

ORIGINAL ARTICLE

Clinical comparison of human and canine atopic dermatitis using human diagnostic criteria (Japanese Dermatological Association, 2009): Proposal of provisional diagnostic criteria for canine atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a common skin disease encountered in both humans and dogs. Canine AD can be used in the analysis of naturally occurring AD; however, details of clinical comparison have been lacking. The purpose of this study is to compare those clinical features using the human diagnostic criteria (Japanese Dermatological Association, 2009). Fifty-one dogs with canine AD were evaluated by the human criteria. Prior to this study, canine AD was basically diagnosed by the fulfillment of two authentic canine AD criteria and a positive reaction against *Demodex phagoides farinae* in serum immunoglobulin E levels and/or in intradermal tests. Among the human AD criteria items, behavior corresponding to pruritus was observed in all 51 dogs. Skin lesions corresponding to eczematous dermatitis were seen in 50 dogs, and symmetrical distribution of skin lesions was noted in all 51 dogs. A chronic or chronically relapsing course was observed in 50 dogs. Based on these results, the concordance rate for the criteria was 96% (49/51). Differential diagnoses of AD were also investigated in the same manner. The concordance rate for the criteria was 0% (0/69) in scabies, 2% (1/50) in pyoderma, 0% (0/50) in demodicosis, 0% (0/9) in cutaneous lymphoma, 0% (0/2) in ichthyosis, 25% (2/7) in flea allergy, 48% (24/50) in seborrheic dermatitis and 75% (3/4) in food allergy. Canine AD is thus indicated as a valuable counterpart to human AD in clinical aspects. In addition, the human AD criteria could be applicable, with some modification, as provisional diagnostic criteria for canine AD.

Key words: animal model, atopic dermatitis, comparative dermatology, diagnosis, dog.

INTRODUCTION

An appreciation of the evolutionary history of skin structure and biochemistry, and knowledge of skin diseases in animals, gives perspective to the human condition but may also provide clues to understanding human skin disease.¹ Some diseases appear to be identical or very similar in humans and animals. Although common skin diseases encountered in both humans and dogs are limited, there are several con-

cordant disorders, such as scabies, seborrheic dermatitis and atopic dermatitis (AD).² AD is pruritic, eczematous dermatitis in humans, and the symptoms are characterized by chronic fluctuation with remissions and relapses. Most individuals with AD have atopic diathesis, which is related to a personal or family history of atopy (asthma, allergic rhinitis and/or conjunctivitis, or AD) and/or a predisposition to overproduction of immunoglobulin (Ig)E antibodies.³ Animal models may give some clues about epidemiology,

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pathogenesis or genetic aspects.¹ Mice offer many benefits, including low cost, short time to maturity, availability of reagents and the opportunity to evaluate the effects of specific genetic alterations. While some mice have been used as an animal model of human AD, their contribution is limited in the analysis of naturally occurring AD.⁴ For this purpose, canine AD (cAD) can be used as an animal model because dogs live in the human lifestyle environment. It is important to investigate the pathological condition and pathogenesis of cAD in comparison with human AD. In cAD, epidermal barrier functions such as discontinuity of lipid lamellae,⁵ decreased transepidermal water loss,⁶ filaggrin expression in the epidermis,⁷ immunological events such as T-helper cell (Th)1/2 imbalance,⁸ expression of chemokines,^{9,10} and association with *Staphylococcus*^{11,12} and *Malassezia*^{13,14} have been investigated, and the majority of findings were similar to those in human AD. In addition, a comparison of the phenotype in human and canine AD is important for investigating the nature of this multifactorial disease, but detailed analyses in terms of clinical comparison have been limited.^{15,16} In general, the use of diagnostic criteria for human disease is considered a valuable approach for identifying its counterpart in animals. However, this has not been applied to AD.¹⁷ In human AD, the diagnostic criteria proposed by Hanifin and Rajka¹⁸ in 1980 are used worldwide, but they are difficult to apply to cAD diagnosis because most of the 23 minor features cannot be determined in dogs. These include keratoconus, anterior subcapsular cataract, facial pallor, pityriasis alba, itch when sweating, and intolerance to wool and lipid solvents, which cannot be assessed in animal dermatology clinics. Based on the above, the simple diagnostic criteria established by the Japanese Dermatological Association (JDA) in 2009 appear to be suitable for application to dogs with cAD in Japan.³ The purpose of this study is to compare the clinical human and canine AD features using the JDA diagnostic criteria to verify cAD as a human counterpart.

METHODS

Fifty-one dogs with cAD were evaluated using the JDA diagnostic criteria (2009) (Table 1).^{3,19} All cases

Table 1. Diagnostic criteria for atopic dermatitis by the Japanese Dermatological Association, 2009

Pruritus
Typical morphology and distribution
Eczematous dermatitis
Acute lesions: erythema, exudation, papules, vesiculopapules, scales, crusts
Chronic lesions: infiltrated erythema, lichenification, prurigo, scales, crusts
Distribution
Symmetrical
Predilection sites: forehead, periorbital area, perioral area, lips, periauricular area, neck, joint areas of limbs, trunk
Age-related characteristics
Infantile phase: starts on the scalp and face, often spreads to the trunk and extremities
Childhood phase: neck, the flexural surfaces of the arms and legs
Adolescent and adult phase: tendency to be severe on the upper half of body (face, neck, anterior chest and back)
Chronic or chronically relapsing course (usually coexistence of old and new lesions)
More than 2 months in infancy
More than 6 months in childhood, adolescence and adulthood
Definitive diagnosis of atopic dermatitis requires the presence of all three features without any consideration of severity. Other cases should be evaluated on the basis of age and clinical course with a tentative diagnosis of acute or chronic, non-specific eczema.
Differential diagnosis (association may occur)
Contact dermatitis, seborrheic dermatitis, prurigo simplex, scabies, miliaria, ichthyosis, xerotic eczema, hand dermatitis (non-atopic), cutaneous lymphoma, psoriasis, immune deficiency diseases, collagen diseases (systemic lupus erythematosus, dermatomyositis), Netherton's syndrome
Diagnostic aids
Family history (bronchial asthma, allergic rhinitis and/or conjunctivitis, atopic dermatitis), personal history (bronchial asthma, allergic rhinitis and/or conjunctivitis), follicular papules (goose-skin), elevated serum immunoglobulin E level.
Clinical types (not applicable to the infantile phase)
Flexural surface type, extensor surface type, dry form in childhood, head/face/neck/upper chest/back type, prurigo type, erythroderma type, combinations of various types are common
Significant complications
Ocular complication (cataract and/or retinal detachment): especially in patients with severe facial lesions, Kaposi's varicelliform eruption, molluscum contagiosum, impetigo contagiosa

were referred to the ASC during the period from February 1997 to August 2009. Prior to this study, cAD was basically diagnosed by the fulfillment of two

Table 2. Diagnostic criteria for canine atopic dermatitis by Willemse (1986, 1988)

Major features
Patient must have at least three of the following features:
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 features
At least three of the following features should also be present:
Onset of symptoms before 3 years
Facial erythema and cheilitis
Bacterial conjunctivitis
Superficial staphylococcal pyoderma
Hyperhidrosis
Immediate positive intradermal test reaction to inhalants
Elevated serum allergen-specific immunoglobulin E
Elevated serum allergen-specific immunoglobulin G

Table 3. Diagnostic criteria for canine atopic dermatitis by Prélard *et al.* (1998)

Major criteria
Patient must have at least three of the following five features:
Corticosteroid-sensitive pruritus
Erythema of pinnae
Bilateral cranial erythematous pododermatitis
Cheilitis
Appearance of first signs between the ages of 6 months and 3 years
Differential diagnosis
Flea allergy dermatitis, adverse food reaction, scabies or other pruritic mite infestation, pruritic bacterial folliculitis, <i>Malassezia</i> dermatitis, cornification disorders, contact dermatitis

authentic cAD criteria (Tables 2,3)^{20,21} and a positive reaction against *Dermatophagoides farinae* in serum IgE levels and/or in intradermal tests (IDT).²² While the precise pathological role of IgE has not been elucidated in dogs, it is customarily used for diagnosis of cAD.²³ Serum was collected and submitted to a commercial laboratory (Saloon, Kyoto, Japan) to measure IgE levels using an FcεRIα-based enzyme-linked immunosorbent assay (ALLERCEPT Definitive Allergen Panels; Heska, CO, USA). The test result was considered positive when the optical density was over 400 U, according to a previous study.^{22,24} In IDT, *D. farinae* at 1/50 000 w/v (Greer Labs, Lenoir,

NC, USA) was used as the antigen.²⁵ The positive control solution was histamine phosphate 1/100 000 v/w, and the negative control solution was physiological saline. Of the control solutions and allergen, 0.04 mL were injected i.d. intradermally at the lateral thorax.²⁶ IDT reactions were read 10–15 min after injection. Reactions were scored positive with the appearance of wheals equal to or greater than those of the positive control. Prior to IDT, all anti-inflammatory drug therapy, including oral and topical glucocorticoids and antihistamines, was discontinued for at least 3 weeks and 10 days, respectively. In order to clarify the differential diagnosis, all differentials in the criteria and any differentials considered in cAD were evaluated.

RESULTS

Pruritus

Behavior corresponding to pruritus such as licking, scratching, biting, chewing and rubbing was observed in all 51 dogs (100%) with cAD.

Typical morphology and distribution

Eczematous dermatitis

Skin lesions corresponding to eczematous dermatitis, such as erythema with or without lichenification, were seen in 50 dogs (98%) with cAD. In only one dog, the history of skin lesions did not correspond to eczematous dermatitis, but there were hyperpigmentation and alopecia. These lesions could be explained as secondary lesions related to eczematous dermatitis.

Distribution

Symmetric distribution of skin lesions including typical flexure sites was seen in all 51 dogs (100%) with cAD (51/51). Lesions were located at the anterior auricle in 63% (Fig. 1), perioral area in 61% (Fig. 2), periorbital area in 49% (Fig. 3), flexural surface of the limbs in 33%, trunk in 33% and neck in 24%. On the trunk, lesions were observed precisely at the axillae (18%), inguinal area (16%), ventral abdomen (16%) and lumbar area (4%). The forehead is one of the predisposed sites in humans, but it is not clearly defined in dogs. Compared to humans, dogs with AD appear to have several different sites of predilection, including

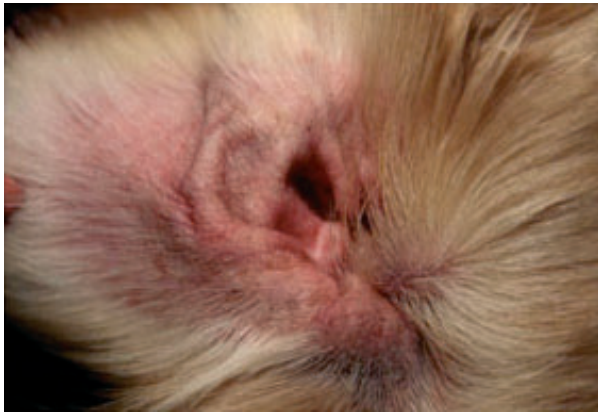


Figure 1. Erythema of the anterior auricle of a dog with canine atopic dermatitis.



Figure 2. Erythema of the perioral area of a dog with canine atopic dermatitis.



Figure 3. Erythema and lichenification of the periorbital area of a dog with canine atopic dermatitis.



Figure 4. Erythema of the interdigital area of a dog with canine atopic dermatitis.

the interdigital area (61%) (Fig. 4), and perianal, perineum or perigenital region (12%).

Chronic or chronically relapsing course

More than 6 months of a chronic or chronically relapsing course was observed in 50 dogs (98%) with AD. Only one dog failed to show such a course. The case was an 8-month-old dog at the time of examination, with a 5-month history of dermatitis. In this study, the mean age of referrals was 4.7 years. However, the age at onset was less than 2 years old in 31% of the cases, and in no cases in this study did the first onset of skin lesions occur at over 6 years old. In addition, summer seasonality was observed at the first onset year in 27.4% of the cases.

Differential diagnosis

We next investigated the differential diagnosis of cAD compared with other canine skin diseases.^{3,21} The concordance rate for the AD criteria was 0% (0/69) in scabies, 2% (1/50) in pyoderma, 0% (0/50) in demodicosis, 0% (0/9) in cutaneous lymphoma, 0% (0/2) in ichthyosis, 25% (2/7) in flea allergy, 48% (24/50) in seborrheic dermatitis and 75% (3/4) in food allergy (Table 4). Contact dermatitis and systemic lupus erythematosus as differentials in human AD are extremely rare in dogs. We did not encounter these disorders in the course of our investigation. Prurigo simplex, miliaria, xerotic eczema, hand dermatitis (non-atopic), psoriasis, immune deficiency diseases, dermatomyositis and Netherton's syndrome are differentials of human AD reported in humans, but not in dogs.

Table 4. Concordance rate of human criteria for atopic dermatitis in dogs with differentials (%)

	Demodicosis (n = 50)	Scabies (n = 69)	Ichthyosis (n = 2)	Pyoderma (n = 50)	Seborrheic dermatitis (n = 50)	Flea allergy (n = 7)	Food allergy (n = 4)
Pruritic behavior	86	100	50	100	100	100	100
Typical morphology and distribution	22	3	0	8	60	29	75
Eczematous dermatitis	22	4	0	22	60	43	75
Distribution	60	35	100	8	100	29	75
Chronic or chronically relapsing course	46	25	50	52	74	72	75
Correspondence rate	0	0	0	2	48	29	75

Table 5. Provisional diagnostic criteria for canine atopic dermatitis

Pruritic behavior (licking, scratching, biting, chewing or rubbing)
Typical morphology and distribution
Eczematous dermatitis
Erythema with or without lichenification that is not characterized by scaling, seborrhea and crusting
Distribution
Symmetrical
Anterior auricle, interdigital area, perioral area, periorbital area, joint area of limbs, ventral abdomen, axilla, inguinal area
Chronic or chronically relapsing course
More than 6 months
Definitive diagnosis of canine atopic dermatitis requires the presence of all three features without any consideration of severity. Other cases should be evaluated on the basis of clinical course with the tentative diagnosis of acute or chronic, non-specific dermatitis
Differential diagnosis (association may occur)
Seborrheic dermatitis, flea allergy, food allergy, contact dermatitis
Diagnostic aid
Elevated immunoglobulin (Ig)E level against <i>Dematophagoides farinae</i> (>400 U with the serum allergen-specific IgE test using the high-affinity IgE receptor)

Diagnostic aids

In general, a reliable family history was not available for pet dogs. In personal histories, bronchial asthma was seen in 0% of the cases, allergic rhinitis in 0% and conjunctivitis in 7.8% (4/51). Follicular papules were not observed in dogs with cAD. No significant complications such as cataracts described in human criteria were seen in dogs.

Concordance rate for JDA criteria on cAD

Among the human AD criteria, the concordance rate for the criteria on human AD on these cAD dogs was

96% (49/51). In general, the pruritic behavior seen in cAD was rare in other canine skin diseases except for seborrheic dermatitis, flea allergy, food allergy and contact dermatitis.

DISCUSSION

This study evaluated the clinical features of cAD to verify its applicability as a counterpart to human AD through the use of diagnostic criteria for human AD (JDA, 2009). This was the first approach to AD in terms of comparative dermatology and the human criteria demonstrated an extremely high concordance rate to cAD. It is therefore indicated that cAD is a valuable counterpart to human AD in clinical aspects, while some modification was required for using the criteria. First, we found that pruritus was not an appropriate descriptive term for use with dogs because it is a rather subjective complaint used more for humans. Pruritic behavior indicated by licking, scratching, biting, chewing and rubbing is more appropriate for describing the symptom in dogs. Second, current veterinary dermatology hesitates to use the term eczema, preferring dermatitis as a pathological description rather than a morphological one. In this study, we specified eczema as erythema with or without lichenification related to pruritic behavior because a doctor can easily recognize these skin symptoms. Another concern was evaluating the distribution of skin lesions because dogs have a different anatomical structure compared to humans. Interestingly, the common sites of skin lesions in cAD were similar to those in human AD, although some lesions seemed to be dog specific. In this regard, sites on the trunk in cAD were precisely the ventral abdomen,

axillae and inguinal, even though the incidence rate was not high. In addition, the interdigital area was predominant in dogs, but not in humans. However, the ventral abdomen and interdigital area were all considered as flexure sites. Distribution of skin lesions in human AD is affected by several factors including barrier dysfunction, local flexion and/or self-rubbing behavior.^{27,28} It is suggested that this scenario is operative in dogs as well as in humans. The last consideration was the difference in lifespan of dogs relative to humans, which might affect the evaluation of their clinical course. In this study, most of the dogs had more than a 6-month history because all cases were referrals with a chronic course. However, approximately one-fourth of the cAD dogs had summer seasonality at least in the first episode. In such cases, follow-up observation is required to finalize the diagnosis of cAD.

The criteria did rule out various non-atopic dermatoses with pruritic behavior, such as scabies, pyoderma, demodicosis and ichthyosis, but not seborrheic dermatitis, flea allergy, food allergy and contact dermatitis. Seborrheic dermatitis is a common dermatitis in humans.²⁷ Its distinctive morphology is characterized by red, sharply-demarcated lesions covered with oily-looking scales, and a distinctive distribution on well-supplied areas of sebaceous glands.²⁹ In dogs, seborrheic dermatitis is characterized by scaling and greasiness, with gross evidence of local or diffuse inflammation.²³ The skin lesions of seborrheic dermatitis in dogs are similar to those in humans, even though their distribution is more generalized, particularly at the flexural and intertriginous area because in dogs the entire body is completely covered with pilosebaceous units.²³ In dogs, the distribution of seborrheic dermatitis is quite similar to that in cAD, but it is crucial to note that seborrheic dermatitis shows predominant scaling and seborrhea compared to cAD. After careful evaluation, we could differentiate seborrheic dermatitis from cAD. Flea allergy is a pruritic skin disease caused by hypersensitivity reactions against flea salivary antigens. The most common onset age is 3–5 years,²³ and skin lesions are typically confined to the dorsal lumbosacral area, caudomedial thighs, ventral abdomen and flanks. Clinical features are basically different from those in cAD, although some cases of cAD may show concurrent features. Food allergy is an adverse reac-

tion to foods or food additives, and is an important exacerbation factor in cAD.³⁰ Although classic cases were scarce, we must always consider the association with cAD. Contact dermatitis is another important differential diagnosis of cAD. It may share its preponderant sites with cAD such as perioral area, anterior auricle, axillae, inguinal area, ventral abdomen and interdigital area, and there is a difficulty in taking a detailed history for contactants.²³ However, symmetrical distribution and chronic or chronically relapsing course in multifocal preponderant regions are the unique diagnostic prerequisites for cAD. Eventually, patch test is a valuable diagnostic tool to conclude contact dermatitis in dogs as well as in humans.

There are several diagnostic criteria for identifying cAD, and two authentic criteria were used in this study. Favrot *et al.*³¹ recently reported a low concordance rate of these two cAD criteria. No reports have compared human AD and cAD. In the present study, we demonstrated that human AD criteria by JDA are readily acceptable for use in dogs, and may be even more useful with some modification and an appendix of diagnostic aids, particularly in dogs with first occurrence. As for diagnostic aids, elevated serum *D. farinae*-specific IgE level might be useful for cAD. The clinical value of the serum allergen-specific IgE test using the high-affinity IgE receptor (ALLERCEPT) in cAD was investigated in our previous study.²⁴ ALLERCEPT against *D. farinae* was measured in 50 dogs with classic cAD and 151 non-cAD dogs with pruritic behavior. Sensitivity was 98% and specificity was 80.8% on cAD with 400 U as the cut-off. Because elevated IgE against *D. farinae* is useful for identifying atopic diathesis, it may be considered a diagnostic aid. We would like to propose provisional diagnostic criteria for cAD based on JDA criteria (Table 5).

In conclusion, cAD is indicated as a valuable counterpart to human AD in its clinical phenotype. Furthermore, the proposed provisional diagnostic criteria could be applicable for identifying cAD, but their validity must be confirmed in additional cases, including mild forms, in veterinary primary care.

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