

What's New in Canine Atopic Dermatitis- Part 1

Michele R. Rosenbaum VMD, DACVD

Canine atopic dermatitis (AD) is a common genetically-based inflammatory and pruritic allergic skin disease with characteristic clinical features associated with IgE; it is most commonly directed against environmental allergens. According to various investigators, the incidence has been reported to be approximately 10% of the worldwide canine population that visits veterinarians.¹ **Atopy** is defined as the inherited predisposition to form allergen-specific IgE antibodies but does not always mean clinical disease (atopic dermatitis) will develop, as normal dogs can have allergen-specific IgE in their skin or serum. Note the **nomenclature change** from allergic inhalant dermatitis to atopic dermatitis (AD) (similar to human atopic eczema) due to recent research which has demonstrated that transcutaneous allergen penetration through a defective skin barrier rather than inhalation is the primary method of allergen absorption.² Inhalation and oral ingestion of allergens are minor routes of exposure.

AD is a clinical diagnosis made by ruling out all other causes of itching, not one made by allergy testing. It is a syndrome triggered by environmental allergens, food allergens, and microbial colonization with *Staphylococcus* and *Malassezia*. In the classic form of AD, it is associated with IgE antibodies to these allergens.

Atopic-like Dermatitis (ALD) is a newly described variant of atopic dermatitis similar to intrinsic AD in humans in which affected dogs show all of the clinical signs of AD without skin or serum testing evidence of IgE-mediated hypersensitivity to environmental or other allergens.³ In people, the disease is thought to have a genetic predisposition. Affected dogs have negative intradermal skin test results, low to negative levels of allergen-specific serum IgE, and no response to home-cooked and commercially prepared hypoallergenic diets. A recent French study reported that French bulldogs were more prone to ALD³; the author has seen cases consistent with ALD most frequently in the Bichon frise. Dogs with ALD appear to be less responsive to cyclosporine than in those with AD.³

Food-induced atopic dermatitis refers to cases of AD in which food allergens may trigger a flare. Up to 23% of atopic dogs may have a concurrent food hypersensitivity.⁴

Genetic factors: Atopic dermatitis can occur in any breed of dog but there is an increased risk reported in Golden and Labrador retrievers, Pit Bull terriers, German shepherd dogs, English bulldogs, boxers, pugs, Irish setters, Dalmatians, West Highland white terriers, Scottish terriers, wirehair fox terriers, Welsh terriers, Boston terriers, cairn terriers, Lhasa apsos, shih tzus, and miniature schnauzers.⁵ Some

authors report a slightly increased incidence in females. A recent study of British guide dogs supported the genetic predisposition of atopic dermatitis in Labrador and Golden retrievers (breeding 2 atopic parents resulted in 65% of the offspring being atopic, breeding 1 atopic parent-21-57 % affected, breeding 2 non- atopics- 11 % affected).⁶ Heritability was found to be 0.47- meaning that ~50 % of risk of developing AD is due to genotype.⁶ A recent paper from Sweden analyzing the genome in atopic German shepherd dogs isolated a locus on a single chromosome with mutations in the genes coding for the epidermal structural protein plakophilin involved in skin barrier function.⁷ Multiple genes are involved with breed and geographical variations; this makes genetic screening tests difficult. In the future, these gene variations in AD may predict response to a particular therapy, and lead to better preventative strategies.

Breed variations: A recent study described breed variations in the clinical manifestations of atopic dermatitis.⁸ Examples include: Boxer- urticaria, otitis; French Bulldog- eyelids, axilla, flexural surfaces; WHWT- yeast infections, oily seborrhea, widespread disease; German shepherd- elbows, thorax, hindlimbs, paws, groin; French Bulldog, Shar pei- onset of disease under 1 year. However, the disease is not limited to these presentations in the listed breeds.

Environmental factors: The hygiene hypothesis states that early exposure to micro-organisms is important in inducing immune tolerance in people and this may be true in dogs as well. A recent Swiss study of Labrador and golden retrievers reported an increased risk for canine AD with urban life and regular bathing of young healthy dogs, and a decreased risk of canine AD with rural life, living with other animals, and forest walks; and, no effect on AD risk with vaccination and deworming.⁹

Updates in pathophysiology of AD: In the past, the clinical manifestations of AD were thought primarily to be due to IgE and mast cell degranulation and release of many pharmacologically active compounds. While mast cells and IgE certainly are involved in AD, new research has shown that it is not that simple. Atopic dogs have a dysregulated cutaneous immune system which favors an acute T-lymphocyte helper type-2 pro-inflammatory reaction to allergens.¹⁰ The release of many pro-inflammatory cytokines after allergen exposure is thought to be the key to the allergic response.¹⁰ In addition, IL-31, a cytokine produced by Th2 cells that acts on cutaneous sensory nerves, is thought to be very important in triggering the perception of itch.¹⁰ These inflammatory cytokines work by signaling the Janus kinase (JAK) enzyme system that sends the cytokine's message to the cell nucleus, triggering gene transcription and protein production.⁹ This may be why antihistamines do not work well in AD (as they only block histamine), and why glucocorticoids, cyclosporine, and oclacitinib, with inhibitory effects on T cells, inflammatory cytokines, and JAK (oclacitinib) are more effective.

In addition, dogs with AD have abnormal skin barrier function¹¹ with an imbalance of stratum corneum ceramides, fatty acids and cholesterol: either primary as a genetic structural defect or secondary to inflammation or protease production from dust mites and staphylococcus bacteria on the skin that degrade the barrier during flare ups. This abnormal barrier function allows excessive transcutaneous absorption of allergens to start the inflammatory cascade as well as increased transepidermal water loss. Think of the skin barrier like “bricks (skin cells) and mortar (lipids, ceramides, fatty acids). Dogs with AD have a “crumbling brick wall” due to a decreased amount/ abnormal composition of “mortar.” A video summarizing the current pathogenesis of the canine AD itch cycle is available at itchcycle.com, and an excellent summary article on our current understanding of the pathophysiological mechanisms of canine atopic dermatitis has been published.¹⁰

Secondary Infection: Many dogs with AD will experience secondary overcolonization of their skin with both *Staphylococcus pseudintermedius* and *Malassezia pachydermatis*. Reasons for this predisposition to infection include: staphylococci adhere to and multiply more easily on the skin of atopics¹², dogs with AD are thought to have a defective cutaneous protective lipid barrier function, and the secondary seborrheic skin disease, hyperhidrosis and self-trauma seen with AD create a micro-environment more conducive to bacterial and yeast over colonization. In addition, staphylococci may produce endotoxins that act as superantigens, leading to the production of IgE and inflammatory cytokines and worsening pruritus. Staphylococcal proteases can break down skin barrier function, thus increasing the overabsorption of allergens and worsening inflammation by triggering the release of pruritogenic and pro-inflammatory cytokines from skin cells. Dogs with AD may develop hypersensitivity reactions with anti-staphylococcal IgE¹³ and anti-*Malassezia* IgE¹⁴, dramatically worsening pruritus when they are overcolonized with these organisms. Although most of the skin lesions seen in AD are secondary to self-trauma, AD can induce a primary skin eruption of erythema and a mild papular eruption that is not due to infection.

Diagnosis: In dogs with AD, pruritus is the primary owner complaint. Most dogs will first show evidence of the disease from 6 months to 3 years of age. Clinical signs may be seasonal or non-seasonal. Specifically, early clinical signs include: face rubbing, foot licking, and scratching of the ears and armpits. Initially there are no clinical lesions other than pruritus. As the disease progresses, erythema and lesions of self-trauma develop. Otitis is commonly seen, and may involve just the medial pinna initially before affecting the ear canals with secondary inflammation and infection. Bacterial pyoderma caused by *Staphylococcus pseudintermedius* and *Malassezia* dermatitis are common. Dogs

may have concurrent allergic conjunctivitis. There is usually a good response to glucocorticoids.

The diagnosis of AD in dogs is made by history and physical examination, and by ruling out ALL other causes of pruritus. Recently, a set of diagnostic criteria for AD has been published.¹⁵ This is helpful as a guide, but should not replace a thorough history, physical examination, and diagnostic tests to **rule out parasites, infections and food-related causes of pruritus** before diagnosing AD. The most common **differential diagnoses** for canine AD includes: scabies, flea allergy dermatitis, food allergy, and less commonly, contact dermatitis (irritant or allergic).

Favrot Criteria*:

- Age of onset < 3 years
- Mostly indoor
- Corticosteroid-responsive pruritus
- Pruritus without skin lesions at onset
- Chronic or recurrent yeast infections
- Affected front feet
- Affected ear pinnae (but not pinnal margins)
- Non-affected dorso-lumbar area

*At least 5 positives = 85% sensitivity (miss 15 %), 79% specificity (falsely diagnose 21%)

References

1. Nuttall T, et al. Canine atopic dermatitis- what have we learned? *Veterinary Record* 2013;172: 201-207.
2. Marsella R, et al. Studies on the role of routes of allergen exposure in high IgE-producing beagle dogs sensitized to house dust mites. *Vet Dermatology* 2006; 17; 306-312.
3. Prelaud P, Cochet-Faivre N. A retrospective study of 21 cases of canine atopic-like dermatitis. *Proceedings, Meeting of the European College of Veterinary Dermatologists, Mainz, Germany;15:15, September 14, 2007.*
4. Jackson HA, et al. The pattern of allergen hypersensitivity (dietary or environmental) of dogs with non-seasonal atopic dermatitis cannot be differentiated on the basis of historical or clinical information: a prospective evaluation 2003-2004. *Vet Dermatology* 2005 16:200.
5. Miller WH, Griffin CE, Campbell KL, eds. Hypersensitivity Disorders. In: *Muller and Kirk's Small Animal Dermatology* 7th ed. St. Louis, MO: Elsevier; 2013:372.

6. Shaw, et al. Estimation of heritability of atopic dermatitis in Labrador and Golden retrievers. *Am J Vet Res* 2004; 65:1014-1020.
7. Tengvall K et al. Genome-wide analysis in German shepherd dogs reveals association of a locus on CFA 27 with atopic dermatitis. *PLOS Genetics* 2013; 9(5) e1002475:May: 1-12.
8. Wilhelm S, et al. Breed-associated phenotypes in canine atopic dermatitis. *Vet Dermatol.* 2010;22:143-149.
9. Meury S, et al. Role of the environment in the development of canine atopic dermatitis in Labrador and golden retrievers. *Vet Dermatol.* 2011; 22:327-334.
10. Marsella R, et al. Current understanding of the pathophysiologic mechanisms of canine atopic dermatitis. *JAVMA* 2012; 241: 194-207.
11. Marsella R, et al. Unraveling the skin barrier: a new paradigm for atopic dermatitis and house dust mites. *Vet Dermatol.* 2009;20:533-40.
12. McEwan NA, et al. Adherence by *Staphylococcus intermedius* to canine corneocytes: a preliminary study comparing noninflamed and inflamed atopic canine skin. *Vet Dermatol.* 2006; 17, 151-154.
13. Morales CA, et al. Antistaphylococcal antibodies in dogs with recurrent staphylococcal pyoderma. *Veterinary Immunology and Immunopathology* 1994; 42(2):137-147.
14. Chen TA, et al. Identification of major allergens of *Malassezia pachydermatis* in dogs with atopic dermatitis and *Malassezia* overgrowth. *Vet Dermatol.* 2002;13(3):141-50.
15. Favrot C, et al. A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis. *Vet Dermatology* 2010; 21: 23-31.