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A COMPREHENSIVE REVIEW ON NON-ALLERGIC RHINITIS (NAR): NARES, NARMA, NARNE, AND NARESMA.

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Short Running Title: ***Current review on cellular NAR.***

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Abstract

Objective: the aim of our paper is to review the up-to-date data on Non-Allergic Rhinitis (NAR), as NAR is becoming an emerging sanitary and economic problem, because of their impact on Quality of Life and patients' productivity.
Data Sources: Web of Science, PubMed and Scopus databases were consulted using a search strategy for "non-allergic rhinitis *or* NAR *or* NARMA *or* NARES *or* NARNE *or* NARESMA".
Review Method: We included all studies irrespectively from their study design (prospective or retrospective), due to the scarcity of data on the subject. Epidemiological, etiopathological and clinical features for each cellular NAR (NARES, NARNE, NARESMA, NARMA) were reviewed and reported.
Results: Thanks to nasal cytology, each NAR is becoming more detailed and more known if compared to the papers of the early '80s, even though there is still a lack of uniformity in their recognition.
Conclusions: NAR is an emerging and challenging medical problem, in which a correct recognition, therapy and follow-ups are fundamental for the so-called "precision medicine".

Introduction

For many years, we have been improperly labeling many forms of rhinitis as aspecific, idiopathic or cryptogenic; medical terms used when the pathology of a disease cannot be framed at the etiopathogenetic

level. In rhinology, much has changed in the last 20 years, largely driven by the introduction of numerous diagnostic tests, such as fiber optic endoscopy, rhinomanometry, olfactometry, and nasal cytology.

In vasomotor rhinitis, especially for non-IgE mediated rhinitis, cytological diagnostics has become key. Based on the cell types present on the nasal mucosa, many of these aspecific forms have acquired a nosological dignity.

Therefore, based on the cytological pattern, it is possible to diagnose eosinophilic rhinitis (nonallergic rhinitis with eosinophils - NARES), neutrophils (NARNE), mast cells (NARMA), and eosinophil-mast cell forms (NARESMA) as reported in the ARIA classification.

Among all cases of rhinitis, these forms have an incidence of 13%, and the diagnosis of these forms is important for prognostic and therapeutic purposes. Recent studies have shown that such nosological entities require different therapeutic approaches and close follow-up. If not properly treated, such cases can progress to more severe forms (e.g., chronic rhinosinusitis with and without nasal polyposis, and rhino-bronchial syndrome). Here we take stock of these nosological entities, which have been largely ignored for too long, and highlight their diagnostic features now available.

We therefore performed a systematic review of the NAR, using medical terms such as "*non-allergic rhinitis or NAR or NARMA or NARES or NARNE or NARESMA"* in the most used medical databases (Web of Science, PubMed and Scopus). We included all studies irrespectively from their study design (prospective or retrospective), due to the scarcity of data on the subject. Epidemiological, etiopathological and clinical features for each cellular NAR (NARES, NARNE, NARESMA, NARMA) were reviewed and reported.

NARES

NARES (*nonallergic rhinitis with eosinophilia syndrome*) is the best-known form of NAR. NARES was first described by Jacobs et al. in 1981 (1) and is described as a clinical condition characterized by a non-atopic patient (by allergen skin testing), with perennial sneezing attacks, profuse watery rhinorrhea, nasal pruritis and nasal obstruction, with diffuse eosinophilic infiltration in nasal cytology.

NARES represents 13–33% of all NAR (2,3), affecting more than 20 million U.S. Americans (4). NARES is a disturbing disease that typically affects women (58–71% of cases) (3, 5), with a classical onset in adulthood; however, considering that NARES is frequently misdiagnosed or underdiagnosed, it is possible that it is as frequent in children as it is in adults, but exact data in the pediatric population remains scarce and limited to single experiences (6).

From a clinical point-of-view, NARES patients have a typical profile: together with the aforementioned nasal symptoms, of which sneezing if the most representative, these patients also often have nasal hyper-reactivity to external triggers, such as air conditioning, active/passive cigarette smoke, detergents, solvents, and (characteristically) during nasal fibroscopy (7). The symptoms of NARES patients tend to be intense, and typically more severe than in patients with allergic rhinitis (AR), and anosmia is more common in NARES patients than in than those with other types of rhinitis. All NAR symptoms tend to worsen in case of exposure to chlorinated water (e.g., swimming pools), and this is especially true for NARES patients (8). Suspicion of NARES can also be raised by family history, where NARES patients show a high prevalence of asthma, nasal polyposis, and sensitivity to acetylsalicylic acid (ASA) (9).

From a clinical point-of-view, NARES is an isolated disorder, but its prompt recognition is essential to avoid its progression towards chronic rhinosinusitis with nasal polyposis (CRSwNP) (10).

Sometimes, NARES can be associated with asthma and ASA-intolerance and, considering that NARES patients can develop CRSwNP during their lifetime, NARES can potentially be considered an early form of Samter's triad. More rarely, NARES can be associated with blood hypereosinophilia (≈900 per mm^3), which together can be defined as the so-called BENARS (Blood Eosinophilia Non-Allergic Rhinitis Syndrome) (2). In these patients, marked blood eosinophilia is associated with nasal eosinophilia and negativity of allergic tests; the frequent progression to CRSwNP is also a characteristic of these patients (10). It is important to remember that NARES can progress into NARESMA, which is a more difficult-to-treat NAR (11).

From a cytological point-of-view, even though NARES is one of the most known NAR, there is no consensus regarding the exact cut-off that should be to define significant eosinophilia in nasal smears to diagnose NARES: according to various authors, this can be 50–70. Even the recent Position Paper on Non-Allergic Rhinitis published by the European Academy of Allergology and Clinical Immunology (15) does not clarify how to diagnose NARES, in which nasal cytology is identified as a 'not recommended' procedure.

Non-Allergic Rhinitis with Neutrophils (NARNE)

Non-allergic rhinitis with neutrophils (NARNE) is a chronic type of rhinitis characterized by an elevated number of neutrophils in the nasal smear (> 30%), without evidence of infection, bacteria or spores.

From a cellular point-of-view, the neutrophil is a type of granulocyte, with a diameter of 12–14 μm and a multi-lobulated nucleus. Neutrophils are phagocytes that are capable of ingesting microorganisms or atmospheric particles attracted by toxic substances or irritancy. The neutrophils migrate toward sites of infection or inflammation, where they release chemical mediators (e.g., neutrophil elastase) that result in the formation of free radicals, subsequent distress of nasal mucosa, and the onset of vasomotor symptoms.

DAMP (damage-associated molecular pattern) are molecules released by stressed cells undergoing necrosis that act as endogenous danger signals to exacerbate the inflammatory response. Neutrophils have a receptor for DAMP, and they are attracted to the site of damage (16). These cells have a short half-life, so it is requested repeated stimulations to find them in the site of recall (17).

NARNE is a non-infectious NAR, most frequently found in patients with professional exposure to irritants (solvents, chemicals), in chronic smokers, and people living in industrialized centers. Gastroesophageal reflux (GERD) has been hypothesized as a possible cause of NARNE because it is a chemical-physical attack on the mucosa (18,19).

Several studies have addressed the relationship between chronic rhinosinusitis and GERD in children and adults, with contradictory results. In the Montreal Definition and Classification of GERD, drawn up in 2006 by a Global Consensus Group (20), GERD was subdivided into esophageal syndromes and extra-esophageal syndromes. Nasal diseases, such as sinusitis, an extra-esophageal syndrome, are proposed associations. However, no high-quality randomized controlled trials have addressed this. Only a few studies have applied the pH-impedance test, the diagnostic gold standard for GERD, and none have used nasal cytology to confirm nasal irritation due to GERD (21, 22). Therefore, we performed a small study on a cohort of patients with NARNE in which we specifically tested for GERD. By pH-impedance test, we studied patients with NARNE and matched them with a control group composed of patients with other ENT symptoms and NAR (NARMA; NARES; NARESMA), who underwent the same diagnostic examination. The results of our study are preliminary but show that NARNE is significantly associated with

GERD. The symptom most related to GERD was nasal obstruction and retronasal mucus, which is in line with the findings of a recent publication that proves that laryngopharyngeal reflux has a negative effect on nasal resistance and nasal congestion (23).

In conclusion, for the diagnosis of NARNE, is essential to have a detailed anamnesis, focusing on cigarette smoke exposure, occupational exposition to an irritant, severe chronic rhinosinusitis, and GERD as possible causes. Therefore, the first therapeutic suggestion is to remove the cause, when possible, and advising the use of protection in the workplace.

Non Allergic Rhinitis with mastcells (NARMA)

In the context of NAR, defined as different and multiple nasal disorders, where an allergic base cannot be found, there is a kind of NAR characterized by the presence of nasal mast cells, that is therefore called NARMA (non-allergic rhinitis with mast cells).

Multiple forms of mastocytosis have been described. Systemic mastocytosis (SM) is a clonal proliferative disorder that causes a pathological accumulation of mast cells in various tissues, such as the skin, bone marrow, and internal organs (liver, spleen, gastrointestinal tract, and lymph nodes). Cases beginning during adulthood tend to be chronic and involve the bone marrow in addition to the skin, whereas, during childhood, the condition is often marked by skin manifestations with no internal organ involvement and can often resolve during puberty.

Many studies have shown that up to 50% of rhinitis symptoms in SM patients are non-allergic and it has been assumed that these nasal complaints in SM patients are due an increased nasal mast cell burden. Nevertheless, to date, there are no data supporting this hypothesis.

Dolner et al. (24) found that the presence of allergy-suggesting nasal complaints in non-allergic SM patients is correlated with an objective measure of nasal mast cell (MC) burden. These authors also found that non-allergic persistent nasal complaints in SM were significantly correlated with elevated nasal tryptase level, as a measure of local MC burden. Elevated nasal tryptase correlated with persistent rhinorrhea, sneezing, and itching as predominant symptoms, which seem to characterize non-allergic mastocytosis-associated rhinitis (NARMA) in SM.

The role of mast cells represent a relevant source for mediator release, mainly histamine and leukotrienes, prostaglandin D2, heparin, chemokines, cytokines, and, together with other cellular mediators, these result in symptomatic episodes, which cause vasodilatation, increased vessel permeability, and stimulation of nerves causing the appearance of symptoms.

Gelardi et al. have demonstrated that both the presence of mast cells and eosinophils are crucial in determining the severity of nasal symptoms and isolated a new nosological type of rhinitis (NARESMA) (25).

The tryptase levels are elevated in both allergic and non-allergic forms. In these patients, the most predominant symptoms are rhinorrhea, sneezing, and itching. All three symptoms were strongly correlated with the nasal tryptase level but not to the level of serum tryptase (26).

Le (26) demonstrated an increase of neuropeptide receptor in nerve fibers containing receptors for mast cells on the nasal mucosa of a patient with perennial allergic rhinitis. These results suggest that targeting or controlling airway sensory nerve function as a modulator of mast cells might prevent allergic airway inflammation.

Mastocytosis can be classified to a specific type depending on the patient's symptoms and overall presentation. According to Gulen (27), mastocytosis can be subdivided into various forms: cutaneous mastocytosis, indolent systemic mastocytosis, systemic mastocytosis with clonal hematologic non-mast cell lineage disease, systemic smoldering mastocytosis, aggressive

systemic mastocytosis, mast cell leukemia, and mast cell sarcoma.

In almost all adult-onset mastocytosis and approximately 80% of children in skin lesions, genetic mutation resulting in the over-activation of the receptor for mast cell growth factor (KIT) has been identified in abnormal mast cells. The most common c-kit mutation in mastocytosis is *D816V*, which is believed to cause the abnormal proliferation and accumulation of mast cells in tissues.

The release of mediators produced by mast cells results in symptomatic episodes. Histamine is a natural chemical released during an allergic event that causes itching, wheezing, dilation of blood vessels, and hypersecretion of stomach acid.

Mastocytosis affects males and females in equal numbers and can begin during childhood or adulthood. Childhood-onset mastocytosis is most common and presents within the first 2 years of life. The symptoms of other disorders can be similar to those of mastocytosis, including inflammatory bowel disease (IBD) irritable bowel syndrome (IBS), and myeloproliferative diseases.

IBD is associated with an abnormal immune response to the natural bacteria in the gastrointestinal tract. IBD patients might experience weight loss, abdominal cramping and pain, nausea and vomiting, fatigue, and irregular bowel movements.

IBS is a gastrointestinal disorder associated with abdominal discomfort, altered bowel patterns, and, in some cases, inflammation of the gastrointestinal tract. Patients with IBS might experience heartburn, abdominal pain, as well as the presence of constipation or diarrhea.

Malabsorption is inclusive of any condition associated with abnormalities occurring during digestion and absorption of food nutrients. Myeloproliferative diseases are a group of disorders associated with the proliferation of one or more distinct cell lines. Patients can experience fatigue, weight loss, abdominal discomfort, easy bruising or bleeding, infections, as well as other symptoms.

Urticaria is a condition of the skin associated with red, elevated patches of the skin that can be itchy and irritating to touch and more commonly referred to as hives. Urticaria is often an isolated event not associated with other systemic symptoms or findings. Endocrine tumors such as carcinoid, pheochromocytoma, and medullary thyroid cancer can cause flushing. These patients have symptoms of mast cell activation, including recurrent anaphylaxis. In patients with idiopathic mast cell activation syndrome, there are episodic symptoms of systemic mast cell activation associated with elevated mast cell mediators, such as tryptase and urinary histamine or prostaglandin metabolites, which respond favorably to treatment with mast cell mediator blocking drugs and have no diagnostic findings of cutaneous or systemic mastocytosis. Other disorders with similar symptoms, such as allergic diseases, should be ruled out before this diagnosis is considered.

In these types of mastocytosis, a correlation with nasal discomfort is not found. In some scientific studies, the levels of nasal tryptase have been measured by Immuno-CAP Tryptase and correlated with symptomatology. The results were that the symptom seems to correlate with the levels of tryptase but that it is independent of nasal localization of mast cells. Furthermore, it was possible to analyze the likelihood that patients with NARMA presented at nasal cytological subsequently develop nasal polyposis, as well as their rate of recurrence. This correlation was lower than in patients with NARES.

Even today, NARMA remains a form of non-allergic rhinitis that is not well-known, and although nasal cytology can provide an accurate diagnosis, the pathogenesis, systemic form correlations, and possible district and systemic complications remain unclear.

NARESMA

NARESMA is a fourth type of NAR (non-allergic rhinitis) that is characterized by

infiltration of eosinophils and mast cells (25).

NARESMA arises from disequilibrium among neuropeptide innervation and neuroendocrine cells, a typical alteration of allergic rhinitis and chronic hypertrophic rhinitis (28). Indeed, making a proteomic analysis of human nasal mucosa, it is possible to identify the disequilibrium among some proteins related to human immune and inflammation response (e.g., ALDH, GSTA2, GSTP1, PRDX5, SERPINB4, and PLUNK) (29).

ALDH is an enzyme that has protective effects on cells during environmental stress. ALDH has an important role in the protective action, in response to external and internal stressors. New studies have detected a direct relationship between eosinophil presence and downregulation of ALDH. This feature might result in the decreased ability of mucosa cells to react to environmental stress (29).

GSTA2 and GSTP1, which play important roles in protecting cells from cytotoxic reactive oxygen species (30), as well as PRDX5, an antioxidant enzyme (31), are downregulated. Thus, it could be assumed the cell ability to counteract stressor action (29). Conversely, SERPINB4 is highly expressed in NARESMA. This protein belongs to the serine proteinase inhibitor family. Overexpression of SERPINB4 could suggest the onset of a pathological process of the respiratory epithelium of the high and lower airways (29).

PLUNC is a protein specifically expressed in the upper airways and mucosa cells in these patients (29) been suggested to be involved in inflammatory responses to irritants and can play a role in innate immune responses. We show that this protein is expressed at a relatively low level in NARESMA. These distinct features could indicate a role for PLUNC in the pathogenesis of nonallergic rhinitis, nasopharyngeal regions. PLUNC has suggesting a decreased immune response to stressors and consequent increase of the inflammatory response of nasal.

In nasal cytology, NARESMA shows eosinophils and mast cells with a relevant degranulation (Fig. 1) (29). Patients with NARESMA are affected by both nasal and nonnasal symptoms. NARESMA patients are more affected by dry nose, nasal obstruction, snoring, nocturnal awakening, and sore throat, than other NAR patients. Moreover, among NAR cases, the NARESMA patients have the worst quality of life, as well as most severe sleep and social problems (25). Nasal polyposis, non-allergic asthma, aspirin intolerance, and rhinosinusitis are more frequent in NARESMA (11), and, in children, NARESMA is associated with a high risk of developing a chronic otitis media with effusion (32). It is interesting to note that some authors have shown an association between allergic and nonallergic rhinitis and skin sensitization to metals (chromium, cobalt, and nickel). In NAR, this skin sensitization is greater in nonallergic rhinitis with eosinophils and mast cells (NARESMA) than in other NARs (33).

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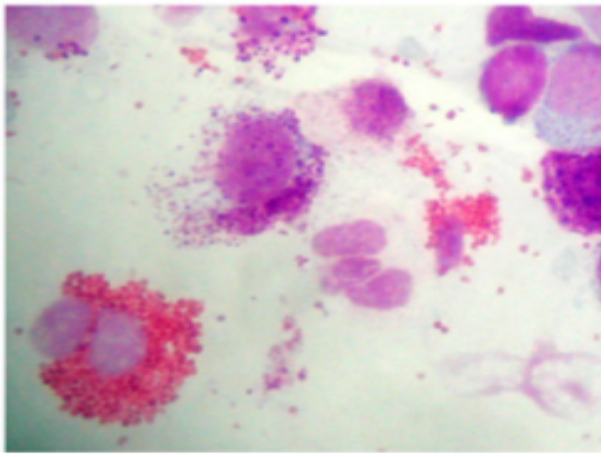

Figure 1. NARESMA: features of nasal cytology. It is possible to identify eosinophils and mast cells with degranulation in Figure 1.

Table 2. Examples of differential diagnoses at NC (Adapted from MELTZER 1988)

Disease	Eosinophils	Mast-cells	Neutrophils	Bacteria	Fungal spores
Healthy	0	0	0–1+	0	0
Allergic rhinitis	2 + /4+	2 + /4+	2 + /4+	0	0
NARES	2 + /4+	0	Variable	0	0
NARESMA	2 + /4+	2 + /4+	Variable	0	0
NARNE	0	0	3 + /4+	0	0
Common cold	0	0	1 + /4+	0	0
Bacterial	0–1+	0	3 + /4+	3 + /4+	0
Fungal	0	0	Variable	0	2 + /4+
Atrophic	0	0	Variable	0	0