

A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis

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Conflict of Interest

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Abstract

Canine atopic dermatitis (CAD) is a multifaceted disease associated with exposure to various offending agents such as environmental and food allergens. The diagnosis of this condition is difficult because none of the typical signs are pathognomonic. Sets of criteria have been proposed but are mainly used to include dogs in clinical studies. The goals of the present study were to characterize the clinical features and signs of a large population of dogs with CAD, to identify which of these characteristics could be different in food-induced atopic dermatitis (FIAD) and non-food-induced atopic dermatitis (NFIAD) and to develop criteria for the diagnosis of this condition. Using simulated annealing, selected criteria were tested on a large and geographically widespread population of pruritic dogs. The study first described the signalment, history and clinical features of a large population of CAD dogs, compared FIAD and NFIAD dogs and confirmed that both conditions are clinically indistinguishable. Correlations of numerous clinical features with the diagnosis of CAD are subsequently calculated, and two sets of criteria associated with sensitivity and specificity ranging from 80% to 85% and from 79% to 85%, respectively, are proposed. It is finally demonstrated that these new sets of criteria provide better sensitivity and specificity, when compared to Willemse and Prélard criteria. These criteria can be applied to both FIAD and NFIAD dogs.

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Introduction

The term canine atopic dermatitis (CAD) is used in veterinary dermatology to describe a pruritic and inflammatory dermatitis, which is driven most commonly by an IgE-antibody-associated reaction.¹ The revised nomenclature for veterinary allergy also takes into account dogs with clinical signs of atopic dermatitis but no demonstrable allergen-specific IgE: the term atopic-like dermatitis (ALD) was coined to describe this group of dogs.¹

In veterinary dermatology, cutaneous adverse food reaction (CAFR) and CAD have been historically considered as two different conditions.² In fact, CAFR includes both immune-mediated and non-immune-mediated food intolerances and may be associated with a wide range of clinical signs such as gastrointestinal disturbances, urticaria, angioedema and signs mimicking those of atopic dermatitis. This latter point has led the International Task Force on Canine Atopic Dermatitis to suggest that some cases of CAFR may trigger flares of atopic dermatitis.³ The clinical signs of CAD may thus be associated with sensitization to environmental (CAD *sensu stricto*), food allergens (CAFR with clinical signs of CAD) or with ALD. It is worth noting that the role of food-specific IgE in the development of FIAD is not firmly demonstrated.

Two sets of criteria have been proposed for making the diagnosis of CAD (Willemse' and Prélard's criteria).^{4,5} Willemse's criteria are usually used in clinical studies but have never been validated. Prélard's criteria were validated but the tested sample was geographically and quantitatively limited. It is generally agreed that both sets of criteria should only be used after ruling out other causes of pruritus. A food trial should also be completed to rule out FIAD. As FIAD and CAD are clinically indistinguishable, one can conclude that criteria used for the diagnosis of CAD could also be used for the diagnosis of FIAD. To the authors' knowledge, this has, however, never been demonstrated.

The historical criteria for the diagnosis of human atopic eczema (Hanifin and Rajka⁶) were also never validated and Williams *et al.* (the so-called UK working party) used a different set of criteria.⁶⁻¹² In order to validate these criteria, interestingly, they did not use the Hanifin and Rajka criteria as the gold standard. On the contrary, they used the 'key physician clinical diagnosis as a gold standard'.¹¹

The same approach has been used in this prospective study. The goals of this study were (i) to describe a large population of dogs with CAD and to compare this population with dogs affected by other chronic pruritic conditions; (ii) to evaluate the predefined sets of criteria (Willemse and

Prélaud) and to determine their sensitivity and specificity; (iii) to determine if other sets of criteria may exist and to evaluate them; and (iv) to compare dogs with FIAD and dogs with CAD *sensu stricto* and test selected criteria on each population.

Material and methods

Definitions

For the purpose of this study we defined CAD as cases with clinical features of atopic dermatitis irrespective of the offending agents (i.e. environmental or food allergens). The diagnosis of CAD was not based on the fulfilment of any criteria but on the exclusion of any resembling disease and on the clinical judgement of each investigator. In this study, CAD encompassed three possible diagnoses:

1. Food-induced atopic dermatitis (FIAD): Dogs with clinical features of atopic dermatitis and a positive response to a six- to eight-week elimination diet and subsequent challenge.
2. Undetermined atopic dermatitis (UAD): Dogs with clinical signs of atopic dermatitis never subjected to an elimination diet.
3. Non-food-induced atopic dermatitis (NFIAD): Dogs with clinical signs of atopic dermatitis and negative response to an elimination diet. ALD dogs were also included in this group.

Study population and record of data

Thirty-four veterinary dermatologists working in 15 different countries located in Europe, North and South America and Japan participated in the study. Dogs included in the study had chronic (more than 2 months) or recurrent (more than two episodes) pruritus.

For every dog entering the study, a set of relevant historical and clinical parameters and the results of diagnostic tests were systematically recorded in a standardized form (Table 1). For every parameter, the information was entered qualitatively as presence or absence or not applicable/unknown when the information was not available. Responses to interventions could also be recorded as good/poor/unknown. Regarding breed predisposition, the list established by Sousa *et al.* was used.¹³

Diagnostic procedure

A standardized diagnostic procedure for chronic pruritus was used, including: diagnosis and control of ectoparasites infections, cytological examinations for bacterial and yeast infections, skin biopsy and histological examination of tissues to rule out diseases such as cutaneous lymphoma or sebaceous adenitis, fungal culture to rule out dermatophytosis and any other test deemed necessary to make the diagnosis. For the diagnosis of CAD *per se*, participants were not asked to use any set of criteria but, on the contrary, to use their clinical judgement. To confirm or exclude FIAD, participants chose themselves the most appropriate type of food for this test and assessed the response as consistent with a diagnosis of FIAD.

Cases were only used for data analysis if a definitive diagnosis could be made. A diagnosis was considered definitive when the participant had carried out the compulsory investigation and was able to assign the case to one of the following predefined diagnoses: CAD (FIAD, NFIAD or UAD) or non-CAD condition (e.g. fleas, *Sarcoptes*, *Demodex*, other ectoparasites, bacterial or yeast overgrowth, dermatophytosis or other pruritic conditions).

In order to provide homogeneous data, investigator diagnoses were verified by one of the authors (CF) by systematically checking the consistency of the recorded parameters with the final diagnosis (i.e. a dog with final diagnosis FIAD should have responded adequately to an elimination diet; a dog with final diagnosis 'sarcoptic mange' should have responded adequately to ectoparasite control). If a discrepancy was found, the case was excluded from the analysis. In addition, cases with more than two diagnoses (e.g. sarcoptic mange and CAD or FIAD and demodicosis) were not included in the data to avoid confounding factors leading to the improper allocation of diagnostic criteria.

Characterization of the dog populations

The analysis of the data was undertaken in several steps. The population of dogs classified as suffering from CAD were first considered

Table 1. Frequency of clinical features in canine atopic dermatitis dogs

1a. Signalment and history

Criterion	No	Yes	Frequency
Sex female	429	414	0.49
Age at onset less than 2 years	403	440	0.52
Age at onset less than 3 years	265	578	0.68
Mostly indoor*	132	706	0.84
Mostly outdoor*	755	76	0.09
Indoor and outdoor*	787	56	0.06
Urban environment*	498	333	0.4
Rural environment*	591	240	0.29
Both environments*	573	258	0.31
Improv./degrad. when moving from usual environment*	89	47	0.35
Familial history of atopic dermatitis*	780	63	0.07
Breed predisposition†	414	429	0.51
Seasonality	641	202	0.24
Seasonality spring/summer	679	164	0.2
Seasonality winter	805	38	0.04
Corticosteroid-responsive pruritus	184	659	0.78
Efficacy of previous antibiotics good*	169	407	0.71
Efficacy of previous antifungals good*	61	153	0.71
Pruritus sine materia at onset	330	513	0.61

1b. Clinical signs and allergy tests

Criterion	No	Yes	Frequency
Dry skin/seborrhea sicca	686	157	0.19
Seborrhea oleosa	724	119	0.14
Chronic or recurrent bacterial infections	283	560	0.66
Chronic or recurrent yeast infections	567	276	0.33
Chronic or recurrent otitis externa	420	423	0.5
Otitis externa, first episode before other signs*	241	182	0.43
Spring/summer conjunctivitis	667	176	0.21
Spring/summer sneezing/rhinitis	787	56	0.07
Previous episodes hot spots	768	75	0.09
Previous episodes of urticaria	815	28	0.03
Concomitant interdigital fistulas	737	106	0.13
Chronic diarrhoea/vomiting	730	113	0.13
Hyperhidrosis	737	106	0.13
Affected front feet	176	667	0.79
Affected hind feet	213	630	0.75
Affected elbows	676	167	0.2
Affected axillae	321	522	0.62
Flexural dermatitis	527	316	0.38
Affected abdomen/inguinae	289	554	0.66
Affected front limbs (other sites)	583	260	0.31
Affected hind limbs (other sites)	581	262	0.31
Affected ear pinnae	355	488	0.58
Affected ear margins	775	68	0.08
Affected lips	491	352	0.42
Affected eyelids	570	273	0.32
Affected face (other sites)	617	226	0.31
Affected genitalia/ventral tail	477	366	0.43
Affected lateral thorax or flanks	657	186	0.22
Affected chest	573	270	0.32
Affected dorso lumbar	687	156	0.09
Positive intradermal test*	76	292	0.79
Positive serology*	59	294	0.84
Positive intradermal test and/or positive serology*	80	494	0.86

*Not all cases were documented.

†List of predisposed breeds was established according to Sousa *et al.*¹³

as a homogenous group and descriptive statistics were performed. This population was then compared with the population of dogs with a non-CAD condition. Frequency of occurrence of all recorded criteria was analysed in both populations. For each individual criterion, sensitivity, specificity and correlation factors were calculated separately.

In a second step, FIAD dogs were compared to NFIAD dogs. Dogs with CAD belonging to the UAD population, namely dogs without information on the elimination diet, were excluded from the analysis. The two populations CAD *sensu stricto* and FIAD were compared to detect statistically significant differences between these two populations.

Selection of sets of diagnostic criteria

Criteria previously proposed by Willemse and Prélaud (three major and three minor criteria for the first set and three criteria for the second one) were first applied to the whole population (dogs with and without CAD) and sensitivity and specificity of these sets of criteria were calculated (see Appendix S1 in Supporting Information). Since the measurement of allergen-specific IgG, one of the Willemse criteria, could not be obtained in all cases, this criterion was not taken into account.

In order to generate new sets of criteria and optimize the diagnosis of CAD, simulated annealing was applied. Simulated annealing is a heuristic method for minimization of 'energy', which is a multidimensional function of the set of diagnostic criteria. The method works by repeated addition and deletion of diagnostic criteria.¹⁴

Series of sets including five to 10 criteria were selected through the statistical procedure described above. These sets corresponded to the highest sensitivity, specificity and combination of both [lowest energy defined as $1 - (\text{sensitivity} \times \text{specificity})$]. All selected sets of criteria were carefully evaluated based on number of selected criteria in a set, sensitivity, specificity, energy and their practicality for use in routine practice such as simplicity and robustness. In order to select a set of criteria which could be used in general practice, sets containing criteria that were difficult to record or rarely recorded were not retained. The procedure resulted in the selection of two sets, one with the criterion 'Corticosteroid-responsive pruritus' and one without.

Sensitivity and specificity of these sets were compared to the predefined sets established by Willemse and Prélaud.

In this last part of the study, criteria selected for the diagnosis of CAD dogs were tested on the dog population diagnosed as suffering from FIAD. Sensitivity, specificity and energy were calculated and compared to those of the whole population.

Statistical procedures

Descriptive statistics and simulated annealing were performed using SAS 9.1.3 (SAS 9.1.3 Help and Documentation, 2004; SAS Institute Inc., Cary, NC, USA). Comparison between NFIAD and FIAD dogs were carried out using chi-squared and Fisher exact tests (GraphPad Instat 3, GraphPad Software, San Diego, CA, USA). Proportions were considered statistically significant when $P < 0.05$ after multiplication of the computed P value by the number of tested parameters.

Results

Animals and diagnoses

One thousand–five hundred and forty-two dogs were initially included in the study with the following final diagnoses (Table 2): CAD (NFIAD or FIAD or UAD) and non-CAD (fleas and flea allergy dermatitis or sarcoptic mange or other ectoparasites (cheyletiellosis, demodicosis, etc.) or other infections (primary pyoderma, pyoderma or yeast infections of unknown origins, other fungal and bacterial diseases) or other diseases (cutaneous lymphoma,

Table 2. Study populations

Diagnosis	Initial population	Used population
CAD	1107	843
NFIAD	759	571
FIAD	248	172
UAD	100	100
Non-CAD	435	253
Fleas	143	80
Sarcoptes	67	37
Other parasites	90	58
Skin infections	57	42
Other diseases	78	36
Total	1542	1096
Excluded dogs	448	

CAD, canine atopic dermatitis; FIAD, food-induced atopic dermatitis; NFIAD, non-food-induced atopic dermatitis; UAD, undetermined atopic dermatitis.

sebaceous adenitis, hyperadrenocorticism with secondary infections, etc.). Four hundred and forty-eight cases with an inaccurate diagnosis and/or more than two diagnoses were excluded from the studies and thus, 1096 were taken into account for the final analysis (Table 2), with 843 in the CAD group and 253 in the non-CAD conditions group.

Clinical features of CAD and comparison between FIAD and NFIAD

Description of the population of dogs with CAD

The population of dogs with CAD consisted of 843 individuals (429 males/414 females sex ratio: 0.49) from more than 80 different breeds. Some breeds appeared more frequently represented, such as West Highland white terrier ($n = 102$), Labrador retriever ($n = 62$), German shepherd ($n = 57$), golden retriever ($n = 45$), boxer ($n = 45$) and bulldogs (French and English together, $n = 37$). Owing to the absence of any control population, it was not possible to determine any breed predisposition. The mean age at onset of the disease was 2.2 years (see Table 1 for this criterion and the following ones), with 68% of affected dogs experiencing the first signs of the disease before 3 years of age. Interestingly, most of the affected dogs were living indoors, spending most of their time in the house. In 35% of animals that changed environments, the owners reported either an improvement or a worsening of the clinical signs and 24% experienced worsening of clinical signs during a specific season. Pruritus was often the first observed clinical sign (pruritus sine materia [(pruritus without any other skin changes)] at onset: 61%) and the pruritus was highly responsive to treatment with glucocorticoids (78%). Allergic dogs were often affected with secondary bacterial or yeast infections (66% and 33%, respectively) and with otitis externa (50%). In 43% of allergic dogs with chronic otitis, the signs of otitis were noticed by the owners before the other signs of allergy. The study also showed the most frequently affected areas were the feet, the axillae, the abdomen and the pinnae. Other signs such as urticaria, rhinitis, areas of pyotraumatic dermatitis or interdigital fistulae were, on the contrary, rarely observed in association with

CAD. Intradermal and serological tests were usually positive (86%) in NFIAD dogs (494 dogs tested).

Comparison of populations with FIAD and NFIAD

The same criteria were compared in populations of dogs diagnosed with FIAD and NFIAD (Table 3). Proportions observed in the two populations were similar; however, a few differences were statistically significant. Age distribution was different between the two populations but were not statistically significant. Dogs with FIAD were more frequently very young (less than 1 year: 46.5% versus 38.6%; $P = 0.06$) or old (more than 6 years: 8.7% versus 3.8%, $P = 0.06$). Compared to NFIAD dogs, FIAD dogs did not usually flare during any specific season (89.5% without seasonality for FIAD dogs versus 71.9% for NFIAD dogs, $P < 0.001$). FIAD dogs experienced more gastrointestinal disturbances than dogs with NFIAD ($P < 0.001$). The eyelids were more frequently affected in NFIAD compared to FIAD ($P = 0.04$) although the occurrence of conjunctivitis was similar in these two populations. Pruritus was less responsive to treatment with glucocorticoids in FIAD compared to NFIAD ($P < 0.001$). Similarly, pruritus sine materia was also more frequently observed in NFIAD dogs ($P < 0.01$).

Diagnosis of CAD

The population of dogs with CAD ($n = 843$) was compared to the population of dogs not suffering from CAD ($n = 253$). Sensitivity, specificity and correlations between the assignment in one or another group and each specific criterion were computed. Results are presented in Table 4. A correlation of > 0.15 was obtained for 10 criteria, this correlation was taken as the threshold for a high association with the disease.

These criteria were (i) age at onset < 3 years, (ii) living indoor, (iii) corticosteroid responsive pruritus, (iv) pruritus sine materia at onset, (v) chronic or recurrent yeast infections, (vi) chronic or recurrent otitis externa, (vii) affected feet (front and hind), (viii) affected axillae, (ix) affected ear pinnae and (x) good efficacy of previous antibiotic therapy.

In contrast, two criteria were highly associated with non-CAD conditions: affected ear margins and affected dorso-lumbar area.

Willemse's and Prélard's criteria were subsequently tested on this population of 1096 dogs. This analysis revealed a sensitivity and specificity of 49.3% and 80.2%, respectively for Willemse criteria, and from 74.3% and 68.4%, respectively for Prélard's criteria.

The procedure of simulated annealing generated numerous sets of criteria associated with energy below or equal to 0.36, and two sets were selected because they include criteria which are readily accessible and easily available (see Appendix S2 in Supporting Information). The criterion 'corticosteroid-responsive pruritus' was included only in the first set. In these two sets, specificity ranged between 79.1% and 83%, which implies that a false positive diagnosis is made in every fifth examined dog. Specificity could be improved dramatically by increasing the number of criteria from 5 to 6 (88.5% and 93.7% for the first and second set, respectively).

The last step of our study consisted of testing these two sets of criteria in FIAD dogs. Applying both sets to

Table 3. Comparison food-induced atopic dermatitis (FIAD) and non-food-induced atopic dermatitis (NFIAD) dogs

	n	Sex ratio Male/ Female	Mean age at onset (year)	Age at onset < 1 (%)	Age at onset < 2 (%)	Age at onset < 3 (%)	Age at onset > 6 (%)	No seasonality (%)	Corticosteroid- responsive pruritus (%)	Pruritus sine materia (%)	Dry skin oleosa (%)	Seborrhea bacterial infection (%)	Chronic or recurrent		Chronic conjunctivitis (%)	Spring summer (%)	Spring summer rhinitis (%)	Previous episodes of hot spots (%)	Previous episodes of urticaria fistulae (%)	
													Chronic or recurrent yeast infection (%)	Chronic or recurrent otitis externa (%)						
FIAD dogs	172	91/81	2.2	46.5	61%	77.3	8.7	89.5	64	47.1	19.2	12.8	69.8	37.8	53	21.5	4	9.3	3.4	16.9
NFIAD dogs	571	278/294	2.1	38.6	69.8	78.8	3.8	71.9	85.2	62.7	16.6	15.2	66.3	32.9	48.8	21.5	8.2	9.3	3.8	11.5
P-value		NS	NS	NS	NS	NS	NS	< 0.001	< 0.001	< 0.001	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

	n	Chronic diarrhoea or soft stools (%)	Hyperhidrosis (%)	Affected front feet (%)	Affected hind feet (%)	Affected axillae (%)	Flexural dermatitis (%)	Affected abdomen sites (%)	Affected other sites (%)	Affected limbs (other sites) (%)	Affected hind limbs (%)	Affected front limbs (%)	Affected face		Affected eyelids (%)	Affected other sites (%)	Affected genitalia (%)	Affected thorax (%)	Affected chest (%)	Affected dorso- lumbar (%)
													Affected pinnae (%)	Affected margins (%)						
FIAD dogs	172	26.2	14.2	177	72.1	15.1	32.1	60.8	29.4	33.7	60.8	9.4	39.1	25.8	29.8	39.2	18.1	35.1	14.6	
NFIAD dogs	571	10.5	11.2	80.9	77	19.2	39.7	67.3	26.4	28	59.3	8.4	45.5	34.3	26.9	45.8	25	31.5	19.2	
P-value		< 0.001	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	0.04	NS	NS	NS	NS	NS	

NS, not significant.

Table 4. Sensitivity, specificity and correlation of all clinical features with the diagnosis canine atopic dermatitis

Criterion	Correlation	P value	Sensitivity	Specificity
Sex female	0.034	0.257	0.491	0.549
Age at onset less than 2 years	0.097	0.0013	0.522	0.593
Age at onset less than 3 years	0.158	< 0.0001	0.686	0.494
Mostly indoor	0.186	< 0.0001	0.837	0.34
Mostly outdoor	-0.118	0.0008	<i>0.91</i>	<i>0.178</i>
Indoor and outdoor	-0.121	0.0009	<i>0.934</i>	<i>0.146</i>
Urban environment	-0.054	0.075	<i>0.605</i>	<i>0.458</i>
Rural environment	0.053	0.0712	0.285	0.771
Both environments	0.005	0.8636	0.306	0.7
Improv./degrad. when moving from usual environment	0.008	0.7844	0.056	0.949
Familial history of atopic dermatitis	-0.001	0.9845	<i>0.925</i>	<i>0.075</i>
Breed predisposition	0.069	0.0215	0.509	0.573
Seasonality	0.046	0.1122	0.24	0.806
Seasonality spring/summer	0.014	0.6474	0.195	0.818
Seasonality winter	0.074	0.0008	0.045	0.988
Corticosteroid-responsive pruritus	0.343	< 0.0001	0.782	0.593
Efficacy of previous antibiotics poor	-0.135	< 0.0001	<i>0.8</i>	<i>0.336</i>
Efficacy of previous antibiotics good	0.192	< 0.0001	0.483	0.743
Efficacy of previous antifungals poor	-0.098	0.0052	<i>0.928</i>	<i>0.138</i>
Efficacy of previous antifungals good	0.143	< 0.0001	0.181	0.941
Pruritus sine materia at onset	0.174	< 0.0001	0.609	0.597
Dry skin/seborrhea sicca	-0.098	0.0027	<i>0.814</i>	<i>0.281</i>
Seborrhea oleosa	0.038	0.1871	0.141	0.889
Chronic or recurrent bacterial infections	0.073	0.0179	0.664	0.419
Chronic or recurrent yeast infections	0.181	< 0.0001	0.327	0.866
Chronic or recurrent otitis externa	0.208	< 0.0001	0.502	0.743
Otitis externa, first episode before other signs	0.082	0.003	0.216	0.862
Otitis externa, first episode concomitant or after	0.149	< 0.0001	0.237	0.905
Spring/summer conjunctivitis	0.133	< 0.0001	0.209	0.913
Spring/summer sneezing/rhinitis	0.078	0.001	0.066	0.976
Previous episodes hot spots	-0.059	0.0762	<i>0.911</i>	<i>0.13</i>
Previous episodes of urticaria	-0.006	0.858	<i>0.967</i>	<i>0.036</i>
Concomitant interdigital fistulas	-0.04	0.2071	<i>0.874</i>	<i>0.158</i>
Chronic diarrhoea/vomiting	0.093	0.0003	0.134	0.937
Hyperhidrosis	0.13	< 0.0001	0.126	0.968
Affected front feet	0.273	< 0.0001	0.791	0.498
Affected hind feet	0.268	< 0.0001	0.747	0.549
Affected elbows	-0.119	0.0003	<i>0.802</i>	<i>0.316</i>
Affected axillae	0.157	< 0.0001	0.619	0.565
Flexural dermatitis	0.111	< 0.0001	0.375	0.751
Affected abdomen/inguinae	0.029	0.3448	0.657	0.375
Affected front limbs (other sites)	0.044	0.1362	0.308	0.739
Affected hind limbs (other sites)	-0.048	0.1228	<i>0.689</i>	<i>0.364</i>
Affected ear pinnae	0.231	< 0.0001	0.579	0.696
Affected ear margins	-0.223	< 0.0001	<i>0.919</i>	<i>0.253</i>
Affected lips	0.119	< 0.0001	0.418	0.719
Affected eyelids	0.028	0.3399	0.324	0.708
Affected face (other sites)	-0.034	0.268	<i>0.732</i>	<i>0.304</i>
Affected genitalia/ventral tail	0.053	0.073	0.434	0.628
Affected lateral thorax or flanks	-0.109	0.0008	<i>0.779</i>	<i>0.332</i>
Affected chest	-0.021	0.4868	<i>0.68</i>	<i>0.344</i>
Affected dorso lumbar	-0.376	< 0.0001	<i>0.815</i>	<i>0.585</i>
Negative intradermal test	0.017	0.5716	0.09	0.921
Positive intradermal test	0.199	< 0.0001	0.346	0.87
Negative serology	-0.054	0.1063	<i>0.931</i>	<i>0.103</i>
Positive serology	0.271	< 0.0001	0.349	0.941
Willemse major criterion 3: affected members or face	0.208	< 0.0001	0.945	0.194
Willemse major criterion 4: breed or familial disposition	0.08	0.0076	0.53	0.565

Figures in italics: negative correlations.

Figures in bold: significant correlations.

FIAD dogs resulted in sensitivities of 80.2% and 70.3%, respectively, and specificities of 85.7% for both sets. Adding one criterion did not result in improvement in specificity with the first set but on the contrary yielded a specificity of 100% for the second set.

Discussion

The goals of the present study were to characterise the clinical features and signs of CAD of a large population of dogs, to identify which of these characteristics could be

different in FIAD and NFIAD and to develop criteria for the diagnosis of this condition.

Numerous studies aiming to describe clinical features of CAD and FIAD dogs have been published previously.^{15–32} Results are, however, sometimes difficult to compare with ours because of different study designs or study groups.^{15–32} This could explain some of the discrepancies observed.

When considering the characteristics of the whole population of dogs with CAD, most studies, including the present one, did not report any sex predilection, male predisposition was reported only once and female predisposition twice.^{20,30,32} Our study also showed that about two thirds of the affected dogs exhibited the first signs before the 3 years of age, which is in agreement with most of the previous studies.²⁰ In only one study was it reported that all atopic Labrador retriever dogs and golden retriever dogs exhibited some dermatological signs as early as 11 months of age and atopic-type skin changes by 15 months of age.¹⁹ However, this study was designed to identify signs predictive of future development of CAD which may explain this discrepancy. In our study, we found that very early or late onset of the clinical signs were more frequently observed in FIAD dogs, when compared to NFIAD, even if the differences did not reach a statistically significant *P* value (*P* = 0.06). First clinical signs were observed before 1 year of age in 46.5% of the dogs and after 6 years of age in 8.7% of FIAD dogs. Early onset of clinical signs in FIAD dogs is also reported by Verlinden *et al.* (31–51%) and by Chesney (37.5%), who additionally reported that FIAD can occur at any age, including aged dogs.^{16,26}

Seasonality of clinical signs is also an important feature of CAD, which was observed in 28.1% of NFIAD dogs in our study. This is less than in previous studies which report a frequency in the range of 32–75%.²⁰ The discrepancy can be explained by the fact that only chronic pruritus cases were included in our study and that we recorded the seasonality of the clinical cases at the time of the clinical examination but not at the onset. In fact, it was already reported that clinical signs of atopic dermatitis are often seasonal at onset and become perennial after several months to years.²⁰

We found a lower frequency of CAD dogs living in an urban environment compared to the non-CAD population (40% of allergic dogs living in cities versus 60.5% of non-atopic dogs). This may appear contradictory with a Swedish study where urban environment was considered a risk factor for the development of CAD.²² One must also keep in mind that we have compared two populations of pruritic dogs and that the Swedish study has compared atopic dogs with healthy ones. Additionally, our study reveals a higher frequency of CAD in the dogs living mostly indoors as reported in Hungary.²⁵ This may reconcile both findings as dogs living in cities probably spend more time indoor than others.

Finally, our study confirmed the pattern of the anatomic distribution of the lesions already described, and the high frequency of association between otitis externa, pyoderma and *Malassezia* dermatitis and CAD which has been frequently observed earlier.

The general agreement between studies is striking in spite of the limitations resulting from the differences in inclusion criteria, diagnostic work-up and study procedures.²⁰

Our study confirmed that FIAD and NFIAD cannot be clinically distinguished. Only a few differences were found in the clinical features of these two conditions but they cannot be used to establish a differential diagnosis on a routine basis. Pruritus was less frequently responsive to glucocorticoid treatments in FIAD than in NFIAD, which has already been reported.^{15,18} The age of onset tending to be earlier or later in FIAD than in NFIAD as mentioned earlier is the only feature which might be used to differentiate the two conditions.

The diagnosis of CAD is difficult because none of the typical signs or features are pathognomonic. The use of sets of criteria to establish a diagnosis of the multifaceted disease is still debated. Some authors consider it should only be a diagnosis of exclusion, with resembling diseases such as ectoparasites (e.g. fleas, *Sarcoptes*) and skin infections being first ruled out.³³ Diagnostic criteria are, however, useful for clinical studies and can also be helpful in clinical practice, if used appropriately and knowing their limitations in terms of sensitivity and specificity.

Our study is the first to test and select sets of criteria based on a large and geographically widespread population of pruritic dogs. It allowed retrospective assessment of the sensitivity and specificity of diagnostic criteria sets already used. It is interesting to note that the sensitivity of Willemse criteria was only close to 50%, which indicate these criteria led to a wrong diagnosis in a substantial number of cases. On the other hand, sensitivity and specificity values measured on Prélud criteria were relatively close to those previously obtained by this author. Simulated annealing, a systematic mathematical approach, generated new sets of criteria with higher sensitivity and specificity. Optimizing energy resulted in sensitivity and specificity ranging from 80.2% to 85.4% and from 79.1% to 85.7%, respectively, which corresponds approximately to an incorrect diagnosis in every fifth pruritic dog. This is adequate for a screening test, which is not supposed to be used alone but in the context of a thorough clinical examination after exclusion of ectoparasites, fungal and bacterial infections. In the context of clinical studies aiming at testing drugs for the treatment of CAD, a high specificity should be searched and more positive criteria are then required for inclusion of dogs into the studies. With six positive criteria instead of five in the screening test, specificity can reach values above 85%.

Simulated annealing not only optimised both sensitivity and specificity but also provided a means to select criteria which are easily accessible in routine practice and not ambiguous. For example it was possible to exclude from our sets the criterion 'corticosteroid-responsive pruritus' without reducing the sensitivity and specificity. Prélud *et al.* with a different methodology could not exclude it without decreasing markedly the overall energy of their set of criteria.⁴ This criterion is rather subjective and subject to the interpretation of both practitioner and dog owner. It is also dependant on the nature and the dosage of the glucocorticoid which is often not precisely known. Practitioners should, however, be aware that only the response of dogs treated with an anti-inflammatory dose of glucocorticoids (i.e. 0.5 to 1 mg/kg once daily of prednisolone) should be interpreted, as higher doses are very likely to decrease pruritus in all itchy dogs.

These criteria have been used on two populations of dogs, the whole population of dogs with CAD and the smaller population of dogs with FIAD, with approximately similar results, which was expected owing to the clinical similarities of both conditions.

NFIAD and FIAD are multifaceted diseases, which are probably associated with several genetic mutations. Breed-associated phenotypes have also been described and criteria corresponding better to each breed would be helpful. They may be associated with higher sensitivity and specificity. These aspects are beyond the scope of this study and will be addressed elsewhere.

In conclusion, we propose to use the first set of criteria (with five positive criteria) in the context of general practice as a screening test (Appendix S2). This set is, however, not intended to replace a proper clinical examination and should be used after exclusion of ectoparasites (appropriate test and/or treatment), bacterial and fungal diseases. Additionally, after the diagnosis CAD has been made, an elimination diet should be carried out to determine whether food allergens play a role in the development of the disease. Using the same first set with six positive criteria could also be very helpful in clinical studies.

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Appendix 1. Criteria proposed by Willemse⁵ and Prélud⁴

Willemse

Major criteria:

- Pruritus
- Typical morphology and distribution: Facial and/or digital involvement or lichenification of the flexor surface of the tarsal joint and/or the extensor surface of the carpal joint
- Chronic or chronic relapsing dermatitis
- Individual or family history of atopy and/or breed predisposition

Minor criteria:

- Onset of signs before 3 years
- Facial erythema and cheilitis
- Bilateral conjunctivitis
- Superficial staphylococcal pyoderma
- Hyperhidrosis
- Immediate positive intradermal test to inhalants
- Elevated serum allergen-specific IgE
- Elevated serum allergen-specific IgG

Prélud:

- Cortico-steroid-sensitive pruritus
- Erythema of the pinnae
- Bilateral cranial erythematous pododermatitis
- Cheilitis
- Appearance of first signs between the ages of 6 months to 3 years

Appendix 2: sets of criteria and associated sensitivities and specificities

Set 1:

1. Age at onset <3 years
2. Mostly indoor
3. Corticosteroid-responsive pruritus
4. Chronic or recurrent yeast infections
5. Affected front feet
6. Affected ear pinnae
7. Non-affected ear margins
8. Non-affected dorso-lumbar area

Set 2:

1. Age at onset <3 years
2. Mostly indoor
3. Pruritus sine material at onset
4. Affected front feet
5. Affected ear pinnae
6. Non-affected ear margins
7. Non-affected dorso-lumbar area

	CAD dogs				FIAD dogs			
	5 criteria		6 criteria		5 criteria		6 criteria	
	sens.	spec.	sens.	spec.	sens.	spec.	sens.	spec.
SET 1	0.854	0.791	0.582	0.885	0.802	0.857	0.541	0.857
SET 2	0.772	0.83	0.42	0.937	0.703	0.857	0.355	1

Résumé La dermatite atopique canine (DAC) est une maladie multifactorielle liée à de multiples allergènes environnementaux et alimentaires. Son diagnostic est difficile puisqu'aucun de ses signes cliniques n'est pathognomonique. Différents critères ont été proposés et sont principalement utilisés pour l'inclusion de sujets dans des études cliniques. Les objectifs de cette étude étaient d'identifier les critères anamnétiques et cliniques d'une large population de chiens atopiques, de déterminer ceux pouvant être attribués aux atopiques sensibilisés aux trophallergènes (FIAD) d'une part, aux atopiques sensibilisés aux aéro-allergènes (NFIAD) d'autre part et d'en déduire les critères de diagnostic. Les critères sélectionnés ont été testés sur une population large et géographiquement étendue de chiens à prurit. L'étude décrit d'abord le signalement, l'anamnèse, les signes cliniques d'une grande population de chiens atopiques, compare les individus FIAD et NFIAD et confirme que les deux conditions sont cliniquement indifférentiables. Des corrélations entre de nombreuses caractéristiques cliniques et le diagnostic de DAC sont ensuite établies. Deux séries de critères associant sensibilité et spécificité s'étendant de 80 à 85% et de 79 à 85% respectivement, sont proposés. Il est finalement démontré que ces nouveaux ensembles de critères sont plus sensibles et plus spécifiques que ceux de Willemse et Prélaud. Ces critères peuvent être appliqués aux FIAD comme aux NFIAD.

Resumen La dermatitis atópica canina (CAD) es una enfermedad con componentes múltiples asociada con la exposición a varios agentes ofensivos tales como agentes del medio ambiente o alérgenos de la comida. El diagnóstico de esta condición es difícil porque ninguno de los signos típicos son patognomónicos. Se han propuesto una serie de criterios que se han utilizado fundamentalmente para incluir los perros en los estudios clínicos. Los propósitos del presente estudio fueron establecer las características y signos clínicos de una amplia población de perros con CAD, identificar cuales de estas características podrían ser diferentes en dermatitis atópica inducida por alimentos (FIAD) y en dermatitis atópica no inducida por alimentos (NFIAD), así como desarrollar criterios para el diagnóstico de esta condición. Utilizando alineamiento simulado, se probaron los criterios de selección en una población geográficamente amplia de perros con prurito. El estudio primero describe la reseña, historia y características clínicas de una población amplia de perros con CAD, comparando FIAD y NFIAD, y confirmó que ambas condiciones son clínicamente indistinguibles. A continuación se calcularon las correlaciones de numerosas características clínicas con el diagnóstico de CAD y se propusieron dos grupos de criterios asociados con sensibilidad y especificidad entre 80–85% y 79–85% respectivamente. Finalmente se demuestra que estos grupos de criterios aportan mayor sensibilidad y especificidad en comparación con los criterios de Willemse and Prélaud. Estos criterios se pueden aplicar tanto a perros con FIAD como con NFIAD.

Zusammenfassung Die canine atopische Dermatitis (CAD) ist eine facettenreiche Erkrankung, die im Zusammenhang mit der Exposition zu verschiedenen krankmachenden Stoffen, wie Umwelt- und Futterallergenen, steht. Die Diagnose dieser Erkrankung ist schwierig, da keines der typischen klinischen Symptome pathognomonisch ist. Mehrere Sets von Kriterien sind vorgeschlagen worden, sie werden aber hauptsächlich zur Aufnahme von Hunden in klinische Studien verwendet. Die Ziele der vorliegenden Studie waren es, die klinischen Merkmale und Symptome einer großen Hundepopulation mit CAD zu charakterisieren, zu identifizieren welche dieser Charakteristika bei Futter-induzierter atopischer Dermatitis (FIAD) und Nicht-Futter-induzierter atopischer Dermatitis (NFIAD) verschieden sein könnten und Kriterien für die Diagnose dieser Erkrankung zu erarbeiten. Mittels simulierter Abkühlung wurden ausgewählte Kriterien an einer großen und geographisch weit verstreuten Population von juckenden Hunden getestet. Die Studie beschrieb zunächst Anamnese und klinische Merkmale einer großen Hundepopulation mit CAD, verglich FIAD und NFIAD Hunde und bestätigte, dass beide Erkrankungen klinisch nicht unterscheidbar sind. Die Korrelationen zwischen den zahlreichen klinischen Merkmalen und einer Diagnose der CAD wurden in der Folge kalkuliert und zwei Sets von Kriterien mit einer Sensitivität von 80% bis 85% und einer Spezifität von 79% bis 85%, wurden vorgeschlagen. Es konnte letztendlich gezeigt werden, dass diese neuen Kriterien, im Vergleich zu den Willemse und Prélaud Kriterien, eine bessere Sensitivität und Spezifität bieten. Die neuen Kriterien können sowohl für FIAD wie auch für NFIAD Hunde angewendet werden.