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Food allergy in canines: A review

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Abstract
Food allergy is an immunological response to the ingested allergen present in food like artificial food additives, beef, canned foods, corn, cow milk, dairy products, dog foods, dog biscuits, eggs, fish, and food preservatives, meat of different species including pork, mutton and horse meat, oat meal, potatoes, rice and commonly occurs in dogs and cats. Among all canine species, Labrador and German shepherd were found to be more prone to food allergy and symptoms are similar to other pruritic skin diseases. These food allergies are broadly classified into two categories (1) IgE-mediated food allergy (2) non-IgE-mediated food allergy. Diagnosis can be done by accurate clinical history**,** parental observations**,** and laboratory tests: Skin scrapping, bacterial/fungal culture examination, thyroid test, fecal examination and skin biopsy, allergic tests: Patch test, Skin Prick Test, Intra-dermal test and Radioallergosorbent test. Management of these allergies can be done by antihistaminics like Hydroxyzine and Chlorpheniramine, antibiotics like Cephalexin, Enrofloxacin, antifungals like Ketoconazole, Griseofulvin, Amphotericin-B and glucocorticoids like Prednisolone, Methyl prednisolone.

Keywords: Food allergy, IgE mediated, non-IgE mediated, Patch test

1. Introduction
Adverse reactions in dogs and cats to allergens present in food is the commonest form of hypersensitivity and frequently reported to occur next to flea allergic dermatitis and atopic dermatitis. It is defined as the clinically abnormal exaggerated immunological reaction/response to the ingested allergen present in food as described by National Institute of Allergy and Infectious Diseases, 2011. Alternatively the food allergy and food/dietary hypersensitivity are used interchangeably. All food reactions are not considered as food allergies [1]. Adverse reactions to food account for 10-20% of all the skin problems been reported till date [2]. It is associated mostly with the protein component present in the food that elicits an immunological response that is capable of bridging the two molecules of IgE thereby triggering degranulation in the mast cells thus causing the release of mediators of inflammation [3].

2. Classification
Broadly untoward reactions to food are classified on the basis of response elicited into two types: immunological and non-immunological. Food allergy/food anaphylaxis is categorized under immunological response which may be IgE mediated or non IgE-mediated. Mostly, it is of type I (immediate) hypersensitivity reactions, mediated by immunoglobulin E (IgE) but in some cases both types III and IV hypersensitivity may also be involved. Glycoproteins with a molecular weight ranging between 10 and 60 kilo Daltons are considered as the antigens which can cause reaction within minutes to hours, days and can even take longer periods to get sensitized to present clinical manifestations. Whereas food poisoning, food intolerance and dietary indiscretion are classified under non-immunological response. Food intolerance is further subdivided namely reaction due to pharmacological active ingredient, reaction due to metabolism of certain ingredients, food idiosyncrasy and pseudo allergy [4]. Pharmacological reaction to food is initiated by stimulation of response to certain pharmacological active agent present in food having drug like action. Mostly response is seen in intestine causing motility disorders manifested as diarrhea. An example is monosodium glutamate used as a flavour enhancer in dogs. In addition, physiological compounds like casomorphins also reported to alter the gut motility and manipulation of the omega-3 and omega-6 ratio in food causes alteration of prostaglandin production [5].

Metabolic reaction to food is due to genetic error of metabolism that is inborn in nature. Chronic hepatitis in Doberman dogs is a classical example. Inability to excrete copper causes copper toxicosis leading to chronic hepatitis in these dogs [6]. Indigestible or unabsorbed products (lactulose), or deficiency of certain enzymes (lactase) can result in a metabolic food reaction [7].

Food idiosyncrasy is mostly mechanical in nature as occurs due to less fibre in the diet or the presence of certain indigestible (bones) products [8]. In contrast production of histamine (ingestion of Tuna fish and Shell fish) which is responsible for mast cell degranulation is categorized under pseudo allergy. [2]. defined Canine food allergy /hypersensitivity as a non-seasonal pruritus (regional or generalized) with involvement of ears, feet, inguinal or axillary areas, face, neck, and perineum. Erythema with a papular rash including alopecia, excoriations, scales, crusts and hyperpigmentation of the affected skin areas. It is very difficult for the clinician to distinguish atopic dermatitis and food allergy based on clinical signs although seasonality of occurrence, response to steroid therapy can give useful hints. In Atopic dermatitis there is a genetic predisposition of developing hypersensitivity reactions (type 1) to substances present in environment such as dust, pollens etc.

3. Predisposition, contributing factors and etiology

3.1 Predisposition and contributing factors

Food allergy has no age predisposition [9], no sex predilection in dogs (Chesney, 2002) with no seasonality of occurrence [10]. Labrador and German shepherd were found to be more prone to food allergy [2] although any breed including mixed breeds may be affected. [11] Reported 33%, 51% and 16% incidence in < 1 year, 1-5 years and 5-11 years of dogs respectively. Protein and carbohydrate source in pet food, certain foods and food ingredients, any disease that increases intestinal permeability (e.g. viral enteritis), selective IgA deficiency, poorly digestible protein and other allergic disease [12].

3.2 Etiology

The offending antigen is usually a basic food ingredient in the animal's diet responsible for the food allergy. A wide range of dietary ingredients responsible for food hypersensitivity includes artificial food additives, beef, canned foods, corn, cow milk, dairy products, dog foods, dog biscuits, eggs, fish, food preservatives, meats of different species including pork, mutton and horse meat, oat meal, potatoes, rice flour, soy, wheat, kidney beans. A prospective study was conducted in 25 dogs to characterize specific food ingredients causing adverse reactions [13]. Single-ingredient stimulation trials were conducted with beef, chicken, chicken eggs, cow milk, wheat, soy and corn. Among all the ingredients, beef and soy were found to cause most cutaneous adverse reactions, although all ingredients induced clinical signs in at least one dog. 36% percent of dogs reacted to one protein and the mean number of suspected allergens per dog was 2.4. Recently in 15 different experimental studies, representing 278 dogs from different continents were assessed to check ingredients that are commonly associated with adverse food reactions. These experimental studies showed beef, dairy products and wheat accounted for 69% of reported cases where as lamb, chicken egg, chicken and soy accounted for 25% of the dogs. In 10 experimental studies conducted on 56 cats, beef, dairy products and fish were associated with food reactions in 80% of the animals [12]. In one beef allergic dog, bovine serum albumin was found to be the target of anti-beef IgE [14]. A study carried on 10 dogs, it was found that major allergen in cow's milk that cause allergic reactions is bovine IgG and because of high homology of bovine IgG with ovine immunoglobulins it can be a possible source of cross-reactivity with beef and lamb (similar to meat allergy in humans). Cow's milk is a wholesome food containing about 20 protein components [15]. The milk-protein fractions are thus subdivided into casein proteins (78-86%) and whey protein (14-24%). β-lactoglobulin is the most allergic component, followed by casein, lactalbumin, and bovine serum albumin. Dogs that were allergic to cow's milk could not eat cheese and vice versa [16]. Hidden allergens can also be a problem with food allergies including a number of oils such as corn and soy. A milk protein (Sodium caseinate), is often added to improve the packaging qualities in canned tuna is also responsible for the allergic reaction.

4. Pathogenesis

A food allergy arises when there is a reproducible reaction to a specific food or food additive with a proven immunological basis. There are two types: an IgE mediated and a non-IgE-mediated response.

4.1 IgE-mediated food allergy

It is commonly believed that food allergy is, in most cases, an IgE-mediated type 1 reaction (Gell & Coombs classification) [7]. However, it is documented and reported to occur by other types also including notably type iii and iv [4]. In type 1 hypersensitivity reaction, specific allergen triggers the IgE sensitized mast cells which causes release its pharmacological mediators thus setting in the process of inflammation. Clinical signs mostly depend on system/tissue in which reaction occurs. It may include dermatological, respiratory, gastrointestinal signs, or a combination. Several reasons are responsible for how an allergen can induce abnormal response in food allergy.

Firstly, the allergen may have the ability to penetrate the physiological mucosal barrier. The components of this barrier include digestive enzymes, gastric acidity, peristalsis, the surface mucus, enterocyte tight junctions, and the immunological barrier of intraluminal IgA. After penetrating the mucosal barrier, the allergen will interact with gastrointestinal associated lymphoid tissue (galt). The galt is formed by the Peyer's patches, diffuse lymphoid tissue in the lamina propria, enterocytes, and intraepithelial lymphocytes [4]. The immune response in the galt usually leads to a Th2-mediated response in which the cytokines interleukin IL-4 and IL-5 stimulate IgA production and immune responses involving mast cells and eosinophils. In a type i reaction, the antigen is presented by an antigen-presenting cell to a Th2 cell, which then produces IL-4 and IL-10. These cytokines stimulate B cell proliferation and induce IgE production. The resultant IgE binds to mast cells and sensitizes them. If the allergen reaches the sensitized mast cell, it releases histamine, proteases, as well as several leukotrienes and prostaglandins. IL-4 produced by Th2 cells influences, among others, tnf-α and tnf-β production [17].

Normally, an antigen will induce oral tolerance, which is an active response and is designed to limit the unnecessary and wasteful activity of galt in response to 'harmless' luminal antigens, such as those from endogenous microbiota. If, for whatever reason, this normal tolerance is abolished, the antigen induces an inappropriate immune response to endogenous flora (resulting in Inflammatory Bowel Disease)

or, in the case of food allergens, food allergy [4]. The food allergens that trigger such an abnormal response are usually soluble protein or glycoproteins resistant to degeneration [4]. In dogs, common allergens are derived from beef, chicken, milk, eggs, corn, wheat, and soy [18]; in contrast, reactions in cats are more commonly to dairy and fish proteins. As such, no particular protein is especially 'allergenic'. Animals are more likely to respond adversely to dietary components to which they are commonly exposed. Factors that contribute to food allergy either interfere with the normal mucosal barrier (viruses, bacteria, parasites, toxins, etc), lead to an abnormal presentation of the antigen to the galt, or cause deregulation of the galt [4].

4.2 Non-IgE-mediated food allergy:
Non-IgE-mediated anaphylaxis or gluten-sensitivity most likely involves a type iii or iv immunological reaction although some believe it to be more an intolerance than immunologic of nature. In gluten-sensitivity, gliadens, one of the four gluten proteins, induce a non-IgE-mediated mast cell response as in IgE-mediated food allergy. Gluten sensitivity was demonstrated in a single cohort of young Irish setters [19]. Hence, the opinion that gluten should be avoided in all cases of gastrointestinal diseases (or in all dog foods) is flawed.

5. Clinical Signs
Reactions to ingested food components can affect many body systems and can produce signs involving the skin, gastrointestinal tract, respiratory tract and central nervous system. Dermatological signs include pruritus, erythma, papular eruptions are common and often seen with a secondary staphylococcal folliculitis infection, otitis externa (unilateral or bilateral), Urticaria. Occasionally, dogs will be non-pruritic and exhibit only seborrhoe [20]. Self inflicted trauma in pruritic cases resulting in excoriation, alopecia and secondary superficial pyoderma are also noticed.

5.1 Food anaphylaxis is an acute response to ingestion of food or food additives resulting in various systemic consequences

- Angioedema or facioconjunctival edema [10].
- Angioedema is typically manifested by large edematous swellings of the lips, face, eyelids, ears, conjunctiva and/or tongue, with or without pruritus [10].
- These reactions usually occur within minutes of allergen exposure and generally subside after one to two hours
- 1/4th of dogs with AFR had lesions only in the region [21].
- Adverse food reactions should always be with pruritic, unilateral or bilateral otitis externa, it may accompanied by secondary bacterial or *Malassezia* infections [10].

Other presentations of food allergy include recurrent superficial pyoderma, pruritic papular eruptions over the trunk and head [2].Adverse food reactions concurrent to flea-allergic or atopic dermatitis accounting for 20% to 30% or more of dogs has been documented [22]. Concurrent GIT signs (vomiting, diarrhea, frequent defecation, colitis etc) were seen to occur in 10-15% dogs with skin infections caused by an adverse reaction to food [23]. Neurological signs, such as seizures, malaise have been reported [24].Although asthma and other respiratory signs have also been reported, these clinical signs are rare [3].

Diagnosis and management
6.1 Diagnosis can be done by
a. Accurate clinical history
b. Parental observations: Clinical symptoms, physical examination
c. Laboratory tests: Skin scrapping, bacterial/fungal culture examination, thyroid test, fecal examination and skin biopsy
d. Allergic tests: Patch test, Scratch tests (Skin Prick Test), Intra-dermal test and RAST (Radioallergosorbent test).
e. Dietary investigation in the form of elimination diets and test meals
f. *Diet selection:* Limited antigen diet, in common use, is of 3 types: Home-cooked diets, commercially available novel protein diets, Hydrolyzed protein diet.
g. *Challenge diet:* Dog should be challenged with old diet. If symptoms do not recur with challenge: improvement would have been coincidental & if symptoms do recur, the diet should be switched back to the elimination diet.
h. Gastroscopic food sensitivity testing (GFST)
i. Endoscopic observation of gastric mucosal reaction following exposure to pure food extracts [25].

h. Colonoscopic food sensitivity test (CFST)

- Allergens injected directly into the mucosa of the colon
- Results observed as wheal and flare reactions.

5.2 Management
5.2.1 ***Antihistaminic drugs:*** They counteract the release of histamine from the mast cells, which is the source of the itching. Some of the common antihistaminics used are: Diphenhydramine hydrochloride @ 2mg/kg B.W, Hydroxazine @ 2.2 mg/kg B.W, Chlorpheneramine @4-8 mg/kg B.W

5.2.2 ***Antibacterial drugs:*** Some dogs scratch so severely that they cause a secondary bacterial infection of the skin called pyoderma (Staphylococcus intermedius), which intensifies the itching. Antibiotics that work best for pyoderma include: Cephalexin @ 22 mg/kg B.W, Enrofloxacin @ 2.5 -5 mg/kg B.W, Erythromycin @ 10 mg/kg B.W, Clavulanic acid + Amoxycillin combination @ 13.5 mg/kg BW. The dog should be bathed with shampoo that will help in controlling the skin infection, eg. Benzoyl peroxide or chlorhexidine containing shampoo.

5.2.3 ***Antifungal drugs:*** Secondary fungal infections can occur, especially when the feet are licked constantly. The commonly used antifungal agents include: Ketoconazole @ 5-10 mg/kg B.W, Griseofulvin @ 25 mg/kg B.W, Amphotericin-B @ 0.5 mg/kg B.W. Bathing the dog with a shampoo containing ketoconazole and chlorhexidine.

5.2.4 ***T-cell inhibitor:*** Cyclosporine @ 5mg/kg B.W, Tacrolimus @ 2 mg/kg B.W

5.2.4 ***Glucocorticoids:*** Prednisolone @ 2-4 mg/kg B.W, Methyl prednisolone @ 1-2 mg/kg B.W

5.2.5 ***Food supplements:*** Feed diets balanced with vitamin, mineral and fatty acid supplements e.g. omega-3 and omega-6.

6. Conclusion
Food hypersensitivity is a relatively common cause of allergic skin disease of dogs Symptoms are similar to other pruritic skin diseases, a methodical approach is required to establish a definitive diagnosis. Secondary infections of the skin and ears are common with food allergy, particularly in the dog. These

infections must be resolved prior to completion of an elimination diet. An 8–12 week elimination diet is the only reliable way to diagnose food allergy in the dog and cat. If improvement or resolution of symptoms is seen, the diagnosis can be confirmed by provocative challenge with the former diet. Long term management of food allergy in the dog requires avoidance of the offending allergen(s). The investigation and diagnosis of food hypersensitivity are laborious and frustrating.

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