PAPULAR URTICARIA:
Insights into non—IgE-mediated hypersensitivity reactions produced by stings of *Culex spp* and *Aedes spp* in patients with Intrinsic Atopic Dermatitis

ABSTRACT

Aims: To evaluate the contribution of non—IgE-mediated hypersensitivity mechanisms in Papular Urticaria produced by *Aedes spp* and *Culex spp* bites in patients diagnosed with Intrinsic Atopic Dermatitis coming from an urban (not beachy) Brazilian region.
Study Design: Through a retrospective chart review, we revisit the precipitins titrations and the *ex vivo* challenge tests against *Aedes spp* and *Culex spp* body extracts performed in patients with non—IgE-mediated Papular Urticaria who also were diagnosed with Intrinsic Atopic Dermatitis.
Place and Duration of Study: Instituto Alergoimuno de Americana – São Paulo – Brazil – between January 2018 and March 2023.
Methodology: We examined the charts of a population of 48 patients diagnosed with Intrinsic Atopic Dermatitis and non—IgE-mediated Papular Urticaria who were investigated through the research of precipitins and/or the Leukocyte Adherence Inhibition Test against *Aedes spp* and *Culex spp* body extracts.
Results: All investigated cases demonstrated laboratory *ex vivo* or *in vitro* evidence of a non—IgE-mediated immune mechanism by the research of precipitins and/or the Leukocyte Adherence Inhibition Test.
Conclusion: Our results support the fact that there is a strong relationship between non—IgE-mediated Papular Urticaria and Intrinsic Atopic Dermatitis, which probably share a common immune physiopathology.

Keywords: Aedes spp; Culex spp; Culicidae; allergy; intrinsic atopic dermatitis; hypersensitivity; immune complexes; mosquitoes; papular urticaria.

1. INTRODUCTION

Hypersensitivity reactions to arthropods are a common cause of allergic disease in the tropics [1]. Vertebrate reactions to arthropod bites can manifest in a variety of ways. Most individuals present a transient wheal and erythema, while others present persistent papular, vesicular, pustular, ulcerated, or even necrotic reactions that appear several hours after the biting [2]. These lesions may be due to mechanical trauma, secondary infections, naturally injurious substances, and/or the presence of harmless substances to which the host had previously developed a hypersensitivity reaction [3]. Papular Urticaria (PU) is the denomination attributed to persistent hypersensitivity reactions elicited by biting, stinging, or urticating arthropods [4]. This disease is produced by a delayed hypersensitivity

reaction characterized by the presence of pruritic skin lesions such as papules (or wheals), vesicles, blisters, and scabs. This clinical presentation is sometimes called "*Prurigo Strophulus*", or simply "*Strophulus*" as it was first described in 1813 when Dermatology was primarily a descriptive science and there was no consensus about the causes of this condition [5-7]. Lesions originating from arthropod biting may resolve after some minutes, or evolve into a chronic condition with secondary infections and scarring with hypo or hyperchromic pigmentation that may persist for years [8]. The delayed non—IgE-mediated immune reactions developed after the arthropods' salivary proteins are quite different from the IgE-mediated immediate reactions produced by the venom proteins inoculated by the Hymenoptera order, which are not produced to facilitate the acquirement of blood, but instead are more adequate to produce pain and inflammation for the defense of the hive or the anthill [9-11]. Hematophagous vectors usually have anticoagulants, platelet aggregation inhibitors, and vasodilators in their saliva [12]. This complex salivary protein mixture injected into the skin of the subject elicits a sequence of immune reactions. Each different immune reaction may be mounted against a different salivary antigen. In 1946 Mellanby proposed a four-stage evolution for the human's reactions to mosquito bites, according to the presence or absence of immediate and delayed reactions after the biting [13]. In most individuals, these reactions are self-limited, in others these reactions may persist through a sequence of hypersensitivity reactions that may be IgE-mediated and/or non—IgE-mediated, as suggested by the immune complexes present at the persistent lesions [14]. The first immune reaction produced by the host against the arthropod saliva is the classical inflammatory triple response of Lewis: pain, redness, and heat [15]. This autacoid-induced vasodilatation reaction usually disappears after a few minutes and may be inhibited by the use of antihistamines and steroids [16]. The subsequent severity and duration of the response are related to the further host's responses against the salivary or contacting proteins. The triple response of Lewis is the basis of the immediate reading skin-allergy tests. The diagnosis of the IgE-mediated reactions can also be inferred by the detection on the patient's serum, by ELISA or Immunoblot, of the free specific IgE able to link to natural or recombinant salivary proteins [17]. However, most patients do not show evidence of serum-specific IgE at all. A Gell & Coombs type III hypersensitivity reaction mediated by Complemented-activated immune complexes is suggested by the presence of granular deposits of C1q, C3, and IgM in the dermal blood vessels with histological vasculitis [18]. Several biting arthropods were reported to present salivary agents liable for producing immune responses associated with PU, such as the cat flea (*Ctenocephalides felis*), the dog flea (*C. canis*), the rat flea (*Xenopsylla cheopis*), the human flea (*Pulex irritans*), the bedbug *(Cimex lectularius*), bush-mites (ticks and chiggers)**,** rodent mites (*Ornithonyssus bacoti*), avian mites (*Germanicus gallinae; Ornithonyssus sylviarum*), and mosquitoes (*Culex sp; Aedes sp; Anopheles sp*), among others [19-26]. The most succeeded hematophagous synanthropic species from the *Culicidae* family (mosquitoes) developing in our tropical urban proximity belong to the genera *Aedes* and *Culex* [27]. Blood-feeding insects from the genera *Culex* and *Aedes* are endemic vectors at our region, which besides the transmission of infectious diseases, may develop hypersensitivity reactions in allergic patients, clinically manifested as PU [28]. The literature describes an association of PU with Atopic Dermatitis (AD) and several allergic comorbidities [29, 30]. In our outpatient clinic, we are visited by several allergic patients with severe AD who also have mild or moderate PU; or, sometimes, allergic patients who have severe PU who also have mild or moderate AD. A few patients present severe AD and severe PU that mixed into an overlapping disease, usually infected by bacteria, that turns into a difficult control condition. The severity of these diseases varies over time. At a given moment, the AD can be more uncomfortable for the patient than the PU, at other times, the PU is more troublesome than the AD. Usually, it seems that one condition aggravates the other, mainly when delayed or non—IgE-mediated hypersensitivity mechanisms are at play [31, 32]. To extrapolate the influence of the IgE-mediated reactions, we focused our attention only on patients with no evidence of increased Total IgE and undetectable specific IgE against every tested allergen, including the mosquitoes' extracts. This might be the equivalent of the diagnosis of the "intrinsic" atopic conditions when the hypersensitivity reactions are not due to the presence of IgE [33, 34]. So, our diagnosis of Intrinsic Atopic Dermatitis (IAD) does not refer to an absence of an eliciting allergen, but to the absence of the Gell & Coombs Type I hypersensitivity mechanism [35]. To explore these hypersensitivity mechanisms which present in common the absence of the influence of the IgE, we select this setting of patients with both diagnosis of IAD and PU. To study this interrelationship, we conducted a retrospective chart review of patients that were diagnosed with these two conditions at our outpatient facility to get insights into their conjoint physiopathology.

2. MATERIALS AND METHODS

2.1 Subjects

After receiving Institutional Review Board approval, from the Instituto Alergoimuno de Americana (Brazil), we proceed with a chart review of a population of 7,035 allergic patients, from which 48 (0.68%) fulfilled the criteria for the diagnosis of non—IgE-mediated PU and IAD. This was a very diversified cohort with 33 females; mean age 26.5 years; SD 22.5 years; range 1 to 73 years; mode = 1 year (appeared 5 times); geometric mean = 13.5 years.

2.2 Antigen Extraction

Whole-body extracts of *Culex spp* and *Aedes spp* were prepared by crushing and grinding whole-body parts of frozen mosquitoes, after which allergen extraction was performed in PBS buffer (pH 7.4) for 24 hours and centrifuged at 8,820 g for 30 min. The supernatant was collected and served for the subsequent procedures [36].

2.3 *In vivo* Investigation: Skin Scrape Test

All patients were submitted to immediate reading allergic skin tests, as previously reported [37].

2.4 *Ex vivo* Investigation: Leukocyte Adherence Inhibition Test

Some patients were submitted to the ex vivo challenge tests monitored by the Leukocyte Adherence Inhibition Test (LAIT), against total body extracts of *Aedes spp* and *Culex spp* to evaluate Gell & Coombs type II and type III hypersensitivity reactions. The LAIT was performed as previously described [38].

2.5 *In vitro* Investigation: Research of tube precipitins

Some patients were submitted to the research of precipitins, according to the suspected allergens identified by anamnesis. The tube precipitins were researched as previously described [39].

3. RESULTS

3.1 Allergic skin tests

The patients were selected by the absence of immediate response to the cutaneous allergic skin tests performed with a panel of common allergens, including insects, foods, and respiratory allergens.

3.2 Total and specific IgE

The patients were selected by detection of the total IgE inside the normal ranges provided by the reference laboratory and undetectable levels of specific IgE against a panel of common allergens, including insects, foods, and respiratory allergens performed by ImmunoCAP®.

3.3 Immunoassay Results

As a retrospective survey, there was no research protocol, therefore we report the incidental immune investigation as registered in the medical charts.

The most investigated *ex vivo* challenge was performed via the TIAL against *Culex spp*. There were 39 tests in which results varied from 0% Leukocyte Adherence Inhibition (LAI) to 100% LAI. See Figure 1.

The *ex vivo* challenge was also performed via the TIAL against *Aedes spp*. There were 18 tests in which results varied from 43% Leukocyte Adherence Inhibition (LAI) to 100% LAI. See Figure 2.

The most intensively investigated case was a 34 years-old woman whose TIAL was 92% LAI for *Culex spp* and 85% LAI for *Aedes spp*. The precipitins research was negative for both allergens.

There were also two female patients (35 and 39 years old) investigated with precipitins for *Culex spp* whose results were both positive for 1:32.

There was a female patient (26 years old) investigated with precipitins for *Culex spp* (positive for 1:8) and for *Aedes spp* (positive for 1:32).

There was a male patient (7 years old) investigated with precipitins for *Culex spp* (positive for 1:128) and for *Aedes spp* (positive for 1:256).

There was a male patient (1-year-old) investigated with precipitins for *Culex spp* (positive for 1:512) and for *Aedes spp* (positive for 1:8).

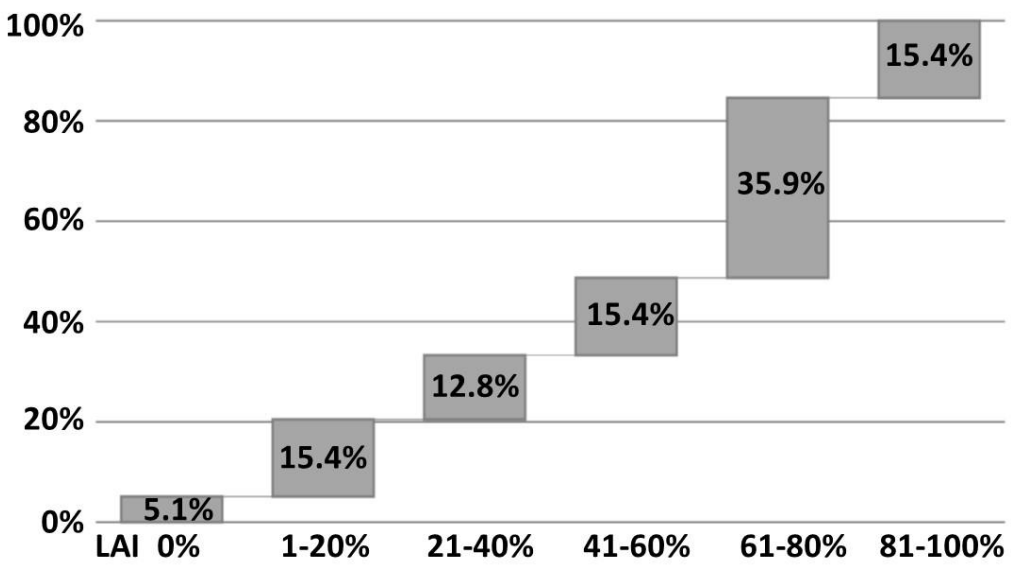

Fig. 1. Cascade distribution chart of the range groups of Leukocyte Adherence Inhibition (x-axis) results (%) of ex vivo *Culex spp* body extract challenges monitored by Leukocyte Adherence Inhibition Tests, according to the respective percentage of results over 39 tests (y-axis) performed on patients with non—IgE-mediated Papular Urticaria and Intrinsic Atopic Dermatitis.

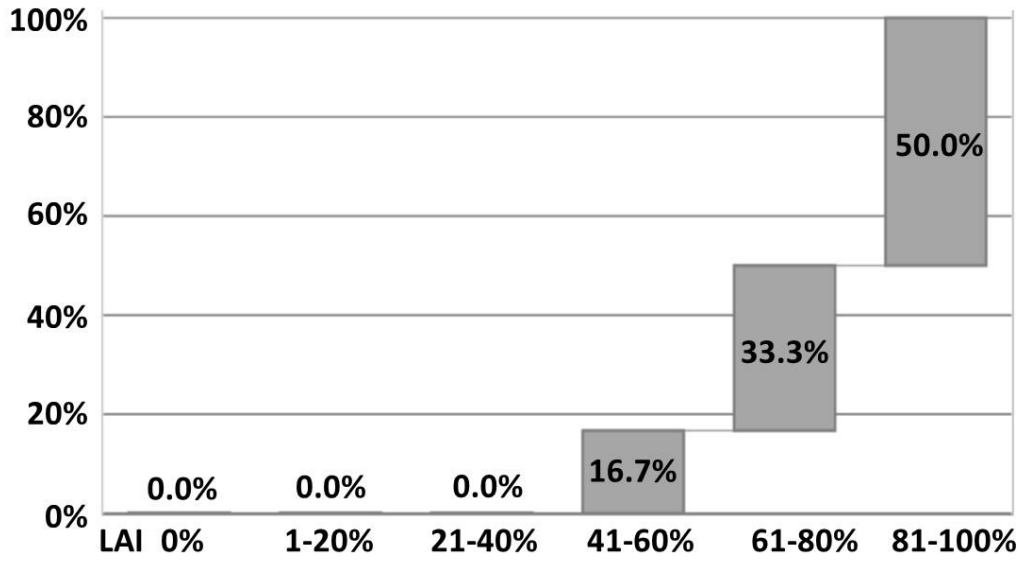

Fig. 2. Cascade distribution chart of the range groups of Leukocyte Adherence Inhibition (x-axis) results (%) of ex vivo *Aedes spp* body extract challenges monitored by Leukocyte Adherence Inhibition Tests, according to the respective percentage of results over 18 tests (y-axis) performed on patients with non—IgE-mediated Papular Urticaria and Intrinsic Atopic Dermatitis.

4. DISCUSSION

The non—IgE-mediated hypersensitivities diseases are a diagnostic challenge to clinicians. Practically every IgE-mediated hypersensitivity reaction has a non—IgE-mediated counterpart that sometimes presents very similar symptoms, almost indistinguishable from the IgE-mediated diagnosed condition [31]. Probably, this is because hardly a hypersensitivity reaction is purely IgE-mediated. The IgE elicits an immediate response, mainly by the release of histamine, a rapidly metabolized autacoid, that after stimulating the histamine receptors is soon degraded by the histaminases. However, IgE-dependent mast cell degranulation releases not only histamine but several other autacoids responsible for the late-phase reactions, such as prostaglandins and leukotrienes, responsible for the persistent symptoms [32]. What experience has shown us is that the IgE-mediated response is not needed for the appearance of the delayed response, which is then called a non—IgE-mediated hypersensitivity reaction [40]. For a long time, the medical community cultivated the “IgE paradigm” that limited the perception of a hypersensitivity reaction to the presence of IgE. Nowadays most physicians have been liberated from this limiting idea but are yet limited by the poverty of resources to perform the etiologic diagnosis of the non—IgE-mediated hypersensitivity reaction. PU is a clinical pathological presentation of a Gell & Coombs type III hypersensitivity reaction mediated by immune complexes, subsequent activation of the Complement System, and the production of anaphylatoxins [41]. The demonstration of the inhibition of the leukocyte adherence by the causative allergen also suggests a Gell & Coombs type II hypersensitivity reaction. The evolution of PU lesions is very similar to the clinical presentation of Intrinsic Atopic Dermatitis that was also diagnosed in our patients. The PU reactions also may produce cutaneous lesions very similar to another Gell and Coombs type III reaction classified as a “vasculitidis”: diseases produced by vascular or peri-vascular inflammation (vasculitis) [42]. Patients with Urticarial Vasculitis (UV) present indurated wheals with a duration greater than 24 hours, palpable purpura, and hyperpigmentation left behind, sometimes indistinguishable from the PU lesions [43]. These three conditions (UV, IAD, and PU) are clinically very similar and constitute a differential diagnosis among themselves. Probably they share a common physiopathology that may be suspected using laboratory tools such as the research of precipitins or

ex vivo challenge tests performed with the help of the LAIT. Our results show that there is a potential for the employ of *ex vivo* tests such as the LAIT and *in vitro* tests such as the research of serum precipitins against the Culicidae allergens in the suspection of Papular Urticaria, mainly in patients with IAD.

5. CONCLUSION

Our preliminary results suggest that there is a big field to be exploited in larger cohorts to prove a relationship between Intrinsic Atopic Dermatitis and Papular Urticaria; as well as the employment of the research of precipitins and the Leukocyte Adherence Inhibition Test to demonstrate a non—IgE-mediated immune mechanism responsible for them.

CONSENT

It is not applicable.

ETHICAL APPROVALS

As per international standards written ethical approval has been collected and preserved by the authors.

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