ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Mixed rhinitis: a new phenotype?

Rinite mista: um novo fenótipo?

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ABSTRACT

Rhinitis is not a homogeneous condition and can manifest in different subtypes, depending on the underlying pathophysiological mechanisms (endotypes) and clinical manifestations (phenotypes). Idiopatic rhinitis (IR) is the most prevalent subtype within the group of nonallergic rhinitis and requires the exclusion of allergic rhinitis (AR) as a diagnosis. Mixed rhinitis (MR) can be considered in patients who present symptoms after exposure to allergens and nonspecific stimuli, representing a combination of Nonallergic rhinitis (NAR) and AR. The PubMed, Google Scholar, EMBASE, and SciELO databases were searched for articles published in English, Portuguese, French, or Spanish in the last decade. The following search strategy was used: mixed rhinitis OR allergic rhinitis OR nonallergic rhinitis OR chronic rhinitis OR nasal irritants AND children OR adults. The prevalence of chronic rhinitis in the general population is estimated to be between 10% and 40%. Among adults, the prevalence of MR corresponds to 30% to 50% of these patients. In children with AR, 42.9% were classified as having MR. Clinically, MR manifests itself in more severe conditions, with worse control and a greater need for medication combinations. The use of a standardized and culturally validated instrument for the study population is essential for the identification of patients with MR, as well as for improving the understanding of this rhinitis endotype in terms of disease progression and pharmacological management.

Keywords: Rhinitis, allergic rhinitis, vasomotor rhinitis, irritants.

RESUMO

A rinite não é uma condição homogênea e pode se manifestar por diferentes subtipos, segundo os mecanismos fisiopatológicos subjacentes (endotipos) e manifestações clínicas (fenótipos). A rinite idiopática (RI) é o subtipo mais prevalente dentro do grupo das rinites não alérgicas e requer a exclusão da rinite alérgica (RA) como diagnóstico. A rinite mista (RM) pode ser considerada em pacientes que apresentam sintomas após exposição a alérgenos e estímulos inespecíficos, uma combinação de RI e RA. Os autores realizaram revisão narrativa de artigos publicados em inglês, português, francês e espanhol, na última década nas bases de dados PubMed, Google Scholar, EMBASE e SciELO. As palavras-chaves usadas nessa busca foram: *mixed rhinitis OR allergic rhinitis OR non allergic rhinitis OR chronic rhinitis OR nasal irritants AND children OR adults*. A prevalência de rinite crônica na população geral está estimada entre 10% e 40%; entre adultos, a prevalência de RM corresponde entre 30% e 50% desses pacientes. Em crianças com RA, 42,9% delas foram classificadas como tendo RM. Clinicamente, a RM manifesta-se por quadros mais graves de rinite, com pior controle e maior necessidade de associação de medicamentos. O emprego de instrumento padronizado e validado para a cultura da população em estudo é primordial para a identificação de pacientes com RM, além de permitir o melhor entendimento desse fenótipo de rinite com relação à evolução e controle medicamentoso.

Descritores: Rinite, rinite alérgica, rinite vasomotora, irritantes.

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Introduction

Rhinitis is an inflammatory condition of the mucous membrane of the nose, characterized by symptoms such as nasal congestion, runny nose, sneezing, and nasal itching.[1,2] It is one of the most common conditions in children and adolescents, significantly affecting their quality of life and general well-being.[3,4] In Brazil, it is estimated that more than one third of the population of children, adolescents, and adults have rhinitis, and its prevalence is increasing.[5,6]

Worldwide, rhinitis causes increased use of health services, poor quality of life, and low performance at work/school. Rhinitis is an independent risk factor for asthma, and several comorbidities may be involved in uncontrolled nasal symptoms: sinusitis, otitis media, eustachian tube dysfunction, chronic cough, obstructive sleep apnea, chronic headache, and fatigue.[7-9] The disease is also a risk factor for behavioral changes and learning difficulties in children.[4,10] Despite their impact, chronic forms of rhinitis have been trivialized and seen as nothing more than a nuisance, both by the general population and by health professionals.

Rhinitis is not a homogeneous condition and can manifest in different subtypes, depending on the underlying pathophysiological mechanisms (endotypes) and clinical manifestations (phenotypes), making it difficult to develop assertive guidelines for its diagnosis and treatment.[10]

Rhinitis classification

The most widely used and accepted classification system for rhinitis divides the disease into 3 main groups according to etiology[11]:

– *infectious rhinitis:* acute, self-limiting, and usually caused by viruses;
– *allergic rhinitis:* induced by a specific allergen in a patient with proven allergic sensitization; and
– *noninfectious and nonallergic rhinitis:* a heterogeneous group without allergic sensitization or signs of infection.

This classification system provides a useful framework for understanding the cause of rhinitis and guides appropriate treatment for each patient.

Infectious rhinitis is usually caused by viruses, its course is self-limiting, and treatment is based on symptom control.[12-15] Also called acute rhinosinusitis, it is characterized by inflammation of the nasal cavity and paranasal sinuses, causing runny nose, nasal obstruction/congestion, and facial pain. Coughing is a very common symptom, especially in children.[16]

Symptoms of uncomplicated viral rhinitis resolve in 7 to 10 days, with significant improvement after day 5. If symptoms persist after 10 days or worsen after a period of improvement, complications with secondary bacterial infection (acute bacterial rhinosinusitis) may be considered, and antibiotics may be indicated. *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Moraxella catarrhalis* are the most frequently involved bacteria in these cases. Coexisting allergic rhinitis (AR) may contribute to persistent nasal symptoms, hindering differential diagnosis with bacterial infection, which occurs in 5% to 13% of pediatric cases.[17,18]

In influenza virus infections, oseltamivir is indicated for at-risk patients (older adults, children < 2 years of age, and individuals with cardiac or respiratory comorbidities).[12,19] Topical corticosteroids may also be considered for their local anti-inflammatory action, especially in more severe cases. They act by neurogenic modulation, reducing edema and mucus production, thus contributing to symptom improvement.[18]

AR is a common, well-defined condition. It is triggered by an immunoglobulin E (IgE)-mediated response after inhalation of environmental allergens, such as pollen, dust mites, cockroach feces, animal dander, rodent dander, and fungi. AR is diagnosed when skin or serological tests demonstrate specific IgE in response to exposure to one or more allergens.[11]

Allergens inhaled through the nose are processed by antigen-presenting cells in the nasal mucosa and are then presented to TCD4+ lymphocytes. During the sensitization phase, T lymphocytes produce cytokines that stimulate the production of a specific IgE against the antigen. This IgE binds to high-affinity receptors on the surface of mast cells and basophils. Upon re-exposure to the allergen, the specific allergen peptides are recognized by IgE bound to mast cells and basophils, resulting in activation of a signaling cascade that leads to the release of preformed and newly synthesized mediators, such as histamine, leukotrienes, prostaglandins, and platelet activating factor. The late-phase reaction occurs approximately 4 to 12 hours after exposure to the allergen, with the release of chemokines that attract type 2 T helper cells, activated eosinophils, and mast cells to the nasal epithelium. These cells

release cytokines, such as interleukin (IL)-4, IL-5, and IL-13, as well as enzymes and other mediators, which perpetuate allergic inflammation, resulting in chronic symptoms such as nasal congestion and runny nose.[10] The response of type 2 T helper cells mainly involves eosinophils and IgE. However, type-2 innate lymphoid cells, which are also present in the nasal mucosa, can produce the same cytokine profile, contributing to local inflammation.[18]

According to the Allergic Rhinitis and its Impact on Asthma guidelines,[1] AR is classified based on symptom duration and severity, namely: mild intermittent, moderate-severe intermittent, mild persistent, or moderate-severe persistent.[1]

Furthermore, the sensitization pattern can be used to differentiate monosensitized vs polysensitized patients. This information can facilitate AR treatment, since polysensitized patients may require more aggressive and individualized treatment.[10]

Noninfectious, nonallergic rhinitis (NAR) is a chronic condition of the nasal mucosa that manifests predominantly with symptoms of nasal congestion and rhinorrhea, without evidence of allergic sensitization (ie, negative skin prick test and/or serum specific IgE). Although the most common symptoms are congestion and anterior and posterior rhinorrhea, other associated symptoms include throat clearing, cough, eustachian tube dysfunction, sneezing, decreased sense of smell, and facial pain/pressure. It is important to note that itchy eyes, throat, and ears are not common symptoms.[1]

NAR is not a single disease with a single underlying cellular mechanism, but rather a group of several different conditions that cause similar nasal symptoms. Some examples of these conditions include: drug-induced rhinitis, rhinitis in older adults, hormonal rhinitis, rhinitis during pregnancy, nonallergic occupational rhinitis, gustatory rhinitis, and idiopathic or vasomotor rhinitis (IR). Several tests may be involved when assessing patients suspected of NAR, such as skin tests, serum IgE levels, nasal provocation tests, pulmonary function tests, X-rays, or computed tomography.[20]

IR is the most prevalent subtype of the NAR group, requiring the exclusion of AR for diagnosis. Different studies have used varying terminologies to refer to this condition, including intrinsic rhinitis, IR, vasomotor rhinitis, and nonallergic rhinopathy. The pathophysiological mechanism of IR is unrelated to allergy, structural defects, or underlying systemic diseases, and it is usually not associated with nasal eosinophilia.[10]

IR symptoms include nasal congestion, runny nose, sneezing, and itchy nose. Treating IR can be challenging because the symptoms can be triggered by a variety of factors, including emotional stress, temperature changes, and alcohol consumption. Treatment options include medications such as decongestants, anticholinergics, and nasal steroids, as well as preventive measures such as avoiding known triggers.[21]

However, in addition to these 3 groups, there is another type: mixed rhinitis (MR), a specific subtype that combines characteristics of AR and NAR and has aroused increasing interest.[10,11]

MR may be considered for patients who present symptoms after exposure to allergens and nonspecific stimuli, a combination of NAR and AR. The degree to which chronic allergic inflammation contributes to hyperreactivity to other stimuli remains unknown, but, in any case, it is believed that other mechanisms trigger symptoms in this type of rhinitis.[7]

The specific endotypes of NAR are not yet fully understood, but the underlying mechanism is believed to be neurogenic.[10] A study assessing the nasal secretions of patients with AR, MR, and NAR in search of biomarkers that could distinguish the disease groups, found no differences in the investigated proteins and peptides. Patients with MR and AR had lower levels of IL-12 than those with NAR, but the groups could not be individually differentiated.[21] The lack of a distinct and consistent cellular inflammatory pattern in the nasal mucosa indirectly supports a neurogenic mechanism. Common symptom triggers include chemical irritants, such as strong odors, tobacco smoke, perfumes/fragrances, and cleaning agents, as well as changes in temperature, humidity, and atmospheric pressure. Other triggers may include changes in position, alcohol consumption, or eating habits.[10]

These irritants are thought to trigger the release of tachykinins, which, by inhibiting sympathetic mediators, result in increased parasympathetic response and nasal congestion and/or rhinorrhea. This neural/vascular pathophysiological mechanism has not yet been clearly documented, and it is now believed that some forms of NRA may be disorders of the non-adrenergic, non-cholinergic (NANC) nervous system.[10,22]

Innervation of the nasal cavity

The neural supply to the nasal mucosa consists primarily of autonomic fibers, including the sympathetic and parasympathetic systems, and NANC neurotransmission mediated by neuropeptides (Figure 1). The sympathetic and parasympathetic components of the autonomic nervous system contribute equally to the delicate homeostasis between vasoconstriction and vasodilation and nasal gland secretion. Imbalance among these components is likely to contribute to the glandular hypersecretion and increased nasal congestion observed in patients with NRA.[20]

Nasal sensory innervation comes from the ophthalmic and maxillary divisions of the trigeminal nerve and supplies the septum, lateral walls, the anterior nasal floor, and the inferior meatus. The parasympathetic fibers travel from their origin in the superior salivary nucleus of the midbrain to the geniculate ganglion, where they join the greater superficial petrosal nerve, which joins the deep petrosal nerve to form the vidian nerve. This nerve then passes to the sphenopalatine ganglion, where preganglionic parasympathetic fibers synapse and postganglionic fibers supply the nasal mucosa. The nasal glands receive direct parasympathetic nerve supply, and their electrical stimulation in animals induces glandular secretions that are blocked by atropine. Furthermore, stimulation of the human nasal mucosa with methacholine, a cholinomimetic drug, produces a marked increase in atropine production in nasal secretion. Stimulation of parasympathetic fibers also causes vasodilation.[20,22]

Sympathetic innervation originates as preganglionic fibers in the thoracolumbar region of the spinal cord, which pass through the vagosympathetic trunk and are relayed to the superior cervical ganglion. Postganglionic fibers also join the petrosal nerves to form the vidian nerve, which passes through the

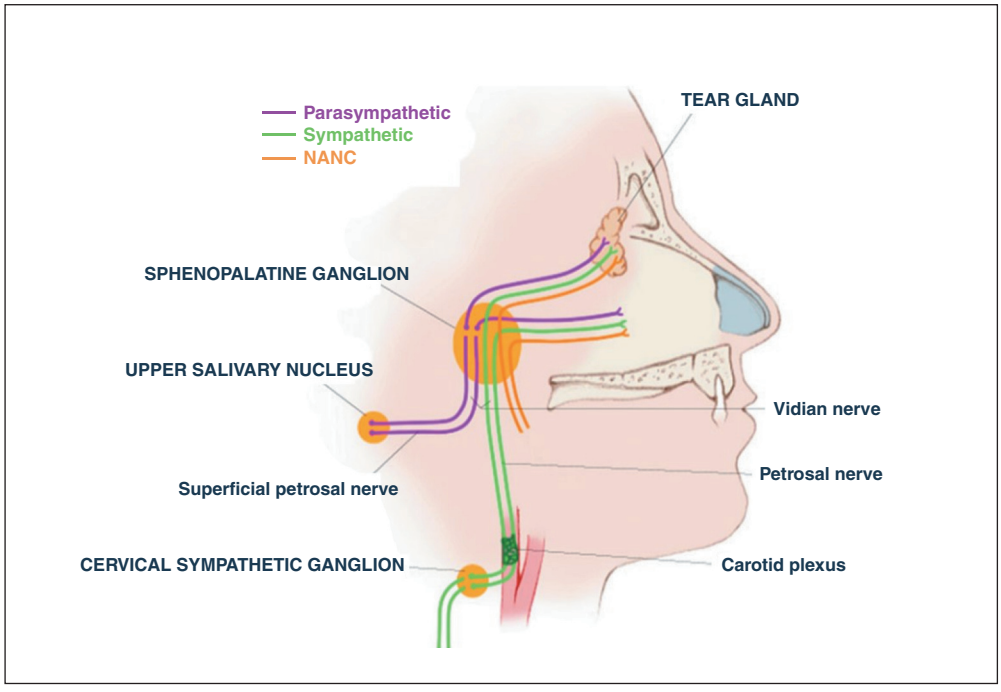

Figure 1
Sympathetic, parasympathetic and non-adrenergic non-cholinergic innervation of the nasal mucosa[22]
NANC = non-adrenergic, non-cholinergic.

sphenopalatine ganglion without synapses and is distributed in the nasal mucosa. Sympathetic fibers supply the nasal vasculature, but do not establish a direct relationship with the nasal glands; their exact role in secretion control is unclear. In animals, stimulation of these fibers causes vasoconstriction and decreases nasal airway resistance. Adrenergic agonists are also commonly used in humans, both topically and orally, to reduce nasal congestion.[20,22]

The presence of sympathetic and parasympathetic nerves and their transmitters in the nasal mucosa has been known for decades, but recent immunohistochemical studies have established the presence of additional neuropeptides. These neuropeptides are secreted by nociceptive unmyelinated C fibers (tachykinins, calcitonin gene-related peptide, neurokinin A, and gastrin-releasing peptide), parasympathetic nerve endings (vasoactive intestinal peptide [VIP] and histidine methionine peptide), and sympathetic nerve endings (neuropeptide Y). Substance P, a member of the tachykinin family, is frequently found as a cotransmitter with neurokinin A and calcitonin gene-related peptide, and high concentrations are present in blood vessels, glandular acini, and the nasal mucosal epithelium, where its receptors are located. High concentrations of calcitonin gene-related peptide receptors are found in small muscular arteries and arterioles of the nasal mucosa. The distribution of VIP fibers in human airways closely corresponds to that of cholinergic nerves. VIP is abundant in the human nasal mucosa, and its receptors are located in arterial vessels, submucosal glands, and epithelial cells, as is the case with substance P. In addition to identifying neuropeptides in the nasal mucosa, several studies have supported its potential contribution to nasal symptoms. VIP stimulates the secretion of serous cells, dilates nasal vessels, and can regulate mucociliary clearance in dogs. Nasal challenge with substance P induces few changes in normal individuals, but it causes a significant increase in vascular permeability, nasal airway resistance, and eosinophil and neutrophil chemotaxis in individuals with rhinitis.[10,20,22]

Nonspecific stimuli can cause the release of substance P, neurokinin A, VIP, and calcitonin gene-related peptide in the nasal mucosa, mainly through sensory C fibers, which are primarily activated by transient response potential (TRP) calcium ion channels, whose ligands are affected by temperature, mechanical or osmotic stimuli, and a wide variety of chemical irritants. For example, TRPV1, for which capsaicin has been shown to be a specific ligand, is activated by high temperatures. Acute exposure to capsaicin can activate TRPV1, whereas continued exposure to it can desensitize this receptor.[10] TRPA1 mediates the effects of noxious stimuli, such as low temperatures and environmental irritants. These channels have been increasingly recognized as an important mediator of nasal response to noxious chemical, mechanical, and osmotic stimuli.[20] These neuropeptides may also stimulate the release of histamine and other inflammatory mediators by local immune cells, resulting in additional IR symptoms, such as itching and sneezing.[22]

Mixed rhinitis

MR, characterized by the coexistence of AR and NAR, can occur in up to 85% of patients with AR and is more common than isolated types of the disease.[23] AR is triggered by exposure to aeroallergens, while NAR can be caused by factors such as weather changes and chemical irritants. MR presents with a combination of allergic and nonallergic symptoms, making its diagnosis and treatment challenging. Understanding the prevalence of MR and its associated factors in children and adolescents is essential for better treatment planning and improved quality of life.

Several studies have investigated the prevalence of MR in different populations, finding variable results. It is important to note that although this condition is relevant in all age groups, it is especially important to study its prevalence and impact on children and adolescents, since it can affect their development. Like all types of chronic rhinitis, MR can negatively affect school performance, sleep, and mental health in affected children and adolescents. Early identification of MR and adequate symptom control are essential to avoid short- and long-term complications. The presence of other respiratory disorders, such as asthma, has been associated with a higher risk of MR in children and adolescents.[24]

Another important aspect to consider is the influence of environment and lifestyle on MR. Factors such as exposure to environmental pollutants, passive smoking, inadequate diet and physical inactivity can contribute to the condition's development and worsening. Understanding these environmental determinants is crucial for effective prevention and treatment initiatives.

Triggering factors

In general, inadequate diet and physical inactivity can play an important role in the development and worsening of any chronic inflammatory disease. Excessive consumption of processed foods and foods rich in saturated fats, refined sugar, and additives, can lead to a chronic systemic inflammatory state, which can affect the upper airways and worsen rhinitis symptoms. Physical inactivity combined with an inadequate diet can lead to weight gain, overweight, and obesity. Excessive adiposity can also lead to changes in the immune system and chronic inflammation, which can exarcebate nasal symptoms.[25,26]

Conversely, diets rich in essential nutrients, such as vitamins, minerals, and antioxidants ensure proper immune function, reduce oxidative stress, and facilitate self-regulation of the inflammatory response.[26,27] Although a direct relationship between inadequate diet, physical inactivity, and rhinitis has not yet been established, a balanced nutrient-rich diet, and an active and healthy lifestyle can help reduce systemic inflammation, strengthen the immune system, and improve respiratory health, reducing rhinitis symptoms.[26]

Several agents and substances can act as direct irritants to the nasal mucosa, promoting local inflammation and worsening rhinitis symptoms. Goblet cells are a type of glandular cell in the nasal epithelium. They are responsible for the production and secretion of mucus, which helps moisten and protect the nasal passages. When the nasal mucosa is irritated, these cells can be stimulated to increase mucus production as part of the protective response, causing nasal congestion and rhinorrhea. The nasal epithelium is also lined with ciliated epithelial cells whose surface contains microscopic cilia. These cilia move in coordinated waves to help move mucus and foreign particles out of the nasal passages. In response to direct irritation of the nasal mucosa, the movement of cilia is increased in epithelial cells to remove irritants and protect the mucosa. However, this movement may decrease upon exposure to tobacco smoke. In both cases, harmony is lost and either the runny nose intensifies or allergens and other irritants can penetrate more easily.[28]

When a local inflammatory response occurs, several types of inflammatory cells are recruited to that area, including neutrophils, eosinophils, and mast cells. These cells release inflammatory mediators, such as histamine, leukotrienes, and cytokines, which act on vasodilation, increase vascular permeability, and activate other components of the immune system, amplifying inflammation.[28] Local chronic inflammatory response can also lead to remodeling of the nasal mucosa.[16]

Mold is a main trigger of rhinitis symptoms and can produce symptoms through allergic and non-allergic responses. Mold spores contain proteins that function as allergens. In sensitized individuals, specific IgEs on the surface of mast cells and basophils bind to these proteins, causing mast cell degranulation and histamine release, which determine the appearance of allergic nasal symptoms. In addition to allergic reactions, contact with mold spores can directly irritate the epithelial cells of the nasal mucosa, leading to local inflammation. Some types of fungi also release mycotoxins, which also cause direct toxic effects on epithelial cells. These response types and sensitization to mold spores can vary between individuals, and symptom severity may depend on factors such as the concentration of mold spores present in the environment and the duration of exposure.[28,29]

Weather changes, which can play a significant role in triggering nasal symptoms, involve variations in temperature, humidity, and air pollutant concentrations. High temperatures and humidity can trigger the direct release of inflammatory mediators by mast cells, such as histamine, causing local vasodilation, increased mucus production, and nasal congestion.[30,31] However, low humidity or exposure to air pollutants can affect the function of the epithelial cells lining the nasal mucosa. Exposure to pollutants can also result in the excessive migration and activation of inflammatory cells, such as eosinophils and type 2 T helper cells. Sensory receptors can also detect changes in temperature, humidity, and other environmental characteristics, influencing airflow regulation, mucus production control, and sneeze reflex response.[32] Some individuals may be more sensitive to certain weather factors than others. It is also important to consider the complex interplay between weather factors and other triggers, such as allergens and irritants.[28]

Many cleaning products contain irritating chemicals, such as bleach, ammonia, acids, and solvents, which act as direct irritants to the nasal mucosa. When these products are used, their volatile chemicals are released into the air and are inhaled, causing irritation and inflammation of the nasal epithelium.

Chronic exposure to these harsh chemicals can lead to chronic rhinitis.[28]

Active or passive exposure to tobacco smoke has detrimental effects on the nasal epithelium. Tobacco smoke contains many irritants and toxic substances, such as nicotine, tar, and carbon monoxide. When inhaled, these agents can directly irritate the nasal epithelium, affecting its integrity and function. As mentioned previously, exposure to tobacco smoke also causes reduced ciliary movement. This can result in less effective removal of mucus and harmful particles from the respiratory system, an increased risk of infection, and easier penetration of allergens and irritants, exacerbating nasal symptoms. Exposure to tobacco smoke can also stimulate increased mucus production. Smoking compromises nasal epithelial function and the overall health of the respiratory system, including the lungs.[28]

Diagnosis

Chronic rhinitis is a very common disease with increasing incidence, especially in Western countries, where the actual prevalence is estimated to be 10%-40% in the general population. Despite this epidemiological burden, the disease is usually considered mild and underestimated.[33] Despite the classic distinction between AR and NAR, thousands of patients meet the diagnostic criteria for AR but have symptoms triggered by primary irritants in addition to allergens, which suggests neural and vascular involvement. For these patients, a diagnosis of MR has been considered, which could apply to 30% to 50% of patients with chronic rhinitis.[24] In these cases, inflammation of the nasal mucosa is exacerbated by IgE-mediated response to allergens, in addition to the entire cascade of neural stimuli described above. Exposure to NAR triggers is difficult to control without depending heavily on the patient's attitude. It is also difficult to control exposure to inhalant allergens, such as dust mites and other aeroallergens. Therefore, controlling NAR symptoms becomes even more challenging. Understanding the cellular mechanisms involved in nasal reactions to irritants is essential for developing appropriate prevention and management strategies to minimize their negative impact on respiratory health.

In an attempt to identify patients with a high response to primary irritants, in 2012, Bernstein et al. developed the Irritant Index Questionnaire.[7] In a population of > 300 adults, the results of this instrument led to reclassifying 25% of those previously diagnosed with AR as having MR. Patients with MR had a higher frequency of symptoms, greater severity, and a higher occurrence of sinusitis and asthma than those who remained diagnosed with AR.[7]

Although the prevalence of NAR in children is unknown, it is estimated that the ratio of NAR to AR is at least 1:3.[34,35] It is known that some of these patients must represent the MR subgroup, but no study has evaluated pediatric populations regarding this diagnosis.[33]

In the Brazilian population, especially children and adolescents, no study has investigated the role of primary irritants as triggers of nasal symptoms. Chronic rhinitis, which is associated with more persistent symptoms, is an important cause of morbidity and affects several aspects of daily life in all age groups, including children and adolescents. An instrument measuring the magnitude of the action of primary irritants as triggers of nasal symptoms has proven effective for assessing chronic rhinitis in adults.[7] It is necessary to understand and quantify the role of primary irritants as a cause of nasal symptoms among children and adolescents.

Nasal irritant questionnaire to identify mixed rhinitis

Based on Bernstein et al.'s Irritant Index Questionnaire,[7,35] our group developed a questionnaire including all of the above mentioned irritants, in addition to several common to our population (makeup, hair dye, nail polish, artificial nail glue, deodorant, fabric softener, and e-cigarette smoke), totaling 27 items, including the following irritants: perfume, hair spray, cosmetics, bleach, washing powder, ammonia, disinfectant, solvent, paint, sawdust, gas stations, cold air, weather changes, cigarette smoke, mold or mildew, periods of severe air pollution, recently printed newspaper, kitchen odors, varnish, and household cleaning products, in addition to the list in parentheses above.[36]

In a pilot study, we asked 40 patients with AR whether they reported discomfort or not when exposed to these irritants. Items receiving < 20% affirmative responses were excluded. This resulted in our Nasal Irritant Questionnaire (Figure 2).[36] To better assess the role of these agents in the final questionnaire, it was decided to increase

NASAL IRRITANT QUESTIONNAIRE

Do you sneeze or have an itchy, runny, or stuffy nose when you come into contact with the following substances? Mark an "X" on the score you give for your symptoms:
0 is no symptoms at all and **10** is unbearable (the worst possible)

	0	1	2	3	4	5	6	7	8	9	10
1) Changes in the weather?	0	1	2	3	4	5	6	7	8	9	10
2) Wall paint or varnish?	0	1	2	3	4	5	6	7	8	9	10
3) Mold or damp indoor spaces?	0	1	2	3	4	5	6	7	8	9	10
4) Cigarette smoke?	0	1	2	3	4	5	6	7	8	9	10
5) E-cigarette or hookah (bong) smoke?	0	1	2	3	4	5	6	7	8	9	10
6) Sawdust?	0	1	2	3	4	5	6	7	8	9	10
7) Severe air pollution (fire, smoke)?	0	1	2	3	4	5	6	7	8	9	10
8) Cold air, cold wind, or air conditioning?	0	1	2	3	4	5	6	7	8	9	10
9) Perfumes?	0	1	2	3	4	5	6	7	8	9	10
10) Paint thinners or acetone?	0	1	2	3	4	5	6	7	8	9	10
11) Bleach or chlorine?	0	1	2	3	4	5	6	7	8	9	10
12) Cleaning products (air fresheners, floor wax)?	0	1	2	3	4	5	6	7	8	9	10
13) Disinfectants?	0	1	2	3	4	5	6	7	8	9	10
14) Ammonia (including hair bleach and dye)?	0	1	2	3	4	5	6	7	8	9	10
15) Cosmetics (lotions) or makeup?	0	1	2	3	4	5	6	7	8	9	10
16) Fabric softener?	0	1	2	3	4	5	6	7	8	9	10
17) Washing powder?	0	1	2	3	4	5	6	7	8	9	10
18) Deodorants?	0	1	2	3	4	5	6	7	8	9	10

Eight or more questions with scores ≥ 5 = **HIGH RESPONSE TO NASAL IRRITANTS**
Fewer than 8 questions with scores ≥ 5 = **LOW RESPONSE TO NASAL IRRITANTS**

Figure 2
Nasal Irritant Questionnaire[36]

the granularity of the responses, changing the options to a numerical scale from 0 to 10, with 10 corresponding to the worst possible reaction. Using the same evaluation criteria as for visual analogue scales, scores ≥ 5 for each question were considered significant. For patients with a high response to irritants (≥ 8 items that scored ≥ 5), an MR diagnosis was considered.[36]

References

1. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol. 2001;108:S147-334.
2. Roberts G, Xatzipsalti M, Borrego LM, Custovic A, Halken S, Hellings PW, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. Allergy. 2013;68:1102-16.
3. Bachert C. Persistent rhinitis – allergic or nonallergic? Allergy. 2004;59(Suppl 76):11-5.
4. Tran NP, Vickery J, Blaiss MS. Management of Rhinitis: Allergic and Non-Allergic. Allergy Asthma Immunol Res. 2011;3:148.
5. Solé D, Rosário Filho NA, Sarinho ES, Camelo-Nunes IC, Barreto BAP, Medeiros ML, et al. Prevalence of asthma and allergic diseases in adolescents: nine-year follow-up study (2003-2012). J Pediatr (Rio J). 2015;91:30-5.
6. Urrutia-Pereira M, Mocelin LP, Ellwood P, Garcia-Marcos L, Simon L, Rinelli P, et al. Prevalence of rhinitis and associated factors in adolescents and adults: a Global Asthma Network study. Rev Paul Pediatr. 2023;41:e2021400.
7. Bernstein JA, Levin LS, Al-Shuik E, Martin VT. Clinical characteristics of chronic rhinitis patients with high vs low irritant trigger burdens. Ann Allergy Asthma Immunol. 2012;109:173-8.
8. Loekmanwidjaja J, Carneiro ACF, Nishinaka MLT, Munhoes DA, Benezoli G, Wandalsen GF, et al. Sleep disorders in children with moderate to severe persistent allergic rhinitis. Braz J Otorhinolaryngol. 2018;84:178-84.
9. Norhafizah S, Salina H, Goh BS. Prevalence of allergic rhinitis in children with otitis media with effusion. Eur Ann Allergy Clin Immunol. 2020;52:121-30.
10. Papadopoulos NG, Guibas GV. Rhinitis Subtypes, Endotypes, and Definitions. Immunol Allergy Clin North Am. 2016;36:215-33.
11. Solé D, Kuschnir FC, Pastorino AC, Constantino CF, Galvão C, Chong e Silva DC, et al. V Consenso Brasileiro sobre Rinites 2024. Braz J Otorhinol. 2024 in press.
12. Kondrich J, Rosenthal M. Influenza in children. Curr Opin Pediatr. 2017;29:297-302.
13. DeGeorge KC, Ring DJ, Dalrymple SN. Treatment of the Common Cold. Am Fam Physician. 2019;100:281-9.
14. De Sutter AI, Eriksson L, van Driel ML. Oral antihistamine-decongestant-analgesic combinations for the common cold. Cochrane Database Syst Rev. 2022;1:CD004976.
15. King D, Mitchell B, Williams CP, Spurling GKP. Saline nasal irrigation for acute upper respiratory tract infections. Cochrane Database Syst Ver. 2015:CD006821.
16. Anselmo-Lima WT, Tamashiro E, Romano FR, Miyake MM, Roithmann R, Kosugi EM, et al. Guideline for the use of immunobiologicals in chronic rhinosinusitis with nasal polyps (CRSwNP) in Brazil. Braz J Otorhinolaryngol. 2022;88:471-80.
17. Ramadan HH, Chaiban R, Makary C. Pediatric Rhinosinusitis. Pediatr Clin North Am. 2022;69:275-86.
18. Piltcher OB, Kosugi EM, Sakano E, Mion O, Testa JRG, Romano FR, et al. How to avoid the inappropriate use of antibiotics in upper respiratory tract infections? A position statement from an expert panel. Braz J Otorhinolaryngol. 2018;84:265-79.
19. Sociedade Brasileira de Pediatria. Departamentos Científicos de Imunizações, Infectologia, Alergia, Otorrinolaringologia e Pneumologia. Atualização no tratamento e prevenção da infecção pelo vírus Influenza – 2020 [Internet]. Available from: https://www.sbp.com.br/fileadmin/user_upload/22445f-Diretriz-_Atualiz_Trat_e_Prev_Infecc_Virus_Influenza_2020.pdf Accessed on May 2024.
20. Baroody FM. Nonallergic Rhinitis: Mechanism of Action. Immunol Allergy Clin North Am. 2016;36:279-87.
21. Segboer CL, Fokkens WJ, Terreehorst I, van Drunen CM. Endotyping of non-allergic, allergic and mixed rhinitis patients using a broad panel of biomarkers in nasal secretions. PLoS One. 2018;13:e0200366.
22. Van Gerven L, Boeckxstaens G, Hellings P. Up-date on neuro-immune mechanisms involved in allergic and non-allergic rhinitis. Rhinology. 2012;50:227-35.
23. Settipane RA, Kaliner MA. Chapter 14: Nonallergic rhinitis. Am J Rhinol Allergy. 2013; 27(Suppl 1):S48-51.
24. Greiwe JC, Bernstein JA. Allergic and Mixed Rhinitis: Diagnosis and Natural Evolution. J Clin Med. 2019;8:2019.
25. Tajima H, Pawankar R. Obesity and adiposity indicators in asthma and allergic rhinitis in children. Curr Opin Allergy Clin Immunol. 2019;19:7-11.
26. Toennesen LL, Meteran H, Hostrup M, Wium Geiker NR, Jensen CB, Porsbjerg C, et al. Effects of Exercise and Diet in Nonobese Asthma Patients-A Randomized Controlled Trial. J Allergy Clin Immunol Pract. 2018;6:803-11.
27. Christ A, Lauterbach M, Latz E. Western Diet and the Immune System: An Inflammatory Connection. Immunity. 2019;51:794-811.
28. Zhang R, Zhang L, Li P, Pang K, Liu H, Tian L. Epithelial Barrier in the Nasal Mucosa, Related Risk Factors and Diseases. Int Arch Allergy Immunol. 2023;184:481-501.
29. Holme JA, Øya E, Afanou AKJ, Øvrevik J, Eduard W. Characterization and pro-inflammatory potential of indoor mold particles. Indoor Air. 2020;30:662-81.
30. Tzivian L. Outdoor Air Pollution and Asthma in Children. J Asthma. 2011;48:470-81.
31. Braat JPM, Mulder PG, Duivenvoorden HJ, Van Wijk GR, Rijntjes E, Fokkens WJ. Pollutional and meteorological factors are closely related to complaints of non-allergic, non-infectious perennial rhinitis patients: a time series model. Clin Exp Allergy. 2002;32:690-7.
32. Reddy KRBK, Gupta N, Bhattacharya BG, Deka NM, Chandane P, Kapoor R, et al. Impact of Air Pollution on Allergic Rhinitis and Asthma: Consensus Statement by Indian Academy of Pediatrics. Indian Pediatr. 2021;58:765-70.
33. Poddighe D, Gelardi M, Licari A, Del Giudice MM, Marseglia GL. Non-allergic rhinitis in children: Epidemiological aspects, pathological features, diagnostic methodology and clinical management. World J Methodol. 2016;6:200-13.
34. Chiang WC, Chen YM, Tan HKK, Balakrishnan A, Liew WK, Lim HH, et al. Allergic rhinitis and non-allergic rhinitis in children in the tropics: prevalence and risk associations. Pediatr Pulmonol. 2012;47:1026-33.

35. Topal E, Bakirtas A, Yılmaz O, Karagöl IHE, Arslan U, Arga M, et al. Predictive factors to differentiate between allergic and nonallergic rhinitis in children. Int Forum Allergy Rhinol. 2014;4:447-52.

36. Manhães IB. Prevalência de rinite mista em crianças e adolescentes acompanhados em um serviço de referência [dissertation]. São Paulo: Universidade Federal de São Paulo, Escola Paulista de Medicina, Programa de Pós-graduação em Pediatria e Ciências Aplicadas à Pediatria; 2023.

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