Asian Journal of Immunology

Volume 7, Issue 1, Page 35-45, 2023; Article no.AJI.98116

Far Beyond the IgE: Insights into the Clinical Profile of Allergic Patients with Selective IgE Deficiency, Urticarial Vasculitis, Allergic Pharyngitis, and Perennial Allergic Conjunctivitis

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Authors' contributions

This work was carried out in collaboration among all authors. Author CEO designed the study and wrote the protocol; the first draft of the manuscript and managed the literature searches. Authors DGP, APMT, JLSS, RPSL, and ESM extract the studied allergens. Authors DGP, APMT, JLSS, and RPSL performed laboratory research. Author RAPGS performed cutaneous tests. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/98116

Original Research Article

Received: 28/01/2023
Accepted: 31/03/2023
Published: 08/04/2023

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ABSTRACT

Aims: Medical literature defines the diagnosis of "selective IgE deficiency" (sIgEd) as the individuals able to produce, at normal amounts, all antibodies' classes, and subclasses, with exception of the IgE, which is not found by the laboratory detection method (usually below 2.0 kIU/L). Patients with sIgEd may present non—IgE-mediated allergies/hypersensitivities, turning them into ideal subjects to study these conditions.
Study Design: To evaluate by a retrospective chart review the allergic conditions of the sIgEd cohort population attended at an Allergy and Immunology medical facility.
Place and Duration of Study: Instituto Alergoimuno de Americana - São Paulo – Brazil – between January 2018 and January 2023.
Methodology: A population of 6.584 allergic patients, from which 44 (0,6%) meet the criteria for the diagnosis of SIgEd. The prevalence of the medically diagnosed allergic conditions was compared between the groups with detectable IgE and non-detectable IgE to extrapolate the Relative Risk (RR).
Results: The RR of Urticarial Vasculitis for the individuals with sIgEd was 64.2 in relation to the individuals with detectable IgE. The RR of Allergic Pharyngitis for the individuals with sIgEd was 2.65 in relation to the individuals with detectable IgE. The RR of Perennial Allergic Conjunctivitis for the individuals with sIgEd was 2.14 in relation to the individuals with detectable IgE.
Conclusion: The comparison of the prevalence of allergic diseases among two cohorts with detectable and undetectable IgE showed a great tendency for Urticarial Vasculitis and a moderate tendency to develop Allergic Pharyngitis and Perennial Allergic Conjunctivitis among the sIgEd population.

Keywords: Allergic conjunctivitis; allergic pharyngitis; allergy; hypersensitivity; IgE; immunodeficiency; selective IgE deficiency; urticarial vasculitis.

1. INTRODUCTION

The great diversity of phenotypes and endotypes of allergen-immunoreactive diseases is astonishing. A long list of conditions that affect several aspects of human physiology, through specific and nonspecific clinical presentations, in diverse graduations of severity (from the almost unperceivable immunoreactive chronic inflammatory conditions, such as gluten-related gastrointestinal disorders, to IgE-mediated life-threatening anaphylaxis) are widely grouped under the general designation of "Allergy" [1]. Although, a more technical keyword is preferred by the Medical Subject Headings of the US National Library of Medicine: "Hypersensitivity" [2]. Most of these conditions, long before the conceptualization of the participation of the immune system in allergic diseases, were studied by their organ-related symptoms, characterizing organ-specific diseases (allergic rhinitis, allergic conjunctivitis, allergic bronchitis, atopic dermatitis, eosinophilic esophagitis, etc.). Most of these diseases and syndromes are dealt with by organ-focused medical specialties, such as Dermatology, Pneumology, Otorhinolaryngology, Ophthalmology, Gastroenterology, and so on, with main attention on the control of the symptoms and the inflammation associated with their affected organs. However, the accumulation of knowledge about the immune system allowed the creation of a new medical specialty known as Allergology, which focuses on A) the diagnosis of the responsible allergens; B) the study of the immune mechanisms (Pathology); and C) their causal treatment (desensitization) [3]. However, the great complexity of the Immune System does not allow a simple and punctual interpretation of allergic diseases [4].

The vertebrate Immune System is primarily divided into two evolutionary arms: the Innate Immune System (more ancient) and the Adaptive Immune System (more recent); both can participate in allergic reactions [5]. As the Adaptive Immune System evolves from and commands the Innate Immune System, this division is more evolutionary than functional [6]. The Immune System can also be divided into two interactive arms: the Humoral and the Cellular; both participating in allergic reactions. As the humoral compound is produced and secreted by the cellular compound, this division is more morphologic/biochemical than functional. The main humoral component of the Innate Immune System is the cascade of proteins known as the Complement System [7]. The main humoral components of the Adaptive Immune System are the several classes of antibodies

(immunoglobulins). Cytokines are soluble substances produced by innate and adaptive immune cells to induce pro- or anti-inflammatory cellular responses and induce cellular migration (a particular subset of the cytokines, called chemokines) [8]. The great majority of the immune cells belong to the Innate Immune System (Macrophages, Neutrophils, Eosinophils, Basophils, Mast Cells, Dendritic Cells, and so on). The main cellular components of the Adaptive Immune System are the Lymphocytes, specialized in orchestrating the immune reaction (T cells) or producing effector antibodies (B cells and Plasma cells). According to the involvement of the Innate, Adaptive, Humoral, and Cellular arms, Gell and Coombs once classified the mechanisms of hypersensitivity into four types: Type I) IgE-mediated; Type II) Antibody-dependent cytotoxicity; Type III) Immune-complexes-mediated and Type IV) Cellular [9]. The last three hypersensitivity reactions are also referred to as the non—IgE-mediated allergic reactions. This classification has a clinical focus, however, as these hypersensitivity mechanisms may concomitantly participate in the same allergic disease, this classification may sometimes be more pragmatic than academic. The inflammation produced by the allergic reactions can also be classified according to the type of cytokines commanding the effector cells, such as A) Type I Inflammation mediated by cytokines generated by and secreted under the influence of the $CD4^+$ T lymphocytes known as T helper 1 cell (Th1); or B) Type II Inflammation, commanded by the cytokines generated by and secreted under the influence of the $CD4^+$ T lymphocytes known as T helper 2 cells (Th2). Other subsets of the Adaptive response are known for their regulatory activity (Th3 and Treg) [10,11]. The allergic inflammation may be also histologically classified according to the cellular participation of the compromised tissue, as it is predominantly caused by Mast cells, Basophils, Eosinophils, Neutrophils, and/or Lymphocytes, for instance [12-15]. The allergen inflammation may also be produced by aggregated and surmounted mechanisms such as described by the Immediate-Phase Immune Response and the Late-Phase Immune Response, both processed in the same location on different timelines, by different players [16]. The Innate Immune System is strongly influenced by the Adaptive Immune system, as one can testify by the massive presence of antibody receptors on the surface membrane of the innate immune cells. Even typically effector cells, such as the neutrophils have on their surface receptors for antibodies typically involved in allergic reactions, such as the IgE and the IgG [17,18]. Lately, innate immune responses such as the Extracellular Nets are gaining crescent interest in the study of infectious and hypersensitivity reactions [19]. The improvement of the innate immune response of the allergic patient by “immune training” is a medical practice used since the eighties, performed by the administration of inactivated bacterial antigens to allergic patients with recurrent infections. Mechanistic studies have demonstrated that one of the effects of this unspecific immunotherapy is the increase of the differentiation of regulatory Lymphocytes (Treg) that produce and stimulate the production of tolerogenic cytokines such as the TGF-beta, that stimulate the production of tolerogenic antibodies, such as the secretory IgA, justifying the prescription of this treatment for IgE-mediated and non—IgE-mediated allergic patients [20-23].

Immunodeficiencies, especially the different kinds of hypo-immunoglobulin syndromes, may contribute to immune dysregulation and the production of diseases. The treatment of these conditions with the therapeutic administration of exogenous gamma immunoglobulins may put light on the understanding of these questions since this reposition may change the profile of a non—IgE-mediated disease to an IgE-mediated condition [24]. One of the more unfathomable immune conditions is familial selective IgE deficiency (sIgEd) [25]. The sIgEd was defined for individuals able to produce, at normal amounts, all antibodies’ classes and subclasses, with exception of the IgE, which is not found by the laboratory detection method, usually below 2.0 kIU/L [26]. This condition has also been erroneously reported as “IgE hypogammaglobulinemia”, while the correct name would be “hypo-immunoglobulin E syndrome”, or, maybe, “hypoepsilonglobulinemia” since the “gamma immunoglobulin” is the IgG and the “epsilon immunoglobulin” is the IgE, both named after their gamma and epsilon heavy chains, respectively [27,28]. However, “hypoepsilonglobulinemia” would be a weird term, since no one calls the “Hyper-IgE Syndrome” like “hyperepsilonglobulinemia”. The main clinical presentations reported in patients with sIgEd are reactive airway diseases and skin manifestations, possibly associated with the innate immune system [27,29,30]. The mechanisms by which the sIgEd cause or is associated with diseases are not elucidated, however, the sIgEd may be seen as a marker of

immune dysregulation [26]. Naturally, patients with sIgEd may present concomitant diseases, which may (or not) be related to the IgE deficiency. Several reports had tried to establish a statistical correlation with allergies, autoimmune diseases, and tumoral diseases, however, it is difficult to differentiate the appearance of these diseases from what is normally expected from the sampled population [31]. This also occurs not only because the quantification of IgE is not a routine exam for most clinicians, but also, when researched, the medical professionals only give credit to the augmented levels, usually despising the report of an undetectable serum IgE [32].

The sIgEd is a phenotype that deserves further studies, however, our primary interest in it is to use the sIgEd as a model for studying the non––IgE-mediated allergic reactions that these patients present, as well as to report the diagnosed clinical allergy syndromes and the allergens associated with the symptoms as elucidated with help of the in vivo tests, ex vivo challenge tests and research of precipitins.

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 6.584 allergic patients, from which 46 (0.7%) presented with indetectable IgE. From these, 2 also had IgA deficiency, and so do not meet the criteria for the diagnosis of SIgEd. The final 44 patients (0,6% of the cohort population) were diagnosed with sIgEd and had their charts retrospectively studied (and compared with the 6.538 patients with detectable IgE). This was a very diversified cohort with 33 females; mean age 33.5 years; SD 23.9 years; range 1 to 85 years; mode = 1 year (appeared 6 times); geometric mean = 18.3 years.

2.2 *In vivo* Investigation

All patients were submitted to immediate reading skin tests, as previously reported [33].

2.3 Laboratory Investigation

To evaluate the presence of elements leading to the suspect of Gell & Coombs type II and type III hypersensitivity reactions we search some of the patients who had been submitted to the Leukocyte Adherence Inhibition Test and the Research of Precipitins against common allergens [34, 35].

2.3.1 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 [36,37].

2.3.2 Leukocyte adherence inhibition test

Some patients were submitted to the Leukocyte Adherence Inhibition Test (LAIT), according to the suspected allergens identified by anamnesis. The LAIT was performed as previously described [38,39].

2.4 Antigen Extraction

Antigen extraction for the skin tests, LAIT, and the research of precipitins was performed as previously described [39,40].

3. RESULTS

Several patients presented more than one diagnosis. To present an amplified chart of conditions we classified our data according to the medical diagnosis, instead of patients, to show the panel of allergic diseases presented by the cohort of patients with sIgEd.

3.1 Allergic Skin Tests

All immediate reading allergic skin tests were “not reactive”.

3.2 Urticarial Vasculitis

Urticarial vasculitis (UV) is a very rare condition. However, there was a disproportional number of patients with this condition that also presented sIgEd. In our cohort population, there were only seven patients with the diagnosis of urticarial vasculitis, out of which, two presented sIgEd (28.5%). When compared with the 0.6% of sIgEd from the total cohort, it is a great disparity. Among the 6.538 patients with detectable IgE, 5 had UV (0.07%). Among the 44 patients with sIgEd, 2 patients had UV (4.5%). Among our population, the relative risk of UV for individuals with sIgEd is 64.2 in relation to the individuals with detectable IgE.

3.3 Allergic Pharyngitis

Among the total enregistered population, 405 (6.1%) patients were medically diagnosed with Allergic Pharyngitis (AP). Out of which, seven patients (1.7%) were medically diagnosed with sIgEd; which is almost triple compared with the sIgEd proportion from the entire cohort (0.6%). Among the 6.538 patients with detectable IgE, 398 had AP (6.0%). Among the 44 patients with sIgEd, 7 patients had AP (15.9%). Among our population, the relative risk of AP for individuals with sIgEd is 2.65 in relation to the individuals with detectable IgE.

3.4 Perennial Allergic Conjunctivitis

Among the total enregistered population, 281 (4.2%) patients were clinically diagnosed with Perennial Allergic Conjunctivitis (PAC). Out of which, four patients (1.4%) were medically diagnosed with sIgEd; which is more than double when compared with the sIgEd proportion from the entire cohort (0.6%). Among our population, the relative risk of PAC for the individuals with sIgEd was 2.14 in relation to the individuals with detectable IgE.

3.5 Other Allergic Conditions

Besides the above, other allergic conditions diagnosed within the sIgEd group were: cow's milk proteins allergy (4 cases); insect allergy (4 cases); oral allergy (1 case); intrinsic asthma (5 cases); gastrointestinal allergy (5 cases); intrinsic atopic dermatitis (14 cases); contact dermatitis (4 cases); intrinsic allergic rhinitis (20 cases); allergic sinusitis (1 case); and chronic urticaria (5 cases).

3.6 Immunoassay Results

As a retrospective survey, there was not a common routine laboratory investigation. Here we report sparse complementary immune investigation performed in some of the cases.

A 49 years-old female with AP and sIgEd was investigated with the LAIT with the following results: A) Airborne fungi: 70% leukocyte adherence inhibition (LAI); B) *Dermatophagoides pteronyssinus*: 74% LAI; C) Cat dander: 74% LAI; D) Dog dander: 0% LAI; and E) beekeeping pollen: 0% LAI.

A 59 years-old female with AP and sIgEd was investigated with the LAIT with the following results: A) *Dermatophagoides pteronyssinus*: 76% LAI; B) Pork meat: 69% LAI; C) Cow's milk: 41% LAI; D) Cocoa: 57% LAI; and E) *Hevea brasiliensis* latex: 36% LAI.

A 50 years-old female with AP and sIgEd was investigated with the LAIT with the following results: A) *Dermatophagoides pteronyssinus*: 82% LAI; B) Airborne fungal extract: 16% LAI; C) Cow's milk: 0% LAI; D) ovalbumin: 81% LAI; and E) *Hevea brasiliensis* latex: 0% LAI.

A 64 years-old female with AP, PAC, and sIgEd was investigated with the LAIT with the following results: A) *Dermatophagoides pteronyssinus*: 61% LAI; B) Airborne fungal extract: 57% LAI; C) Cat dander: 84% LAI; D) Dog dander: 82% LAI; and E) beekeeping pollen: 80% LAI. She was also investigated with the research of precipitins that showed positivity for: A) *Dermatophagoides pteronyssinus* 1:128; B) Peanuts 1:64; C) Pork meat: 1:32; D) Dog dander 1:128; E) Carmine cochineal extract 1:8.

A 1-year-old female with PAC and sIgEd was investigated with the LAIT with the following results: A) *Dermatophagoides pteronyssinus*: 63% LAI; B) Avocado: 92% LAI; C) Banana: 13% LAI; D) Cocoa: 72% LAI; and E) *Hevea brasiliensis* latex: 38% LAI.

4. DISCUSSION

4.1 Urticarial Vasculitis

Urticarial Vasculitis (UV) is a rare clinicopathologic presentation of a Gell & Coombs type III hypersensitivity reaction [41]. Classified as a "vasculitidis": a disease produced by a "vasculitis" (vascular inflammation), UV differs from the common Urticaria by the extension of the vascular damage produced by the immune complexes deposition [42]. Patients with UV may present typical indurated wheals that disappear in less than 24 hours, however, the main characteristics of the vasculitis lesions are their longer duration, the palpable purpura, and the hyperpigmentation left behind [43]. Diascopy is a useful method for revealing inapparent purpura or hyperpigmentation occulted by the erythematous halo which disappears by vitropression [44]. Inflammation is the main distinction between UV and Chronic Urticaria, and the quantification of the C-Reactive Protein and the Erythrocytic Sedimentation Rate may be useful for differential diagnosis [45]. The

tissue deposition of immune complexes activates the Complement cascade, consuming their components, in such a way that UV may be classified as "normocomplementemic" or "hypocomplementemic" [46,47]. The hypocomplementemic state may rather be reflecting the activity and the severity of the disease since after the "consumption" of the serum Complement components, the liver will provide the proteins to replenish systemic circulation again [48]. The Complement cascade originates the anaphylatoxins (C3a and C5a components), that bind through specific receptors (C3aR, C5aR, and C5L2) on mast cells (eliciting degranulation) and other immune cells (producing and amplifying inflammation) [49]. The skin biopsy typically shows a dynamic angiocentric infiltrate with leukocytoclastic neutrophils (or eosinophils). There is also endothelial swelling and fibrinoid necrosis in blood vessels [50]. Several antigens have been associated with UV, including food allergens [51-53]. Antigen-Antibodies immune complexes may be assembled with any bivalent antibody, including the IgE [54]. At low concentrations, the immune complexes are adsorbed by the red cells' membranes and eliminated via the reticuloendothelial system [55]. However, at high concentrations, the immune complexes may deposit in the vascular bed, activating the Complement cascade and producing inflammation and clinical symptoms, depending on the affected organs, such as the cutaneal, digestive, musculoskeletal, renal, pulmonary, gastrointestinal, and ocular systems [56]. The digestive inflammation can aggravate the intestinal hyperpermeability (leaky gut syndrome) increasing the undesirable absorption of undigested proteins, producing more immune complexes, and perpetuating the disease in a vicious circle [57,58]. Secondary infections may also be diagnosed in UV patients. Skin infection may aggravate the inflammatory condition, turning systemic antibiotics into a common first-line medication for UV patients [42]. Our total cohort presented a little number of patients with UV. However, among the sIgEd patients, a much greater proportion of patients presented UV. Our cohort presented a relative risk of 64.2 for UV comparing patients with indetectable and detectable IgE, suggesting that UV may be rather a non—IgE-mediated hypersensitivity condition. Our little sample does not allow us to take statistical significance from the results, but it gives us a strong suggestion about a possible relationship between UV and sIgEd.

4.2 Allergic Pharyngitis (AP)

The pharynx is a common way for air and food. The nose-inhaled air, the mouth-inhaled air, as well all the ingested food constantly in contact with the mucous membrane lining the pharynx and its associated lymphatic tissue, concentrated mainly within the Waldeyer lymph ring, referred to in some studies as NALT (Nose Associated Lymphoid Tissue) [57]. While acute pharyngitis is more common in infancy, chronic pharyngitis is more common through adulthood [58]. Several causes may be held responsible for chronic pharyngitis: acid reflux, a persistent bacterial infection of the sinuses and tonsils, breathing through the mouth instead of the nose, pollutants, food allergies, and allergies to inhalants [59]. Chronic pharyngitis is one of the most common conditions diagnosed at ENT practice, however, the diagnosis of its etiology as allergic is restrained by some issues [60]. Patients with Allergic Pharyngitis (AP) complain about persistent or recurrent burning and pruritus at the oropharynx [61]. To the clinical examination, they present hyperemic elevated plaques of reactive lymphoid tissue in the oropharynx [62]. Allergic pharyngitis is a condition recognized by the US National Library of Medicine and categorized under the code MedGen UID: 664143 [63]. Recognizing that no respiratory organ is free from allergies, ENT specialists also know allergic pharyngitis as "allergic chronic pharyngitis" or "allergic sore throat" [64,65]. Most of our patients diagnosed with AP also presented occasional episodes of acute laryngitis, with hoarseness, hacking cough, inspiratory dyspnea, and paradoxical vocal fold motion demonstrated by the nasal allergen challenge monitored by spirometry [66]. AP is a condition usually diagnosed only by doctors with personal experience with its symptoms since the absence of unified diagnostic standards, treatment guidelines, and epidemiological data, produces a poor awareness of the condition, mainly when the oropharynx is not the main anatomical site of the symptoms [67]. However, when actively researched through anamnesis and a detailed physical examination, the number of patients with this diagnosis progressively increases in daily clinical practice. When the hypersensitivity is IgE-mediated, the relationship between chronic pharyngitis and allergies is easier to establish. However, the diagnosis of a non—IgE-mediated hypersensitivity is much more difficult to demonstrate. Our cohort presented a relative risk of 2.65 for AP comparing patients with indetectable and

detectable IgE, suggesting that AP may be rather a non—IgE-mediated hypersensitivity condition.

4.3 Perennial Allergic Conjunctivitis

Allergic Conjunctivitis is a condition caused by the conjunctival inflammatory response to specific allergens [68]. Allergic Conjunctivitis has been classified by different authors, in different ways, according to their experience, resources, and current understanding of the immunologic mechanisms behind the disease's physiopathology [69]. Anamnesis is a simple way to first classify ocular allergies as seasonal or perennial, according to the persistence of the symptoms. The second pass to classify ocular allergies is the ophthalmic examination, which will determine the sole involvement of the conjunctive, or a concomitant corneal and/or palpebral commitment. The prevailing laboratory resource for the practical allergist is currently specific IgE research. Hence, the third pass is to classify the ocular allergy as IgE-mediated (Gell & Coombs type I) or non—IgE-mediated hypersensitivity. This is a simplistic classification, and one must also consider mixed conditions, where IgE-mediated and non—IgE-mediated mechanisms participate together. The typical ocular Gell & Coombs type I hypersensitivity reaction is Seasonal Allergic Conjunctivitis, an immediate (acute) response produced after the degranulation of histamine from the conjunctival Mast Cells, elicited by the cross-linking of surface IgE bound to allergens. Less frequent, there is Perennial Allergic Conjunctivitis (PAC), which may be (or not) elicited by IgE-mediated mechanisms but is maintained as chronic conjunctival inflammation, as described by the Gell & Coombs type II hypersensitivity reaction, characterized by the infiltration of neutrophils, eosinophils and T cells responsible for the release of proinflammatory cytokines [70]. Our cohort presented a relative risk of 2.14 for PAC comparing patients with indetectable and detectable IgE, suggesting that the IgE is not a predominant participant in this condition.

4.4 Selective IgE Deficiency (sIgEd)

Familial sIgEd has not yet had the official status of a Primary Immunodeficiency. Broader studies are in need to be planned and executed to understand the pathophysiology of diseases produced or influenced by this condition, especially allergic ones. This particularity resides in the fact that normal IgE-producers and hyper IgE-producers may present the same conditions found in patients with sIgEd. Additionally, there is no clear physiopathologic mechanism able to explain a link between sIgEd and any disease since there is no animal model to study this condition. Most physicians simply don't pay attention to a result of indetectable IgE, just considering it a "negative" result inside the context of the triage of allergic diseases. As most studies are performed retrospectively, if the physician doesn't register this detail, the diagnosis must be lost, turning impossible to compare the clinical characteristics of populations with and without the capacity to produce IgE. At our outpatient facility, the diagnosis of sIgEd is a concern in the investigation of allergic symptoms, and a comparative study is possible, based on the two cohort populations. The increase of the relative risk for AP and PAC, comparing the IgE-producers' cohort with the non—IgE-producers' cohort is not quite representative information when considering the low number of subjects, but represents a clue for more detailed investigations. However, what called our attention was the disproportional number of patients with UV inside the group with sIgEd. The reason for that eludes our understanding. Maybe some multiligand superantigen or superallergen like an IgE-specific Cross-Reactive Carbohydrate Determinant (CCD) or an IgE-specific "protein Fv", sequestering all the circulating IgE into the assemblage of the immune complexes [71]? This is just speculation. The appearance of antibodies against CCD is a phenomenon taken into account to dismiss false-positive reactions inside the laboratory investigation of IgE-mediated hypersensitivity diseases [72]. The CCDs are immunogenic glycoproteins that can cross-react with antibodies directed against diverse allergens. Glycoproteins were already described to produce severe non—IgE-mediated delayed anaphylaxis [73]. Would these multiligand superallergens be acquired to blood circulation through a highly permeable leaky gut [74,75]? More studies, with a larger number of patients, must be done to answer these questions.

5. CONCLUSION

The comparison of the prevalence of allergic diseases among two cohorts with detectable and undetectable IgE showed a great tendency for Urticarial Vasculitis and a moderate tendency to develop Allergic Pharyngitis and Perennial Allergic Conjunctivitis among the sIgEd population.

CONSENT

It is not applicable.

ETHICAL APPROVALS

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

ACKNOWLEDGEMENTS

This work was funded by the Instituto Alergoimuno de Americana.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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