

NEW SCIENTIFIC SYNERGIES TO MANAGE PATIENTS WITH SEVERE RHINITIS: ALLERGY DIAGNOSIS AND TREATMENT FOR ENT SPECIALISTS

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Introduction

Allergic rhinitis (AR) is a global health problem because of its steadily increasing incidence and prevalence that currently concerns about 30% of the world's population. Although AR is not a disease that reduces the life expectancy, it is a disorder with a major impact on the quality of life of patients, resulting from an impaired social life, school performance and work productivity. Furthermore, AR produces significant costs for its treatment.

AR is a pathology of the nasal mucosa induced by IgE-mediated inflammation that follow the exposure to the culprit allergen and is clinically characterized by rhinorrhoea, sneezing, nasal itching and obstruction, which are reversible spontaneously or after treatment. The environmental allergens, after binding to specific IgE receptors on the surface of mast cells and basophils, trigger the degranulation of these cells in sensitized individuals, followed by a cascade of immunologic events resulting in the release of pre-formed mediators, with a major role for histamine, and the synthesis of further mediators that maintain the inflammatory response.

The document Allergic Rhinitis and its Impact on Asthma (ARIA), that was endorsed by WHO, has definitively certified the importance of AR in the context of respiratory disease. Recently, the international scientific community has identified a serious form of rhinitis associated with upper airways involvement: the SCUAD (severe chronic upper

airways disease), a complex clinical condition that is generally poorly responsive to usual drug treatment and thus requires highly specialized management. Recent scientific evidence also confirms that patients suffering from the most severe forms of AR are turning to highly qualified specialists. The ENT specialist experienced in allergy is the physician that, more than others, is able to diagnose and consequently to cure these severe AR types. Actually, the nasal district is not an isolated compartment, but is connected with other structures that are concerned by any variations occurring in the nasal mucosa by proximity such as bronchi, lungs, paranasal sinuses and ears. It is therefore necessary to have a broader vision of the pathology and cooperation among specialists in order to manage the pathology. These were the premises leading us to organize a Master of Allergology for ENT specialists, with the aim to give a theoretical and practical background, useful in linking their expertise to allergy and immunology, enabling them to deal with clinical cases requiring both capacities. In particular, from the allergist's point of view, an appropriate use of innovative diagnostic and therapeutic tools such as molecular diagnosis, nasal cytology and their management, is more feasible; this influences when and how to use allergen specific immunotherapy to treat patients with severe rhinitis unresponsive to the usual drugs, keeping in mind that such treatment is the only one able to alter the natural history of allergy.

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HUMAN NASAL IMMUNE SYSTEM: A SPECIAL SITE FOR IMMUNE RESPONSE ESTABLISHMENT

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The mucosal immune system located in correspondence to the olfactory organs in adult humans is not well identifiable but has proven important in establishing an effective immune response against inhaled antigens, including the generation of Helper 1 (TH1)- and TH2-cells, cytotoxic T lymphocytes (CTLs), plasma cells (PCs) and memory B cells. It is constituted by a diffused network of cells of epithelial and immune origin, as well as organized lymphoid tissue, where each component has a role in the initiation and maintenance of a long-lasting immune response, which is evoked not only in the oral and nasal cavities but also in the respiratory, intestinal and genito-urinary tracts. These peculiarities, in association to the easy anatomical accessibility of such immunological site, render the nasal mucosa a good candidate for the development of vaccine, even if a better understanding of the mechanism of the immune response induction as well as finding a safe adjuvant are necessary.

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MECHANISMS OF ALLERGIC DISEASES IN OTORHINOLARYNGOLOGYE. RIDOLO¹, I. MARTIGNAGO¹ and S MASIERI²¹*Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy*²*Department of Sense Organs, Sapienza University, Rome, Italy*

Allergic rhinitis (AR) is an IgE-mediated hypersensitivity disease caused by inhalation of an allergen to which the patients is sensitized. Etiopathogenesis of AR comprises a sensitization phase, an immediate phase and a late phase. In the sensitization phase, inhaled allergens are processed in peptides and come into contact with the nasal mucosa cells. Antigen-presenting cells (APCs), especially represented by dendritic cells (DCs), capture them through the interaction with their own MHC class II complexes and migrate to lymph nodes. Then, allergenic peptides are presented to naïve CD4+ T lymphocytes and a differentiation of T cells in Th2 subset takes place. After Th2 lymphocyte induction due to allergen exposure, the most relevant cytokines that are produced are represented by IL-3, IL-4, IL-5, IL-9, IL-10, and IL-13 that are able to promote IgE synthesis and mast cell proliferation. The allergen reaction, when allergen meets its specific IgEs on mast cells surface, causes an early inflammatory reaction determined by mast cells and basophils degranulation with release of preformed mediators from the intracellular granules, resulting in symptoms such as rhinorrhea, itching and sneezing. This phase is followed by a late phase characterized by the release of newly formed mediators, like leukotrienes, chemokines and adhesion molecules, and by the recruitment of eosinophils, neutrophils, macrophages, mast cells, lymphocytes B and T in the nasal mucosa. Such mechanism is responsible for continuing inflammation sustained by chemoattractants, cytokines and adhesion receptors that induce cellular infiltration of eosinophils, basophils, Th2 lymphocytes and mast cells and is clinically mirrored by the prevalence of nasal congestion over sneezing, itching and rhinorrhea.

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POLLENS CAUSING ALLERGY AND THEIR MONITORING BY AEROBIOLOGY AND PHENOLOGY

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Allergies caused by inhalant allergens, particularly pollens, are steadily increasing in urban centers. It is known that atmospheric pollution is strongly related to the inflammatory disease of the upper and lower airways but it is equally important in the development of sensitization towards pollens. Particulate Matter (PM), sulfur dioxide (SO₂) and nitrogen dioxide (NO₂) have an enhancement function on the persistence of pollens in the air, increasing the concentration and duration of pollinosis. It is therefore essential to use air quality control methods in urban centers to monitor the presence of pollen and fine dust that can drive the doctor and the patient to improve prevention, a step of primary importance in the treatment of allergies. Aerobiology and phenology are essential tools to monitor pollen production. The opportunity for the patients to use social media as information sources, including teletext, sms, mail and social networks, as well as a wide range of apps, allows to have reliable information on the air we breathe and therefore to better manage the methods of prevention at our disposal.

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THE SKIN PRICK TEST

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The skin prick test (SPT) is the most common test for the diagnosis of allergy. SPT is performed by pricking the skin, usually in the volar surface of the forearm, with a lancet through a drop of an allergen extract and is usually the first choice test in the diagnostic workup for allergic diseases because of its reliability, safety, convenience and low cost. SPT is minimally invasive and has the advantage of testing multiple allergens in 15 to 20 min. In children, SPT is far less disturbing than venipuncture and is used to obtain a sample of serum to measure specific IgE through *in vitro* tests. There is a good correlation (about 85-95%) between SPT and *in vitro* tests. Globally, SPT is an excellent diagnostic tool, with a positive predictive value ranging from 95-100%. SPTs can identify sensitivity to inhalants, foods, some drugs, occupational allergens, hymenoptera venom and latex. However, the relevance of such sensitivity to allergens should always be carefully interpreted in the light of the clinical history, because sensitization and clinical allergy may not coincide. In regards to safety, though the reports of systemic reactions, and particularly anaphylaxis, are very rare, *in vitro* IgE tests should be preferred if previous severe reactions emerge from the patient's clinical history.

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LABORATORY TESTS FOR ALLERGY DIAGNOSIS

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The introduction of highly purified natural and recombinant single allergenic molecules represented an important improvement in the diagnosis of IgE sensitization. The identification of specific IgE against cross-reacting molecules such as profilin, lipid transfer proteins, calcium binding proteins or against “genuine molecules”, represents an added value and allows to distinguish between true and false polysensitization. *In vitro* tests add information to recognize patients with sensitization to genuine molecules that cause allergic diseases and to evaluate in childhood the spreading of sensitization for each molecule in order to choose the best treatment and to identify the ideal patient for allergen immunotherapy. Also, in order to detect patients with sensitization to pan-allergens it is important to manage the risk of anaphylaxis for patients allergic to latex and to identify IgE to particular molecules involved in occupational allergy. In patients with negative skin prick tests (SPT), that results in a lower sensitivity compared with *in vitro* tests, the negative test may be caused by the lack of some important allergenic molecules in the extract used for SPT.

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ENT TESTS FOR ASSESSING THE ALLERGIC PATIENT

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Allergic rhinitis (AR) is a disease that afflicts a large percentage of the world population. It concerns both allergists and otolaryngologists, therefore it is important for both specialists to be aware of the characteristics of a patient who suffers from AR. Often, patients complain of nasal breathing difficulty only, initially not reporting any other symptoms typical of AR. In this brief review, the most important investigations, physical examination, nasal endoscopy, nasal peak flow and rhinomanometry, are described. All these investigations allow us not only to make the correct diagnosis, but also to monitor the course of the disease and the effects of therapy.

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NASAL CYTOLOGY

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Nasal cytology represents a useful, inexpensive and easy-to-apply diagnostic method to better detail the phenotypic characteristics of rhinitis. In fact, it allows to detect and quantify the cell population within the nasal mucosa at a given time. The technique involves sampling, processing and microscope reading. Sampling requires the collection of cells from the surface of nasal mucosa that is usually done by a sterile disposable curette. Samples should be collected from the middle portion of the inferior turbinate where the ratio ciliate/mucinous cells is expected to be well balanced. This totally painless procedure is performed under anterior rhinoscopy, with an appropriate light source. The sample staining is executed using the common May-Grünwald-Giemsa (MGG). The stained sample is read at optical microscopy with a 1000x objective and with oil detecting the presence of inflammatory elements (eosinophils, mast cells, neutrophils and lymphocytes) in nasal mucosa, as in the case of allergic and non-allergic rhinitis. Nasal cytology is easy to perform, non-invasive, inexpensive and repeatable in the same subject, also at short time intervals. For these reasons it represents an affordable diagnostic technique that can be applied in all age ranges, to better differentiate pathological conditions and also to evaluate the effects of various stimuli (allergens, infectious, irritants) or the effect of treatments.

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ROLE OF IMAGING IN ALLERGIC RHINOLOGY

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Rhinitis is an underestimated clinical condition, which has a considerable impact on the quality of life of the affected patients. The subject of this review focuses on three fundamental aspects: the development of knowledge concerning anatomic landmarks, the development of radiological imaging technology, and developments that can make a difference in the treatment of allergic rhinitis. The anatomical study of paranasal sinuses has been conducted since the time of the ancient Egyptians. Development of radiological equipment from the early 1900s has helped to improve information on the morphology of paranasal sinuses, sufficient to be considered valuable information regarding frontal anatomy and its variability. Imaging has become increasingly important in the diagnosis and treatment of inflammatory diseases of the paranasal sinuses. In recent decades, radiology has helped to study this region as we have progressed from plain radiography to high-resolution Computed Tomography (HRCT). Subsequently, from radiologic imaging, digital volume tomography (DVT) has been developed, in high resolution and narrow section width. Currently, experience with third generation Cone-Beam Computed Tomography (CBCT) technologies provides useful information about bones, and it is now possible to highlight anatomical variants that involve bone structures. We still lack the ability to make a qualitative evaluation of soft tissues, as there are no Hounsfield levels in CBCT. However, this is a new area of research, and its application is evolving in an interesting manner, especially for soft-tissue allergic-inflammatory diseases.

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ALLERGIC CONJUNCTIVITIS: CURRENT CONCEPTS ON PATHOGENESIS AND MANAGEMENT

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Allergic conjunctivitis (AC) includes a wide spectrum of clinical entities characterized by different incidence, age of onset, natural course, clinical outcome and response to treatment. Taken together, they represent one of the most frequent ocular surface diseases affecting more than 30% of the young-adult population and show an increasing incidence over the years. Moreover, comorbidities with other systemic atopic conditions such as asthma, atopic dermatitis and rhinitis require a multidisciplinary approach. Recent advances in the knowledge of the pathogenic mechanism overcome the classic role of type I hyper-sensitivity and mast cells' activation, demonstrating an involvement of innate immunity and neuroinflammation in the pathogenesis of the most severe forms such as atopic keratoconjunctivitis (AKC) and vernal keratoconjunctivitis (VKC). Ocular itching, swelling and tearing are the most frequent symptoms complained by patients with all forms of AC, while photophobia and pain are typical of the most severe forms, such as VKC and AKC, due to the frequent corneal involvement. Upper tarsal papillary reaction represents the main clinical sign of AC associated with conjunctival hyperemia and mucous secretion. Diagnosis is based on clinical history and eye evaluation and can be confirmed through allergological tests. Additional ocular exams include specific allergen conjunctival provocation tests and the presence of eosinophils in the conjunctival scraping. Current treatments of AC include the use of antiallergic eye drops for mild forms, while recurrences of ocular surface inflammations with corneal involvement in severe forms require the use of topical steroids to avoid visual impairment. Novel steroid sparing therapies such as Cyclosporine A eye drops or topical Tacrolimus have been proposed to improve VKC and AKC management.

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ALLERGIC RHINITIS

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Allergic rhinitis (AR) was long considered a quite trivial disease, but the advance in epidemiological and clinical knowledge, with a major role for Allergic Rhinitis and its Impact on Asthma (ARIA) initiative, substantially changed the scene. Now we know that AR has significant effects on patients' quality of life and also has a relevant economic burden. The ARIA phenotypes related to the duration of symptoms and to the severity of AR are very useful in establishing the optimal strategy in each patient with AR, also according to the kind of allergens that cause rhinitis. When traditional allergy testing, including skin prick tests and *in vitro* of specific IgE antibodies are not sufficient for the diagnosis, modern techniques such as molecular diagnostics may be used. Also the management of AR may be tailored to single patients according to the clinical expression of AR, that may vary from mild to moderate-severe stage, with the aim of achieving the best possible control of the disease.

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ASTHMA ASSOCIATED TO RHINITIS

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A large amount of data show that AR and asthma are associated both epidemiologically and clinically, introducing the definition of “united airway disease”. The mechanisms underlying such association were initially suggested to start from the nose, including the loss of the protective and homeostatic effects of nasal function, the activation of a naso-bronchial reflex and the spread of allergic inflammation from the nose to the lower airways. Later, other factors such as microbial stimuli and systemic inflammatory mechanisms, involving bloodstream and bone marrow, were advocated. The advance in knowledge made it clear that the link between asthma and AR is multifactorial, with particular importance for inflammatory cells and especially eosinophils. By the model of nasal challenge, important immunological responses were revealed, with particular importance for the increased expression of adhesion molecules (ICAM-1, VCAM-1 and E-selectin) and of cytokines such as interleukin (IL)-13, that was accompanied by a rise of eosinophils in blood and development of bronchial hyper-responsiveness. The occurrence in AR of a concomitant sinusitis is frequently associated with worse asthma outcomes, as assessed by a lower pulmonary function, increased asthma symptoms and poorer quality-of-life compared to patients with asthma alone.

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