 89.5% and 68.4% of cats, respectively. Those were followed by strong reactions to HDM (*Dermatophagoides farinae* and *D. pteronyssinus*) and flea in 47.4% and 42% of cats, respectively. Strong reactions to moulds (15.8%), storage mites (5.3%), mixed feathers (5.3%) and grain mill dust (5.3%) were present in a minority of the cats. Most of the cats in the study had multiple positive reactions mainly to pollens and insects.[15] In another study of 20 cats with spontaneous asthma, IDTs were performed in 18 cats with positive results to aeroallergens in 15.[104] The allergens identified were HDM *D. farinae* (eight of 15) and *D. pteronyssinus* (four of 15), storage mites *Acarus siro* (six of 15), *Glyciphagus domesticus* (four of 15) and *Tyrophagus putrescentiae* (four of 15), cockroach (two of 15) and pollens (eight of 15).[104] As far as allergens commonly identified via ASIS, one study[14] reported the presence of positive reactions in 63.3% (19 of 30) of sera from atopic cats; of those, 23.3% had positive reactions to indoor allergens alone. Although in another study reactivity to HDM was similar in normal and FASS cat groups,[21] 30% of cats had reactions to a combination of indoor allergens, grass/weed and tree. Very few cats had positive reactions to either grass/weed and tree (6.7%) or indoor allergens and grass/weed combinations (3.4%).

Do any drugs interfere with IDT, PPT and/or ASIS?

A possible influence of anti-inflammatory medications on the results of allergen tests in cats has been hypothesised based on canine studies.[105] However, such studies have not been undertaken in cats and detailed withdrawal guidelines are not available. Thus, the same guidelines used for dogs[105] have been generally adopted for cats; for IDT, the withdrawal time for antihistamines is seven days, 14 days for short-acting oral and topical glucocorticoids, and at least 28 days for long-acting injectable glucocorticoids. Short-term (six weeks or less) ciclosporin does not require withdrawal for IDT. Although very few studies have been published on the effects of anti-inflammatory drugs and ASIS, it is generally thought that the results of ASIS are not influenced by anti-inflammatory drugs. Currently no studies have analysed the influence of drugs on PPT in dogs or cats.

In an experimental model,[106] asthma was induced in 18 cats using Bermuda grass allergen (BGA). Cats (n = 6/group) were randomised to receive oral GCs (10 mg prednisolone once daily), inhaled GCs (600 μg budesonide once daily) or oral placebo (once daily) for one month. Intradermal testing and serum BGA-specific IgE were measured before, during and after treatment. A two week withdrawal for glucocorticoid therapy (both oral and inhaled) was adequate to restore IDT reactivity.[102]

The effects of sedatives on IDT in cats are unknown, too, yet clinicians typically use the same drug selection as is used for dogs.[3]

Summary

This review highlights the complexity of the FAS and how this syndrome involves multiple organs including skin, gastrointestinal and respiratory systems. It is essential to remember that contrary to dogs (in which the atopic disease manifests mainly with cutaneous signs), asthma may play an important role in atopic cats, and this is often underestimated by dermatologists and general practitioners. This review emphasises the strong connection between cutaneous, gastrointestinal and respiratory systems in allergic cats. Because of the strong clinical similarities between cats with food allergy and cats with FASS, if perennial clinical signs are present, food allergy has to be excluded via one or more strict food trial(s). In particular, it is worth remembering that in cats, extracutaneous clinical signs can occur in both FASS and food allergy: respiratory signs 8.3%[1,10,11,15] versus 11.5%,[35] ocular signs 4.8%[1,11,15] versus 12%[1,31] and gastrointestinal signs 3.9%[1,11,15] versus 18.1%, respectively.[31,33,34,39,43]

Likewise, in order to rule out flea allergy dermatitis, it is critical to perform very strict flea control, typically by increasing the frequency of the flea prevention medications for nine to 12 weeks.

Furthermore, it is important to remember that the diagnosis of FASS is both clinical (compatible history and clinical signs) and by exclusion of diseases with similar clinical features. Because similar clinical signs and reaction

patterns characterise several skin diseases in cats, the presence of compatible clinical signs or reaction patterns alone should not justify the diagnosis of FASS.

Finally, in this review we want to emphasise how little research has been done in cats with allergic conditions and remind the reader that much of what we do and know in feline allergies is extrapolated from dogs and humans. More studies are required in order to better assess the phenotypical variations of FAS and how different clinical manifestations respond to different treatments. This is an absolute prerequisite to enable the design of better tailored treatments.

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Résumé

Contexte – le syndrome atopique félin (FAS) décrit un spectre d'hypersensibilités caractérisées par diverses présentations cliniques comprenant la peau, le système digestif et le système respiratoire. Parmi ces atteintes, il y a le syndrome cutané atopique félin (FASS), pour lequel l'hypersensibilité est typiquement associée à des allergènes environnementaux, bien que l'allergie alimentaire puisse coexister. D'autres organes (par exemple asthme) peuvent être aussi impliqués. En raison de cette grande hétérogénéité clinique, le diagnostic du FASS peut être un défi.

Objectifs – Un sous-groupe de l'ICADA (International Committee on Allergic Diseases of Animals) a été chargé de résumer les informations les plus actuelles sur les présentations cliniques du FASS et de développer des recommandations de diagnostic.

Méthodes – Les citations des bases de données en ligne et les résumés des congrès internationaux ont été recherchés pour les publications en lien avec les allergies félines. Ceci a été combiné avec des opinions d'experts quand nécessaire.

Résultats – Un total de 107 publications pertinentes a été identifié. La compilation de ces données a permis le développement d'une description détaillée des critères cliniques du FASS et le développement de recommandations ciblant une élimination systématique des autres atteintes cutanées avec des caractéristiques cliniques semblables. Alors que les tests allergiques sont fréquemment utilisés par les dermatologues pour soutenir le diagnostic clinique du FASS, une revue rapide de ces méthodologies a aussi été réalisée.

Conclusions et importance clinique – De façon semblable à la dermatite atopique canine, le FASS est un diagnostic clinique basé sur la présence compatible avec les signes cliniques et l'exclusion d'autres maladies ayant des critères cliniques semblables. L'élimination ou l'exclusion des puces/de l'allergie aux puces, d'autres parasites, des infections et de l'allergie alimentaire est necessaire avant d'établir un diagnostic de FASS.

Resumen

Introducción – el síndrome atópico felino (FAS) describe un espectro de trastornos de hipersensibilidad caracterizados por presentaciones clínicas muy diversas que incluyen la piel, los sistemas gastrointestinal y

respiratorio. Entre estos trastornos se encuentra el síndrome de piel atópica felina (FASS), en el que la hipersensibilidad se asocia típicamente con alérgenos ambientales, aunque la alergia alimentaria puede coexistir. También puede producirse la afectación de otros sistemas orgánicos (por ejemplo asma). Debido a su presentación clínica altamente heterogénea, el diagnóstico de FASS puede ser difícil.
Objetivos – Se encomendó a un subgrupo del Comité Internacional sobre Enfermedades Alérgicas de los Animales (ICADA) que resumiera la información más actual sobre las presentaciones clínicas de FASS y que desarrollara pautas de diagnóstico recomendadas.
Métodos – Se realizaron búsquedas en la red de bases de datos de referencias y resúmenes de reuniones internacionales relacionadas con alergias felinas. Éstos se combinaron con la opinión de expertos cuando fue necesario.
Resultados – Se identificaron un total de 107 publicaciones relevantes para esta revisión. La recopilación de estos datos permitió el desarrollo de una descripción detallada de las características clínicas de FASS y el desarrollo de pautas centradas en la eliminación sistemática de otras afecciones de la piel con características clínicas similares. Dado que los dermatólogos utilizan con frecuencia las pruebas de alergia para respaldar un diagnóstico clínico de FASS, también se realizó una breve revisión de estas metodologías.
Conclusiones e importancia clínica – De manera similar a la dermatitis atópica en perros, FASS es un diagnóstico clínico basado en la presencia de signos clínicos compatibles y la exclusión de otras enfermedades con características clínicas similares. La eliminación o exclusión de pulgas/alergia a pulgas, otros parásitos, infecciones y alergia alimentaria es necesaria antes de llegar a un diagnóstico de FASS.

Zusammenfassung
Hintergrund – Das Feline atopische Syndrom (FAS) beschreibt ein Spektrum von Hypersensibilitätserkrankungen, die durch sehr unterschiedliche klinische Präsentationen auf der Haut, dem Gastrointestinaltrakt und dem Respirationstrakt charakterisiert sind. Unter diesen Erkrankungen ist auch das Feline Atopische Haut Syndrom (FASS), bei dem eine Hypersensibilität typisch mit Umweltallergenen in Zusammenhang steht, obwohl eine Futterallergie gleichzeitig bestehen könnte. Es können auch andere Organsysteme mit involviert sein (z.B. Asthma). Aufgrund der hochgradig heterogenen klinischen Präsentation kann die Diagnose der FASS eine Herausforderung darstellen.
Ziele – Eine Untergruppe des International Committee on Allergic Diseases of Animals (ICADA) sollte die gängigste Information über die klinischen Präsentationen vom FASS zusammenfassen und diagnostische Richtlinien entwerfen.
Methoden – Es wurden Online Literaturstellen und Abstracts von internationalen Treffen auf Publikationen über Allergien der Katze durchsucht. Diese wurden, wenn nötig, mit einer Expertenmeinung kombiniert.
Ergebnisse – Es wurden insgesamt 107 Publikationen, die für dieses Thema relevant waren, identifiziert. Eine Erfassung dieser Daten erlaubte die Entwicklung einer detaillierten Beschreibung der klinischen Merkmale des FASS und die Entwicklung von Richtlinien, die sich auf die systematische Eliminierung von anderen Hauterkrankungen mit ähnlichen klinischen Charakteristika konzentrieren. Da Allergietests von Dermatologen häufig verwendet werden, um eine klinische Diagnose des FASS zu untermauern, wurde eine kurze Review dieser Methoden durchgeführt.
Schlussfolgerungen und klinische Bedeutung – In einer ähnlichen Weise wie bei der atopischen Dermatitis der Hunde, ist das FASS eine klinische Diagnose, die auf dem Vorkommen von kompatiblen klinischen Zeichen und einem Ausschluss anderer Krankheiten mit ähnlichen klinischen Merkmalen beruht. Eine Eliminierung von Flöhen/Flohspeichelallergie, anderer Parasiten, Infektionen und Futterallergie sind zwingend notwendig, bevor die Diagnose einer FASS getroffen werden kann.

要約
背景 – ネコアトピー症候群 (FAS) は、皮膚、胃腸、呼吸器系を含む非常に多様な臨床症状を特徴とする一連の過敏症を説明している。これらの障害の中には、食物アレルギーが共存する可能性があるものの、過敏症が通常環境アレルゲンと関連しているネコアトピー性皮膚症候群 (FASS) がある。他の臓器系 (喘息など) の関与も発生する可能性がある。その非常に不均一な臨床症状のために、FASSの診断は困難な場合がある。
目的 – 動物のアレルギー性疾患に関する国際委員会 (ICADA) のサブグループは、FASSの臨床症状に関する最新情報を要約し、診断ガイドラインを作成する任務を負った。
方法 – オンライン引用データベースと国際会議の要約を検索して、猫アレルギーに関連する出版物を探した。これらは、必要に応じて専門家の意見と組み合わされた。
結果 – このレビューに関連する合計107の出版物が特定された。これらのデータの編集により、FASSの臨床的特徴の詳細な説明の開発および、同様の臨床的特徴を持つ他の皮膚状態の体系的な排除に焦点を当てたガイドラインの開発が可能になった。アレルギー検査はFASSの臨床診断をサポートするために皮膚科医によって頻繁に使用されるため、これらの方法論の簡単なレビューも行われた。
結論と臨床的重要性 – 犬アトピー性皮膚炎と同様に、FASSは、互換性のある臨床徴候の存在と、同様の臨床的特徴を持つ他の疾患の除外に基づく臨床診断である。 FASSの診断に達する前に、ノミ/ノミアレルギー、他の寄生虫、感染症、および食物アレルギーの排除または排除が義務付けられている。

摘要

背景 — 猫特应性综合征(FAS)涵盖了一系列超敏反应疾病，以高度多样化的临床表现为特征，包括皮肤、胃肠道和呼吸系统。这些疾病包括猫特应性皮肤综合征(FASS)，其中超敏反应通常与环境过敏原相关，尽管食物过敏可能同时存在。也可能累及其他器官系统(如哮喘)。由于其高度异质性的临床表现，FASS的诊断可能具有挑战性。

目的 — 国际动物过敏性疾病委员会(ICADA)的一个亚组的任务是总结FASS临床表现的最新信息，并制定诊断指南。

方法 — 检索在线引文数据库和国际会议摘要中与猫过敏相关的出版物。必要时结合专家意见。

结果 — 共找出107篇与本综述相关的出版物。汇编这些资料能够制定FASS临床特征的详细描述和制定指南，重点是系统性消除具有相似临床特征的其他皮肤疾病。由于皮肤科医生经常使用过敏试验来支持FASS的临床诊断，因此还对这些方法进行了简要综述。

结论和临床重要性 — 与犬特应性皮炎相似，FASS的临床诊断是基于相符的临床症状，并排除具有相似临床特征的其他疾病。在确诊FASS之前，必须消除或排除跳蚤/跳蚤过敏、其他寄生虫、感染和食物过敏。

Resumo

Contexto – A síndrome atópica felina (SAF) descreve um espectro de distúrbios de hipersensibilidade caracterizados por uma apresentação clínica altamente diversa, incluindo a pele, sistema gastrointestinal e respiratório. Dentre esses distúrbios está a síndrome atópica cutânea felina (FASS, *feline atopic skin syndrome)*, na qual hipersensibilidade é tipicamente associada a alérgenos ambientais, apesar de alimentos poderem coexistir. O envolvimento de outros sistemas (ex: asma) pode também ocorrer. Devido a essa apresentação clínica altamente heterogênea, o diagnóstico da FASS pode ser desafiador.

Objetivos – Um subgrupo do *International Committee on Allergic Diseases of Animals (ICADA)* foi designado a sintetizar as informações mais recentes sobre as apresentações clínicas da FASS, e a desenvolver diretrizes diagnósticas.

Métodos – Bancos de dados de citações online e resumos de congressos internacionais foram utilizados para buscar publicações relacionadas a alergias em felinos. Quando necessário, estes foram combinados com as opiniões dos experts.

Resultados – Um total de 107 publicações relevantes a essa revisão foram identificados. A compilação desses dados permitiu o desenvolvimento de uma descrição detalhada das características clínicas da FASS e o desenvolvimento de diretrizes focando a eliminação sistemática de outras dermatopatias com características similares. Como os testes alérgicos são frequentemente utilizados por dermatologistas para apoiar o diagnóstico clínico de FASS, uma rápida revisão destas metodologias foi realizada.

Conclusões e importância clínica – Semelhante à dermatite atópica em cães, a FASS é um diagnóstico clínico baseado nos sinais clínicos compatíveis e exclusão de outras doenças com características clínicas similares. A eliminação de pulgas/alergia à picada de pulgas, outros parasitas, infecções e alergia alimentar é mandatória antes de se fechar o diagnóstico da FASS.

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