Vet Clin Small Anim 36 (2006) 175–184
VETERINARY CLINICS
SMALL ANIMAL PRACTICE

Food Allergies: Update of Pathogenesis, Diagnoses, and Management

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Food allergies have been defined in human beings. Possible reactions include type I, type III, and type IV hypersensitivities. An oral allergy syndrome has also been described. Oral allergy syndrome is a form of contact allergy affecting the oropharynx that is associated with local IgE-mediated activation of mast cells. The term *food allergy* describes an immune-mediated process that may include any or all of the aforementioned reactions. Nonimmunologic adverse food reactions may also occur, such as food intolerance, which is an abnormal physiologic response to an ingested food item or food additive. Also, toxic reactions may occur because of the ingestion of bacterial or fungal toxins. Food intolerances probably account for most human adverse food reactions (eg, "jitters" from too much caffeine) [1].

Dogs may present with cutaneous clinical signs of food allergy. These may be attributable to immunologic or nonimmunologic causes. Because it is sometimes difficult to define the true pathogenesis, the term *cutaneous adverse food reactions* should be used [2]. The term *food allergy* is used when immune-mediated disease is discussed, regardless of the type of hypersensitivity reaction.

PATHOGENESIS

The major food allergens have been identified as water-soluble glycoproteins ranging from 10,000 to 60,000 d [3]. They are generally stable to treatment with heat, acid, and proteases. The most common food allergens include beef, chicken, corn, wheat, cow's milk, soy, eggs, and fish, but virtually any ingested food item may induce a cutaneous adverse food reaction [4]. Type I (immediate hypersensitivity) and type IV (delayed hypersensitivity) reactions have been reported in dogs. Mixed IgE-mediated, non–IgE-mediated, and late-phase IgE reactions may also be implicated [5]. The true pathogenesis of food allergies in dogs has not been defined.

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0195-5616/06/$ – see front matter
doi:10.1016/j.cvsm.2005.09.012

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The best protective mechanism for the development of tolerance is an intact intestinal mucosal barrier. Oral tolerance is a state of immunologic unresponsiveness to potential allergens. It has been shown that anergy and active suppression are the principal mechanisms of oral tolerance in mice under experimental circumstances [6]. Secretory IgA binds allergens and removes them in the mucus. Those antigens that pass through the intestinal barrier are bound by IgA and secreted through the liver into bile.

A type I reaction is characterized by the production of IgE antibodies and the activation of mast cells. Antigens may pass through a disrupted mucosal barrier or may enter circulation as antibody or antigen complexes. The allergens are processed by antigen-presenting cells and are subsequently presented to T cells. CD4+ T cells may be categorized into T helper (Th) 1 and Th2 subsets. The Th2 cells play a role in the activation of B cells, leading to the production of antibodies in which Th1 cells activate macrophages and a "cell-mediated" response. Most Th cells recognize processed antigen in association with major histocompatability complex (MHC) II molecules on the surface of antigen-presenting cells (eg, dendritic cells, macrophages) and bind to the T-cell receptor (TCR). This interaction leads to T-cell activation. Concurrently, antigen may bind directly to B cells via the B-cell receptor, which is, in fact, an IgD or IgM antibody, leading to B-cell activation. Activated T cells provide "help" to the activated B cells by cell-cell interactions and the production of cytokines. The secreted cytokines of an activated Th2 cell include interleukin (IL)-4, IL-5, IL-6, IL-10, and IL-13. These promote the class switching of B-cell antibodies to the formation of antigen-specific IgE. IgE antibodies bind to mast cells via the fixed complement ϵ high-affinity receptor (FcϵRI). When specific antigen "cross-links" IgE molecules on a mast cell, a signal is sent to release chemical mediators of inflammation, such as histamine and leukotrienes. The development of allergy is caused by a breakdown of oral tolerance.

The oral allergy syndrome has been described in a dog with Japanese cedar allergy. Cross-reactivity between Japanese cedar and tomato allergens was demonstrated by enzyme-linked immunosorbent assay (ELISA) inhibition. When the patient was fed fresh tomato, salivation, tightness, and swelling of the lips and quivering of the tongue occurred within 15 minutes after provocation. A similar finding was not observed when the same dog was challenged with tomato juice that was heated [7]. This study clearly demonstrated cross-reactivity between cedar and tomato antigens. To date, this is the only published report of the oral allergy syndrome in a dog. Similar oral allergy syndrome reactions could partially explain why some dogs with adverse food reactions exhibit pruritus of the muzzle region after eating, however. Numerous cross-reactions between environmental allergens and food allergens have been implicated in the oral allergy syndrome in human beings (Table 1) [8,9].

The role of type 1 hypersensitivity as a cause of canine food allergy has been investigated using an atopic dog model [10–12]. Dogs were selected based on their ability to produce higher than normal levels of IgE. Selected dogs were then purposefully bred [13]. Their puppies were sensitized to various food

Table 1
Pollens and foods causing oral allergy syndrome in human being

Pollen	Cross-reacting foods
Alder	Almonds, apples, celery, cherries, hazelnuts, parsley, pears, peaches
Birch	Almonds, apricots, apples, buckwheat, caraway, carrots, celery, cherries, coriander, dill, fennel, hazelnuts, honey, kiwi, lentils, nectarines, parsley, parsnips, peanuts, peppers, plums, potatoes, prunes, spinach, sunflower seeds, spinach, walnuts, wheat
Grasses	Melons, oranges, peanuts, swiss chard, tomatoes, watermelons, wheat
Mugwort	Apples, carrots, celery, coriander, fennel, kiwi, melons, parsley, peanuts, peppers, sunflower seeds, watermelons
Plane	Apples, chickpeas, green beans, hazelnuts, kiwi, lettuce, maize, melons, peanuts
Ragweed	Apples, bananas, cantaloupes, chamomile tea, cucumbers, honeydews, zucchini, watermelons

Data from Vieths S, Scheurer B, Ballmer-Weber B. Current understanding of cross-reactivity of food allergens and pollen. Ann NY Acad Sci 2002;964:47–68; Zarkadas M, Scott FW, Salminen J, et al. Common allergenic foods and their labeling in Canada—a review. Can J Allergy Clin Immunol 1999;4:118–41.

allergens via subcutaneous injections. Later in life, these dogs demonstrated cutaneous or gastrointestinal signs when challenged orally with the food items to which they had been sensitized. It was shown that these dogs had elevated IgE to the sensitized food items, had wheal and flare reactions with intradermal injections of the relevant food extracts, and had immediate and late-phase reactions when relevant food extracts were injected into gastric mucosa via an endoscope [14]. These findings suggested that sensitized dogs producing high IgE could be useful as a model of canine food allergy. Additional studies with this model helped to elucidate the hypothesis of genetic predispositions for the development of high levels of IgE [10,11,13].

This canine model producing high IgE has been used in additional investigations. One finding is that these dogs have a statistically significant difference in IgE levels detected by ELISA for individual food items compared with control dogs. These differences were not altered when sensitized allergens were given as food items in the diet or when an elimination test diet was used [14]. Further, only the sensitized dogs exhibited wheal and flare when whole-food allergen extracts were injected subcutaneously. None of the atopic food allergen–sensitized dogs exhibited cutaneous or gastrointestinal signs when challenged with soy- or corn-based diets, however, even though they had been sensitized to these items via subcutaneous injections. These results differed from the data obtained from previous studies [11,13].

A spontaneous dog model of IgE-mediated food hypersensitivity has also been investigated. These test dogs exhibited cutaneous and/or gastrointestinal signs when challenged with cow's milk or dairy products, and their symptoms resolved when fed an elimination test diet. Relative concentrations of serum IgE detected by ELISA to wheat, corn, and cow's milk were elevated in test dogs compared with control dogs. These dogs also had an increase in IgE to corn when a corn-based diet was fed. A concurrent increase in the severity of clinical signs was seen during the feeding of the corn-based diet [15]. From an investigative standpoint, the spontaneous food-allergic dog model may prove to be better than the atopic dog, food allergen–sensitized model for the study of type I hypersensitivity reactions as a parallel to dogs with cutaneous adverse food reactions.

Investigations support the hypothesis that dogs with concurrent gastrointestinal disease may also have associated elevations in serum IgE to food items. In one study, atopic dogs had more food allergen–specific IgE than control dogs. Also, dogs with gastrointestinal disease had more food allergen–specific IgG compared with atopic and control dogs. It was summarized that increased antigen exposure follows increased mucosal permeability [16]. In another study, it was shown that normalization of intestinal permeability followed by an elimination test diet helped to define dietary hypersensitivity, whereas those dogs with persistent abnormalities in gastrointestinal permeability are more likely to have underlying intestinal disease and food intolerance [17]. Together, all these studies help to define that true IgE-mediated adverse food reactions are dependent on genetic predisposition and an abnormality in gastrointestinal function.

Although the IgE hypersensitivity reaction is assumed to be the most common cause of cutaneous adverse food reactions in dogs and people, there is some recent evidence to support the finding that elevated levels of serum IgE may not always be present. In one study, it was shown that people diagnosed with food hypersensitivity based on a double-blind, placebo-based, controlled food challenge (DBPCFC) exhibited localized IgE responses when symptomatic without statistically significant differences in serum IgE compared with control patients [18]. This finding may help to explain why serum testing and intradermal skin testing with food allergens in dogs have been inaccurate–the IgE-mediated response may be occurring at the intestinal level and may not be reflected in serum or cutaneous mast cell reactivity.

DIAGNOSIS

There is no evidence that there is any sex predilection for cutaneous adverse food reactions. The age of onset is variable, and clinical signs maybe seen in dogs less than 6 months of age and greater than 11 years of age [4]. There is some evidence to support the finding that certain breeds have an increased risk for the development of food allergy [19,20]. In dogs, the most common signs associated with cutaneous adverse food reactions include nonseasonal pruritus of the face, feet, ears, axillae, forelegs, or perianal regions. Any or all of these regions may be affected, or the dog may have generalized skin

disease [4,21,22]. Additionally, dogs may present with chronic or recurrent otitis or pyoderma [4,21,22].

The "gold standard" for diagnosis of food allergy in human beings is the DBPCFC. During the challenge, capsules of food items are ingested and the patient is evaluated. The oral allergy syndrome causes a burning or tingling sensation of the oral cavity and sometimes tinnitus [1]. Clearly, these subtleties could not be evaluated in canine patients. The oral allergy syndrome may partially explain facial pruritus in the dog, however. Skin prick testing using whole-food items has demonstrated a negative predictive value in human beings. Serum allergy testing for IgE antibodies is sometimes used but may only be helpful in evaluating type I hypersensitivity reactions.

The only accurate diagnosis of canine food allergy is based on an elimination test diet leading to the resolution of clinical signs, followed by a provocative food challenge. Clinical signs may recur in minutes to hours or up to 2 weeks after the challenge item is fed [23]. The duration required to perform an elimination test diet is not clearly defined. The length of time recommended for the elimination diet is variable, and a period ranging from 3 to 10 weeks has been suggested [19–21]. It has been demonstrated that an 8-week food trial is adequate in most situations [19]. Some authors contend that there is usually some evidence of improvement of clinical signs within the first month, although all the signs may not have completely resolved. Also, there have been other reports of food-allergic dogs failing to show clinical improvement until the food trial was extended for 12 full weeks [19].

One of the most difficult challenges in achieving an accurate diagnosis of food allergy is owner compliance. In a recent study, suspected food-allergic dogs were to be fed a homemade diet elimination food trial for 6 to 8 weeks. Of the 28 dogs enrolled in the study, 10 did not complete the food trial as prescribed [24]. There are many reasons for noncompliance in general. These may include cost, time of preparation, intolerance or dislike of the selected food items, inability to limit exposure to other items (treats), exacerbation of clinical signs, poor doctor and client communication, or a client who does not believe that food is a cause of the clinical signs.

The selection of an appropriate elimination test diet is dependent on the dietary history. Most dogs have eaten commercial diets containing a variety of different ingredients from protein and carbohydrate sources. Selecting items that are unique to the diet can be challenging. Ideally, the test diet would be free of preservatives or additives, although documented adverse reactions to preservatives and food additives in canine patients are rare [25]. Studies have suggested that commercial diets are not as accurate in diagnosing food allergy as home-prepared diets [19,23,25]. Therefore, it is recommended that a home-cooked elimination diet should be considered the gold standard for diagnostic purposes.

There are profound limitations associated with a home-prepared diet using a unique or novel protein source. First, some protein sources may be expensive for the owner to purchase or may only be found in limited quantities. Second,

home-cooked diets entail some work by the owner that he or she might find tedious. Finally, home-prepared diets are not usually complete and balanced [26]. For clinically healthy dogs, the short duration of the feeding trial should not lead to major nutritional deficiencies. Dogs with concurrent metabolic illness should be carefully evaluated before recommending a home-cooked diet, however. Most home-prepared diets are low in calcium [27]. Nondietary calcium, vitamins, and essential fatty acids should be added to the diet [4,26].

Many "novel" protein sources can be considered for an elimination test diet. A short list of fresh food items includes pinto beans, tofu, venison, duck, rabbit, fish (various species), squid, ostrich, alligator, and other wild game. Canned tuna in water or salmon is also an option. Care should be taken if selecting fish as a test diet. One study suggests that a home-cooked diet containing fish and potato was inadequate in diagnosing food allergy in four of eight cases and that there may be an emergence of fish allergies in canine food-allergic patients [24]. This may be attributable to the presence of fish and fish meal in many commercial diets. In another study, it was found that the two most common canine food allergens identified were beef and soy [23]. This would suggest that tofu might not be the best protein source for a dietary trial.

The selection of a carbohydrate source is also based on dietary history. Food elimination diets have been performed using rice or potato, but these ingredients have found their way into many commercial diets and may not be suitable as test ingredients. Sweet potato or brown rice should be considered as a novel carbohydrate source at this time. New commercial diets available through mail order may contain these items as well.

The test diet may be composed of a 50:50 protein-to-carbohydrate source by volume, although less protein may be used for financial reasons. This diet should be fed for a minimum of 10 to 13 weeks or until clinical signs abate [4,19]. A partial improvement in clinical signs may be seen in some cases because of resolution of concurrent problems such as atopy, flea allergy, or concurrent infection with bacteria or *Malassezia* yeast. Recurrence of clinical signs may occur in 3 to 7 days on dietary food challenge. Once a documented reaction is noted, the dog should be placed back on the test diet. It may only take a few days for the pruritus and lesions to improve. It is recommended to use individual food items for the identification of offending allergens. This should aid in the long-term management of the patient. In one study, it was found that the mean number of offending allergens per dog was 2.4, with 80% of dogs reacting to one or two items and 64% reacting to two or more tested proteins [23]. Once the offending allergens are identified, strict avoidance is essential. Sensitivity to commercial dietary products based on the same ingredients as those used in home-cooked diets has been noted [20,28].

Home-prepared test diets are not without potential adverse reactions. Some dogs may not tolerate a home-cooked diet and may exhibit vomiting or diarrhea. Some dogs may be reluctant to eat the chosen diet. Also, weight gain or weight loss should be carefully monitored during the dietary trial. Hungry dogs are likely to scrounge for food and may accidentally ingest items that negate the food trial.

During the food trial, it is imperative that nothing passes the dogs lips except for the selected diet and water. Flavored heartworm preventive should be changed to a nonflavored tablet or alternative product. By the same token, chewable flavored antibiotic or vitamin tablets must be avoided. All treats, including rawhide chews and pig's ears, are also off limits. Part of the difficulty in achieving an accurate food trial stems from the client's desire to offer the dog treats. Children within the household who do not understand the implications of an elimination test diet can also affect the outcome of the trial. Even treats that are labeled "hypoallergenic" should be avoided.

Several commercial diets have been formulated for the diagnosis and management of food-allergic dogs. Novel protein sources, such as rabbit, venison, duck, kangaroo, and others, are available from commercial producers. Potato and oats have been used in combination with the various protein sources. These diets seem to be a reasonable alternative to home cooking when cost or owner effort is the limiting factor. Commercial diets containing lamb were once considered effective as testing and management sources for canine food allergy. Because of the prevalence of lamb-based diets (including puppy formulations), however, this protein source has lost its "novel" status. There are also many commercial diets available that contain fish (eg, catfish, whitefish, salmon). Recent data suggest that fish is no longer considered to be a novel protein [24].

Within the past few years, new diets have emerged that extend beyond the novel protein concept. Diets containing hydrolyzed proteins are now commercially available. It had been demonstrated that modification of wheat proteins led to the mitigation of allergic responses in a colony of highly inbred and sensitized research dogs [29]. These findings helped to introduce the idea of formulating hypoallergenic diets for dogs. Hydrolyzed diets have been shown to be beneficial for human beings with known allergic reactions [30]. Enzymatic hydrolysis of proteins can lead to smaller protein peptide fragments that are more digestible and less allergenic. Small proteins may still be immunogenic, however.

Hydrolyzed diets have been investigated for dogs suspected of having food allergy. In one study, 34 of 36 dogs improved during the test period when fed a commercially prepared soy isolate hydrolysate and rice diet and relapsed when challenged with the original diet. Interestingly, 1 dog did not respond to the hydrolyzed soy diet but did improve when a home-prepared soy diet was fed [31]. These findings suggest that a commercially prepared hydrolyzed soy diet could be used as an elimination test diet for many dogs. The percentage of dogs with a favorable response was high, although this may reflect the selection process for inclusion in the study.

Hydrolyzed chicken-based diets are also commercially available. In one study using a hydrolyzed chicken and corn starch diet as a test diet for dogs suspected of having adverse food reactions, 9 of 46 dogs were diagnosed with an adverse food reaction as the sole cause of nonseasonal pruritus. Concurrent gastrointestinal signs were noted in 21 of these dogs, and they all improved during the test diet [32].

The colonoscopy allergen provocation test has recently been described to evaluate the type I hypersensitivity reaction in human beings [33]. Allergens are directly injected into the mucosa of the colon, and observations are made of wheal and flare reaction. This procedure has been evaluated using the atopic dog model and showed good reproducibility [34]. The preliminary results of this diagnostic test on dogs with adverse food reactions seem to be promising [34]. Colonoscopy allergen provocation testing demonstrated sensitivity and specificity of 75% and 73%, respectively, when evaluated in nine food-allergic dogs (atopic dog model). This novel approach to the diagnosis of adverse food reactions is only useful for detecting the type I reaction. Further data must be collected before conclusions can be drawn on the usefulness of this procedure. A similar procedure has been described for injecting food allergens into the gastric mucosa using an endoscope [35]. This procedure has limitations with reproducibility and sensitivity.

Skin prick testing using whole-food allergens is used to rule out IgE-mediated food hypersensitivity in human beings [1]. This test is associated with low sensitivity and high specificity (few false-positive reactions). It is sometimes used for infants and young children who may not be amenable to oral food challenge [36]. Skin prick testing is not commonly used in dogs. Intradermally injected food allergens have been investigated in dogs. This procedure showed low sensitivity and high specificity similar to skin prick testing in people [37].

MANAGEMENT

Long-term management of the food-allergic dog requires strict avoidance of the offending food items. Some dogs may exhibit new dietary sensitivities within 1 to 3 years [22]. Therefore, it might be best to limit the variety of items fed to the patient in case a new elimination test diet is needed. The owner should keep a journal of offending foods and note any adverse reactions, including pruritus, infections, or seizures.

FUTURE CONSIDERATIONS

We are a long way from understanding the complete pathogenesis of cutaneous adverse food reactions in dogs. Further investigations may lead to better and easier diagnostic tests.

It has been hypothesized that there is an immunologic window of opportunity for dogs to become sensitized to food allergens [20]. If it is shown that dogs become sensitized at a young age, it might be possible to limit sensitization to those food items that affected dogs are not likely to consume during the remainder of their lives. Feeding a novel protein antigen at a young age may lead to sensitization, but this protein could easily be avoided at an older age [12]. There might still be a chance of new sensitivities developing later in life, however [22]. Hydrolyzed protein diets could also be considered instead of novel proteins. Hydrolyzed diet formulas are given to atopy-prone people to reduce allergenic activity [38]. Also, reduced exposure of human infants to allergenic foods caused by food allergen avoidance on the part of the reactive mother has been shown to decrease food

sensitization, primarily during the first year of life [38]. Additional studies are needed to investigate whether hydrolyzed diets or limited antigen exposure to proteins of the nursing bitch would be of benefit in reducing the risk of development of cutaneous adverse food reactions in dogs.

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