Timely Topics in Nutrition

Use of atopic dogs to investigate adverse reactions to food

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The *JAVMA* welcomes contributions to this feature. Articles submitted for publication will be fully reviewed with the American College of Veterinary Nutrition (ACVN) acting in an advisory capacity to the editors. Inquiries should be sent to Dr. John E. Bauer, Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843-4474.

Food allergies are a recognized clinical entity in dogs. Affected dogs may have nonseasonal pruritus, enteropathies, or both. Because the pathophysiologic mechanisms have not yet been elucidated, the term allergy may not always be appropriate. Urticaria, fever, malaise, seizure, and recurrent otitis are a few of the other clinical manifestations that have been associated with adverse reactions to dietary exposure. The objective of the information provided here is to review current knowledge on the immunologic aspects of food allergies in dogs (with a focus on IgE-mediated hypersensitivity) and the use of atopic dogs to study these conditions.

Description of the Condition

Terms used to describe adverse reactions to food can be confusing. Proposed definitions that were based on mechanistic classifications have been used in the human literature but have not been fully accepted by the veterinary community. Adverse reactions to food are defined as an aberrant reaction after the ingestion of food or a food additive. Adverse reactions may be the result of toxic or nontoxic mechanisms. Nontoxic reactions depend on the susceptibility of each animal and may be the result of immune mechanisms attributable to allergic hypersensitivity responses. Other nontoxic reactions may relate to intolerance attributable to pharmacologic properties of the food, metabolic disorders, or idiosyncratic responses. In many cases, it is difficult to determine the cause of an adverse reaction in a dog with clinical signs. Thus, it is probably most correct to use the term adverse reaction to food in dogs until further clarification is established.

In humans, intolerance to food probably accounts for most adverse reactions to food, but specific IgE-mediated immediate-hypersensitivity reactions have been clearly documented.[1] These reactions are most prevalent in young children and people with atopic disease. Generally, dermatologic, respiratory, and gastrointestinal disorders are recognized within minutes to hours after ingesting the offending food. Oral allergy syndrome is a form of contact allergy affecting the oropharynx that is associated with local IgE-mediated activation of mast cells. Clinical symptoms in humans may include oral pruritus, a tingling sensation, angioedema, or a pruritic sensation in the ears. Such symptoms may be associated with individuals who are allergic to pollen reacting to ingested fresh fruits or vegetables that have cross-reactivities with pollen antigens. Cooking the offending food usually prevents oral allergy syndrome in affected humans.

It is interesting that ingested food items are associated with dermatologic signs. In humans, immunologically active food proteins can enter the circulation.[2] These proteins may stimulate a localized immunologic response in distal organs including the skin. Altered gastrointestinal permeability may lead to an increase in food proteins in the circulation. The allergenic fraction of foods generally comprises heat-stable, water-soluble glycoproteins ranging in size from 10 to 70 kd.[1] Several new commercially available diets for dogs take advantage of decreased protein size by hydrolyzing proteins prior to processing. This may make the proteins less allergenic.

Diagnosis of Adverse Reactions to Foods

In dogs, ingestion of food items can result in acute urticaria associated with IgE-mediated hypersensitivity. Mixed IgE-mediated, non-IgE-mediated and late-phase IgE reactions may also be implicated.[3] Dogs with adverse reactions to foods may develop pruritus of the face (muzzle and chin) and ears. Owners have described acute onset of scratching or rubbing of the face soon after affected dogs have eaten. One can hypothesize that some of these dogs may be having a reaction similar to the oral allergy syndrome described in humans.

Adverse food reactions in dogs are associated with dermatologic signs, gastrointestinal signs, and sometimes both.[4] Nonseasonal pruritus affecting the ears, feet, or inguinal region is most commonly reportedly.[5] Other affected regions include the face, rump, perianal region, medial or lateral aspects of the thighs, or flank.

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In some cases, pruritus is generalized. Age of onset varies, but many dogs develop clinical signs before they are 1 year old. This time course is in contrast with that for inhaled allergies in which clinical signs are uncommonly seen in dogs < 1 year of age.

A diagnosis of dietary hypersensitivity in dogs may be difficult to establish because of overlapping clinical signs attributable to other allergies, secondary infections, or inaccurate historical data from clients. The only consistently accurate diagnostic tool is to feed an elimination test diet. An established protocol for this approach has been published.[6] Differentiating dietary hypersensitivity from intolerance may be clinically irrelevant if there is an adequate response to feeding of an elimination test diet.[7] However, when there is sufficient evidence of an IgE-mediated hypersensitivity reaction, then diagnostic tests may be developed to aid in establishing a definitive diagnosis, hopefully superseding the need for lengthy dietary trials that involve the use of meals prepared by the owners.

Advances in the Study of Adverse Reactions to Foods by the use of Atopic Dogs

Atopic dogs have been used to study IgE-mediated hypersensitivity. It has been documented that these dogs are predisposed to developing IgE concentrations that are higher than concentrations found in clinically normal dogs.[8] Furthermore, this predisposition appears to be inherited in a dominant manner, which may partially explain the reason that certain breeds seem to develop adverse reactions to food more frequently than other breeds. Dogs can be sensitized to various allergens, including food items, when treated in accordance with defined protocols.[9] Briefly, 1-day-old dogs are injected SC with selected allergens and an alum adjuvant. When dogs are 3, 7, and 11 weeks old, a modified-live virus combination vaccine against canine distemper, adenovirus type 2, and parainfluenza virus is administered to stimulate sensitization to the allergens injected into the 1-day old dogs. One and seven days after each vaccination, the dogs again are injected SC with the same allergens. They are then maintained by SC administration of the allergens at 8-week intervals. Vaccinations are administered annually.

This method of sensitization has been used to validate IgE-mediated sensitivity in dogs for specific allergens, as determined by the use of an ELISA, western blot analysis, and intradermal testing. Gastroscopic-aided injection of selected allergens into the gastric mucosa causes an increase in reactivity, compared with injections in a control population.[9] Some of the sensitized dogs also develop acute onset of vomiting or diarrhea after food items are administered orally. Occasionally, anaphylactic reactions are observed that require medical assistance. Considered together, this dog model seems reasonable as a research tool for use in investigating IgE-mediated hypersensitivity to selected food items.

Several questions exist regarding this method of sensitization. Because these dogs have been sensitized by the use of SC injections, it is not known as to the extent that they represent dogs with naturally occurring dietary hypersensitivity. Dogs with adverse reactions to food may not be mediated by IgE or may only be partially mediated by IgE. Several investigators[10,11] have looked at the validity of intradermal testing, results of ELISA, or radioallergosorbent test (RAST) testing as diagnostic tools for use in detecting dietary hypersensitivity. Low sensitivity and high specificity (few false-positive reactions) were found in 1 study,[10] leading to the conclusion that these tests were not useful.[11] These diagnostic tools are sometimes used as a screening tool for humans with suspected dietary hypersensitivity, and they are useful for their negative-predictive value. The criterion-referenced diagnostic test is the **double-blind, placebo-controlled, oral food challenge** (**DBPCFC**). The use of sensitized atopic dogs may be a useful method for the development of DBPCFC testing protocols that can be used in suspected cases of dietary hypersensitivity.

In dogs with dietary-responsive intestinal disease, intestinal permeability normalized after an elimination diet was fed to dietary hypersensitive dogs.[12] Using monosaccharide and disaccharide sugars to measure gastrointestinal permeability and mucosal function, the dogs in that study had improvement in permeability values, whereas those with food intolerance did not have improvement in permeability values. However, all dogs clinically improved when fed elimination diets. Permeability tests have been applied to sensitized atopic dogs,[a] and it was revealed that there was an inability to differentiate food allergen sensitized dogs from control dogs after feeding an elimination test diet for 6 weeks. Analysis of these findings suggests that atopic dogs may be similar to those with naturally occurring dietary hypersensitivity. Additional studies investigating gastrointestinal permeability and function after dietary challenges are currently being conducted in atopic dogs to evaluate the hypothesis that permeability and function are altered after challenge exposure with an offending allergen. Such a response might be related to an increase in immunologically active proteins in circulation, leading to clinical signs.

It has been documented in humans that some individuals have IgE-mediated food hypersensitivity without detectable allergen-specific circulating IgE.[13] This diagnosis was determined on the basis of an adverse reaction to the offending allergen and examination of gastrointestinal biopsy specimens. Although these patients had negative results for a skin-prick test and an allergen-specific ELISA, examination of intestinal biopsy samples revealed an inflammatory response. Immunohistochemical staining revealed a T-helper 2-subset with increases in interleukin-4 in dietary hypersensitive patients after challenge exposure, compared with results for control groups. Analysis of these results indicated that the IgE-mediated response might be localized to the gastrointestinal tract. These data may explain the reason that results of intradermal testing and serum ELISA may be misleading as a diagnostic tool for dietary hypersensitivity. If such findings also exist in dogs, it may help explain the reason that some dogs have dietary hypersensitivity of only the gastrointestinal tract without concurrent dermatologic manifestations.

Future Considerations

Ultimately, the aforementioned use of sensitized atopic dogs represents only the IgE-mediated hypersensitivity aspect of a range of possible adverse reactions to food. Because these dogs are genetically predisposed to developing concentrations of IgE that are higher than those in clinically normal dogs, it may be possible to sensitize them by oral administration of antigens. One advantage of this route for sensitization is that it will more closely mimic the development of dietary hypersensitivity in the canine population at large. It has been hypothesized that there is an immunologic window of opportunity for dogs to become sensitized to food allergens.[14] Thus, over time, developmental changes such as mucosal IgA concentrations, altered gastric pH, and decreased gastrointestinal permeability may be protective mechanisms used to develop tolerance to ingested proteins. Additional investigations are needed to evaluate these possibilities. For example, if it can be determined that dogs are sensitized at a specific early age, then dietary modifications could be used to limit sensitization to those food items that affected dogs are likely to consume for the remainder of their lives. Feeding novel protein sources at a young age may still lead to sensitization, but these proteins may easily be avoided at a later age, thereby preventing the onset of clinical signs. To reduce suspected allergenic activity, hydrolyzed artificial formulas are given to atopy-prone newborn humans.[15] Further, reduced exposure of infants to allergenic foods caused by food allergen avoidance on the part of the reactive mother has been reported to decrease food sensitization primarily during the first year of life.[15] The use of atopic dogs may be beneficial in determining whether a similar phenomenon occurs in neonatal dogs.

[a]Kennis RA, Baltzer WI, Steiner JM, et al. Inability to differentiate non-challenged food allergen sensitized dogs from control dogs using gastrointestinal permeability and mucosal function testing (abstr), in *Proceedings*. 20th Annu Vet Med Forum 2002;762.

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