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Invited review

Adverse food reactions: Pathogenesis, clinical signs, diagnosis and alternatives to elimination diets

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Read this annotated article paying close attention to the clinical signs of cutaneous adverse food reactions and the diagnostic process used to diagnose it. Focus on learning information in the highlighted passages and material in red boxes. Do not try to memorize data from the various studies that are reviewed.

ABSTRACT

This review summarises available information about adverse food reactions in dogs and cats. Much of the published information on the pathogenesis of adverse food reactions in these species is transferred from what is known in mice and human beings. Clinical signs affect mostly the integument and gastrointestinal system. Pruritus of the distal limbs, face, ears and ventrum is the most common cutaneous presentation in dogs, although urticaria has also been reported. In cats, all so-called 'cutaneous reaction patterns' may be due to adverse food reactions. The most common gastrointestinal signs in both species are diarrhoea and vomiting. An elimination diet over several weeks using a protein source and a carbohydrate source previously not fed is still the diagnostic tool of choice. Improvement on such a diet, deterioration on re-challenge with the old food and improvement again on the elimination diet confirms the diagnosis of adverse food reaction, whereas alternative tests of blood, serum, saliva and hair have been found to be unsatisfactory. Patch testing with food antigens has been recommended as an aid to choose the elimination diet ingredients, since it has a reasonable negative predictability and likelihood ratio, but is laborious and costly.

Introduction

Skin and gastrointestinal problems are two of the most common presenting complaints in small animal practice and allergies are a frequent cause of pruritus in dogs and cats (Lund et al., 1999; Hill et al., 2006; Klinger et al., 2016). Atopic dermatitis in the dog shows identical clinical signs whether caused by environmental or by food allergens (Hillier and Griffin, 2001; Picco et al., 2008), although environmental allergies are reported more commonly than adverse reactions to food antigens (Picco et al., 2008). Similarly, cats with allergic dermatitis present with a range of clinical changes, frequently referred to as 'feline cutaneous reaction patterns', irrespective of the type of causative allergen (Hobi et al., 2011). Thus, adverse food reaction (AFR) is a differential diagnosis for pruritus with or without gastrointestinal signs in dogs and cats.

Diarrhoea in small animals may have a plethora of causes, of which food-responsive diarrhoea is frequent (Volkmann et al., 2017). Thus, a systematic diagnostic approach to animals with pruritus and gastrointestinal problems frequently includes the ruling out of an AFR. There is a great deal of confusion and contrasting information about the diagnosis and management of AFRs in small animals, whether with gastrointestinal and/or cutaneous clinical signs. Diets of different types and durations have been recommended, and many different blood, skin, saliva and hair tests are marketed as 'useful' diagnostic aids.

This review will summarise our current understanding of the pathogenesis and epidemiology of AFRs in the dog and cat, and outline the clinical presentations seen with this disease. Currently available diagnostic tests and evidence for their reliability will be discussed. Problems associated with the diagnostic approach, as well as reasons for failure to identify AFR, will be presented. Finally, tips for the long term management of animals with confirmed AFRs will be provided.

Pathogenesis of adverse food reactions

On the basis of research in human beings and animals, AFRs can be due to true hypersensitivities or can occur without direct involvement of the immune system. The latter group includes metabolic, pharmacological, toxic or idiosyncratic food reactions (Mueller and Jackson, 2003). An example of a metabolic food reaction is lactose intolerance, leading to maldigestion, malabsorption and osmotic diarrhoea (Deng et al., 2015). Pharmacological food reactions include vasoactive and biogenic amines, such as histamine found in fish, including tuna and mackerel, which may

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cause clinical signs within minutes of ingestion (Ridolo et al., 2016). Since pet foods are typically low in histidine, a precursor of histamine, such reactions are seen more frequently in raw and spoiled home-made fish diets. Chocolate poisoning in dogs with methyl xanthins is another example of a pharmacological food reaction (Bates et al., 2015). Bacterial and fungal toxins contaminating diets may lead to acute enteritis; causative bacteria are not uncommon in raw foods marketed for dogs (Nemser et al., 2014; van Bree et al., 2018). Food allergy or hypersensitivity is caused by an exaggerated immune response to food antigens, most commonly in the form of diarrhoea in dogs and cats, pruritus associated with atopic dermatitis in dogs or various 'cutaneous reaction patterns' in cats.

In human beings, food allergens that elicit an immune response are typically water soluble and heat stable glycoproteins with a molecular weight >10 kDa (Verlinden et al., 2006). The most frequently reported food allergens involved in AFRs are beef, dairy products, chicken and wheat in dogs, and beef, chicken and fish in cats (Roudebush, 2013; Mueller et al., 2016).

The most common food hypersensitivities in human beings are immunoglobulin E (IgE)-mediated (type I) reactions (Pali-Scholl et al., 2017). In the sensitisation phase, food antigens are encountered by T cells and lead to a T helper type 2 (Th2) response, with upregulation of interleukin (IL)-4, IL-5 and IL-13, and subsequent class switching of antibody production to IgE. In the effector phase, cells with surface Fc-e receptors, such as mast cells, basophils and eosinophils, bind the food-specific IgE and, upon exposure to food antigens, release inflammatory mediators. This classically occurs within minutes following exposure and leads to clinical angioedema and/or urticaria (Pali-Scholl et al., 2017). In dogs and cats, food-specific serum IgE has been demonstrated in many studies and was assumed to be an indicator of a clinically relevant type 1 hypersensitivity. However, a number of studies with client-owned dogs have failed to identify a reliable correlation between serum IgE concentrations and clinical exposure to the offending allergens (Mueller and Olivry, 2017). Similarly, intradermal, gastric or colonoscopic testing was deemed to be unreliable (Mueller and Olivry, 2017). Furthermore food-induced urticaria and angioedema is rarely reported in animals (Rostaher et al., 2017a,b).

Alternatively, dendritic cells with food-specific IgE on their surface bind the antigen and initiate a cell-mediated delayed type Th1 response, which clinically may present as pruritus or diarrhoea, histologically associated with a lymphocytic, mastocytic and plasmacytic infiltrate. Stimulation of lymphocyte cultures with food antigens apparently correlates better with clinical observations, but is time-consuming, complicated and still unsatisfactory (Mueller and Olivry, 2017). Patch testing with food antigens has been reported in dogs and has a high negative predictability, although positive reactions to food antigens are meaningless (Bethlehem et al., 2012; Johansen et al., 2017). It is postulated that a breakdown in oral tolerance due to increased intestinal permeability and dysbiosis, especially at a young age, results in food hypersensitivity in people (Plunkett and Nagler, 2017).

Epidemiology

The prevalence of AFRs in veterinary medicine is unclear and an exact evaluation is hampered by the same obstacles as in human medicine. Owner reported food allergies are very common, but often are based on spurious and incomplete responses to diet modifications. Confirmed AFRs require a systematic work-up, often hindered by low owner compliance. Based on available data, the reported prevalence of AFR is 0.22–6% of cats with cutaneous signs and 17–22% of cats with gastrointestinal signs (Hobi et al., 2011). In dogs with clinical signs suggestive of allergic dermatitis, the reported prevalence of AFR (including immunological and non-immunological conditions) is 7.6–25% (Chesney, 2002; Picco et al., 2008; Proverbio et al., 2010); however, AFRs were diagnosed in only 1.7% of the total canine population presented to a veterinary teaching hospital over 12 months (Proverbio et al., 2010). Approximately 50–60% of dogs with chronic enteropathies respond to dietary changes (Allenspach et al., 2016; Volkmann et al., 2017). Thus, food responsive enteropathy represents the most frequent cause of chronic diarrhoea/chronic primary enteropathy in dogs.

In dogs with AFR, young (<1 year) and older dogs (>6 years) are overrepresented (Chesney, 2002; Picco et al., 2008; Proverbio et al., 2010). German shepherd dogs, West Highland white terriers, Boxers, Rhodesian ridgebacks and Pug breeds are also overrepresented among breeds developing AFR (Picco et al., 2008). In cats, the mean age of onset of AFR is 4–5 years, but with a wide range from 3 months to 11 years (Bryan and Frank, 2010). Concurrent environmental hypersensitivities and AFRs have been reported more frequently in the cat than in the dog. In 45 cats with diagnosed environmental antigen-induced dermatitis, additional involvement of food antigens was seen in six animals (13%) (Ravens et al., 2014).

Clinical signs of adverse food reactions

Cutaneous food reactions may be seen in dogs from <6 months of age to as old as 10 years; however, the peak incidence seems to be in younger dogs (<1 year of age) (Picco et al., 2008; Proverbio et al., 2010). Dogs with cutaneous signs due to AFRs are frequently presented with signs of atopic dermatitis that cannot be differentiated clinically from environmental allergy (Hillier and Griffin, 2001; Olivry et al., 2007; Picco et al., 2008). Affected dogs exhibit pruritus, erythema and frequently secondary lesions due to self-trauma. Salivary staining and, in more chronic cases, alopecia, lichenification, hyperpigmentation and excoriations, are seen variously affecting the interdigital aspects of the paws, carpi, tarsi, face, axillae, ventrum, inguinal and perianal area, and may be generalise. Otitis externa is seen in half of affected dogs and may also be the only presenting sign. Secondary infections are common. Bacterial infections (most commonly *Staphylococcus pseudintermedius*) may lead to follicular papules, pustules, epidermal collarettes, and crusts; with yeast infections (typically *Malassezia pachydermatis*), erythema may be exacerbated and oily or greasy skin may be present. Pruritus may be exacerbated with both. In severely affected animals, a deep pyoderma may be characterised by draining tracts. In rare cases, urticaria, vasculitis, erythema multiforme and generalised erythroderma may also be caused by AFRs (Itoh et al., 2006; Cain et al., 2017; Rostaher et al., 2017b).

Food-responsive diarrhoea is a well-known entity in dogs. Other gastrointestinal signs seen with food reactions include vomiting, abdominal discomfort, flatulence, frequent defaecation and borborygmi. Concurrent gastrointestinal and dermatological signs are seen in 6–44% of affected dogs (Picco et al., 2008; Proverbio et al., 2010; Johansen et al., 2017; Volkmann et al., 2017), with diarrhoea being most commonly reported, followed by an increased number of daily defaecations (Johansen et al., 2017). This correlates with a study showing a positive correlation with the number of daily bowel movements and pruritus in apparently healthy dogs (Stetina et al., 2015).

Inflammatory bowel disease (IBD) is a multifactorial, chronic and relapsing inflammatory disorder of unknown cause. Possible pathomechanisms include a genetic predisposition, intestinal barrier dysfunction, aberrant immune response and functional changes within the microbiota (Craven et al., 2004; Xavier and Podolsky, 2007; Vazquez-Baeza et al., 2016). The exact role of diet in IBD is unknown. Lymphocytic-plasmacytic infiltration is the most common type of chronic intestinal inflammation. Histopathological

evaluation of intestinal biopsies does not help to differentiate between food-responsive and other forms of enteropathies (Allenspach et al., 2016; Volkmann et al., 2017). In addition, histopathological grading scores, total numbers of inflammatory cells and numbers of $CD3^+$ cells do not allow differentiation between food and steroid-responsive diarrhoea, and do not correlate with clinical response to therapy (Schreiner et al., 2008). Although significantly more dogs in a food-responsive diarrhoea group (62%) compared to an IBD group (23%) were positive for perinuclear anti-neutrophilic cytoplasmic antibodies, this marker as well, as other serological markers for intestinal inflammation, are not useful to accurately detect dogs with AFR in a clinical setting (Luckschander et al., 2006; Sattasathuchana et al., 2017).

Breed predispositions for subsets of AFRs with specific clinical signs have been reported in dogs. An inherited hypersensitivity against gliadin and glutenin has been reported in Irish setters and leads to clinical signs at a young age; the condition is completely reversible with a gluten-free diet (Hall et al., 1992; Daminet, 1996; Garden et al., 2000). Canine 'epileptoid cramping' syndrome in six Border Terriers was triggered and perpetuated by gluten and is responsive to a gluten-free diet (Lowrie et al., 2015). AFR was diagnosed in Soft coated wheaten terriers affected with protein-losing enteropathy (Vaden et al., 2000).

In cats, the common cutaneous reaction patterns associated with AFRs are self-induced alopecia, miliary dermatitis, head and neck excoriation, and eosinophilic skin lesions, such as eosinophilic granulomas and plaques, and indolent ulcers (White and Sequoia, 1989; Guaguere, 1995; Hobi et al., 2011; Bryan and Frank, 2010). These reaction patterns are non-specific and may be associated with ectoparasite infestations and food or environmental allergens (Bryan and Frank, 2010; Hobi et al., 2011). Mite infestations include feline scabies, cheyletiellosis and demodicosis; thus, a thorough diagnostic approach to the suspected allergic cat should always include a good ectoparasite control of all animals in the household. Cats with AFRs may also present with gastrointestinal signs, most frequently vomiting and diarrhoea, along with anorexia, weight loss, flatulence and abdominal bloating (Bryan and Frank, 2010; Guilford et al., 2001). Urticaria, angioedema, plasmacytic pododermatitis and conjunctivitis may be food-induced in some cats (Bryan and Frank, 2010; Hobi et al., 2011).

Diagnosis of adverse food reactions with elimination diets

Elimination diets have been considered the gold standard to diagnose AFR for many years. Ingredients are chosen based on the dietary history of the individual animal and the diet should only contain ingredients to which the animal was not previously exposed. This diet is then fed exclusively for at least 8 (Olivry et al., 2015) to 12 weeks (Rosser, 1993) for animals with cutaneous clinical signs. In previous studies, animals with gastrointestinal disease underwent an elimination diet for 2–4 weeks (Guilford et al., 2001; Sauter et al., 2006). However, a standardised duration for diet trials in animals with chronic gastrointestinal signs has not been established. Although a partial response is expected in the first 2 weeks in case of AFR, complete resolution of clinical signs may take 6 weeks in dogs with significant intestinal inflammation. Owners need to be instructed carefully that, apart from the food sources chosen for the elimination diet, no other proteins should be available. This includes food supplements, medications, animal protein-containing chew toys and treats which, for better palatability, may be flavoured with beef or pork proteins not listed on the label (Parr and Remillard, 2014). If the pet is accustomed to receiving treats, then recommending specific treats made from the same sources as the elimination diet, such as dried meat or jerky, may increase client compliance, but care must be taken to ensure these treats are pure and are not, for example, coated with maize (corn) flour. Regular telephone calls to assist owners with the diet are recommended and often indispensable for achieving a successful outcome. If the animal improves during that time, as occurs in 90% of cases of AFRs (Olivry et al., 2015), then re-challenge with the old diet is extremely important, since the improvement may be due to other concurrent treatments or changes in season or environment. Deterioration within days to maximally 2 weeks on the previously fed diet, and subsequent improvement when the elimination diet is again strictly fed, confirms the diagnosis of AFR (White, 1986; Harvey, 1993). It may be important to remember that a number of atopic dogs have a combination of offending environmental and food antigens and thus may only improve partially on the diet (Picco et al., 2008).

It is more difficult to conduct diet trials with cats. Firstly, cats may have free access to the outdoors and thus to other food sources. Thus, feeding an elimination diet without improvement does not rule out AFR. However, locking such cats indoors for 8 weeks is usually difficult, if not impossible. Secondly, in contrast to dogs, refusal to eat the new diet for several days may predispose those animals to hepatic lipidosis (Dimski, 1997; Center, 2005). To identify an elimination diet the cat likes to eat may be a challenge and the authors always suggest two protein sources, so that in the event the cat stops eating, there will be an alternative exclusion diet at hand.

Principally, there are three choices for an elimination diet for dogs and cats: (1) home cooking (using a selected protein); (2) a commercial selected protein diet; and (3) a commercial hydrolysed diet.

Home-cooked elimination diets

Home-cooked elimination diets for dogs typically consist of one meat source and one carbohydrate source, with both ingredients not present in previously fed diets (Bethlehem et al., 2012). Over 95% of home-cooked elimination diet recipes are not balanced (Stockman et al., 2013). Many home-cooked diets are deficient in calcium, zinc, copper and vitamins D and E. Ideally, a veterinary nutritionist should be consulted for optimal formulation (Stockman et al., 2013); particularly in young and rapidly growing dogs, home-cooked elimination diets should not be conducted without such input. The diet should gradually replace the normal food over a 3–4 day period to avoid diarrhoea and to achieve optimal compliance. Whether the meat is raw or cooked will depend on owner and pet preference. However, if uncooked meat is chosen, extensive client education is necessary to avoid possible infections and to explain the risk of contraction of zoonotic diseases. The meat should be frozen for more than 24 h at −20 °C to kill *Toxoplasma* tachyzoites (Dubey, 1996). Also, in a recent study, commercially acquired 'biologically appropriate raw food' (BARF) meats were not infrequently contaminated with bacterial pathogens (Nemser et al., 2014; van Bree et al., 2018). Pork and chicken should never be fed raw due to the potential to contain *Salmonella* spp. or, in the case of pork, Aujeszky's disease virus. Since diet trials are more difficult in cats, it may be sensible to choose only a meat source to increase the chances of compliance through better palatability. Cats are obligate carnivores and cannot be fed a vegetarian diet. Cats with healthy kidneys typically do well on an all meat diet.

Commercial selected protein diets

An increasing number of selected protein diets from many different manufacturers is available on the market and can be used for elimination diets in many practices. However, in four studies, proteins not listed on the label were identified in the majority of those foods (Raditic et al., 2011; Ricci et al., 2013; Willis-Mahn

et al., 2014; Horvath-Ungerboeck et al., 2017). In one study, 3/4 'over the counter' diets and 4/7 veterinary diets which claimed 'no soy' on the label, contained soy protein detectable by ELISA (Willis-Mahn et al., 2014). Similarly, in another study of 'over the counter' diets, 3/4 tested positive for soy and 1/4 tested positive for beef by ELISA, even though the label claimed that these proteins were absent (Raditic et al., 2011).

In the study by Ricci et al. (2013), 11 selected protein diets underwent PCR testing and microscopic evaluation for bone fragments of mammals, birds and fish. In 10/11 diets, bone fragments were identified from one or two unpredicted zoological classes; 6/10 contained avian fragments, 5/10 contained fish fragments and 4/10 contained mammal bone fragments. Furthermore, an additional unexpected zoological class was detected by PCR in two samples (Ricci et al., 2013). PCR testing of 12 commercial canned and dry dog foods for DNA of animal origin revealed contamination with beef ($n = 8$) and pork ($n = 6$) in 9/10 'over the counter' diets (Horvath-Ungerboeck et al., 2017).

However, in none of the above studies was the clinical relevance of these contaminations confirmed through feeding provocation in known sensitive animals. When three different commercial selected protein diets were administered to 40 dogs with AFRs, 95% could be maintained free of pruritus on one of the diets, although 48–85% of dogs had recurrence of clinical signs on at least one of the three (Leistra et al., 2001).

In some cats with a high suspicion of an AFR and no response to an elimination diet, a second diet may be needed to confirm the diagnosis; of 20 cats with AFR, 35% and 60% could be maintained in remission with one of the two diets, respectively (Leistra et al., 2001). On the basis of currently published information, commercial diets containing selected proteins seem to be more suitable as maintenance diets following a diagnosis than as a diagnostic tool for AFR.

Commercial hydrolysed diets

When proteins are hydrolysed, their allergenicity is decreased. Cave and Guilford (2004) showed that hydrolysis decreased 97% of chicken protein to a molecular weight <10 kDa. An inhibition ELISA using IgG demonstrated a residual antigenic mass of 1.5% compared with the intact chicken protein (Cave and Guilford, 2004). In human beings, the allergenic fraction of food is generally comprised of heat stable, water soluble glycoproteins with a molecular weight of 10–70 kDa (Sampson, 1999). Sensitised research dogs which were challenge exposed with hydrolysed soy protein had a reduced inflammatory response after intradermal injection and no clinical response after an oral challenge exposure, compared with responses after intradermal and oral challenge exposure with native soy protein (Puigdemont et al., 2006).

Exclusive feeding of hydrolysed diets to dogs and cats suspected of having AFR in clinical practice has resulted in improvement in many of those animals. When 10 dogs allergic to soy or maize were exposed to hydrolysed soy and corn antigens, veterinarian-assessed pruritus was reduced by 60% and 80% in dogs allergic to soy ($n = 6$) and corn ($n = 4$), respectively, compared to feeding intact corn or soy (Beale and Laflamme, 2001). In a randomised, double blinded, cross-over study, 10 dogs reacting to chicken meat, but not maize, were exposed to hydrolysed poultry feather and chicken liver diets. The hydrolysed poultry feather diet did not induce pruritus flares in dogs allergic to chicken, in contrast to the hydrolysed chicken liver diet, which led to pruritus flares in 40% of these dogs (Bizikova and Olivry, 2016).

In a food trial using a diet containing chicken hydrolysate in 63 pruritic dogs with possible AFR, 39% were diagnosed with AFR on the basis of improvement with the diet, deterioration upon re-challenge with the previous food and remission when fed the diet once again (Loeffler et al., 2004). Commercial hydrolysed diets were also shown to be of benefit in dogs and cats with chronic small bowel disease (Mandigers et al., 2010a,b). However, a systematic review of the trials evaluating hydrolysed diets in dogs with suspected cutaneous AFRs concluded that a proportion of dogs with cutaneous AFRs had worsening of clinical signs when fed partial hydrolysates and that diets containing hydrolysates are probably best used in dogs suspected not to be sensitive to the parent protein (Olivry and Bizikova, 2010). Thus, although hydrolysed diets seem to result in improvements in many dogs with AFRs, on the basis of published, data they are not completely reliable in ruling out this disease. For the authors, hydrolysed diets are the second best choice after a home-cooked elimination diet when evaluating dogs and cats with possible AFRs.

Diagnosis of adverse food reactions with other tests

Serum testing for food-specific immunoglobulin E

Many studies have evaluated food-specific serum IgE in normal dogs and dogs with skin or gastrointestinal diseases. In one study, dogs with proven cutaneous AFR, normal controls, dogs with non-allergic skin disease and dogs with atopic dermatitis due to environmental allergens and no food involvement were tested by ELISA for food-specific serum IgE. Positive reactions were found only in one dog with dermatophytosis and one dog with environmental allergies (Mueller and Tsohalis, 1998). In another study, the IgG and IgE responses of normal dogs, dogs with atopic dermatitis and with various types of gastrointestinal disease were compared; normal dogs produced more IgE against chicken and lamb, while atopic dogs had more IgE against egg, fish, pork, turkey, rice, soy and yeast antigens than the other two groups, respectively (Foster et al., 2003). In a study by Hardy et al. (2014), the paired sera of dogs with AFR, with environmental allergies without food involvement, with allergic dermatitis not further diagnosed, with non-allergic skin diseases and nine healthy control dogs were submitted to two laboratories for food-specific IgG and IgE testing; there were no clear differences between groups. In addition, the agreement between the results of the two laboratories was 'moderate' for one antigen, 'fair' for four, 'slight' for eight and 'less than chance' for the remaining six antigens (Hardy et al., 2014). Another study evaluating food-specific IgE and IgG responses of dogs with allergic skin disease also showed an unsatisfactory repeatability of those tests (Wilhelm and Favrot, 2005). The limited value of serum food-specific IgE and IgG has been confirmed in a number of other studies (Jeffers et al., 1991; Fujimura et al., 2011; Zimmer et al., 2011; Ishida et al., 2004; Bethlehem et al., 2012; Favrot et al., 2017; Mueller and Olivry, 2017; Udraite Vovka et al., 2017); currently serum testing cannot be recommended for the diagnosis of AFRs.

Intradermal testing with food antigens

Fewer studies have evaluated intradermal testing with food antigens in dogs suspected of having cutaneous AFR (Jeffers et al., 1991; Kunkle and Horner, 1992; Ishida et al., 2004). In the study by Jeffers et al. (1991), well-defined food allergic dogs underwent intradermal testing with a range of food antigens. As a result of true and false positive reactions, both a low sensitivity and a high specificity were found. Neither the positive nor negative predictive values adequately predicted positive and negative reactions, respectively (Jeffers et al., 1991). In the study by Kunkle and Horner (1992), 100 dogs with atopic dermatitis presumably caused by food or environmental allergens, or both, were intradermally tested with nine food antigens; 48 had positive reactions to at least

one of those antigens. Three of 30 dogs with positive reactions responded to an elimination diet, while 6/35 dogs did not react to any food antigen but improved on an elimination diet (Kunkle and Horner, 1992). Unfortunately, results of provocation were not reported. In one further study, 11 dogs with known AFRs and six healthy control dogs were intradermally tested with eight common food antigens (Ishida et al., 2004). Only 2/18 offending allergens in the dogs with clinically identified food hypersensitivities showed strong positive reactions, one of the control dogs also showed a reaction to milk antigen; however, this was tolerated without clinical signs by the animal (Ishida et al., 2004). On the basis of these studies, intradermal testing with food antigens does not reliably identify dogs with AFR.

Patch testing with food antigens

Two studies evaluated patch testing with food antigens in dogs with cutaneous hypersensitivities (Bethlehem et al., 2012; Johansen et al., 2017). In both studies, multiple food antigens, including raw and cooked meats, and carbohydrate sources were placed on the skin in Finn chambers for 48 h. In the first study, reactions were evaluated after 24, 48 and 72 h (Bethlehem et al., 2012). Three positive reactions were seen on average per dog, erythema was the only reaction noted, and only 1/68 positive reactions occurred solely at the last evaluation after 72 h. Positive reactions against the meat sources were against either raw or cooked meat, or both. In this study, the negative predictability was very high (99.3%), while the negative likelihood ratio was 0.04, decreasing the likelihood of a clinically relevant allergic reaction to this antigen by at least 50% (Bethlehem et al., 2012).

In the second study, which included 25 dogs, more antigens were tested. Positive reactions were seen either with raw meat proteins or with both the raw and cooked form of the same protein, with a mean number of 14 positive reactions per dog (Johansen et al., 2017). The overall negative predictability was lower with 83.1%, but all false negative reactions were to carbohydrates and the negative predictive value for protein sources, irrespective of cooked or raw, was 100% which was much higher than that for carbohydrates (70%). Patch testing with commercial foods was also attempted, but the low number of positive reactions precluded any interpretation (Johansen et al., 2017). Both studies concluded that patch testing may be helpful in selecting the ingredients of the elimination diet, but cannot be used for the diagnosis of AFR.

Other diagnostic tests for adverse food reactions

Lymphocyte proliferation test

Lymphocyte proliferation responses to food antigens have been evaluated in a series of Japanese studies (Ishida et al., 2004, 2012; Fujimura et al., 2011; Kawano et al., 2013). In the study by Ishida et al. (2004), dogs with clinically proven AFR and known offending food antigens and healthy control dogs were tested; in 9/11 dogs with AFR, results of lymphocyte proliferation tests (LPTs) correlated with the oral food provocation tests and normalised after the dogs had been fed an elimination diet until clinical remission. None of the control dogs had a proliferation index indicating a positive reaction (Ishida et al., 2004). In the study by Fujimura et al. (2011), food allergic dogs, dogs with environmentally induced atopic dermatitis and control dogs were subjected to the LPT; lymphocyte blastogenesis reliably differentiated allergic from healthy control dogs, but not environmentally-induced from food-induced atopic dermatitis. In a larger study, 97/138 dogs with allergic dermatitis had a positive LPT (Kawano et al., 2013). In 12 of these 97 dogs, no serum IgE against environmental allergens was identified and an elimination diet was chosen based on the LPT; all 12 animals improved and the authors concluded that the test could be used to choose the ingredients for an elimination diet (Kawano et al., 2013).

In a study evaluating LPT in three cats, 12/15 antigens with known clinical provocation results were correctly identified (Ishida et al., 2012). The tests were repeated after the cats were in remission on the replacement diet for at least 3 weeks and were all negative. Although the numbers are small, the results suggest that lymphocytes were likely to be involved in the pathogenesis of the skin disease in those three cats and that further studies are warranted (Ishida et al., 2012).

In summary, LPTs seem to be more accurate than serum testing for food-specific IgE, but not sufficiently accurate to replace an elimination diet in the diagnosis of AFR. To the authors' knowledge, these tests are currently not commercially available.

Salivary immunoglobulins A and M

Salivary testing for food-specific IgA and IgM has been recommended (Dodds, 2014), but a recent larger study evaluating this test showed a higher number of reactions in the control group than in dogs with AFRs (Udraite Vovka et al., 2017). In addition, there was no good correlation between clinical data and test results, and the authors concluded that this test currently cannot be recommended for the diagnosis of AFRs in the dog.

DNA testing of hair

Hair testing for food allergy is also offered by various laboratories. Companies advertise 'epigenetic DNA testing' of the hair root,[1] claim to measure 'bioenergetic forces' from the body[2] or simply describe the method of analysis as 'proprietary' (Coyner and Schick, 2016). One study evaluated such hair testing by sending in hair from an allergic dog, a normal dog and artificial hair from toy animals (Coyner and Schick, 2016). The test results were similar from all specimens, including the toy dog artificial hair. Currently, there is no solid data supporting such testing.

Gastroscopy and colonoscopy

More than two decades ago, gastroscopic testing was developed and subsequently evaluated for canine AFR (Olsen et al., 1991; Elwood et al., 1994; Guilford et al., 1994; Vaden et al., 2000). In one published study, six atopic dogs were tested gastroscopically and challenged orally with seven different food antigens. Only three oral challenges were clearly positive and all three were also positive on gastroscopic testing; three other gastroscopic tests were false-positive (Guilford et al., 1994). In another study, only 50% of positive gastroscopic tests were substantiated by oral challenges; false negative results were also seen in a number of Soft coated wheaten terriers (Vaden et al., 2000); thus gastroscopic testing does not seem to be useful for the diagnosis of AFR.

Colonoscopic testing was evaluated in nine research dogs with AFR and five controls (Allenspach et al., 2006). Dogs were tested and orally challenged with seven food antigens. None of the control dogs showed positive reactions. In the dogs with AFR, 17/23 offending allergens were correctly identified by the testing, six were missed, and 12 test results were false positive (Allenspach et al., 2006). The authors considered that colonoscopic testing superior to gastroscopic testing, but a recent review concluded that the accuracy was not sufficient to recommend either of those tests to diagnose AFR in dogs or cats, due to the false positive and false negative reactions seen in both (Mueller and Olivry, 2017).

[1] See: Shohet, S., 2012. The Integral Health Pet DNA Hair Test. http://www.integralhealth.org/integralhealth/general/pet-and-animal-hair-test.html (accessed 27 December 2017).

[2] See: Allman, K.B., 2017. Bioscan for Allergies and Organs. http://www.naturalhealingforanimals.com.au/bio-scan (accessed 27 December 2017).

Long term management of animals with adverse food reactions

In the long term, the best management of dogs and cats with AFR is through avoidance of the offending allergens (Verlinden et al., 2006). Ideally, this is achieved by challenging the animals with individual food antigens (Jeffers et al., 1991), thus identifying the offending foods and enabling subsequent avoidance. However, sequential provocations can be challenging and many owners may discontinue the systematic provocations after a short time and choose alternatively to feed the home-cooked or commercial elimination diets life-long. However, home-cooked diets need to be balanced and consulting a veterinary nutritionist for input may be useful. Short term medical treatment may be necessary to limit clinical signs due to allergic flares following (sometimes inadvertent) challenges. Antihistamines and glucocorticoids have been reported as successful interventions for food allergic animals with gastrointestinal signs and urticaria, respectively (Luckschander et al., 2006; Rostaher et al., 2017b).

Conclusions

AFR is a common cause of both cutaneous and gastrointestinal problems in dogs and cats, and should be considered as a differential diagnosis for dogs and cats presenting with compatible clinical signs. Although there are a number of studies evaluating alternative diagnostic methods, such as testing saliva, hair or serum, currently the most reliable method to diagnose AFR is an elimination diet with a novel protein source (and in dogs an accompanying carbohydrate source) to which the pet was never previously exposed. If such a diet leads to clinical improvement, if subsequent re-challenge with the old food leads to clinical deterioration and if the feeding of the elimination diet again results in improvement, then a diagnosis of AFR is confirmed. In the long term, offending allergens need to be identified and avoided to the best of the owner's ability and therapy in response to clinical signs may be needed to help control clinical flares.

Conflict of interest statement

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