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Perspective

Allergic Sinusitis, Allergic Migraine, and Sinus Headaches

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Abstract

Sinus headache, sinusitis, and migraine are phenotypic diagnoses frequently elaborated by otolaryngologists, neurologists, and primary care general practitioners under different per-spectives. These conditions present with very similar phenotypes that are investigated, diagnosed, and treated according to the physician's perspective. Some patients present fluid phenotypes that sometimes appear to be one condition and, sometimes, another condition. Due to the similarity of the phenotypes, a multidisciplinary approach is highly recommendable. To prescribe an adequate treatment, defining the endotypes responsible for the phenotypes is essential. The role of hy-persensitivity conditions is better understood, especially the role of non-IgE-mediated hyper-sensitivities. The eosinophil is a typical type II Gell and Coombs hypersensitivity marker. However, it is not the sole one. Personalized approaches to identify non–IgE-mediated hyper-sensitivities dwelt in the in vivo and ex vivo provocation tests. A suggestion from an allergologist to colleagues from other specialties is to ensure, at least, a minimum investigation for allergic eti-ology in patients complaining of sinus headaches and/or migraines. This approach aims pre-scribing proper eviction measures and curative treatments, such as one of the several available presentations of allergen-specific, multiallergen group-specific, or allergoid immunotherapies. Here, the author provides the perspective of an allergologist updating an immunological point of view under the premises of IgE-mediated and non–IgE-mediated hypersensitivities.

Keywords: Allergy; Diagnosis; Headache; Hypersensitivity; Migraine; Immunoreactivity; Preci-sion Medicine; Sinus; Sinusitis; Rhinosinusitis

Abbreviations: CHES: Chronique Hyperplastic Eosinophilic Sinusitis; Der p 2: Allergen 2 from *Dermatophagoides pteronyssinus*; IgG: Immunoglobulin G; IgE: Immunoglobulin E; ILC2s: Group 2 Innate Lymphoid Cells; MD-2: Myeloid Differentiation Factor 2; SPECT: Single Photon Emission Computerized Tomography; TLR: Toll-like receptors

Background: Definition of Phenotypes

Sinus headache

Sinus headache (headache of rhinogenic origin or midfacial pain syndrome) is a phenotypic diagnosis frequently elaborated by otolaryngologists, neurologists, and primary care general practitioners under different perspectives [1]. Sinus headache is a nonspecific diagnosis elaborated by clinical anamnesis and physical examination (fa-cial pain elicited by pressure) that sometimes becomes a "label" that most patients use to self-diagnose when suffering from recurrent headache episodes [2]. When "labeling" a patient like this, most physicians and patients usually stay satisfied with this succinct diagnosis, avoiding further etiologic investigations despite the paucity of nosologic criteria to distinguish a differential diagnosis, such as migraine or sinusitis [3].

Migraine and Allergic Migraine

The migraine phenotypes englobe a heterogeneous spectrum of diseases identified by their clinical presentations since no biological marker exists to diagnose them [4]. Allergic migraine is a phenotype diagnosed when patients report migraine headaches associated with exposure to known allergens to which they are sensitized, and that also elicits concomitant symptoms pertinent to allergic conditions such as rhinitis, bronchitis, and urticaria [5].

Sinusitis and Allergic Sinusitis

Sinusitis (a term frequently substituted by rhinosinusitis) is primarily associated with sinus headaches and comprises a spectrum of diseases affecting the nose and paranasal sinuses [6]. The acute sinusitis is associated with viral or bacterial infections [7]. Several chronic sinusitis phenotypes have already been established [8]. However, the contribution of immune and inflammatory endotypes must also be evaluated when diagnosing patients with chronic sinonasal phenotypes [9]. Allergic sinusitis was first defined as a clinical condition associated with fungal colonization [10]. Aspergillus fumigatus is a sensitizing agent that colonizes sinuses, causing IgE-mediated and non-IgE-mediated sinusitis, with and without aspergillomas [11-13].

Relationship Among the Phenotypes and with the Allergies

Sinus headache, sinusitis, and migraine are overlapping phenotypic conditions that are frequently associated and confused, mainly because it is rare that a patient presents only one characteristic clinical picture [14]. When properly inquired, most patients report that sometimes they feel a light facial congestive headache and sometimes moderate or intense crises of cephalalgia, which raises two questions:

A. It would be appropriate for these conditions to be seen as distinct monolithic clinical disorders, able to be easily differentiated?

B. What would the role of immune hypersensitivity mechanisms be on overlapping endotypes for these not-so-distinct phenotypes?

Some epidemiological surveys have shown a significant association between migraine headaches and hypersensitivity diseases (especially allergic rhinitis), revealing that migraine is more common in allergic patients and allergy is more frequent in migraineurs [15-17]. The association of allergy with migraine depends upon factors such as age, degree of allergic sensitization, and administration of desensitization immunotherapy. Higher degrees of hypersensitization are associated with more frequent disabling migraine attacks, while the administration of immunotherapy decreases the prevalence, frequency, and disability of migraine episodes [18]. However, allergic migraine is not necessarily associated with IgE-mediated mechanisms [19]. For sharing biochemical pathways and based on epidemiology, it is thought that allergy and migraine are comorbid conditions with superposable underlying mechanisms [20]. The primary mechanism associated with migraine is the increased neurogenic vasodilation leading to stimulation of the peptidergic trigeminal sensory system [21]. The shared mediator between migraine and allergic diseases is histamine, a potent vasodilator and a releaser of nitric oxide, a vasorelaxant and elicitor of nociceptive impulses [22, 23]. Several textbooks of neurology taught that food and pharmacologic agents in foods are provokers of migraine [24]. Sulfites and alcoholic beverages are associated with headaches in sensitive individuals [25, 26]. The percentage of patients reporting that foods precipitate their migraine attacks ranges from 12 to 60 % [27].

Several studies associate foods as migraine triggers and a decrease in migraine attacks with elimination diets [28]. It is usually the patients themselves who report an immediate association between the intake of certain foods and the triggering of migraine attacks. The “post hoc ergo propter hoc” reasoning (after this, therefore, because of this) obliged migraineurs to avoid selective foods such as cheese, chocolate, nuts, citrus fruits, processed meats, monosodium glutamate, aspartame, coffee, alcohol, and others [29-31]. When the patient presents an IgE-mediated condition, it is relatively easy for the assistant physician to suggest a causal etiology with the help of a laboratory investigation [32, 33]. However, the IgE-mediated hypersensitivity reactions are only a fraction of the universe of the allergic diseases. Until now, immunology societies have recognized at least eight non-IgE-mediated hypersensitivity mechanisms [34]. Some studies with migraineurs showed that a diet restriction based on high titers of specific IgG antibodies against foods reduces migraine attacks [35, 36]. The IgG-mediated reactions may participate in type II and type III Gell & Coombs hypersensitivity reactions, the last one a known histamine-releaser through the intermediation of anaphylatoxins (C3a and C5a) formed during enzymatic activation of the Complement System due to the tissue deposition of immunoglobulin-antigen complexes [37]. However, the Mast Cells can degranulate with the presence of immune complexes through their Fc receptors, even when the Complement System is not activated [38, 39].

The association of IgE-mediated allergy and sinus inflammation is hardly evocated by imagery resources [40]. However, with the help of Single Photon Emission Computerized Tomography (SPECT), the sinuses’ metabolic activity and dynamic physiology may be followed after the injection of a radioactive tracer. The SPEC images of allergic rhinitis patients studied during ragweed season showed significant sinus hyperemia, with delayed imaging demonstrating a marked increase in bone uptake around the sinuses. These patients had robust positive skin tests for ragweed, were highly symptomatic, had nasal mucosa markedly edematous, and had normal sinus radiographs. When performed again after the ragweed season, the SPECT showed normal bone uptake, demonstrating that hypersensitivity reactions also affect paranasal sinuses during allergic crises, proving and defining the genuine concept of the allergic sinusitis phenotype [41].

Chronic hyperplastic eosinophilic sinusitis (CHES) is among the most challenging to evaluate sinusitis phenotypes. CHES is regarded as an allergic response (not necessarily IgE-dependent)

characterized by eosinophilic infiltration of sinus tissues [42]. Both innate and adaptive immunity are activated in chronic rhinosinusitis immunopathogenesis [43]. Innate immune cells are nowadays better understood about their capacity to orchestrate persistent non-IgE-mediated allergic inflammation resulting in chronic respiratory diseases [44]. This paradoxical allergic innate host defense, activated in response to environmental allergens, is an enigmatic feature of type 2 immunity [45]. Group 2 Innate Lymphoid Cells (ILC2s) are also recognized as participants of several allergic phenotypes, including chronic sinusitis with nasal polyps or eosinophilia [46-48]. Innate sensors such as the Toll-like receptors (TLR) participate in recognizing aeroallergens such as mites and fungi, leading to innate hypersensitivity responses [49]. The mite allergen Der p 2 has structural homology with Myeloid Differentiation factor 2 (MD-2), the lipopolysaccharide binding component of the TLR-4 signaling complex, producing a non-IgE-mediated hypersensitivity response due to a functional mimicry that acts as an immune adjuvant [50]. Several non-IgE-mediated allergic phenotypes are being investigated using cellular techniques that provide evidence of the cellular responses to respiratory allergens by ex vivo challenging techniques [51-53].

Perspectives for Clinical Practice

Due to its feasibility, non-invasiveness, and universal access, most physicians begin to investigate these phenotypes with imagery resources. This is a good policy since imagery exams are essential to identify (or rule out) the most severe diseases, subject to treatment with interventionist treatments. Also easy to access are some serum biomarkers, such as the leucogram, that help to diagnose bacterial (neutrophilia), viral (lymphocytosis) or parasitic (eosinophilia) infections. Also easy to access are the dosages of total and specific IgE to help diagnose Gell and Coombs type I hypersensitivity. Performed by an allergologist, an allergic skin test panel may also help diagnose immediate (type I) hypersensitivity reactions [54].

In the current medical practice, diagnosing non-IgE-mediated hypersensitivities in allergic patients demands painstaking attention to detail [55]. The human immune response to the individual exposome and metaexposome is not restricted to IgE antibodies insofar as comprehensive innate and adaptive immune systems are recruited to identify and restrict the multifactorial exogenous threats that affect allergic diseases' complex nature [56, 57].

Due to the similarity of the phenotypes, a multidisciplinary approach is highly recommendable. A suggestion from an allergologist to colleagues from other specialties is to reassure, at least, a minimum investigation for allergic etiology in patients complaining of sinus headaches and/or migraines and, in suspected cases, to refer these patients to an allergologist able to perform provocation tests to discard or confirm the possibility of an immune hypersensitivity as the cause of the patient's symptoms, especially when a non-IgE-mediated hypersensitivity mechanism is under suspicion.

Several in vivo and ex vivo challenging tests with the suspected allergens may be necessary to diagnose non-IgE-mediated hypersensitivity. Sophisticated personalized laboratory testing such as the Leukocyte Adherence Inhibition Test and the Tube Research of Precipitins can be performed at Precision Medicine laboratories to endotype non-IgE-mediated hypersensitivity [58]. Nasal or bronchial provocation tests may clarify the cases when there is doubt about the gap between laboratory diagnosis of hypersensitivity and a causal relationship with the disease [59, 60].

Radiological patterns of "centrally limited sinus disease" are highly suggestive in a mucosal allergic condition; however, they are not a primary diagnostic criterion [61].

When investigating the diseases produced by hypersensitivity reactions, it is essential to consider that the proper diagnosis may lead to the prescription of proper eviction measures and curative treatments, such as one of the several available presentations of allergen-specific, multiallergen group-specific or allergoid immunotherapies [62, 63].

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Conflicts of Interest

The author declares no conflicts of interest.

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