Infection or Allergy

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Patients are frequently seen in our practices with nasal complaints, unable to distinguish between the symptoms of allergic rhinitis (AR) and airway infections (AI). What is the relationship between allergic rhinitis and airway infections? Could one lead to the other? In order to understand the links between them, some epidemiological and pathophysiological concepts must be taken into consideration.

In Sweden, a study of 1,200 adults evaluated the economic impacts of allergic rhinitis and airway infections. Absenteeism, presenteeism and career absenteeism rates reached 5.1 days per person a year, at an individual cost of € 653, totaling € 2.7 billion a year. [1]

By definition, rhinitis is an inflammation of the mucous tissue lining the nasal cavities, characterized by the presence of symptoms such as nasal blockage, anterior or posterior rhinorrhea, nasal pruritus and sneezing. The symptoms must occur for more than an hour on at least two consecutive days. [2]

There are several ways of classifying rhinitis. Didactically, they may be subdivided into infectious (viral, bacterial and others) and non-infectious (allergic, drug-induced, hormonal, irritative, non-allergic eosinophilic, idiopathic etc). [3]

It is estimated that between 30% and 50% of airway infections are caused by rhinovirus, generally twice a year for adults, while children may present 8 to 12 episodes a year. [4]

Among non-infectious types of rhinitis, the allergic form is undoubtedly the most prevalent, at rates varying from place to place worldwide. In some countries, this is estimated at close to 50%, hovering around 15% in Brazil. [2,3,5]. An assortment of factors underpins these variations, such as those aired by the theory of hygiene, air pollution etc. [6]

In order to determine the actual prevalence of allergic nasal disease, it must be accurately diagnosed from both the clinical and laboratorial standpoints, measuring the agent involved (specific IgE). Unfortunately, this is not feasible for large populations, as studies are based on questionnaires such as the International Study of Asthma and Allergies in Childhood (ISAAC); Allergies in America (AIA); Allergies in Latin America (AILA) etc. [5,7,8]

Basically, these studies investigate symptoms by tracing clinical links to trigger factors. The accuracy of this methodology is poor, as nasal symptoms in allergic patients are caused by agents that may be either specific (mites, fungus, pollen, animal antigens) or non-specific (strong smells, air pollution, variations in temperature and air humidity), in addition to those for which no IgE is produced.[9] In allergic and non-allergic patients, there is a disorder of the autonomic system that controls nasal physiology that is characterized by local sympathetic hypo-

reactivity and parasympathetic hyper-reactivity, consequently leading to high levels of nasal blockages and rhinorrhoea. [2] As a result, the symptomatology of the various types of rhinitis is similar, thus requiring particularly close attention when taking clinical histories.

According to the theory of hygiene, there would be an increase in the prevalence of allergic IgE-mediated episodes through a drop in the number of childhood infections. From the immunological standpoint, Type 1 auxiliary lymphocytes (Th1) release cytokines that mediate responses to viruses and bacteria, while Type 2 (Th2) cytokines do so for parasitoses and IgE production. At the start of our lives, viral and bacterial infections stimulate the immunological system to produce responses that are eminently Th1 type. By "protecting" children through immunizations, sterilized foods and early antibiotic use, we "release" the immune system for Th2 type responses. Corroborating this theory, a study in the USA showed that some infections (hepatitis A, *Toxoplasma gondii* and *Herpes simplex*) are associated with a lower prevalence of allergic rhinitis and asthma. [10]

On the other hand, there are several papers in the medical literature that contradict this theory. In a cohort of more than 1000 people, the authors did not note any increase in the relative risk when relating the number of airway infections before two years of age, between two and four years of age and between four and eight years of age, to the development of allergic rhinitis and asthma. [11] Similarly, another study with children under four years of age showed that among those going to daycare centers while still very young, the prevalence of wheezing, night coughing, asthma, rhinitis and eczema was higher than among those who stayed at home until they were older. In other words, children in contact with infectious agents presented more allergic episodes. [12]

The innate immunity of the nasal cavities is composed of a ciliary mucus barrier, bacterial peptides dissolved in the mucus and the junction complex between the cells constituting the epithelium (hair, serum, globular and basal cells). [13]

Chronic airway inflammation among allergic patients undermines the ciliary barrier, exposing receptors and consequently paving the way for more serious diseases caused by rhinovirus.

A recent study of lung cells showed that allergic inflammation exposes the Cadherin-Related Family Member 3 (CDHD3), an intercellular adhesion molecule in the junction complex. Additionally, CDHD3 is also related to rhinovirus C binding and its replication. The authors suggest that allergic information may foster greater adherence and replication of these viruses, thus resulting in a disease that is more severe. [14]

In order to understand another possible link for a predisposition to airway infections among patients with allergic rhinitis, it is necessary to recall its pathophysiology [15], which is quite complex, including two very important characteristics. After the interaction between antigens and the IgE molecules, a wide variety of chemical mediators is released, such as histamine, leukotrienes and cytokines. These substances are involved in the genesis of symptoms during the immediate phase and the development of the late phase, including the attraction of inflammatory cells such as eosinophils. Moreover, patients sensitized to perennial agents

(mites) present a phenomenon known as minimal persistent inflammation. One of the markers in this process is the expression of the intercellular adhesion molecule 1 (ICAM-1) associated with eosinophil attraction, even when asymptomatic. [2] As the ICAM-1 is the main rhinovirus receptor, there is a predisposition to airway infections among these patients. [16] It is worthwhile stressing that rhinovirus is the main infectious agent associated with airway infections among children under two years old. [17]

Another important point is that the influenza virus boosts ICAM-1 expression in the nasal epithelium cells, thus potentiating allergic inflammatory conditions. [18] In other words, during the allergic process, ICAM-1 expression facilitates rhinovirus adhesion, while for influenza virus infections, induction of the expression of this adhesion molecule potentiates the allergic process.

We know that local leukotriene concentration rises during rhinovirus infections. [19,20] In allergic processes, these mediators are associated with eosinophil chemotaxis. The viral process feeds back into the nasal allergy condition, which in turn facilitates the appearance of airway infections through ICAM-1 expression.

Another link between airway infections and the nasal allergy process lies in the fact that 80% of acute bacterial rhinosinusitis are due to viral infections. [21] The influenza virus and the human parainfluenza virus 3 (HPIV-3) buttress the adhesion of *the Streptococcus pneumoniae* to the nasal epithelial cells. [22]

We must suspect a bacterial process when airway infection symptoms last for more than ten days, or weaken and then return. The prevalence of acute bacterial rhinosinusitis is not higher among allergic patients, although tending to be more aggressive when this occurs. In animal models, the presence of polymorphonuclear cells is greater, together with the release of chemical mediators such as tumoral necrosis factor alpha (TNF-alpha) in allergic groups, compared to non-sensitized groups. [23] In human beings with airway infections caused by rhinovirus, higher scores are noted for computerized tomography alterations in allergic patients, compared to their non-allergic counterparts. [24]

We normally use clinical parameters to distinguish nasal allergies from viral infections. With infections, there are systemic aspects other than nasal symptoms, such as fever, malaise and loss of appetite. However, among children under two years old with only nasal symptoms, rhinoviruses are also the most prevalent agents, at 40% of these cases. It is stressed that wheezing and coughing is present for both conditions, with no difference for allergic patients. [17]

It is thus very difficult to diagnose allergic rhinitis in this age bracket. Although children can already produce IgE, the importance of this mechanism in triggering systems become significant only after two years of age. Consequently, caution is required when interpreting the presence of specific IgE, particularly for inhaled antigens (mites, fungus, pollen, etc).

In conclusion, distinguishing between allergic rhinitis and airway infections among small children is not an easy task, as they are very similar from the clinical standpoint and each tends to feed over into the other. We must thus base our suspicions on detailed clinical histories and studies demonstrating that the cause of an infection is more important during the first few years of life.

References

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