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Review: Clinical and histological manifestations of canine atopic dermatitis

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Background – Many studies focusing on clinical and histological signs of canine atopic dermatitis (AD) have been published since its early descriptions decades ago. Findings of these studies contributed to our current knowledge about the disease pathogenesis and allowed establishment of diagnostic criteria used by clinicians and researchers.

Objectives – This review serves as an update on the clinical and histological features of canine AD published by the American College of Veterinary Dermatology Task Force on Canine Atopic Dermatitis in 2001 and summarizes the recent discoveries in these fields.

Results – The overall findings of studies focusing on clinical features mirrored those published by the Task Force in 2001. The novelty was the larger number of animals included in these studies, which allowed establishment of a new set of diagnostic criteria that exceeded the sensitivity and specificity of the previous criteria. The same study uncovered some clinical differences between dogs with food-induced and nonfood-induced AD; however, the authors concluded that these two entities cannot be distinguished based on clinical signs only. Another study demonstrated some major breed-specific phenotypes. Several publications addressed the histological features of canine AD skin lesions in experimental models of AD, but none of those addressed naturally occurring lesions. Nevertheless, the histopathological description of the skin reactions was generally similar to that published by the Task Force in 2001.

Conclusions – Considerable work has been done in recent years to provide a better definition of the clinical appearance and histopathology of canine AD. New sets of diagnostic criteria have been developed, and additional breed-associated differences in phenotypes have been demonstrated.

Introduction

Canine atopic dermatitis (AD) has been the object of investigation for many decades. Discoveries in the clinical, histological, immunological and epidemiological aspects of the disease led to the definition of canine AD as a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features

associated with immunoglobulin E (IgE) antibodies, most commonly directed against environmental allergens.¹ Despite the many years of research, investigations of clinical and histological features of AD in dogs are still of interest to many clinicians and researchers because they allow us not only to diagnose the disease more precisely, but also to obtain an insight into the possible pathomechanism of the condition.

Clinical manifestations of canine atopic dermatitis

Historical perspective

Since the early descriptions of canine AD more than seven decades ago, several studies focusing on clinical signs and, later, their reliability as diagnostic criteria have been published and reviewed.² Pruritus, especially of the feet, face and axillae, was described in some of the early publications focusing on the cutaneous manifestations of canine AD.^{3,4} The following 10 years brought studies orientated more specifically on the types of skin lesions

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and their quantification.^{5–7} As a result, clinical criteria for canine AD were proposed by Willemse (1986) and were later amended by Prélaud *et al.* (1998)^{8,9} The latter criteria included a steroid-responsive pruritus, erythema of the pinnae, bilateral cranial erythematous pododermatitis, cheilitis and appearance of first signs between the ages of 6 months and 3 years. Prélaud's criteria were validated but were based on a small population of dogs with a limited geographical distribution.

In 1999, the American College of Veterinary Dermatology (ACVD) Task Force on Canine AD undertook a review of the available literature on canine AD. As a result, a series of manuscripts, including one on the clinical phenotype of canine AD, were published in 2001. This manuscript established the picture of 'typical' clinical manifestations of canine AD.² This valuable information, together with the identification of diagnostic criteria by Willemse and Prélaud, have been important steps in creating the first validated scoring system for use in clinical trials, called the Canine Atopic Dermatitis Extent and Severity Index (CADESI-03).¹⁰ Although rigorously validated, CADESI-03 has shown limited use by veterinarians because of its time-consuming nature. Indeed, multiple clinical trials have published so-called 'modified CADESI-03' to allow for more convenient assessment of the enrolled cases. Such scoring systems are, however, not validated, which needs to be taken into account when interpreting the study results or conducting systematic reviews.

A handful of studies focusing on clinical manifestations of canine AD have been published since 2001.^{11–17} These studies have included a total of 2880 dogs from North and South America, Europe, Japan and Australia and enhanced our current knowledge about the clinical phenotype of canine AD. In addition, a new set of diagnostic criteria was proposed in 2010 (Table 1, criteria set 1).¹² In contrast to the previously proposed criteria, selection of these criteria and their validation were based on data analysis from a large number of dogs (1096 dogs) and included 15 different countries worldwide. This set of criteria has been shown to have 85% sensitivity and 79% specificity for the diagnosis of AD in dogs exhibiting five of the criteria, which exceeds the sensitivity and specificity of previously proposed criteria by Willemse and Prélaud *et al.*^{8,9,12} The growing knowledge about the clinical phenotypes of canine AD and the need for a more convenient validated scoring system led subsequently to the development of two additional validated scoring systems, Canine Atopic Dermatitis Lesion Index (CADLI) and CADESI-04.^{18,19}

Update on clinical manifestations of canine atopic dermatitis

Review of the literature focusing on clinical aspects of canine AD published after 2001 strongly supports previously published data in most instances.² Although historically, cutaneous adverse food reaction and canine AD have been considered as separate entities, the majority of the recent publications focusing on clinical description of canine AD included dogs with so-called food-induced AD in their data analysis and clearly demonstrated only negligible clinical differences between

Table 1. Favrot's two proposed criteria sets for the diagnosis of canine atopic dermatitis¹²

Criteria set 1:
Age at onset under 3 years of age
Dog living mostly indoors
Glucocorticoid-responsive pruritus
Chronic or recurrent yeast infections
Affected front feet
Affected ear pinnae
Nonaffected ear margins
Nonaffected dorsolumbar area
Sensitivity for five criteria, 85.4%; specificity for five criteria, 79.1%
Sensitivity for six criteria, 58.2%; specificity for six criteria, 88.5%
Criteria set 2:
Age at onset under 3 years of age
Dog living mostly indoors
Pruritus without lesions at onset
Affected front feet
Affected ear pinnae
Nonaffected ear margins
Nonaffected dorsolumbar area
Sensitivity for five criteria, 77.2%; specificity for five criteria, 83.0%
Sensitivity for six criteria, 42.0%; specificity for six criteria, 93.7%

the AD associated with environmental allergens and that of the food-induced AD.^{12,14–17} Overall, these studies included a total of 2880 dogs with either AD associated with environmental allergens or food-induced AD from all around the world and provided additional information on canine AD.^{11–17}

Age of onset

Review of the literature confirmed that the majority of dogs developed signs of atopic dermatitis before the age of 3 years, with the mean age of onset being 1.7, 2.2 and 2.7 years, depending on the publication.^{11–17} A publication focusing on breed-related differences reported that French bulldogs and shar-pei dogs appeared to develop AD earlier in their life than other breeds.¹⁶

Another study using the same population of dogs assessed the differences in the age of onset between canine AD associated with environmental allergens and food-induced AD.¹² This demonstrated that dogs with food-induced AD were more likely to be very young (<1 year, 46.5 versus 38.6%) or older (>6 years, 8.7 versus 3.8%) in comparison to dogs with AD associated with environmental allergens.¹²

Breed predisposition and breed-specific phenotypes

Although there were some minor geographical differences in the breed predisposition, most studies agreed that West Highland white terrier (WHWT), Labrador retriever, golden retriever, boxer, French bulldog, German shepherd and cocker spaniel dogs represented the most commonly affected breeds.^{11–17} It is suspected that the regional popularity of some particular breeds or the different genetic background in different geographical areas affected the proportions of some breeds in these reports. For example, the Vizsla was one of the most commonly affected breeds in a study from Hungary, while the Cavalier King Charles spaniel, great dane and silky terrier were breeds found to be predisposed to canine AD based on a population study from Australia.^{13,15}

Sex predilection

In contrast to the inconclusive results on sex predilection in the 2001 review, all reviewed studies published after 2001 agreed that canine AD, in general, does not exhibit sex predilection.^{2,11–17} Breed-related exceptions, however, were noted in one study, which reported that female boxers and male golden retrievers suffered with canine AD more frequently.¹⁶

Seasonality

While food-induced AD presents with strictly nonseasonal signs, seasonality can be appreciated in some dogs with AD associated with environmental allergens. Moreover, it remains a well-accepted fact that, in some dogs, seasonality can be appreciated initially, but it might be lost eventually with the disease progression.²

All but one publication focusing on clinical aspects of canine AD published after 2001 included data on the seasonal character of the disease.^{11,12,14–17} The percentage of dogs exhibiting seasonal signs varied from 15 to 62%, with the median being 30%. The high variability in seasonality could be explained by the geographical differences or possibly by the fact that some studies included only chronic cases, in which the seasonality of the disease was recorded at the time of presentation but not at disease onset.

According to studies in which information about the specific seasonal distribution could be found, the majority of seasonally affected dogs exhibited clinical signs in the spring and/or summer.^{11,14,17}

Clinical features of canine atopic dermatitis

The most common feature of canine AD is pruritus, which in the majority of analysed dogs appears to precede other clinical signs (this has been termed pruritus sine materia in some publications) and is steroid responsive.^{11,12,16} The most commonly involved body regions included distal limbs (62–81% of dogs), face (27–57% of dogs), ventrum (39–66% of dogs) and ears (48–60% of dogs).^{11–17} The involvement of flexural areas was reported in 38% of dogs with AD.^{12,16} Some breeds appeared to exhibit more specific phenotypes, including shar-pei and WHWT dogs with more frequent pruritus and lesions on the dorsolumbar area or German shepherd dogs with lesions affecting elbows, hindlimbs and thorax.¹⁶

It is well accepted that, in addition to pruritus, dogs with AD can present with a variety of primary or secondary skin lesions. Some of the most common lesions seen in canine AD are erythema, erythematous macular or papular eruptions, self-induced alopecia, excoriations, hyperpigmentation and lichenification.² Additionally, yeast and bacterial infections have been reported as frequent complications affecting dogs with AD.² This statement was confirmed by recent studies, in which a concurrent yeast or bacterial infection was reported in 28–33 or 55–66% of dogs, respectively.^{12,14–17} Some less common clinical features, such as urticaria (2–3%), hot spots (1–11%), hyperhidrosis (4–13%), interdigital fistulae (13–22%) and seborrhoea oleosa (8–14%), were assessed in the recent publications.^{12,14–16} Significant dog breed differ-

ences were noted for some of these lesions; for example, urticaria was more often seen in boxers, interdigital fistulae were more common in Labrador retrievers, pyotraumatic dermatitis was detected more often in German shepherds, golden and Labrador retrievers, and seborrhoea oleosa with hyperhidrosis were more frequent in West Highland white terriers and German shepherds (Table 2).¹⁶ Interestingly, no major differences in clinical phenotype were noted between AD associated with environmental allergens and food-induced AD.¹⁴

Noncutaneous conditions associated with canine AD. Canine AD can present with concurrent nondermatological signs, such as rhinitis or conjunctivitis. Some of the recent publications focusing on the clinical phenotype of canine AD included assessment of such presentations in their data. Concurrent signs of conjunctivitis were reported in 21–30% of dogs with AD, while rhinitis was recorded in ~7% of included dogs.^{12,14–16} This prevalence of atopic conjunctivitis was lower than previously reported, and it was also lower than that reported in an ophthalmology study.^{5,6,20} The latter investigators detected ~60% prevalence of an allergic conjunctivitis in dogs with AD.²⁰ The variations in the prevalence of conjunctivitis could be due to differences in the population or environment or to study design, particularly when the assessment of the prevalence of the ocular disease represents the priority of the study.

Additionally, one study showed that bacterial colonization of the conjunctival sac of dogs with AD was more frequent than in healthy dogs and that the most frequently cultured bacteria was *Staphylococcus pseud-intermedius*.²¹ In addition, atopic dogs had significantly higher numbers of keratinized epithelial cells and lymphocytes on cytology from the conjunctival sac, and eosinophils were seen only in the cytology from dogs with AD.

Table 2. Examples of breed-specific clinical phenotypes in canine atopic dermatitis¹⁶

Breed-specific distribution of clinical signs	Breed-specific clinical lesions
Dalmatians – lips	Boxers – increased urticaria and otitis
French bulldogs – axillae, eyelids and flexor surfaces	Dalmatian – decreased frequency of pruritus without lesions
German shepherd dogs – elbows, hindlimbs, thorax and generalized	German shepherd dogs – increased seborrhoea and hot spots, decreased pruritus without lesions
Shar-peis – thorax, hindlimbs, flexor surfaces and dorsolumbar skin	Golden retrievers – increased hot spots
West Highland white terriers – dorsolumbar skin, feet, flexor surfaces, lips, face, genitals and generalized	Labradors – increased dry skin and hot spots, increased incidence of interdigital fistulae
	Shar-peis – increased otitis and decreased pruritus without lesions
	West Highland white terriers – increased seborrhoea, <i>Malassezia</i> dermatitis, decreased frequency of conjunctivitis

Histopathological manifestations of canine atopic dermatitis

Historical perspective

Histopathological features of canine AD have been under-reported over the years. The first detailed description of histological features of canine AD established epidermal hyperplasia, orthokeratotic and parakeratotic hyperkeratosis, hypergranulosis, spongiosis, melanosis and leucocyte exocytosis as the most common histological findings.⁵ In this study, mast cells appeared to be increased in number and eosinophils were detected in only 15% of evaluated cases. Additional studies involving histological and immunohistochemical stains further characterized the cell types of the inflammatory infiltrate in canine AD.²² Briefly, the perivascular infiltrate seen in canine AD was mixed, composed of T cells, dendritic cells, eosinophils and hyperplastic mast cells. Epidermal infiltrate was composed of T cells, Langerhans cells and some eosinophils.²²

Update on histopathological manifestations of canine atopic dermatitis

Since the last review, several publications have addressed the histological features of canine AD skin lesions using experimental models of AD.^{23–28} None of those, however, evaluated histological features of naturally occurring lesions, and the histopathological descriptions were often adjunctive to the primary immunological questions addressed by the authors. Nevertheless, the histopathological description of the skin reaction after an epicutaneous or intradermal delivery of a relevant allergen or anti-canine IgE antibody injection was generally similar to that reviewed by the ACVD Task Force in 2001.²² All the studies focused on the late-phase skin reaction (e.g. erythema, thickening), which is believed to resemble lesions seen in dogs with AD. In general, the late-phase skin reaction was characterized by an inflammatory pattern consisting of superficial perivascular to interstitial mononuclear dermatitis with neutrophils and eosinophils. Degranulation of mast cells and eosinophils was reported upon allergen challenge.^{24–28} An irregular epidermal hyperplasia with lymphocytic and eosinophilic exocytosis resulting in an occasional formation of eosinophilic micro-abscesses and infiltration of the lesional skin with epidermal and dermal dendritic cells were also reported.^{24–27}

Conclusions

In summary, considerable work has been performed in the past 10 years to provide a better definition of the clinical appearance and histopathology of canine AD. New sets of diagnostic criteria have been developed, which offer an enhanced sensitivity and specificity over older criteria. This information has led to the development of two new scoring systems for assessment of lesion severity, tools necessary for a generation of high-quality medical evidence. Significant breed-associated differences in phenotypes have also been demonstrated. However, these investigations have also demonstrated that food-induced AD and purely environmental allergen-induced AD may be clinically indistinguishable in dogs. These limi-

tations imply that a 'one-size-fits-all' set of diagnostic or descriptive criteria for canine AD may not be possible.

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Résumé

Contexte – De nombreuses études portant sur les signes cliniques et histologiques de la dermatite atopique canine (AD) ont été publiées depuis ses premières descriptions, il y a plusieurs dizaines d'années. Les données de ces études contribuent à notre connaissance actuelle de la pathogénie de la maladie et nous permettent de déterminer des critères de diagnostic utilisés par les cliniciens et les chercheurs.

Objectifs – Cette revue sert de mise à jour des critères cliniques et histologiques de l'AD canine publiés par la Task Force de la dermatite atopique canine du Collège Américain de Dermatologie Vétérinaire en 2001 et résume les découvertes récentes de ce domaine.

Résultats – Les données globales des études portant sur les signes cliniques correspondent à celles publiées par la Task Force en 2001. La nouveauté était le plus grand nombre d'animaux inclus dans ces études, permettant ainsi de déterminer un nouvel ensemble de critères améliorant la sensibilité et la spécificité des critères précédents. La même étude a permis de mettre en évidence des différences entre les chiens atteints d'AD liée à l'alimentation et non-liée à l'alimentation; cependant, les auteurs ont conclu que ces deux entités ne pouvaient pas être distinguées sur la seule base des signes cliniques. Une autre étude a démontré des spécificités phénotypiques de certaines races. Plusieurs publications ont pris en compte les critères histologiques des lésions cutanées de l'AD canine sur des modèles expérimentaux d'AD mais aucune ne portaient sur des modèles naturels. Néanmoins, la description histopathologique des réactions cutanées était généralement semblable à celle publiée par la Task Force en 2001.

Conclusions – Un travail considérable a été fait récemment pour fournir une meilleure définition clinique et histopathologique de l'AD canine. De nouveaux critères de diagnostic ont été développés et des différences phénotypiques associées à des races ont été démontrées.

Resumen

Introducción – muchos estudios enfocados en los signos clínicos e histológicos de la dermatitis atópica canina (AD) han sido publicados desde las descripciones más tempranas hace décadas. Los hallazgos de estudios contribuyeron a nuestro conocimiento actual acerca la patogenia de la enfermedad y permitieron establecer un criterio diagnóstico para ser utilizado por los clínicos y los investigadores.

Objetivos – esta revisión sirve como una puesta al día de las características clínicas e histológicas de la dermatitis atópica canina publicadas por el colegio americano de dermatólogos veterinarios en el grupo de trabajo de la dermatitis atópica canina en el año 2001, y resume los descubrimientos más recientes en estos campos.

Resultados – los hallazgos de los estudios enfocados en los signos clínicos semejan aquellos publicados por el grupo de trabajo del año 2001. La novedad fue el mayor número animales incluidos en estos estudios, lo cual permitió establecer un nuevo conjunto de criterios diagnósticos que excedían la sensibilidad y la especificidad de los criterios previos. El mismo estudio descubrió algunas diferencias clínicas entre los perros con dermatitis atópica inducida por comida o por otras causas. Sin embargo los autores concluyen que estas dos entidades no se pueden distinguir basados solamente en los signos clínicos. Otro estudio demostró algunos fenotípicos específicos de raza. Varias publicaciones estudian las características histológicas de las lesiones de dermatitis atópica en modelos experimentales, pero ninguno estudia las lesiones por causa natural. Sin embargo, las descripciones histopatológicas de la reacción de la piel fueron similares a las publicadas por el grupo de trabajo en e año 2001.

Conclusiones – se han realizado bastantes trabajos en años recientes para aportar una mejor definición de la presentación clínica y de las características histopatológicas de la dermatitis atópica. Se han desarrollado nuevos conjuntos de criterios diagnósticos, y se han demostrado diferenciación fenotípicas dependiendo de la raza.

Zusammenfassung

Hintergrund – Viele Studien, die sich auf die klinische und histologische Symptomatik der atopischen Dermatitis (AD) des Hundes konzentrieren, sind seit der Beschreibung ihrer Charakteristika vor Jahrzehnten veröffentlicht worden. Die Ergebnisse dieser Studien haben zu unserem momentanen Wissen über die Pathogenese der Erkrankung beigetragen und ermöglichten die Erstellung diagnostischer Kriterien, die von Klinikern und Wissenschaftlern verwendet werden konnten.

Ziele – Diese Review dient als Update der klinischen und histologischen Merkmale der caninen AD, die von der Task Force des American College für Veterinärdermatologie 2001 über die atopische Dermatitis des Hundes publiziert worden war und fasst die letzten Entdeckungen auf diesem Gebiet zusammen.

Ergebnisse – Insgesamt entsprachen die Ergebnisse dieser Studien, die sich auf die klinischen Merkmale bezogen denen von der Task Force 2001 publizierten. Die Neuheit daran war die größere Anzahl an Tieren, die in diesen Studien untersucht worden waren, was es ermöglichte, ein neues Set an diagnostischen Kriterien zu erstellen, welches die Sensibilität und Spezifität der vorherigen Kriterien übertraf. Dieselbe Studie zeigte einige klinische Unterschiede zwischen Hunden mit Futter-induzierter und Nicht-Futter-induzierter AD; die Autoren wiesen jedoch darauf hin, dass diese zwei Einheiten nicht alleine aufgrund ihrer klinischen Zeichen unterschieden werden können. Eine weitere Studie zeigte einige große Rasse-spezifische Phänotypen. Mehrere Publikationen bezogen sich auf die histologischen Merkmale der Hautveränderungen bei der caninen AD in experimentellen Modellen, aber keine der Studie beschrieb natürlich auftretende Läsionen. Nichtsdestotrotz waren die histopathologischen Beschreibungen der Hautreaktionen generell ähnlich wie die von der Task Force 2001 publizierten.

Schlussfolgerungen – Eine bedeutende Arbeit wurde in den letzten Jahren geleistet, um eine bessere Definition der klinischen Erscheinung und der Histopathologie der AD des Hundes zu liefern. Neue Sets an diagnostischen Kriterien sind entwickelt worden und zusätzliche rasse-spezifische Unterschiede der Phänotypen wurden gezeigt.

要約

背景 – イヌアトピー性皮膚炎(AD)の臨床的および組織学的な所見に注目した多くの研究が数十年前に初めに解説されて以来、発表されている。これらの研究の所見は疾患の病院に関する我々の知識に貢献し、臨床家や研究者によって使用される診断基準の制定を可能にした。

目的 – この総説は2001年に American College of Veterinary Dermatology Task Forceによって発表されたイヌADの臨床的および組織学的な特徴のアップデートを扱うとともに、これらの分野での最近の発見を要約する。

結果 – 臨床的な特徴において、全体的な研究の報告は2001年のTask Forceで発表されたものに類似していた。新しい知見としては、新しい診断基準の制定を認めたこれらの研究に含まれる多数の動物が、以前の基準の感度と特異度を超えていることである。同じ研究では食物誘発性および非食物誘発性ADのイヌの間のいくつかの臨床的な違いを明らかにしたが、しかし、筆者らはこれらの2つは臨床所見のみでは区別できないと結論づけた。他の研究はいくつかの主要な犬種-特異性の表現系を立証した。複数の発表ではADの実験モデルにおけるイヌADの皮膚病変の組織学的な特徴について取り上げているが、いずれの記載も自然発生性のものではない。それにもかかわらず、皮膚反応の病理組織学的な記載は2001年のTask Forceで発表されたものに概ね類似している。

結論 – イヌのADの臨床症状および病理組織学によりよい説明を示すための多くの仕事が近年に行われていた。新しい診断基準が開発され、さらなる表現型の犬種-関連性の違いが示めされた。

摘要

背景 – 早在几十年前,就有很多聚焦于犬异位性皮炎(AD)的临床及病理学症状的研究发表。这些研究提供给我们关于该病的病理学知识,并建立供临床医生和研究人员使用的诊断标准。

目的 – 本综述更新了犬AD临床及病理学特性,这是由美国大学的兽医犬异位性皮炎工作组发表于2001年。本文还总结了目前该领域近期的研究成果。

结果 – 所有研究的全部结果都集中于临床特征,与工作组于2001年的发表文章相符合。这些新研究包含了大量动物,建立出一套新的诊断标准,其特异性及敏感性均高于之前的标准。相同研究发现有食物诱导和没有食物诱导AD的一些临床不同点;然而,作者得出结论,两者不能只靠临床症状区别。作者研究证明一些主要品种特异性表型。一些实验用AD实验模型来研究犬AD皮肤病变的病理学特征,但是其中没有自然发生的病变。然而,皮肤反应的组织病理学描述与工作组2001年发表的几乎一致。

总结与临床意义 – 为更好的描述犬AD临床表现及组织病理学特征,近年有相当大的工作需要去做。已经形成新的诊断标准,品种相关的表型差异也已经被证明。