Dietary hypersensitivity in cats and dogs

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Overzichtsartikel

SUMMARY

Adverse reactions to food or dietary hypersensitivity are frequently seen problems in companion animal medicine and may be difficult to differentiate from inflammatory bowel disease (IBD). Dietary hypersensitivity can be divided into two subgroups: immunological and non-immunological problems. Non-immunological problems can be subdivided into food intolerance, food poisoning, and dietary indiscretion. The immunological group can be subdivided into true food allergy (IgE mediated) and anaphylaxis (non-IgE mediated). This article gives an outline of what dietary hypersensitivity is, and more specifically food allergy and how to deal with patients with possible dietary hypersensitivity.

SAMENVATTING

Voedselovergevoeligheid bij katten en honden

Een afwijkende respons op voedsel of een voedselovergevoeligheid is een veel voorkomend probleem in de gezelschapsdierenpraktijk en het kan erg lastig zijn het verschil te onderscheiden met een inflammatoire darmaandoening (inflammatory bowel disease (IBD)). Voedselovergevoeligheid kan verdeeld worden in twee hoofdgroepen: immunologisch en niet immunologisch. Deze laatste groep kan weer worden onderverdeeld in voedselintolerantie, voedselvergiftiging en voedselindiscretie. De immunologische groep wordt onderverdeeld in voedselallergie (veroorzaakt door een abnormale IgE-productie) en een voedselanafylaxie (Niet door IgE veroorzaakt). Dit artikel geeft een overzicht van wat voedselovergevoeligheid is en gaat dieper in op het begrip voedselallergie en hoe het is om te gaan met patiënten die mogelijk een voedselovergevoeligheid hebben.

INTRODUCTION

Clinical signs associated with adverse reactions to food are a common reason for owners to consult their veterinarian. Not uncommonly, this 'adverse reaction to food' is translated by the owner into the existence of a 'food allergy'. However, this terminology is not correct since an 'adverse reaction to food' simply means any type of reaction to food that leads to a clinically abnormal response attributed to an ingested food or food additive, and its aetiology can be diverse (9, 15, 19).

Dietary hypersensitivity can be divided into two major groups: non-immunological, which includes the categories of food intolerance, food poisoning, and dietary indiscretion, and immunological, which is true food allergy (9, 19, 29, 40). The clinical signs of food allergy, food intolerance, food poisoning, and dietary indiscretion overlap, and for this reason it is not possible to separate the two groups clinically (19, 29). In all cases owners may seek veterinary help for dermatological, gastrointestinal, or other signs (19, 29). It has been suggested that the majority of adverse reactions to food are due to food intolerance rather than genuine food allergy (21), although there are no data to support this supposition directly.

THE GROUP OF NON-IMMUNOLOGICAL PROBLEMS

Food intolerance

Food intolerance is a non-immunological adverse reaction to a specific food (or food additive) that, in contrast to dietary indiscretion and food poisoning, is reproducible. Since signs are associated with the ingested food, it is more difficult to distinguish from food allergy. Food intolerance can be subdivided into four groups (9, 19, 29, 40).

1) Metabolic food reaction

Metabolic food reactions may occur from, for instance, an inborn error of metabolism or excess of a food ingredient. An example of a presumably genetic inborn error of metabolism is chronic hepatitis in Doberman dogs. Some dogs lack the ability to excrete copper and develop a copper-associated chronic hepatitis due to copper toxicosis (32). Unabsorbed or indigestible products (for example, lactulose), or an enzyme deficiency (lactase) can also result in a metabolic food reaction (19, 47).

2) Food idiosyncrasy

This may be partly mechanical (lack of fibre or ingestion of non-digestible material such as bones). But many other items ingested by dogs (and cats) can cause food idiosyncrasy (7).

3) Pharmacological reaction to the food

Pharmacological stimulation can occur when compounds in the food have a drug-like action or stimulate such a response in the intestine. An example is monosodium glutamate in vetsin (10). In addition, physiological compounds such as casomorphins can alter the motility of the gut. Another example is the alteration of prostaglandin production by manipulation of the omega-3 and omega-6 ratio in food (13).

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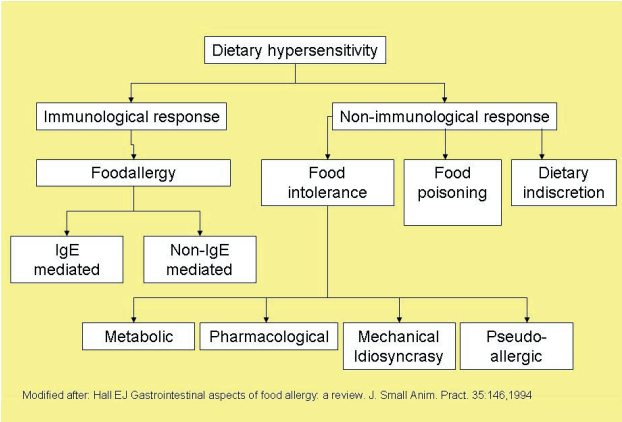

Fig 1. Dietary hypersensitivity can be divided into two major groups: immunological and non-immunological. Each group is again subdivided.

4) Pseudo-allergic

Pseudo-allergic responses induce histamine- (for instance, in Tuna fish) or non-IgE-mediated mast cell degeneration (for instance, in shellfish) (43). This type of non-IgE-mediated mast cell degeneration is different from that in non-IgE food allergy such as coeliac disease (discussed later).

Dietary indiscretion & food poisoning

A dietary indiscretion is seen after, for instance, scavenging or pica and it is not related to the ingested food itself (9, 19, 29, 40). There is, of course, some overlap with food idiosyncrasy. The term food idiosyncrasy may suggest a single event, whereas scavenging or pica may be a more normal food pattern for an individual. A dog or cat that is known to eat abnormal material (for instance, plant particles) may show this behaviour repeatedly despite the fact that it gives rise to gastrointestinal signs.

Food poisoning results from a direct non-immunological action of a toxin ingested, a toxin released (by an ingested organism, e.g., bacteria), or an infection caused by an ingested organism (9, 19, 29, 40). Normally, it has an acute presentation and will rapidly resolve by itself. For this reason, it is easy to distinguish food poisoning from food allergy, because signs resulting from the latter will not rapidly resolve by themselves.

THE GROUP OF IMMUNOLOGICAL PROBLEMS

Food allergy

A food allergy arises when there is a reproducible reaction to a specific food or food additive with a proven immunological basis (9, 19, 29, 40). There are two types: an IgE-mediated and a non-IgE-mediated response.

IgE-mediated food allergy

It is commonly believed that food allergy is, in most cases, an IgE-mediated type I reaction (Gell & Coombs classification) (9, 19, 24); however, there may be instances when other types of hypersensitivity may occur, most notably type III and IV responses (9). With type I hypersensitivity reactions, IgE-sensitized mast cells are triggered by a specific allergen. When the mast cell releases its pharmacological mediators, an inflammatory response will follow. Observed clinical signs depend upon the tissue in which the reaction occurs and may include dermatological, respiratory, gastrointestinal signs, or a combination.

A food allergy can arise when an allergen induces an abnormal immunological response, and this can occur for several reasons. Firstly, the allergen may have the ability to penetrate the physiological mucosal barrier (figure 2). The components of this barrier include digestive enzymes, gastric acidity, peristalsis, the surface mucus, enterocyte tight junctions, and the immunological barrier of intraluminal IgA (figure 2). 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 (9, 44). 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, TNFα and TGFβ production (1, 3, 9, 34, 37, 44).

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

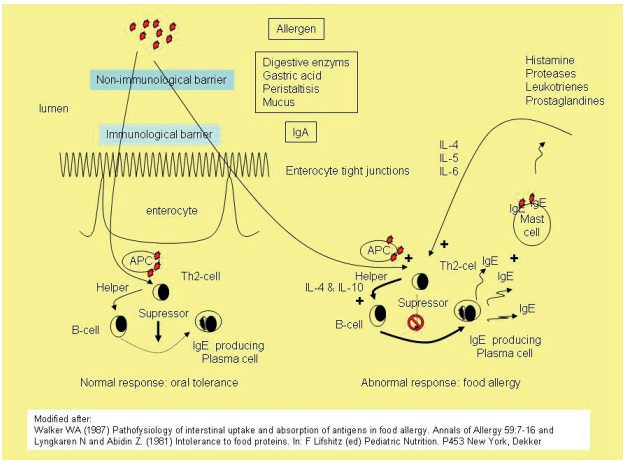

Fig 2. The normal response leading to oral tolerance and the abnormal response. In the abnormal response the ingested allergen is presented by an antigen presenting cell to the Th2 cell. Due to among others IL-4 and IL-10 it leads to plasma cells that produce abnormal IgE. This can bind to mast cells and hence this may lead to excretion of histamine, proteases, leukotrienes and prostaglandins.

Systemic	Gastrointestinal tract	Skin	Other organs
	Vomiting	Pruritis	
Fatigue	Small bowel diarrhoea	Non-specific dermatitis	Joint disease
Food-aversion	Large bowel diarrhoea	Pyodermia	Respiratory disease
	Abdominal pain	Crusting lesions	Behavioural problems (?)
Anaphylaxis	Weight loss	Otitis externa	Epilepsy (?)
	Eating problems		

Table 1. Possible clinical signs caused by food allergy.

response to endogenous flora (resulting in Inflammatory Bowel Disease; IBD) or, in the case of food allergens, food allergy (9). The food allergens that trigger such an abnormal response are usually soluble protein or glycoproteins resistant to degeneration (9). In dogs, common allergens are derived from beef, chicken, milk, eggs, corn, wheat, and soy (46); 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 dysregulation of the GALT (19).

Non-IgE-mediated food allergy: anaphylaxis

Non-IgE-mediated anaphylaxis or gluten-sensitivity (known in humans as coeliac disease) (9, 20, 41, 42) most likely involves a type III or IV immunological reaction although some believe it to be more an intolerance than immunologic of nature. Coeliac disease is nowadays called, in humans, gluten-intolerance and not gluten-allergy. But as in veterinary medicine it is still categorized in this group it is discussed here.

In gluten-sensitivity, gliadens, one of the four gluten proteins, induce a non-IgE-mediated mast cell response as in IgE-mediated food allergy. In humans, coeliac disease may be accompanied by no or a variety of clinical signs, such as diarrhoea, abdominal pain, weight loss (due to malabsorbtion), fatigue, and depression. It is also associated with other immune-mediated diseases (e.g., hypothyroidism) and a possible slightly higher incidence of enteric lymphoma (8;12;28). The incidence is estimated to be 0.5-2% in humans. Histopathology is marked by villous atrophy and crypt hyperplasia (8, 12, 28). Although gluten is commonly cited as a food allergen in dogs, there is little evidence for this. Gluten sensitivity was demonstrated in a single cohort of young Irish setters. However, the pathogenesis was found to be different from that of human coeliac disease, and in many cases the disease resolved as dogs got older (20). Hence, the opinion that gluten should be avoided in all cases of gastrointestinal diseases (or in all dog foods) is flawed.

CLINICAL SIGNS

The clinical signs of food allergy, food intolerance, food poisoning, and dietary indiscretion overlap, and for this reason it is not possible to separate the two groups clinically (9, 19, 29, 40). Dermatological, gastrointestinal, and other signs have been described (2, 6, 35, 46). In most cases, the gastrointestinal signs are caused by dietary indiscretion, food poisoning, and food intolerance. Only in 10-15% of cases it is caused by a food allergy (2, 19, 29, 39).

DIAGNOSING FOOD ALLERGY AND FOOD INTOLERANCE

Both food intolerance and food allergy will, in principle, respond when the abnormal food is withheld. When a patient is no longer fed on a diet containing the offending ingredient, it should respond, in most cases within days. Further, challenge with the suspect diet should lead to recurrence of clinical signs (16, 22, 23, 29, 30, 47). Diagnostic aids, such measurement of antigen-specific IgE and gastroscopic food sensitivity testing, have been used in dogs. However, currently they are either not reliable (in the case of antigen-specific IgE) (9, 19) or too elaborate for routine use in private practice (16-18). Currently, the gold standard for diagnosis remains provision of an exclusion diet and subsequent challenge (see above); either a home-prepared diet using a novel and rare protein source (22, 25, 26, 29, 38) or a commercially available diet can be used (4, 11, 31, 33). In the past, many commercial hypoallergenic diets contained novel proteins, such as lamb, white fish, rabbit, but these proteins are nowadays used in normal pet foods. This may lead to a lower efficacy (19, 39).

In recent years, several hydrolysed protein-based diets have been developed and shown to be effective (4, 11, 31, 33). In the Netherlands, at least five different brands of hydrolysed protein diets are available, based on fish, soy, and chicken. Although soy protein was long considered immunogenic, a recent study showed that a hydrolysed diet based on soy protein did not interfere with normal GALT responses and thus can be used as a hypoallergenic diet (36).

DEALING WITH GI PATIENTS WITH POSSIBLE FOOD INTOLERANCE AND FOOD ALLERGY

When presented with patients with GI symptoms, veterinarians should take a thorough history and perform a clinical examination. Ideally clinical signs are scored using the Canine Chronic Enteropathy Disease Activity Index (CCEDAI) (5). Faecal examination and other laboratory testing (blood samples and urinalysis) are recommended. In many cases, a dietary trial could be considered before performing gastrointestinal endoscopy or initiating antimicrobial or glucocorticoid therapy.

If gastroduodenal scopy or coloscopy is performed, one should realize that the exact histological changes in the gut associated with food allergy are not known, and that it is not possible to diagnose food allergy based on histopathology alone (9, 29, 45). In both food allergy and IBD, villous atrophy, lymphoplasmacytic infiltrates, eosinophilic infiltrates, and an abnormal intraepithelial lymphocyte infiltration may occur (4, 9, 11, 33, 45). It is recommended to use, for histopathology, the recently published guidelines of the WSAVA gastrointestinal standardization group (45). Moreover, although obtaining biopsies from animals with possible food allergy may be of interest, it can lead to misdiagnosis if cases are treated solely on the basis of histopathology findings. Likewise, initiating antibiotic or glucocorticoid therapy may lead to an incorrect diagnosis or may complicate diagnosis at a later stage, because these agents may influence the clinical features and histopathology (9, 14).

A complete diagnosis can only be made on the basis of a systematic approach to each patient and careful testing with a home-prepared novel protein diet or a commercially available hydrolysed protein diet. If a response is not observed at once, then another hydrolysed protein diet should be tried.

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