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EDITORIAL

Hives: The target of itching



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The first documents describing cases of urticaria were written in China between the years 1000–200 BC, where it was known as *Fen Yin Zheng* or “snaking hidden erythema”.¹ Posteriorly, Hippocrates (460–377 BC) described lesions arising from the skin and which originated upon contact with nettles or as a result of mosquito bites. He thus referred to this condition as *cnidos* (from the Greek term *cnidos*, referring to nettles). On the other hand, Pliny the Elder (23–79 BC) introduced the term *uredo* (burning). Other references to urticaria come from Ibu Al-Abba Ali in the X century, who used the term *essera* (bulge in Persian), while Thomas More described the condition in detail in his book “King Richard III”.

However, we owe the current term to Zedler, in his work “Grosses Vollständige Universallexikon” (1730–1740). This author changed the term *uredo* to *urticatio*, and in 1769 William Cullen used the term *urticaria* in his book “Synopsisae Nosologiae Methodica”. Finally, in 1813, Robert William and his pupil Thomas Bateman published the book “Practical Synopsis of Skin Diseases,” describing various types of urticaria (*febrilis*, *evanida* and *perstans*), but not everyone accepted their classification system. In this regard, Jean Louis Alibert preferred the Greek word *cnidos*, and advocated classification based on the etiology of the disease.

Today, urticaria or hives is defined as a disease characterized by the development of wheals (hives), angioedema, or both.²

The disease is currently classified according to its evolution as either acute (<6 weeks) or chronic urticaria (>6 weeks), though it can also be classified according to the underlying cause as either immune IgE-mediated or non-immune urticaria (physical, associated to paraproteinemia, or familial angioneurotic edema), urticarial vasculitis (associated to autoimmune diseases or hepatitis B or C infection) or idiopathic urticaria.

Chronic urticaria affects about 300,000 people in Spain and is more prevalent in women than in men (2:1). It is estimated that of every 100 cases of urticaria, 50% last at least one year, 20% last three years, and 20% persist for up to 5 years. Patient quality of life is affected by the disease itself and by the associated health expenditures. In fact,

urticaria is one of the diseases resulting in most emergency care visits, and in children it is the disorder that causes most psychological alterations. Their true economic impact of urticaria is not known, since it is a disease that manifests in the form of outbreaks; however, it is known to have an important spending impact for the affected families. We therefore must try to understand the underlying etiology in order to correct the root cause of the condition and not only afford symptomatic treatment.

The causal factors of chronic urticaria are diverse, but can be summarized as comprising food additives, drugs, inhaled allergens, contact allergens, and viral, parasitic, protozoan and fungal infections. In less frequent cases, urticaria is caused by the parasite *Anisakis*, present in fish and ingested by people who eat raw or undercooked fish.³

Documentation referred to a bacterial etiology is less abundant, though most commonly reported causal agents are beta-hemolytic *Streptococcus* and *Helicobacter pylori*. In the case of *H. pylori* infection different pathogenic mechanisms have been postulated. One purported mechanism involves immune IgE-dependent reactions that improve after eliminating the bacteria,⁴ though some studies have not obtained significant results in this regard. Another possibility is that the presence of the bacterium in the gastric mucosa causes the activated eosinophils to secrete cytotoxic proteins that favor the appearance of urticaria. In fact, *H. pylori* infection favors the production of proinflammatory cytokines and the expression of inflammatory cell adhesion epitopes that would activate a systemic immune response.⁵

Other cases of urticaria have been associated to vasculitis, hormones, mental and physical stress, tissue diseases, physical agents, malignancies, latex, vaginal fluid, insect venom, vaccines, erythropoietic protoporphyria, C3b inactivator deficiency, and genetic disorders such as Muckle-Wells syndrome (urticaria, deafness and amyloidosis) and Ascher syndrome (recurrent edema of the lips and eyelids, skin atrophy and laxity).⁶

The pathogenesis of urticaria manifests in the form of hives or wheals produced by immunological and non-immunological stimuli that induce plasma extravasation in the papillary dermis.⁷ In IgE-mediated urticaria, the presence of this immunoglobulin on the surface of mast cells and

basophils triggers the release of leukotrienes, prostaglandin D₂, platelet activating factor, eosinophil chemotactic factor and histamine (the main mediator), which binds to the H1 receptors inducing skin erythema, edema and pruritus.⁸

An association has been established between high levels of B cell activating factor (BAFF) in patients with chronic urticaria and positive autologous serum skin testing, the presence of antithyroid antibodies, antinuclear antibodies, high total IgE titers, and severity of the disease.⁹ Autoimmune chronic urticaria is due to the strong affinity of the anti-FcRI autoantibodies (and to a lesser degree also of anti-IgE autoantibodies) for the IgE receptors.¹⁰ Another purported pathogenic mechanism underlying chronic urticaria involves IL-3, which would activate basophils, inducing an increase in neutrophil presence and in C-reactive protein.¹¹

On the other hand, it has been seen that IL-6 and C-reactive protein increase to a greater extent in patients with severe chronic urticaria than in patients with mild disease, though it is not clear whether this increase is only an epiphenomenon or also contributes to the pathogenesis of chronic urticaria.¹²

Likewise, in cases of chronic urticaria associated to other autoimmune disorders – particularly autoimmune thyroiditis – the diagnostic evaluation should include the determination of antithyroglobulin antibodies, ANA, etc.¹² However, the human leukocyte antigen (HLA) system, implicated in immune recognition processes and in signaling between immune system cells, as well as in genetic polymorphism, have no strong implication in the pathogenesis of this disease.

The evolution of our knowledge of the physiopathology of urticaria has witnessed key moments, such as the demonstration that inflammation is due to edema secondary to local obstruction, described by the founder of modern dermatology and histology, Astruc (1684–1766); the triple response described by Marey (1858); and the contribution of Dale and Laidlow, who in tissues identified the presence of an amine capable of affecting the smooth muscle of blood vessels, and which they called histamine.

The main effector cell in the physiopathology of urticaria is the mast cell, which releases inflammatory mediators (either preformed or *de novo*), giving rise to tissue responses involving other effector cells such as basophils, Th2 lymphocytes and, to a lesser degree, neutrophils and eosinophils.¹³ Only in cases of neutrophilic urticaria has an association to rheumatic diseases been demonstrated.¹⁴

From the immunopathological perspective, urticaria is characterized by the intervention of proinflammatory cells such as mast cells, eosinophils, neutrophils, monocytes, macrophages and T lymphocytes that release different mediators – the fundamental representative of which is histamine (beta-imidazole-ethylamine). This mediator binds to the H1 receptors of blood vessels, causing vascular dilatation, decreased blood pressure and increased capillary permeability, with an outflow of exudate, antibodies, macrophages and other components of the complement system into the interstitial fluid compartment, thereby favoring the development of edema.

Another released mediator is platelet activating factor (PAF), which in turn would cause other cells to release serotonin – one of the factors responsible for chronic

urticaria. Eosinophil chemotactic factor would induce such cells to migrate towards the inflammatory site. The activated eosinophils release cationic protein (ECP), peroxidase (EPO) and protein X (EPX). In particular, eosinophils are activated by IL-5, transforming into larger cells which are selectively recruited in late-phase inflammatory reactions. They also bind to endothelial cells expressing E-selectin, but furthermore express VLA-4 (very late antigen type 4 or CD49d/CD29), which allows them to firmly adhere to the endothelial cells that express vascular cell adhesion molecule-1 (VCAM-1 or CD106). Following recruitment of the eosinophils, they act as effector cells of reactions initiated by IgE. In this regard, their main proteins – major basic protein and eosinophil cationic protein – damage the target tissue of allergic reactions.

On the other hand, a second group of mediators represented by arachidonic acid metabolites and leukotrienes C and D, are synthesized by the surrounding cells or tissues through direct action of the primary mediators. These secondary mediators appear in later phases and their actions are prolonged in time.

Complement activation releases anaphylotoxins (C3a, C4a, C5a), which by directly acting upon the cell surface contribute to release more histamine. In this regard, factor C5a is the factor with the strongest impact upon vascular permeability, since its inhibition mediated by anaphylotoxin inhibiting factor occurs in a later stage, allowing it to not only favor permeability but also to act as a chemotactic factor for eosinophils and neutrophils that arrive at the inflammatory site. By acting upon the blood vessels, the mediators increase vascular wall permeability, resulting in fluid extravasation and the production of edema. At the same time, a local spinal cord reflex (antidromic reflex) induces arteriolar vasodilatation followed by erythema. Thus, one same etiological factor can produce urticaria through different mechanisms.

Although histamine is the most important mast cell mediator, non-mast cell mediators can also intervene. Mast cell activation moreover can be induced by other stimuli such as cytokines, opiates, heat, pressure and vibration, as well as by stem cell factor (SCF), which constitutes an IgE-independent mechanism.¹⁵

Thus, as we have seen, there are multiple underlying causes and physiopathological mechanisms, and a variety of complementary tests undoubtedly must be used in these patients, as described by the authors of the article: “Ten-year follow-up study of patients with chronic urticaria” – an interesting study comprising a total of 100 adult patients with urticaria in which the cause of the disease was investigated.

In coincidence with most publications, the authors concluded that in almost 55% of all cases it is possible to identify a cause of the disease, leaving a 45% of cases in which the etiology is considered to be unknown.^{16,17}

In this regard, in dealing with chronic urticaria patients, we should not give up if the first evaluations do not allow us to identify the underlying cause of the disease. Follow-up over time will gradually afford additional information that will help us to discover the cause.

As a final comment serving as food for thought for all investigators, we wish to cite the words of Dr. Chang (co-discoverer of the anti-IgE molecule talizumab): “If you

really believe in a project, the best thing you can do is spend all the effort to get it”.

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