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Trabajo Fin de Grado en VETERINARIA

LA REACCIÓN DE HIPERSENSIBILIDAD TIPO I EN LA ESPECIE CANINA

Dermatitis Atópica Canina y otras enfermedades alérgicas

TYPE I HYPERSENSITIVITY REACTION IN THE CANINE SPECIES

Canine Atopic Dermatitis and other allergic diseases

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***Título*:** *La reacción de hipersensibilidad tipo I en la especie canina: Dermatitis Atópica Canina y otras enfermedades alérgicas*

La reacción de hipersensibilidad tipo I (hipersensibilidad inmediata) es una reacción inmediata que se produce cuando un antígeno se combina con un anticuerpo (IgE) preformado (creado por una exposición sensibilizante al mismo antígeno) y se une a los mastocitos provocando una reacción instantánea: sustancias inflamatorias y vasoactivas son liberadas por esas células, causando vasodilatación, edema, quimiotaxis eosinofílica, prurito y broncoconstricción. Los ejemplos más importantes de reacciones de hipersensibilidad inmediatas en medicina veterinaria van desde trastornos alérgicos sistémicos (anafilaxis) hasta trastornos alérgicos específicos tales como alergias respiratorias y oculares (rinitis alérgica, bronquitis y conjuntivitis), alergias alimentarias y alergias cutáneas. Los trastornos alérgicos de la piel son los más relevantes en la especie canina, especialmente un síndrome multifactorial denominado Dermatitis Atópica Canina, sufrido por entre el 10 y el 15% de la población canina. En la primera década del siglo XX, el científico austriaco Clemens von Pirquet introdujo el término "alergia" en el mundo de la medicina humana. Posteriormente el concepto se extendió al campo veterinario y ya en 1941 se informó de un caso de manifestaciones clínicas compatibles con atopia canina en un perro afectado de rinitis alérgica estacional. Justo en 1971 se describieron inicialmente los signos clínicos de CAD. Las condiciones alérgicas suelen ser multifactoriales y en ellas intervienen tanto factores intrínsecos, únicos del animal, como factores extrínsecos, relacionados con el medio ambiente y con el microambiente cutáneo. Una comprensión completa de estos factores es necesaria si la condición se quiere abordar con éxito desde el punto de vista diagnóstico y terapéutico.

Palabras clave: alergia; hipersensibilidad; atopía; alérgeno; dermatitis atópica canina; CAD; alergia alimentaria; alergias respiratorias; alergia ocular

Title: *Type I Hypersensitivity reaction in the canine species: Canine Atopic Dermatitis and other allergic diseases*

Type I Hypersensitivity reaction (immediate hypersensitivity) is an immediate reaction that occurs when antigen combines with preformed antibody (IgE) (created by a sensitizing exposure to the antigen) that is attached to mast cells triggering an instant reaction: inflammatory and vasoactive substances are released from mast cells granules, causing vasodilatation, oedema, eosinophil chemotaxis, pruritus and bronchoconstriction. Important

examples in veterinary Medicine of Immediate Hypersensitivity reactions include from systemic allergic disorders (anaphylaxis) to specific allergic disorders such as respiratory and ocular allergies (allergic rhinitis, bronchitis and conjunctivitis) and food and skin allergies. Skin allergic disorders are the most relevant in dogs, including a multifactorial syndrome suffered from 10 to 15% of dogs named Canine Atopic Dermatitis (CAD). In the first decade of the 20th century the Austrian scientist Clemens von Pirquet introduced the term 'allergy' into the world of human medicine. Later the concept was extended to the veterinary field and in 1941 clinical manifestations of canine atopy first were reported in a dog affected with seasonal allergic rhinitis. It is only in 1971 that the clinical signs of CAD initially were described. Allergic conditions usually are multifactorial involving both intrinsic factors, unique to the animal, and extrinsic factors, relating to both the environment and cutaneous microenvironment. A thorough understanding of these factors is needed if the condition wants to be managed successfully via current diagnostic and therapeutic tools.

Key words*:* allergy; hypersensitivity; Type I Hypersensitivity; atopy; allergen; atopic dermatitis syndrome; CAD; food allergy; respiratory allergies; ocular allergies

4. INTRODUCTION AND JUSTIFICATION

4.1. Introduction: Establishment and use of the concept of “allergy” and other terms

Allergies, also known as *allergic diseases*, are a number of conditions caused by hypersensitivity of the immune system (Type I Hypersensitivity) to something in the environment that usually causes little or no problem in most animals and people (McConnell, 2007). In the canine species, these conditions include systemic disorders (anaphylaxis) and specific disorders such as respiratory and ocular allergies (allergic rhinitis, bronchitis and conjunctivitis), food hypersensitivities and skin allergies. Currently, allergies are common both in people and dogs and cats (Guaguere, et al., 2008). However, allergies exist in all animal species (Miller & Willemse, 1997). As in human, the first case reports published, although anecdotal, were to foods. In 1941, a case of allergy was reported on a dog with recurrent seasonal pruritus that coincided with the ragweed season (Wittich, 1941) but it is only in 1971 when the clinical signs of Canine Atopic Dermatitis (CAD) initially were described (Guaguere, et al., 2008). Despite these later discoveries, the term *allergy* was initially introduced in 1906 by the Viennese paediatrician Clemens von Pirquet.

In dogs, the most relevant skin allergic disease is Canine Atopic Dermatitis (CAD). The incidence of CAD is still unknown, though some authors cite an incidence of 10-15% of the

canine population (Tizard, 2009). CAD is a common chronic pruritic dermatitis of the face and limbs, responsive to glucocorticoids and linked to a predisposition to develop allergic reactions to environmental allergens (Guaguere, et al., 2008). The terms *atopic dermatitis* and *allergic dermatitis* should not be used interchangeably. Allergic dermatitis is a form of dermatitis (also called *eczema*) characterized by spontaneous and occasional onsets of pruritus and hives on the skin in response to an allergen. In contrast, the concept of atopic dermatitis goes further. Atopic Dermatitis is typically a more specific set of associated conditions occurring in the same animal including chronic eczematous skin disease and a predisposition to develop other type of allergies (atopy) (Cole, 2016).

In addition to the confusion between the terms atopic dermatitis and allergic dermatitis, there are other concepts that should not be confused in any case when talking about veterinary allergology (Olivry, et al., 2001; Guaguere, et al., 2008; Regueiro González, et al., 2010):

- **Hypersensivity**: reproducible clinical signs, triggered by exposure to a stimulus which, at the same dose, produces no effect in a normal individual.
- **Allergen**: an antigen that favours the development of a hypersensitivity response
- **Allergy**: hypersensivity of immunological origin. A disease state characterized by hypersensitivity responses to allergens and oftentimes mediated by IgE antibodies.
- **Atopy (atopy state)**: predisposition to develop allergic reactions. It is the tendency to develop IgE-mediated allergy to environmental allergens.
- **Atopic disease:** any clinical manifestation of atopy. In the dog, atopic dermatitis is the most commonly diagnosed atopic disease. Other poorly defined and uncommon atopic diseases of dogs include atopic conjunctivitis, atopic rhinitis and experimental atopic asthma. An **atopic individual** is a patient who suffers from an atopic disease.
- **Atopic dermatitis (AD)**: a genetically-predisposed inflammatory and pruritic allergic skin disease characterized by particular patterns of lesion distribution and frequent association with allergy to aeroallergens. Canine Atopic Dermatitis (CAD) is a classic example in the dog.

4.2. Justification

This literature review aims to detail the most important aspects related to nosography (description of the disease: aetiology, pathogenesis, nosobiotic, semiotics and nosognosis (clinical trials such as diagnosis and treatment, and their sources, types and tools) of the immune system disorders related to the process of Type I Hypersensitivity, allergy and atopy, paying particular attention to the condition on the dog (due to the enormous importance of

these conditions in canine species). This task seeks to clarify different key points used during the clinical approach of these conditions and to deepen in the study of immediate hypersensitivities, justifying the importance of all factors involved in the allergic condition, with special emphasis on those involved in Canine Atopic Dermatitis.

5. OBJECTIVES

Then, once the subject has been introduced and justified, the goals of the present review can be summarized with the following points:

- To gain background knowledge of the Type I Hypersensitivity reaction
- To identify potential areas and hypothesis for research in the field of allergology
- To make a classification scientifically based of the main allergic diseases of the dog
- To identify tested and potential tools for the diagnosis and treatment of allergic conditions

6. METHODOLOGY

The theoretical framework of this literature review is based on the collection of information related to the physiopathological and clinical study of those diseases of the immune system connected to the process of hypersensitivity, allergic reaction and atopy in domestic animals, valuing especially that scientific contribution coming from studies realized in the dog. The search for scientific literature related to the topic has been carried out in an inductive way. First it has been revised all the information focused on a theoretical point of view coming from great works created by current specialists in Immunology, Internal Medicine and Dermatology such as Ian R. Tizard, José Ramón Regueiro González-Barros and Eric Guaguere. Then, in order to enrich the theoretical part of the review, a rigorous search of current articles has been done using databases such as the *Nation Centre for Biotechnology Information* (NCBI) and *Scholar/Academic Google*.

The review also includes a real clinical perspective with the presentation of cases collected in two veterinary practices: the Department of Dermatology of the Veterinary Hospital of Ghent University (Faculteit Diergeneeskunde) and EMVET Emergencias Veterinarias de Zaragoza. These clinical cases have been addressed first-hand during the period from September 2016 to June 2017. The presentation of these subjects aims to exemplify some theoretical references cited during the writing of this review.

7. RESULTS AND DISCUSSION

7.1. Classification of Immune Disease: Hypersensivity reactions

Immune-mediated disorders occur when the protective immune response is activated inappropriately, resulting in organ injury. Pathologic immune reactions may occur in response to infectious pathogens and contribute to the clinical disease presentation for that pathogen or be stimulated by otherwise innocuous foreign substances (allergens) or by self-antigens (Nelson & Couto, 2014). Even though there is no completely satisfactory system for categorizing immune disease, the big picture can be described by the proposal of Gell and Robin Coombs (1963) that is still the basis for our understanding of most allergic disorders (Miller & Willemse, 1997; Rajan, 2003). Gell and Robin Coombs classified the hypersensitivity reactions into four groups (Table 1) on the basis of every hypersensitivity reaction (whether an allergy on autoimmune disease) involves one of four basic immune mechanisms (McConnell, 2007). This classification helps in the understanding of the immunology of allergy (Types I and IV) and immune mediated diseases (Types II and III).

Table 1. Gell and Coombs classification of hypersensitivity: mechanisms of immunopathologic injury **(Miller & Willemse, 1997; McConnell, 2007; Nelson & Couto, 2014)**

TYPE	IMMUNE SYSTEM EFFECTORS	MECHANISMS	EXAMPLES
B-cell reactions			
Type I, immediate hypersensitivity (allergic reaction*)	Humoral immune system (T-helper cells, B cells), IgE, mast cells, inflammatory mediators	IgE-mediated degranulation of mast cells following antigen binding and cross-linking of IgE	Acute anaphylactic reactions, atopy, allergic bronchitis, food allergies
Type II, cytotoxic hypersensitivity	Humoral immune system, IgG and IgM	IgM/IgG antibody antigen interactions on target cell surfaces	Immune-mediated haemolytic anaemia, immune-mediated thrombocytopenia, myasthenia gravis, pemphigus foliaceus
Type III, immune complex hypersensitivity	Soluble immune complexes	Immune complex formation and deposition in tissues leading to local or systemic inflammatory reactions	Glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis
T-cell reactions			
Type IV, cellular (delayed) hypersensitivity	Sensitized T lymphocytes, cytokines, neutrophils, and macrophages	Sensitized T_H1 cells activated to release cytokines upon binding to antigen, resulting in macrophage and cytotoxic T cell accumulation	Lymphocytic thyroiditis, myositis, contact dermatitis, chronic transplant rejection

* The majority of authors when discussing allergies only refer to Type I Hypersensitivity. However, Type IV hypersensitivity must also be present since cellular hypersensitivity can also produce allergic pictures; animals do not always respond to allergens of arthropods with a type I hypersensitivity, for example, the response to *Demodex* mites and to components of flea saliva may be cell-mediated (Type IV hypersensitivity) (Tizard, 2009).

7.2. Mechanisms, cellular and molecular components of Type I Hypersensitivity reaction

Once the general aspects of immune disorders and different types of hypersensivity have been presented, the attention will be focused in Type I Hypersensitivity reaction, which is the main responsible of allergies.

Most individuals constantly inhale certain allergens (e.g. pollen) without an immune response or, in any case, small amounts of IgG are produced against the inhaled allergen. However, as was said in the introduction, certain individuals, called atopic patients, have a genetic tendency to develop intense IgE-mediated responses (Type I Hypersensitivity reaction) against these allergens. Multiple molecular and cellular components take place in the mechanisms by which this excessive production of IgE is generated.

IMMUNOLOGICAL MECHANISMS

Type I Hypersensitivity reaction depends on the production of IgE antibodies against a certain allergen and the consequent activation of the mast cells sensitized to these IgE. These certain allergens have no common pattern, except that they are usually low molecular weight glycoproteins that diffuse easily through skin and mucous membranes (Regueiro González, et al., 2010).

In the mechanisms described for the Type I hypersensitivity reaction, two stages can be distinguished:

- Sensitization stage
- Re-exposure or elicitation stage (followed by a delayed reaction)

The sensitization stage occurs the first time that an individual comes in contact with these allergens (Randall, 2005). Allergens that are inhaled or pass through the skin or mucous membranes are picked up by the antigen-presenting cells, mainly the Langerhans cells, which transport them to the lymph nodes where allergens are presented to Th2 cells through Class II Major Histocompatibility Complex (MHC II). Th2 cells promote the proliferation and differentiation of allergen-specific B cells and stimulating cytokine secretion, mainly IL-4 and IL-13, what favour their change from isotype to IgE-producing cells. The result of the sensitization phase is therefore the production of specific IgE that will bind to the high affinity FcεRI receptor on the surface of the mast cells which are located below the skin and mucous membranes and associated with blood vessels.

The sensitization phase does not produce any clinical signs, but if a previously sensitized individual is re-exposed to the same allergen (re-exposure or elicitation stage), its recognition by IgE will cause the mast cells degranulation producing an immediate inflammatory reaction (in a few seconds or minutes). The immediate reaction depends fundamentally on the secretion of vasoactive molecules preformed and stored in the granules of mast cells such as histamine and tryptase, and lipid mediators derived from its membrane such as leukotrienes, prostaglandins and platelet activating factor. Their release produces a rapid increase in local blood flow, increased vascular permeability, and smooth muscle contraction. This response is identical to that which produces an infection, and is intended to recruit elements of the immune response to the site of inflammation. The contraction of the smooth muscle attempts to expel the pathogen, in this case from the allergen, and its manifestations range from mucus secretion (by contraction of the smooth musculature of the mucous glands) to cough, vomiting or diarrhoea.

The elicitation stage is followed by a delayed reaction (with a peak at 6-12 hours) more or less intense depending on the amount of allergen and the degree of sensitization. The late reaction is induced by the synthesis of new mast cell inflammatory mediators (prostaglandins, leukotrienes and platelet activating factor) that produces their biological effect over the following hours. Also due to the production of chemokines and cytokines such as IL-4, IL-5, IL-9, IL-13, TNF-α, etc., the inflammatory reaction is prolonged, eosinophils are recruited, and vasoactive molecules are secreted what produce the late damage and mucus production, oedema, skin redness and pruritus associated with allergic reactions (Tizard, 2009; Regueiro González, et al., 2010).

The mechanism by which atopic dermatitis (AD) (in our case, Canine Atopic Dermatitis) develops is similar to other allergic processes (Randall, 2005). However, some aspects of this multifactorial disease should be especially mentioned such as the role of cytokine IL-31 and the JAK-STAT pathway. IL-31 is a recently described cytokine that plays an important role in CAD and the pruritus cycle (chronic itching is one of the most important and distressing features of atopic skin disease). It is detected in more than 50% of dogs with DAC, but not in dogs with other inflammatory diseases (Artola Magallon & Verde Arribas, 2016). In atopic dermatitis, when a dendritic cell (such as Langerhans cells) is exposed to the same allergen and T-cell activation is triggered rapidly, pruritogenic cytokines such as IL-31 are also released (Tizard, 2013). IL-31 travels and binds to receptors found on the surface of neurons. This interaction leads to the activation of Janus Kinase (JAK) enzymes, which stimulates the

transmission of the signal along the nerve to the brain, promoting pruritus. The JAK-STAT (Janus kinase/signal transducer and activator of transcription) pathway has been shown to play an essential role in the dysregulation of immune responses in atopic dermatitis, including the exaggeration of Th2 cell response, the activation of eosinophils, the maturation of B cells, and the suppression of regulatory T cells. In addition, the JAK-STAT pathway, activated by IL-4, also plays a critical role in the pathogenesis of atopic dermatitis by upregulating epidermal chemokines, pro-inflammatory cytokines, and pro-angiogenic factors as well as by downregulating antimicrobial peptides (AMPs) and factors responsible for skin barrier function (Bao, et al., 2013).

IMMUNOLOGICAL COMPONENTS

Once the mechanism is exposed, a more detailed description of the cellular and molecular agents involved in the reaction is almost essential in the understanding of the immediate immunity.

IMMUNOGLOBULIN E

IgE is an immunoglobulin with a conventional four chain structure, with a molecular weight of about 200 kDa. It is found in serum in extremely low amounts (9 to 700µg / ml in dogs), and its half-life is only 2 days. Most of the IgE in the body is not localized in the bloodstream, but is tightly bound to Fcε receptors on mast cells, where it has a half-life of 11-12 days (Tizard, 2013). IgE production is initiated when Th2 lymphocytes generate interleukins 4 (IL-4) and interleukins 13 (IL-13). Atopic individuals are predisposed to generate Th2 lymphocytes that produce these compounds. These cytokines, together with the stimulation of the Cluster of Differentiation 40 (CD40), initiate the synthesis of IgE by B lymphocytes. B lymphocytes start with an IgM molecule on its surface that is specific for the antigen. Then, T helper (Th2) cells assist B cells in making antibody by producing cytokines (IL-4) that are partially responsible for causing the isotype switch from IgM to IgE.

Once formed, IgE seeks to bind to either the inciting allergen or to IgE receptors located on a variety of cell types (e.g. mast cells) (UTHealth, 2008). Mast cells have high affinity IgE receptors and once stimulated, they produce IL-4 in important amounts. This may alter the helper cell balance and enhance yet more Th2 cell production and IL-4 release (Tizard, 2009). Therefore, the whole mechanism of IgE production is destined to ensure its survival and maintenance during the response.

MAST CELLS

When IgE binds to Fcε on the surface of mast cells, it does not have an immediate evident effect on the cell. However, if an antigen enters the tissue a second time, finds the mast cell and cross-links two of fixed IgE molecules on the surface of the cell, the mast cell will be activated to remove the contents of its secretory lysosomes and their inflammatory mediators to the surrounding tissues (Tizard, 2009). This rapid activation of exocytosis begins when an antigen molecule cross-links two mast cell receptors and activates several tyrosine kinases which, in turn, activate phospholipase C, which causes the production of diacylglycerol and inositol triphosphate. These mediators elevate intracellular calcium and activate more protein kinases that phosphorylate the myosin in the cytoskeleton, causing the migration of the secretory lysosomes to the cell surface, fusing their membranes with cell-membrane phospholipids, and releasing their contents into the extracellular fluid. The cross-link of two IgE mast cell receptors by the antigen also activates phospholipase A, which acts on membrane phospholipids to produce arachidonic acid. Subsequently, other enzymes convert arachidonic acid into leukotrienes and prostaglandins. Finally, protein kinases promote the transcription and expression of the genes encoding many different cytokines, as well as the genes for cyclooxygenase and lipoxygenase (Hill & Martin, 1998).

EOSINOPHILS

One characteristic of tissues suffering from Type I Hypersensitivity reactions is the presence of large numbers of eosinophils. These cells are attracted to the degranulation sites of mast cells, where they also degranulate and release their own biologically active molecules. Eosinophils can be considered as the ultimate effector cells of the allergic reaction, so probably they are the main responsible of the delayed stage of an allergic reaction.

Several mechanisms are involved in the mobilization of eosinophils. One of the most important is produced by Th2 lymphocytes and mast cells, which produce IL-5 and chemokines, known as eotaxins that stimulate eosinophil output from the bone marrow. Once eosinophils reach the degranulation site of mast cells, they increase their ability to eliminate parasites, a fact that supports the theory that the main function of IgE-mediated responses is the control of helminth parasites. Mast cells and eosinophils interact extensively in allergic reactions (Tizard, 2009) and it is clear that on balance, eosinophils exacerbate the inflammation triggered by mast cells (Tizard, 2013).

SOLUBLE MEDIATORS

The soluble mediators released from degranulating mast cells, eosinophils and also basophils release a complex array of molecules that contribute to the acute inflammatory process and it will mainly characterize the clinical picture of Type I Hypersensitivity reactions which will be described later.

Soluble mediators from degranulation of mast cells can be found at high levels in tissue fluids during allergic reactions and may be classified in three categories and: molecules released from exocytose granules (histamine, serotonin, tryptase, kallikreins, proteases and proteoglycans), lipids (ecosanoids) synthesized within minutes (leukotrienes, prostaglandins, platelet-activating factor), and proteins synthesized over several hours (IL-4, IL-5, IL-6, IL-13, TNF-α, MIP-1α) (Tizard, 2013).

In addition to soluble mediators released from degranulating cell components, another cytokine of the IL-1 family plays an important role in inflammation and promotes Th2 responses leading to allergies. This is the IL-33. It is produced by smooth muscle cells, epithelial cells, fibroblasts keratinocytes, dendritic cells, and activated macrophages. In the presence of IgE, IL-33 binds to a receptor on mast cells, basophils, and Th2 cells and produces the production of inflammatory cytokines. IL-33 is probably therefore a major mediator of Type I hypersensitivity (Tizard, 2013).

Although the importance of mast cell degranulation, it has been seen that fatal allergic reactions can be induced in mast cell-deficient mice, possibly measured by platelets (Cara, et al., 2004). Analysis indicates that this is mediated by IgG acting through IgE receptors on platelets and neutrophils. Their role in allergies in other species is unclear (Cara, et al., 2004; Tizard, 2013).

7.3. Factors involved in the onset of Type I Hypersensitivity reaction

As has already been said, allergens and some immune mechanisms are the root causes of the allergic disorders. Although this is important, sometimes the condition is multifactorial involving both intrinsic factors unique to the animal, and extrinsic factors, relating to both the environment and cutaneous microenvironment (Guaguere, et al., 2008). These factors are extremely important when we talk about Canine Atopic Dermatitis and, therefore, we shall devote special attention to this disease.

Atopic dermatitis has a multifactorial, incompletely understood pathogenesis in both dogs and people. Until a few years ago, the traditional pathogenetic view of atopic dermatitis focused on the interpretation that it was due to genetic alterations of the immune system leading to abnormal immunological response (e.g. increased allergen-specific immunoglobulin E (IgE) to innocuous allergens (*inside-outside* theory). More recently, a theory focused on the fundamental role of the epidermal barrier has been proposed (*outside-inside* theory). The outside-inside theory proposed that an abnormal skin barrier in atopic patients facilitates the penetration of allergens (and microbes) though the epidermis, increasing their contact and exposure to epidermal immune cells (Wolf & Wolf, 2012). Such theories are not mutually exclusive and they have been integrated into a more comprehensive theory (*outside-inside-outside* theory) based on the view that a primary defect in the epidermal barrier leads to a higher penetration of allergens and microbes that overstimulate the local immunity (innate and adaptive). Such excessive stimulation triggers the release of inflammatory mediators that further exacerbate the barrier dysfunction (Santoro, et al., 2015).

The following is a description of those factors involved in the allergic reaction. A thorough understanding of these factors is needed if the condition is to be managed successfully (Guaguere, et al., 2008).

INTRINSIC FACTORS

GENETIC PREDISPOSITION

Studies involving lines of atopic dogs or dogs that have been artificially sensitised show that the allergen-specific IgE response, total IgE concentration and the clinical expressions of CAD depend on different genes. This suggests that in dogs, genetic predisposition to allergies is probably multiallelic (Sousa & Marsella, 2001; Guaguere, et al., 2008). However, genetics of atopy and allergy is complex: if both parents are atopic, most of their offspring will also be atopic and will suffer allergies, but if only one parent is atopic, the percentage of atopic offspring varies (Tizard, 2009).

Genetic or breed predispositions to CAD are very significant in the dog. Breeds commonly affected in America, Europe and Japan include Shar pei, Fox terrier, Jack Russel terrier, Labrador retriever, French bulldog, West Highland White terrier, Boxer and Dalmatian (Sousa & Marsella, 2001; Guaguere, et al., 2008). Cross breeds may also be affected. Additionally, not only the development of this disease but also its clinical phenotype vary between breeds; some breed may develop lesions in specific areas (e.g. French bulldog develop lesions in the

axillae, eyelids, and flexural surfaces, German Shepherds, in contrast, tend to develop lesions in the elbows, hind limbs, and thorax) (Wilhem, et al., 2011).

In addition, there are some indications that the allergic status of parents, especially mothers, has a direct influence on the development of allergies in offspring. Fact which suggests that there is vertical transmission of allergies in dogs. The mechanisms of this effect are unknown, but it is possible that certain factors ingested with the colostrum of allergic mothers may favour the change towards a Th2 type response in their puppies (Barret, et al., 2003).

IMMUNE RESPONSE

Each atopic individual evokes an IgE immune response to environmental antigens. This abnormality is due to a deviation in the cellular immune response, thought to be a Th2 response, characterized by production of cytokines that favour the allergic response: increased IgE production, expression of high-affinity receptors by antigen-presenting cells (Langerhans' cells) and mast cell pre-activation. This creates a vicious circle perpetuating the allergic response. The IgE-laden antigen-presenting cells present a large quantity of epitopes to lymphocytes, favouring an IgE response. Pre-activated mast cells are very readily activated by immunological and non-immunological stimulation (Guaguere, et al., 2008).

Many bacteria and viruses elicit a Th1-mediated immune response, which down-regulates Th2 responses (Folkerts, et al., 2010). Thus, these types of microorganisms may be related in the modulation of the immune response, predisposing to the appearance of allergic diseases. The *hygiene hypothesis* was developed to explain this observation in a study which reveals that hay fever and eczema, both allergic diseases, were less common in children from larger families and individuals from the developing world, which were; it is presumed, exposed to more infectious agents through their siblings, than in children from families with only one child or individuals from the industrialized world (Gibson, et al., 2003). In the same field, studies in the third world demonstrate an increase in immunological disorders as a country grows more affluent and, it is presumed, cleaner (Addo-Yobo, et al., 2007). The use of antibiotics in the first year of life has also been linked to asthma and other allergic diseases (Marra, et al., 2006). The use of antibacterial cleaning products has been associated with higher incidence of asthma, as has birth by caesarean section rather than vaginal birth (Thavagnanam, et al., 2007; Zock & Plana, 2007). Although many aspects of the hygiene hypothesis have been extensively investigated by immunologists and epidemiologists and have become an important theoretical framework for the study of allergic disorders in humans (Gibson, et al., 2003), findings have

been found to show some differences in the canine species. It has been suggested that contact with allergens in the first days of life predisposes pups to develop significantly higher IgE levels than pups sensitized at 4 months of age. Additionally, normal animals infested by helminths and insects parasites also produce large amounts of IgE, so it is believed that the IgE response has evolved specifically to counteract these organisms. It is interesting to note that atopic and parasitized dogs may have reduced levels of IgA, an observation that supports the idea that IgA deficiency could presuppose a compensatory increase in IgE production (Tizard, 2009).

SURFACE HYDROLIPID BARRIER AND KERATINISATION ABNORMALITIES

In the atopic dog, surface hydrolipid barrier abnormalities lead to increased water loss and greater adherence of allergens and infectious agents such as staphylococci and *Malassezia spp*. In breed such as the West Highland White terrier and Shar pei, keratinisation disorders sometimes dominate the clinical picture (Guaguere, et al., 2008).

In humans with atopic dermatitis (AD), the epidermal lipid barrier is abnormal because of combined insufficient extrusion of lipid-containing organelles into the superficial epidermal intracellular spaces as well as skin lipid metabolic defects. Studies investigating skin hydration and lipids in atopic dogs are scarce and unfortunately have yielded conflicting data. Whether or not dogs with AD exhibit dry skin and an inadequate stratum corneum barrier (Olivery & B.Hill, 2001).

EXTRINSIC FACTORS

Allergic individuals may overreact to a large number of different allergens, any antigen, most often eaten (food allergens) or inhaled (aeroallergens), that is recognized by the immune system and causes the allergic reaction (Guaguere, et al., 2008). The presence of these allergens in the environment and diet are considered as extrinsic factors.

In addition to allergens, parasitic and infectious agents will often have a direct relationship with the pathogenesis and clinical course of some allergic conditions. Agents such as *Ctenocephalides felis, Staphylococcus intermedius* and Malassezia *spp.* have to be considered in the study of the clinical course of CAD. In fact, atopic dermatitis is the main cause of *Malassezia* dermatitis (Table 4) (Boer & Marsella, 2001; Guaguere, et al., 2008). In the case of allergic bronchitis and allergic conjunctivitis, infectious agents will also act as complicating agents and should be considered during the clinical approach (King, 2004).

AEROALLERGENS

In every continent, house dust mites are the most commonly encountered aeroallergens. The most allergenic in the dog is *Dermatophagoides farinae*. Sensitivities of other pyroglyphid mites, *D. pteronyssinus* and *D. microcera*, are a lot less common. The difference in sensitivity to that seen in the human population sharing the same habitat is probably explained by the fact that the major allergens in dogs and people are different. On the other hand, the incidence of forage mite sensitivity is also high in atopic dogs. It is difficult to know if this apparent sensitivity is due to cross reactivity with *Dermatophagoides mites* or a genuine sensitivity in its own right.

The importance of allergies to hair and epithelia, human or animal, is unclear in dog. Cases of cockroach sensitivity have been reported in Europe. They have always been associated with pyroglyphid mite allergy and the inclusion of cockroach allergen in anti-allergen vaccines has never been found to worthwhile. The allergic pollens are, as in human medicine, anemophilous pollens. Mould spores are often incriminated. Linen, wool, cotton and kapok are now known to be non-allergenic in the dog (Guaguere, et al., 2008).

FOOD ALLERGENS

About 2% of ingested proteins are absorbed as peptide fragments large enough to be recognized as foreign. Foods most commonly incriminated in food hypersensitivity studies in the dog are meat (beef, chicken and lamb), egg, dairy products and soya, but any dietary protein is potentially allergenic (Martín, et al., 2004). The IgG is the main allergen in foods from ruminants (Jeffers, et al., 1991). Either of these antigens can be spread by the blood and reach the mast cells of the skin in a few minutes (Tizard, 2009).

Food allergens are particularly important in the atopic dog. Through the establishment of an elimination diet in atopic dogs (in which hypoallergenic foods are administered) clinical signs are controlled in 30% of cases (Shaw, et al., 2004).

7.4. Major allergic diseases in dogs: systemic and specific allergic disorders

The route of entry (inhalation, food and blood), dose of the allergen and the sensitization status of the animal will determine the location and amount of cells that respond to the antigen and, in turn, the development of different forms of allergic reactions with a very varied symptomatology (Regueiro González, et al., 2010). As we already known, the clinical signs of Type I Hypersensitivity derive from the abrupt and excessive release of inflammatory

mediators by mast cells, eosinophils and basophils in response to the presence of an antigen (Tizard, 2009).

Two large groups of allergic reactions can be established (Table 2). In the first place, those that are generated systematically and extensively in the animal (anaphylaxis) and secondly, those that tend to occur more localized in the individual.

Table 2. *Major allergic diseases in dogs: systemic and specific allergic disorders* (Type I Hypersensitivity)

CONDITION	ORIGIN
Systemic allergic disorder	
Anaphylaxis	Aerosol exposure to antigens, blood inoculation, allergen ingestion
Specific allergic disorder	
Eye allergies: allergic conjunctivitis and allergic blepharitis	Aerosol exposure to antigens
Respiratory allergies: allergic rhinitis and allergic bronchitis (asthma)	Aerosol exposure to antigens
Food allergies: gastrointestinal disorders (vomits and diarrhoea) and allergic dermatitis (urticarial)	Allergen ingestion
Skin allergies: allergic dermatitis, atopic dermatitis	Allergen ingestion, aerosol exposure to antigens
Allergy to drugs and vaccines	Drug ingestion, antigen blood inoculation
Allergy to parasites	Exposure to parasites (e.g. helminths)
Allergy to other organisms	Exposure to other organisms (e.g. *Thaumatopoea processionea*)

Despite the particularities of each allergic reaction, some may share similarities in the clinical picture. For example, urticaria, angioedema, and anaphylaxis all are Type I Hypersensitivity reactions and may occur in different allergies (i.e., a classic example of the appearance of urticarial is in allergic dermatitis, however, food allergies can also produce this injury). Urticarial lesions are focal and superficial reactions where wheals (hives) develop on the skin (Fragio, 2011). Lesions may be single or multiple and may affect the whole body. Angioedema reactions can be thought of as deep wheals. Deep blood vessels are affected and the oedema causes diffuse swelling, typically of one area such as the head (Figure 1). If the clinical picture manifested in the form of urticaria or angioedema evolves to a more severe form, the anaphylactic reaction will appear (Miller & Willemse, 1997).

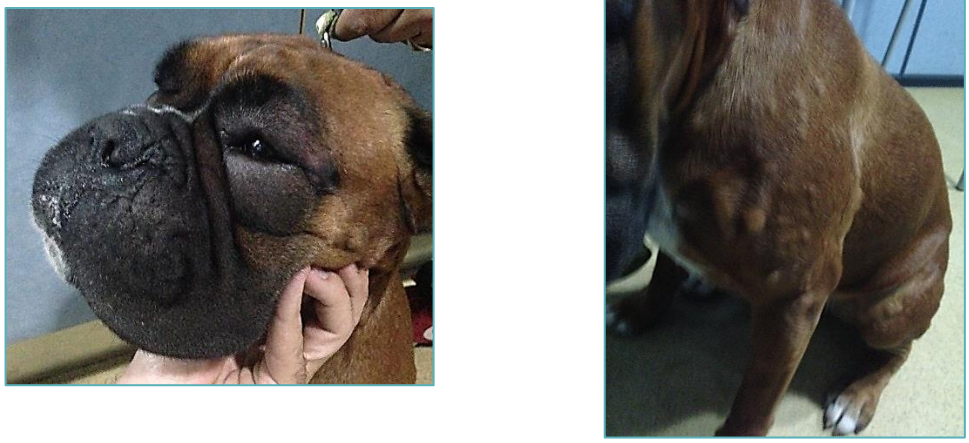

Figure 1. *On the left: Boxer, non-neutered female, 4 years old: evident swelling face due to angioedema. On the right: Bumps visible in the same dog as a consequence of hypersensitivity reaction*. The signs of allergy suddenly appear (5 minutes) after a routing walk through a park with abundant floral gardens. No ingestion of any allergic component is suspected (Emergencias Veterinarias de Zaragoza EMVET, Zaragoza-Spain, 2017).

SYSTEMIC ALLERGIC DISORDERS

ANAPHYLAXIS

Anaphylaxis or anaphylactic reaction is an especially severe type I reaction that results in immediate and widespread release of inflammatory and vasoactive substances from mast cells, provoking widespread vasodilatation and oedema. Vasodilatation causes flushing, low blood pressure, and fainting or shock, and accumulation of oedema that can produce airway obstruction. In some cases smooth muscle spasm can occur and cause severe bronchial restriction (bronchospasm). Death can occur because of vascular collapse or to asphyxiation from laryngeal oedema or bronchospasm (McConnell, 2007).

The clinical signs of anaphylaxis are determined by the organic system involved. Dogs differ from other domestic animals in that the main organ affected is not the lung but the liver, especially the hepatic veins. Dogs suffering from allergic anaphylaxis show initial excitement followed by vomiting, defecation, and urination. As the reaction progresses, the dog collapses, with muscle weakness and respiratory depression, goes into coma and convulsions, and dies in about an hour. At necropsy, the liver and intestine are very dilated, containing up to 60% of the animal's total blood (visceral haemorrhage). These signs come from occlusion of the hepatic vein due to the combination of smooth muscle contraction and hepatic oedema, which leads to hypertension and visceral oedema, in addition to a decrease in venous return, cardiac output and blood pressure. The mediators identified are histamine, prostaglandins and leukotrienes (Tizard, 2009). Acute hepatic venous congestion may result in swelling of the

gallbladder wall and thus the sonographic creation of the *gallbladder halo sign* (Figure 2). However, there many other causes of gallbladder wall oedema (pancreatitis, cholecystitis, pericardial effusion, etc.) (Lisciandro, 2016) .

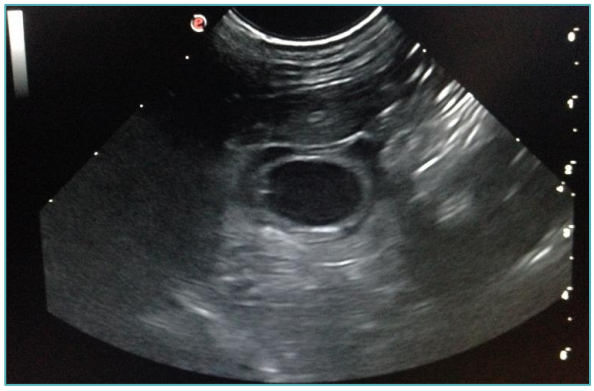

Figure 2. *Ultrasonographic image (within minutes of patient arrival) of the gallbladder in a Pug, non-castrated male, 4 years old, with classic clinical signs of hypovolemic shock compatible with an acute allergic reaction: decrease in venous return, low blood pressure and pale mucous. Note the gallbladder wall oedema referred to as the "Gallbladder Halo Sign". In the same examination, the intestines are very dilated, containing large amounts of blood (*Emergencias Veterinarias de Zaragoza EMVET, Zaragoza-Spain, 2017).

SPECIFIC ALLERGIC DISORDERS

EYE ALLERGIES

Type I hypersensitivity reactions located in the eye are usually caused by exposure of small doses of allergen in aerosol in atopic animals.

Allergic conjunctivitis

Allergic conjunctivitis occurs when the conjunctiva, the clear membrane covering the white part of the eye, comes in contact with an allergen. This phenomenon produces inflammation and intense tearing. Several causes can produce conjunctivitis (infectious agents, viruses, parasites, systemic infections) but the allergic component is common and usually originates in atopy (Morgan, 2008; Lourenço-Martins, et al., 2011)

Allergic blepharitis

Allergic blepharitis is the inflammation of the eyelids due to a reaction that an allergen triggers when contacts with eyelids, Meibomian glands and the glands of Zeis and Moll. As in the case mentioned above, different causes can also produce blepharitis but atopy, contact allergies (Type IV hypersensitivity) and food hypersensitivity are common immune-mediated disorders that can cause this inflammation (Morgan, 2008).

RESPIRATORY ALLERGIES

Allergic rhinitis and bronchitis

Type I hypersensitivity reactions located in the airways are usually caused by inhalation of small doses of allergen in aerosol (pollen, mites...). If the inhaled allergen comes into contact with the nasal mucosa it causes spring allergic rhinitis or hay fever in people, characterized by sneezing, nasal mucus, itching, etc., which is produced by degranulation of the mast cells of the nasal and upper airways mucosa (Regueiro González, et al., 2010). Allergic rhinitis is an unusual or an underdiagnosed condition in dogs (King, 2004; Tizard, 2013).

When the allergen penetrates into lower airways produces a more severe syndrome called allergic asthma. The contraction of the smooth muscles of the lower airways and the exaggerated secretion of mucus in the bronchial cavities can compromise breathing. An inevitable consequence of chronic asthma is the hyperreactivity of the airways to nonspecific agents (cold, pollution, exercise, etc.), which perpetuate the inflammatory reaction even in the absence of a re-exposure of the allergen; consequently the discrimination what is the cause of this type of reactions is very difficult (Regueiro González, et al., 2010). Individuals of the canine species can also develop a kind of 'asthma', duly called Chronic Bronchitis. However, the pathophysiology of this disease is even more unexplained than in humans and cats. In fact, this condition in dogs should not be called asthma because the aetiology is not only allergic, but different possible causes trigger bronchitis in dogs: atmospheric pollution, passive smoking, respiratory tract infections, genetic or acquired defects and hypersensivity (allergic) lung diseases (King, 2004; Morgan, 2008). When the main cause is an allergic reaction to something in the environment, the disorder can be named allergic bronchitis (Bright, 2011). Whatever the cause, the most common functional sequela of chronic bronchitis is chronic airflow obstruction, which is generally referred to as chronic obstructive pulmonary disease (COPD).

Although chronic bronchitis is common in dogs, especially in smaller breed dogs in middle age to older (age greater than 5 years) (King, 2004), allergic causes are less likely. However, Basenji dogs have extremely sensitive airways and suffer from a disease similar to that of people with asthma (Tizard, 2009).

FOOD ALLERGIES

Many different names are used to describe adverse reactions to foods, including food intolerance and food allergy. It is important not confuse these concepts. Food allergy is a

reaction caused by the immune system's reactions to a food, causing distressing and often severe symptoms. On the other hand, food intolerance does not involve the immune system but its mechanism includes metabolic reactions and food idiosyncrasies (Homeier, 2005).

In the present case of food allergies, when the allergen is ingested, the degranulation of the mast cells of the intestinal mucosa produce vomiting and diarrhoea. If allergens are absorbed through the intestinal mucosa and pass into blood they can trigger the degranulation of the mast cells of the subcutaneous connective tissue, resulting in urticaria (Regueiro González, et al., 2010). Therefore, clinical consequences of food allergies are seen both in digestive tract and on the skin.

It is claimed that up to 30% of skin diseases are due to allergic dermatitis, and that reactions to allergens ingested account for up to 1% of skin diseases in dogs and cats, although the actual prevalence is unknown. Between 10 and 15% of dogs with food allergies have gastrointestinal disorders. The intestinal reaction may be moderate, manifesting only as an irregularity in the consistency of the faeces, or it may be severe, with vomiting, colic and intense diarrhoea, sometimes haemorrhagic, occurring soon after eating. At least half of these affected dogs have non-seasonal and non-sensitive to corticosteroids pruritic dermatitis, usually popular and erythematous and can affect legs, eyes, ears, armpits and perineal area. In chronic cases the skin may be hyperpigmentated, with lichenification and infection, leading to pyoderma. Chronic pruritic otitis can also develop (Jeffers, et al., 1991; Tizard, 2009).

SKIN ALLERGIES

Allergic dermatitis

Allergic dermatitis is a type of cutaneous eczema that manifests as a skin lesion characterized by the appearance of lesions called allergic-type skin rashes and intense pruritus. It is a kind of allergy that arises in response to one or more allergens both of environmental origin or food precedence.

Atopic Dermatitis (Canine Atopic Dermatitis)

As we have already said on several times in previous points, atopic dermatitis, termed in the dog as Canine Atopic Dermatitis (CAD) is a common chronic multifactorial syndrome that is characterized by a skin with inflammation and chronic pruritus of the face and limbs, responsive to glucocorticoids (Table 4) and linked to a predisposition to develop allergic reactions to environmental allergens (Figure 3) (Guaguere, et al., 2008). Although it is not

known with certainty the percentage of the canine population that suffers from the disease, it is estimated that between 10 and 15% of dogs are affected.

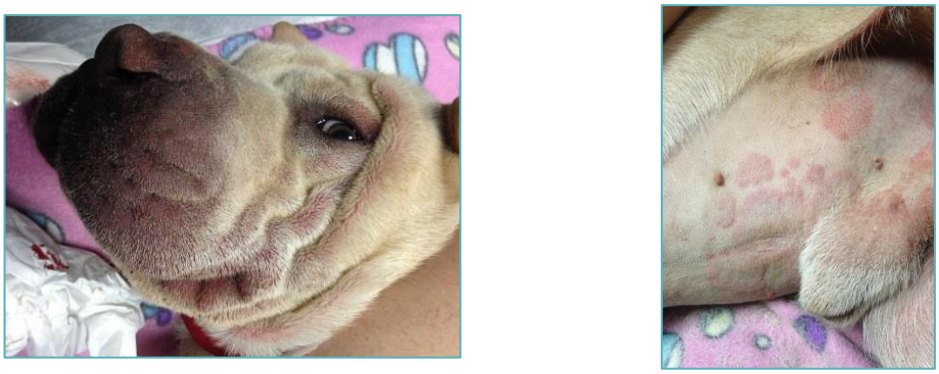

Figure 3. *On the left: atopic dermatitis in a Shar Pei: muzzle and periorbital erythema and excoriations around the lips. On the right: the same dog after a shaving and spreading a gel over the area being tested by an abdominal ultrasound. The appearance of urticaria in a skin predisposed to react to any stimuli can be seen* (Emergencias Veterinarias de Zaragoza EMVET, Zaragoza-Spain, 2017).

Lesions that are generated due to the atopic dermatitis are secondary to pruritus and range from acute erythema and oedema to more chronic secondary changes such as crusting, scaling, hyperpigmentation, lichenification and secondary infections (*Malassezia* spp.). Some animals may present external otitis or conjunctivitis as a consequence of atopic dermatitis (Tizard, 2009)

Canine atopic dermatitis includes hypersensitivity to both environmental antigens and food antigens and produces lesions that will often be identical to those produced in chronic cases of allergic dermatitis or food allergies. For this reason, it is impossible to distinguish atopic dermatitis causes by food allergens from atopic dermatitis caused by aeroallergens. When there is no demonstrable evidence of allergy, or more precisely, atopy, despite a clinical history consistent with this condition, the term “atopic dermatitis-like” is sometimes used. The multiplicity of clinical forms and causes of CAD is such that today in human medicine, the term “atopic dermatitis syndrome” is used. Such variety also exists in the dog and we have chosen to use the term canine atopic dermatitis syndrome (Guaguere, et al., 2008).

OTHER ALLERGIC REACTIONS

Allergy to vaccines and drugs

If the allergen is given intravenously (a drug, for example), they can be distributed throughout the body and cause degranulation of the mast cells of the connective tissue that are associated with blood vessels, causing an anaphylactic syndrome with serious consequences such as systemic vasodilation associated with a great loss of pressure of all the blood vessels and

constriction of the airways. In some patients with IgE antibodies against penicillin, for example, administration of intravenous penicillin can cause anaphylactic shock and even death within minutes (Regueiro González, et al., 2010).

The IgE response may occur following administration of any antigen, including vaccines. It is more likely to occur in vaccines containing traces of foetal bovine serum, gelatine or casein, which should always be taken into account when animals are vaccinated. The IgE response may also occur following drug administration, although most drug molecules are too small to be antigenic but they may bind to the host proteins and thus act as haptens. Allergies to many drugs have been reported in domestic animals, especially antibiotics and hormones (Tizard, 2009). Even allergies can be caused to the substances used to preserve leather from harnesses, catgut sutures, compounds such as methylcelulose or carboxymethylcellulose used as stabilizer in vaccines and dextrans used as synthetic colloids in fluid therapy (Carrillo Poveda, et al., 2006).

Allergies to parasites and other organisms

Helminths

Many studies have hypothesized that there is some relationship between the response generated against allergens and against some parasites such as helminths. Possibly, the IgE response to a certain antigen was initially developed to combat parasites against helminth parasites (Tizard, 2009). It has been suggested that the possible similarity with the molecular patterns that are recognized by the immune system in these parasites may favour such allergic responses against other allergens (Regueiro González, et al., 2010).

Arthropods

Allergies are also commonly associated with exposure to arthropod antigens. Insect bites cause many human deaths each year due to acute anaphylaxis following poison sensitization. In animals if an allergic reaction to saliva antigens is generated by these arthropods, an allergic dermatitis characterized by urticaria and intense pruritus may occur. This is the case of scabies by *Sarcoptes scabiei* in dogs and by *Octodectes cyanotis* in cats, whose allergy may contribute to the development of skin lesions. However, as we said at the beginning of the review, animals do not always respond to allergens with a Type I Hypersensitivity, but they can also respond by a Type IV Hypersensitivity reaction. Examples of Type IV Hypersensitivity reaction are the allergic response to *Demodex* and components of flea saliva. Flea Allergy Dermatitis

(FAD) is one of the most important allergic skin diseases in veterinary medicine. There is no racial or sex predisposition, but atopic animals, as well as those exposed intermittently to fleas, tend to present a more serious disease, while continued exposure to fleas at an early age seems to result in a form of hyposensitization (Dryden & Rust, 1994; Guaguere, et al., 2008; Tizard, 2009).

In addition to the importance of FAD, in Europe (Italy, France, Spain, Belgium, and the Netherlands) the processionary caterpillar (*Thaumatopoea processionea*) is an increasing cause of urticaria, angioedema, or even anaphylactic reaction. Each caterpillar has approximately 700.000 to one million of *hairs*, which contain substance responsible for the acute contact reaction after touching skin and mucosa (Miller & Willemse, 1997; Bonamonte, et al., 2013).

2.1. Clinical approach of the allergic patient: diagnostic and therapeutic tools

Effective management of allergic diseases relies on the ability to make an accurate diagnosis. Allergy testing can help, confirm or rule out allergies (Portnoy & Amado, 2006). A correct clinical approach of the patient, combining allergy testing and allergen avoidance, reduces the incidence of symptoms and need for medications, and improves quality of life. Nevertheless, the use of drugs and allergen immunotherapy will continue to be necessary in many cases of allergen since the complete avoidance of the allergen is very complicated and not always practical (NHS, 2016).

It seems reasonable to think that each allergy must be diagnosed with disparate methods. However, the diagnosis of different allergic diseases is often similar or even identical. Instead, the therapeutic guidelines will differ depending on the patient's symptoms.

DIAGNOSIS

HISTORY AND CLINICAL DIAGNOSIS

Contrary to a far too widely held belief, diagnosis of allergic diseases is not based solely on the results of allergy testing. Allergy test results should only be interpreted in the light of appropriate history and clinical signs. About 20-30% of atopic dogs produce negative allergy test results whereas a similar or even greater percentage (<50%) of normal dogs may test positive (Codner & Tinker, 1995).

In addition to the data collected during the anamnesis (age, sex, breed, etc.), most important questions to ask to the owner relate to diet, stools, in-contact animals, habitat, itchy score,

seasonal variation and changes when the animal is taken to another location (Guaguere, et al., 2008). Moreover, an elimination diet must be carried out and followed strictly at the beginning of the clinical approach of chronic and repetitive pictures. A third of atopic dogs can be controlled with diet but compliance is not always perfect (Chesney, 2002). A dietary history must be taken and all items listed and that is not easy given the abundance of food sources.

ALLERGY TESTING: SEROLOGICAL AND INTRADERMAL TESTING

Allergy tests are not usually done in cases of spontaneous allergies (e.g., allergic reaction to insect bites, spontaneous urticaria, etc.), but they are usually performed in cases of chronic allergies in atopic dogs, such as dogs with CAD. Once a clinical diagnosis of allergy is made, allergy test can be performed to identify potential causative allergens for allergen-specific immunotherapy (Hensel, et al., 2015). Allergy testing is more focused on the identification of aeroallergens.

There are two basic types of allergy testing: serological testing and intradermal skin testing. Serological methods of measuring the level of specific IgE in body fluids include the RAST (radioallergosorbent test), ELISA test (enzyme-linked immunosorbent essay) and FEIA (Fluorescent enzyme immunoassay) (Tizard, 2013). Intradermal skin testing is the other type of allergy testing especially used for the diagnosis of CAD (Tizard, 2013). Each method has pros and cons (Foster & Smith, 1995) and even though both are recommended due to their similar diagnostic value (Boyce, 2010; Cox, 2011), there are poor correlation between the results obtained by serology or skin testing. The reason for this poor correlation between direct IgE measurements and in vivo methods are debatable but probably reflect the fact that the skin microenvironment is much more complex than in the bloodstream. For these reasons many veterinary dermatologists prefer skin testing (Tizard, 2013).

Another type of test can also be performed in cases of suspected food allergy in which it was not possible to identify the food that causes the allergy through an elimination diet. These quick tests, whose effectiveness is not evaluated in this review, have recently been developed and are based on the detection of IgA and IgM in the dog's saliva. The mission is to help establish a hypoallergenic diet suitable for the patient (Dodds, 2013). In the case that this kind of test is to be applied, as with allergy tests, a detailed medical history must always be made.

TREATMENT AND MANAGEMENT

Management of allergies typically involves avoiding what triggers the allergy, routine measures and medications to improve the symptoms. Allergen immunotherapy may be useful for some types of allergies (Anon., 2015).

AVOIDING EXPOSURE TO ALLERGENS

The best way to prevent an allergic reaction is to avoid the substance that the animal is allergic to, although this is not always easy (NHS, 2016). A hypoallergenic diet can be continued beyond the time needed to diagnose food hypersensitivity but the possibility of the patient developing hypersensitivity to an item in the hypoallergenic diet cannot be discounted. Aeroallergens avoidance concerns mainly house dust mites and for it be effective, the mites must be killed or have their life cycle broken. In addition, proteins in their cuticle and faeces must be denatured (Guaguere, et al., 2008).

ROUTINE MEASURES

Certain simple steps can significantly reduce the development of allergies. Particularly in CAD the clinician has to take into account that the condition is multifactorial. Basic hygiene measures (flea control, feeding a well-balanced diet, use of shampoos, emollients and topical ear products, grooming, etc.) applicable to every atopic dog, will control pruritus lesions in most mild cases and reduce the need for drugs in more serious cases (Guaguere, et al., 2008).

MEDICATIONS

It is difficult to consider a classification of all drugs used in practice to combat allergies. However, special mention can be made of those current medications which are most frequently used to treat allergic symptoms (Table 3).

Table 3. *Most commonly used medications for the treatment of allergies in dogs*

Pharmacological group	Purpose or use	Indications*	Considerations	
Topic anti-inflammatory agents				
Glucocorticoids	Topical steroids can be used in hairless areas for well-circumscribed non-infected lesions due to allergic reactions.	Canine Atopic Dermatitis Allergic dermatitis Allergic blepharitis Allergic conjunctivitis	Hairy coat limits their usefulness. Topical glucocorticoids can be effective and well tolerated but are not suitable for generalized pruritus due to CAD.	(Guaguere & Bansignor, 2002; Guaguere, et al., 2008; Morgan, 2008; Cosgrove, et al., 2013)

Tacrolimus	A 0.1% tacrolimus gel can be used to bring about a significant reduction in lesion severity	Canine Atopic Dermatitis	When treatment is first started, irritation may increase	(Marsella, et al., 2004; Guaguere, et al., 2008)
Other topical agents (glycerine, chlorhexidine, piroctone olamine, analgesics, antihistamines, essential fatty acids, vitamin E, anti-pruritic agents)	Depending on the agent, one or other objective is pursued	Canine Atopic Dermatitis Allergic conjunctivitis Allergic blepharitis	These topical agents have to be used very frequently (daily) for benefit to be obtained	(Guaguere, et al., 2008; Morgan, 2008)
Systemic treatments				
Glucocorticoids (prednisone, prednisolone, methylprednisolone, fluticasone, etc.)	Glucocorticoids are potent anti-inflammatories. They supress cyclooxygenase expression and inhibits prostaglandins and leukotrienes.	Canine Atopic Dermatitis Anaphylactic shock Urticaria and angioedema (Table 4) Allergic bronchitis	For prolonged treatment (CAD), a minimum effective dose must be sought. They are highly effective, but adverse effects are common so regular monitoring is essential Short-term administration of corticosteroids may be warranted to decrease airway inflammation in severe case of bronchitis.	(Dhupa, 2005; Guaguere, et al., 2008; Morgan, 2008; Cosgrove, et al., 2013; Anon., 2015)
Antihistamines (amitriptyline, astemizole, cetrizine, chlorpheniramine, clocinizine, cyproheptadine, dexachlorphenirамine, diphenydramine, mydroxyzine, loratadine, mequitazine and promethazine)	Antihistamines oppose the activity of histamine receptors (H1 and H2) in the body. The role of H2-Antihistamines, such as ranitidine, in the treatment of allergic conditions is less clear than H1-Antihistamines.	Night time pruritus (for anxiolytic activity of first generation antihistamines) Urticaria and angioedema (Table 4) Anaphylaxis Canine Atopic Dermatitis (responses to antihistamines in dogs with CAD are unpredictable) Allergic blepharitis	H1-Antihistamines are commonly used, both as single agents, and as synergistic medications used to reduce required dosage of glucocorticoids.	(Olivry & Mueller, 2003; Cook, et al., 2004; Morgan, 2008; Guaguere, et al., 2008; Kupczyk, et al., 2008; Canoninca & Blaiss, 2011; Fragio, 2011)
Epinephrine	Stimulation of alpha adrenoceptors improves blood pressure and coronary perfusion; stimulation of beta-1 adrenoceptor has both positive inotropic and chronotropic cardiac effects; stimulation of beta-2 adrenoceptors	Anaphylaxis (first line treatment)	In anaphylactic shock, epinephrine is best administered either intramuscularly or as an intravenous constant rate infusion. Bolus administration of IV epinephrine has	(Dhupa, 2005; Fragio, 2011)

	causes and reduces the release of inflammatory mediators		been associated with the induction of fatal cardiac arrhythmias and myocardial infarction.	
Bronchodilators (Beta-2 agonists: albuterol and terbutaline, methylxantines derivatives: theophylline and aminophylline, and anticholinergics: atropine and ipratropium bromide)	The purpose is the dilatation of the bronchi and bronchioles, decreasing resistance in the respiratory airway and increasing airflow to the lungs. In the case of anticholinergic drugs, they relax airway smooth muscle and reduce mucus production through blockage of vagal nerve transmission to airway smooth muscle and submucosal gland and globet cells.	Allergic bronchitis (canine chronic bronchitis)	Beta-2 agonists and methylxanthine derivatives seem to act synergistically with glucocorticoids to control airway inflammation. Anticholinergics are widely used for the treatment of COPD in humans, but it has not proven to be an effective bronchodilator in dogs.	(King, 2004; Gosens, et al., 2006; Tilley, 2010)
Cough suppressants (antitussives) (dextromethorphan, codeine, buthorphanol, hydrocodone, etc.)	Depending on the agent, the mechanisms by which it acts is different.	Prolonged or exhausting non-productive coughs in Allergic bronchitis (canine chronic bronchitis)	Cough suppressants are not used if the cough is productive, or if the transtracheal wash suggests infection	(King, 2004; Anon., 2015; Morgan, 2008)
Cyclosporin A	Cyclosporin A inhibits the activation of cells capable of inducing (T lymphocytes and Langerhans's cells) and effecting (mast cells and eosinophils) the allergic inflammatory response	Canine Atopic Dermatitis Allergic blepharitis	Cyclosporin A can effectively control atopic dermatitis, but the delayed onset of action makes it impractical as a stand-alone therapy for the rapid management of pruritus. However, at two weeks of treatment, its efficacy is comparable to that of glucocorticoids.	(Guaguere, et al., 2004; Guaguere, et al., 2004; Guaguere, et al., 2008; Morgan, 2008; Cosgrove, et al., 2013)
Anti-pruritics (Oclacitinib, Canine Atopic Dermatitis Immunotherapeutic CADI)	The treatment of pruritic dogs has the following two goals: to reduce or eliminate the pruritus, which breaks the itch cycle, allowing the skin to heal, preventing chronic inflammatory changes and secondary infection, and reducing patient and owner discomfort and distress; and to diagnose and manage the cause of the pruritus.	Canine Atopic Dermatitis (Table 5) Allergic dermatitis and other pruritic skin diseases (with pruritic component).	These drugs reduce highly effective pruritus but it has to take into account that they are not anti-inflammatory but only takes away signs of itchiness, so the dog still need to be appropriately treated with medications as needed to control the atopy.-	(Cosgrove, et al., 2013; Zoetis, 2013; Zoetis, 2017; Lee, 2017)
Antimicrobial treatments				
Antibiotics	Depending on the agent, the mechanisms by which	Bacterial proliferation	Antibiotherapy ideally based on	(King, 2004; Anon., 2015;

	it acts is different.	syndrome and associated pyoderma due to CAD Secondary infections due to allergic bronchitis, allergic blepharitis and conjunctivitis.	culture and sensitivity testing	Guaguere, et al., 2008; Morgan, 2008)
Antifungals (ketoconazlole, itraconazole, posaconazole)	Depending on the agent, the mechanisms by which it acts is different.	*Malassezia* dermatitis due to CAD		(Guaguere, et al., 2008)

* According to the use of these medications, it is important to say that each patient has to be treated individually and, if necessary, make use of other medical tools such as oxygen therapy or fluid therapy, especially in acute allergic reactions (anaphylaxis) with life-compromising outcomes (Dhupa, 2005).

Table 4. *Proposed treatment plan for urticaria and angioedema in a Cocker Spaniel, castrated male, 7 years old* (Emergencias Veterinarias de Zaragoza EMVET, Zaragoza-Spain, 2017).

In the first place, the cause should be eliminated if known. However, many times the cause of urticaria and angioedema will be unknown. In this case, the process was related to a walk in the park 10 minutes before the reaction occurred but the exact cause was unknown. The patient had facial angioedema and erythematous rashes on the skin of the abdominal area. Airways were not compromised.
Antihistamines - Diphenhydramine (*Syva*®) 0.5-1 mg/kg IM - Ranitidine: 1-2 mg/kg SC
Glucocorticoids - Methylprednisolone (*Urbason*®) 1 mg/kg IM
After the administration of drugs and discharge the patient, owners are advised to keep an eye on the animal, in search of relapses or clinical signs that could occur as a consequence of the late phase of the allergic reaction: vomits, diarrhea, etc.

Table 5. *Proposed treatment plan for Canine Atopic Dermatitis (CAD) with secondary skin infection (Malassezia spp.) in a French Bulldog, neutered female, 1 year 2 months old* (Department of Dermatology of the Veterinary Hospital of Ghent University (Faculteit Diergeneeskunde), Ghent-Belgium, 2016).

The patient, already diagnosed of CAD, needs veterinary assistance because of an intense itching episode. Since she is diagnosed, she takes a hypoallergenic diet. She has been taking prednisolone orally during 4 weeks but 1 week ago corticotherapy has ended. During the treatment with steroids the itching was controlled (steroid responsive) but after stopping prednisolone dosage, pruritus has appeared again, especially on the legs and around the mouth. The patient often shakes her head and the right ear is painful. An ear swab is performed and a considerable amount of *Malassezia spp*. is detected (*Malassezia* otitis).
Anti-pruritic drugs: - Oclacitinib (*Apoquel*®): 0.4-0.6 mg/kg PO daily during 4 weeks (allergy testing will be performed if itching is not gone during these 4 weeks)
Treatment for Malassezia otitis due to CAD: - Orbifloxacin, mometasone furoate and posaconazole (*Posatex otic suspension*®)

ALLERGEN-SPECIFIC IMMUNOTHERAPY (DESENSITISATION THERAPY)

Allergies may be controlled by allergen-specific immunotherapy; particularly it is indicated whenever allergen avoidance does not produce significant improvement; only aeroallergens are indicated. Desensitisation therapy involves the regular subcutaneous injections of allergic extracts to which the animal is allergic. Allergen selection is based on allergy test results, intradermal or in vitro (Guaguere, et al., 2008). The best results are obtained with mite and

pollen extracts. Insect, epithelia and mould spore extracts have not been found to give good results. The number of allergens to which the animal is sensitised is not a significant prognostic factor (Griffin & Hiller, 2001; Zur & White, 2002).

Multiple controlled studies have shown that this therapy is effective in humans. It appears to be most effective for the treatment of allergic rhinitis (hay fever), asthma, and allergies to insect stings. However, there is often an element of confusion with regard to the definition of improvement or success of allergen-specific immunotherapy in the treatment of food allergies and allergic dermatitis. In veterinary medicine multiple open studies have suggested that this therapy is effective in the treatment of atopic dermatitis (Tizard, 2013), although few randomized controlled trials have been published. It has been estimated that up to 80% of dogs have a good to excellent response to this procedure (Griffin & Hiller, 2001; Tizard, 2013). The improvement may take the form of longer intervals between flares, a less extensive distribution, reduced lesion severity or a marked reduction in drug consumption.

Immunologic changes that occur during allergen-specific immunotherapy are complex and not completely understood. However, successful immunotherapy has been associated with a shift from T helper cell type-2 (Th2) immune responses, which are associated with the development of atopic conditions, to Th1 immune responses (Shida, et al., 2004; Moote & Kim, 2011). It is also associated with the production of T regulatory cells that produce the anti-inflammatory cytokine, interleukin 10 (IL-10), amongst others such as transforming growth factor (TGF) - beta. IL-10 has been shown to reduce levels of allergen-specific immunoglobulin E (IgE) antibodies, increase levels of immunoglobulin G (IgG) (blocking) antibodies that play a role in secondary immune responses, and reduces the release of pro-inflammatory cytokines from mast cells, eosinophils and T cells. Allergen-specific immunotherapy has also been found to decrease the recruitment of mast cells, basophils, and eosinophils to the skin, nose, eye, and bronchial mucosa after exposure to allergens, and reduces the release of mediators, such as histamine, from basophils and mast cells (Cox, et al., 2008; Frew, 2010).

3. CONCLUSIONES/ CONCLUSIONS

Español:

1. El conocimiento completo de los procesos inmunológicos que acontecen en la reacción de hipersensibilidad de tipo I es esencial para abordar clínicamente con éxito a un paciente alérgico, evitando confusiones cuando se aborda un proceso de hipersensibilidad determinado en la especie canina.

2. La hipersensibilidad inmediata es un trastorno del sistema inmunológico en el cual intervienen varios factores (tanto intrínsecos al animal como extrínsecos) y, aunque las pautas de diagnóstico a menudo son similares, será necesario conocer todas las herramientas terapéuticas para poder establecer un tratamiento adecuado para cada condición.
3. En la especie canina, la Dermatitis Atópica Canina (CAD) lleva el término "alergia" a su máxima expresión, siendo un síndrome multifactorial que nos permite estudiar las evidencias que explican la razón por la cual un perro es alérgico y por qué manifiesta un cuadro clínico tan característico.

English:

1. The full knowledge of the immunology of Type I Hypersensitivity reaction is essential to successfully approach clinically an allergic patient, avoiding misunderstandings when we are talking about different processes of hypersensitivity in the canine species.
2. Immediate hypersensitivity is a disorder of the immune system in which several factors figure (both intrinsic to the animal and extrinsic) and, although the diagnostic guidelines will often be similar, it will be necessary to know all the therapeutic tools to be able to establish a suitable treatment for each allergic condition.
3. In the canine species, Canine Atopic Dermatitis (CAD) represents the term 'allergy' with its maximum expression, being a multifactorial syndrome which enable us to study the evidences that explain the reason why a dog is allergic and why they manifest such a typical symptomatology in practice.

4. PERSONAL VALUATION

The decision to choose a topic for my final degree thesis closely related to the allergy reaction was not arbitrary. From the age of 10 the allergy accompanies me almost daily to all over the places where I go. It was during my first year of studies at CEU Cardenal Herrera University when the Professor Maria Isabel Guillén began to explain the lesson of hypersensitivity and allergies. At that moment, apart from feeling identified with everything she was explaining, I was fascinated to know how the immune system of animals works. Throughout my career as a veterinary student I have not only felt attracted to immunology, but I have also done so by pharmacology. Doing this review on allergies, it has allowed me to put into practice and deepen on much knowledge of immunology and pharmacology. In addition, find out what

other have studies and researched about allergies has allowed me to improve my ability to analyze different sources of information. This all has been really successful for me and my career.

Once this work is almost completed, I would like to highlight that I still have the desire to go deeper into some aspects that have been treated. Topics such as the hygiene hypothesis - could it really apply in a certain way to the canine species?, and issues relating the influence of platelets in the allergic reaction - do they play a more important role than we realize?. In addition, it would be interesting to know more about allergen-specific immunotherapy, and fortunately researches surrounding the mechanisms of this therapy are still ongoing and will help further elucidate how this therapy exerts its beneficial effects in allergic diseases. Perhaps in a near future I will be able to resume this review with more force and time.

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