ORIGINAL ORTILCE

When sneezing indicates the cell type

Matteo Gelardi[1], Nicola Quaranta[1] and Giovanni Passalacqua[2]

Background: **Nasal hyperactivity is the symptomatic expression of vasomotor rhinitis. This study describes a typical nasal reaction, represented by a "volley of sneezes" found in some patients during nasal endoscopy, and to assess the possible correlation between hyperactivity and a particular clinical and cytological condition.**

Methods: **We studied 671 rhinological subjects, 344 male, mean age 35.7 ± 13.76 standard deviation (SD) years. All were submitted to medical histories and clinical and instrumental investigations (skin prick test, nasal endoscopy, and nasal cytology). While performing endoscopy, particular attention was paid to the possible signs of nasal hyperactivity, in particular "volley of sneezes" both during and immediately after the diagnostic procedure.**

Results: **Out of 671 endoscopies performed, 130 (17.1%) patients presented signs of hyperactivity during and/or immediately after nasal endoscopy. The ratio of positive vasomotor reaction was 10.6% in the nasal polyposis (NP) group, 19% in the allergic rhinitis (AR) group, 70.6% ($p < 0.01$) in nonallergic rhinitis with mast cells (NARMA), 76% ($p < 0.01$) in nonallergic rhinitis with eosinophils and mast cells (NARESMA), and 83% ($p < 0.01$) in nonallergic rhinitis with eosinophils (NARES). In the AR subjects hyperreactivity was more frequent during the pollen season, compared to the period of absence of pollen (87.5% vs 12%).**

Conclusion: **The onset of hyperactivity (sneezing) can be considered an important "sign" in nasal symptomatology, whose sensitivity and specificity for nonallergic "cellular" rhinitis are 79% and 93%, respectively.** © 2012 ARS-AAOA, LLC.

Key Words:
vasomotor rhinitis; nasal cytology; hypereactivity; eosinophils; NARES; NARESMA; nasal endoscopy

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Nasal hyperreactivity is the symptomatic expression of the capacity of nasal mucosa to respond to specific (allergenic) or nonspecific stimuli (temperature, humidity, or odors).[1] The mechanisms underlying this hyperreactivity are well known in the case of allergic rhinitis (immunoglobulin E [IgE]-mediated reaction), and less in the case of nonspecific stimuli. Understanding the pathophysiology and, consequently, the possible therapeutic interventions still ranks high in the interest of ear, nose, and throat (ENT) research.[2–4] Symptoms of nasal hyperreactivity are represented by nasal obstruction, itching, rhinorrhea, and sneezing, sometimes associated with watery eyes, cough, headache, fatigue, malaise, and low quality-of-life.[5,6] From a cytologic point of view, the condition is associated with an increase of some cellular elements (neutrophils, eosinophils, mast cells, lymphocytes, or plasma cells) and their mediators (eosinophil cationic protein [ECP], major basic protein [MBP], histamine, tryptase). This is well-defined in IgE-mediated conditions such as allergic rhinitis (AR). Otherwise, the mechanisms linking cellularity and clinical expression are less known in nonallergic "cellular" vasomotor rhinitis, such as nonallergic rhinitis with neutrophils (NARNE), nonallergic rhinitis with eosinophils (NARES), nonallergic rhinitis with mast cells (NARMA), or nonallergic rhinitis with eosinophils and mast cells (NARESMA).[7–11]

According to our clinical observation, this study describes a particular nasal hyperreactivity, represented by a "volley of sneezes," specifically observed during nasal endoscopy, and its possible correlation with the involved cells. The main aim was to determine whether nasal reactivity can be considered an important sign in the diagnosis of rhinological diseases.

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Patients and methods

Patients

Consecutive outpatients, referred to the Rhinology ENT Clinic of the University of Bari between March 2011 and June 2012 for nasal diseases, were studied. After a careful medical history was taken, subjects underwent allergy testing (skin prick test), fiber-optic endoscopy, and nasal cytology. Particular attention was paid to the occurrence of a "volley of sneezes," during the endoscopic examination of the nasal cavity, both during and immediately after endoscopy.

Fifty subjects, with evidence of rhino/nasal diseases, were also studied as a control group.

Nasal endoscopy was carried out by means of a flexible device (Vision Science ENT 2000; diameter 3.4 mm) to detect the presence of changes in nasal anatomical structures (septal cartilage, turbinates, nasal secretions, polyps, etc.). None of the patients received local anesthesia or nasal decongestion. All subjects who presented signs of vasomotor reaction (volleys of sneezes) during and/or immediately after endoscopy were recorded on the medical chart. All nasal endoscopy procedures were carried out by the same operator, and with the same technique.

Skin-prick test

Allergic sensitization was assessed by the presence of skin-prick test positivity to the most common aeroallergens. Skin-prick tests were carried out and read in accordance to the European Academy of Allergy and Clinical Immunology. Results were considered positive when the wheal diameter was equal or greater than 3 mm.[12] The panel of allergens used included: house dust mite (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grass mix, *Compositae* mix, *Parietaria judaica*, birch, hazel tree, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix. The concentration of allergen extracts was 100 index of reactivity (IR)/mL (Stallergenes, Milan, Italy). Individuals with uncertain skin tests were further investigated by a CAP-RAST assay (Phadia, Uppsala, Sweden).

Nasal cytology

Nasal cytology was performed by anterior rhinoscopy, using a nasal speculum and good lighting. Scrapings of the nasal mucosa were collected from the middle portion of the inferior turbinate, using a Rhino-Probe®.[13] Samples were placed on a glass slide, fixed by air drying, and then stained by the May-Grunwald Giemsa (MGG) method (Carlo Erba®, Milan, Italy). MGG staining is the most widely used method in diagnostic nasal cytology, because all of the cellular components of the nasal mucosa, from inflammatory cells (neutrophils, eosinophils, mast cells, and lymphocytes) to bacteria, spores, fungal hyphae, and mucous secretions are easily stained. The slide was observed under a Nikon E600 light microscope (Nikon, Canada) equipped with a digital camera (Nikon Coolpix 3:34) for the acquisition of microscopic images.

For the rhinocytogram analysis, 50 microscopic fields were read at a magnification of ×1000 to assess the presence of normal and abnormal cellular elements, along with any microscopic features (spots, special inclusions, etc.) important for the diagnosis. Cell counts, bacterial analysis, and fungal analysis were carried out by a semiquantitative grading, as proposed by Meltzer and Jalowayski.[14] In particular, bacteria and fungal spore assessment was determined as follows:

Grade 0 (not visible);
Grade 1 + (occasional groups);
Grade 2 + (moderate number);
Grade 3 + (easily visible);
Grade 4 + (many of which cover the entire field of view).

Patients with nasal disorders were subdivided on the basis of the skin-prick test and of nasal cytology, into subjects with AR or nonallergic rhinitis. Cellular forms were further subdivided based on their cytotype: NARNE (neutrophils >50% with absent spores and bacteria); NARES (eosinophils >20%); NARMA (mast cells >10%); and NARESMA (eosinophils >20% and mast cells >10%);

Statistical analysis

Absolute and relative frequencies of diseases in the sample were taken into consideration. The association between pathology and sneezing was evaluated with a chi-square test. The sensitivity and specificity of sneezing as a test for nasal diseases (NARES, NARMA, and NARESMA) were calculated. The relationship between eosinophils and mast cells with the "volleys of sneezing" was evaluated using a logistic regression model.

Results

Patients and diagnoses

We studied 671 outpatients, 344 male, 327 female, mean age 35.7 ± 13.76 years. Out of 671 subjects 47 (7%) showed no signs of nasal diseases, 32 (4.8%) had rhinosinusitis, 205 (30,6%) septal deviation, 142 (21.2%) AR (positive result with at least 1 extract of the panel tested), 69 (10.3%) NARES, 17 (2.5%) NARMA, 25 (3.7%) NARESMA, 66 (9.8%) nasal polyposis, 25 (3.7%) catarrhal rhinitis, and 16 (2.4%) had obstructive adenoidal hypertrophy. A group of 27 (4%) patients had more rare disease, as summarized in Table 1. The 50 subjects with no history or evidence of rhino/sinonasal disease, clearly proved negative at diagnostic tests.

Nasal cytology, which considered immunoinflammatory cells, bacteria and/or spores staining, substantially confirmed the diagnosis of AR (Fig. 1A), rhinosinusitis (Fig. 1B), and "cellular" rhinitis represented by NARNE, NARMA, NARES, and NARESMA (Fig. 1C-F).[15]

Q11

TABLE 1. Distribution of diagnoses

Diagnosis	n	%
Negative	47	7
Rhinosinusitis	32	4.8
Septal deviation	205	30,6
Allergic rhinitis	142	21.2
NARES	69	10.3
NARESMA	25	3.7
NARMA	17	2.5
Polyposis	66	9.8
Catarrhal rhinitis	25	3.7
Adenoid hypertrophy	16	2.4
Antrochoanal polyps	4	0.6
Septal perforation	4	0.6
Post viral anosmia	5	0.7
Rhinitis medicamentosa	6	0.9
Multiple chemical hypersensitivity	2	0.3
Rhinoliquoral fistula	2	0.3
Churg-Strauss	2	0.3
Hereditary telangiectasia	1	0.15
Nasopharynx carcinoma	1	0.15
Total	671	100

NARES = nonallergic rhinitis with eosinophils; NARESMA = nonallergic rhinitis with eosinophils and mast cells; NARMA = nonallergic rhinitis with mast cells.

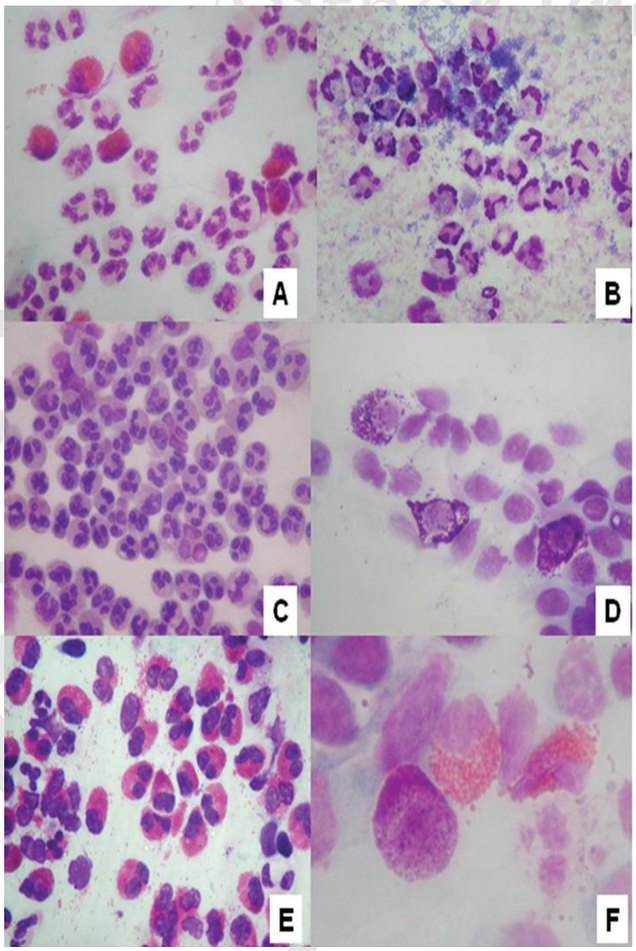

FIGURE 1. Nasal cytology: AR (A), rhinosinusitis (B), NARNE (C), NARMA (D), NARES (E), and NARESMA (F). May-Grünwald-Giemsa staining, original magnification ×1000.

On average, perennial AR showed the characteristic presentation of a "minimal persistent inflammation" characterized by numerous neutrophils, some eosinophils and rare mast cells, with few signs of degranulation.[16] At variance, the pollen-induced forms had more eosinophils and mast cells frequently degranulated (not shown). The rhinocytograms of patients suffering from nonallergic "cellular" rhinitis were characterized by numerous degranulated eosinophils and/or mast cells. The distribution of neutrophils, eosinophils, and mast cells in the various nasal disorders is reported in Table 2.

Among the 671 endoscopies performed, 130 (17.1%) patients had signs of nasal hyperreactivity during and/or immediately after the endoscopy, represented by a "volley of sneezes," sometimes associated with tearing and/or runny nose.

Correlation between nasal hyperreactivity and nasal disorders

Of the 130 subjects who presented hyperreactivity during nasal endoscopy, 1 (0.8%) was normal at examination, 1 (0.8%) had rhinosinusitis, 6 (4.6%) had septal deviation, 27 (20.8%) AR, 57 (43.8%) NARES, 12 (9.2%) NARMA, 19 (14.6%) NARESMA. and 7 (5.4%) had nasal polyps.

Extrapolating from 130 subjects with nasal hyperreactivity only the disease groups with the highest percentage of vasomotor reactions such as AR, NARMA, NARES, NARESMA, and NP, and comparing them with the other subjects belonging to the same groups of diseases, but who had not shown signs of nasal hyperreactivity, the ratio of the percentage of positive vasomotor response were 10.6% in the NP, 19% in the RA, 70.6% ($p < 0.01$) in NARMA, 76% ($p < 0.01$) in NARESMA, and 83% ($p < 0.01$) of NARES (Table 3).

Q12

For the group with AR, endoscopy had evoked hyperreactivity in 3 of 25 (12%) patients with sensitivity to mites, in 8 of 56 (14.3%) with pollen allergies, and in 16 of 61 (26.2%) with positivity to mites and pollens. However, considering every single allergy only during the pollen season, in the acute phase, nasal hyperreactivity was more frequently present: in 7 of 8 (87.5%) subjects positive to

TABLE 2. Neutrophils, eosinophils, and mast cells for each of the most-represented diseases*

Disease	Neutrophils median (IQR)	Eosinophils median (IQR)[a]	Mast cells median (IQR)[a]
NARES (n = 69)	146 (172–189)	33 (49–57)	0 (0–0)
NARESMA (n = 25)	145 (165–197)	35 (45–56)	22 (32–39)
NARMA (n = 17)	148 (158–177)	0 (0–0)	21 (27–33)
NP (n = 66)	155.5 (178.5–198)	14.3 (19–26)	0 (0–0)
AR (n = 142)	154.3 (182–207)	8 (14–19)	0 (0–1.5)
Total (N = 319)	154 (176–199)	12 (19–39)	0 (0–3)

*Values are median (25–75 IQR).

[a]The distribution of eosinophils and mast cells are statistically different for each disease (F-test, $p < 0.01$).

AR = allergic rhinitis; IQR = interquartile range; NARES = nonallergic rhinitis with eosinophils; NARESMA = nonallergic rhinitis with eosinophils and mast cells; NARMA = nonallergic rhinitis with mast cells; NP = nasal polyposis.

TABLE 3. Distribution of sneezing/no sneezing in different diseases

Disease	n/Total (%)	No sneezing	Sneezing	p[a]
Allergic rhinitis	142/671 (21.2%)	115 (81%)	27 (19%)	0.94
NARES	69/671 (10.3%)	12 (17.4%)	57 (83%)	<0.01
NARMA	17/671 (2.5%)	5 (29.4%)	12 (70.6%)	<0.01
NARESMA	25/671 (3.7%)	6 (24%)	19 (76%)	<0.01
Nasal polyps	66/671 (9.8%)	59 (89.4%)	7 (10.6%)	0.25

[a]The statistical significance is considered to be 0.01, given the correction for multiple comparisons.

NARES = nonallergic rhinitis with eosinophils; NARESMA = nonallergic rhinitis with eosinophils and mast cells; NARMA = nonallergic rhinitis with mast cells.

aeroallergens only, and in 13 of 16 (81.2%) subjects allergic to both mites and aeroallergens.

Correlation between nasal hyperactivity and cell type

Regarding to the correlation between nasal hyperreactivity and types of inflammatory cells, we found that for the AR, NARES, and NP, in the absence of mast cells, the number of "threshold" eosinophils to trigger sneezing was 30 cells per 50 microscopic fields at ×1000 magnification. In the presence of mast cells, the "threshold" number of eosinophils was reduced to 27 in AR, and 20 in the NP. For nonallergic rhinitis (NARMA, NARESMA) the presence of mast cells was the only factor that caused sneezing (Fig. 2). Therefore, in light of the results reported, nasal hyperactivity (sneezing) can be considered an important "sign" of nasal symptomatology, in particular for the "cellular" rhinitis group, whose sensitivity and specificity were 79% and 93%, respectively. Q13

Control group

Of the 50 subjects examined, none had signs of hyperactivity during nasal endoscopy. Q14

Allergy tests and nasal cytology were totally negative.

Discussion

"Symptoms" and "signs" are an indispensable aid in clinical diagnosis. In fact, since ancient times, the terms indicate the different diagnostic elements. In the mind of F.J. Double, the "sign" is nothing more than the objective finding of the clinician. The term "symptom" is any detectable change in the sick body. "Sign" is instead all that is recognized by the physician as belonging to the clinical disease.[17] In the clinical setting, an exaggerated reactivity of the patient, in the course of a particular instrumental investigation, in addition to being an obstacle to the investigation, may also "irritate" the operator, especially if the operator is impatient and unsympathetic. On the other hand, if it is shown that this hyperreactivity is not only an expression of a particular pathophysiologic condition, this "symptom" could be included as a "sign" of great clinical significance and diagnosis, and should be sought after even by endoscopists.

This review demonstrates a direct link between nasal hyperreactivity ("sneezing"), evoked during endoscopic investigation, and a specific clinical-cytological condition in rhinological diseases.

Although the results have shown that only 17.1% of the cases examined were nasal hyperactivity, the data should not be considered irrelevant. Indeed, in our opinion, if properly studied and understood, the "signs" assume an important value of great interest in analyzing the symptoms. Q15

If we examine the correlations between hyperreactivity and rhinological diseases, the most significant data regarding "cellular" rhinitis are represented by NARMA, NARES, and NARESMA ($p < 0.01$) (Table 1). For these forms the vasomotor reaction occurring during or immediately after an endoscopic maneuver is considered a symptomatological "sign," whose sensitivity and specificity was found to be 79% and 93%, respectively. Just as interesting was the observed correlation between the presence of hyperreactivity and cell type, with the identification of a "threshold" for the number of eosinophils and/or mast cells, beyond which a vasomotor reaction is triggered (sneezing) (Fig. 2).

This is in accordance with the pathophysiological mechanisms of nasal hyperreactivity correlated with the detrimental actions of inflammatory cell types in the course of degranulation causing epithelial damage.[18] In particular, the MBP is the more cytotoxic enzyme. By acting

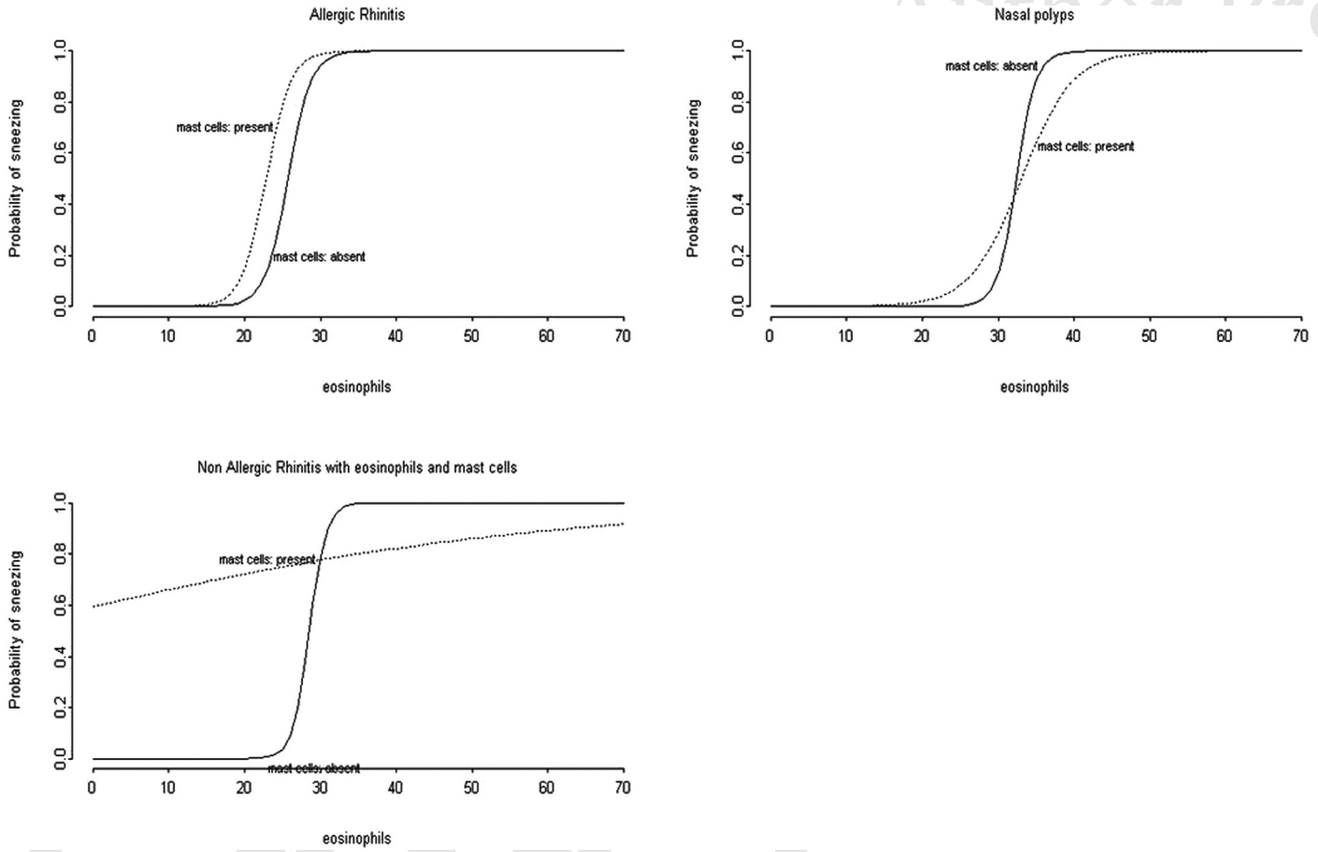

FIGURE 2. Relationship between sneezing and the presence of mast cells and eosinophils in allergic rhinitis (A), nasal polyps (B), and nonallergic "cellular" rhinitis (C).

directly on the junctional systems of the columnar cells of the nasal respiratory epithelium, it is responsible for the breakup and the subsequent de-epithelialization.[19] The discontinuous respiratory mucosa causes the loss of 1 of the main functions of the mucosa, a barrier to the outside world. This condition determines a greater exposure to chemical-physical-atmospheric stimuli of the "irritant trigeminal receptor," located immediately below the basal membrane, which also explains the exaggerated reactivity of these patients with respect to subliminal stimuli (small temperature changes, perfumes, humidity, chlorine in swimming pools, endoscopies etc.).[20,21]

A further confirmation of the existence of a direct correlation between cell type and nasal hyperreactivity was detected by our group in allergic rhinitis. In fact, the percentage of the presence of nasal hyperreactivity ranged from 14.3% of patients examined outside the pollen season, to 87,5% of those examined during the period of maximum pollination, with greater increase in both eosinophil-mast cell cellularity and the degree of degranulation.

Conclusion

Describing a new symptomatological "sign" confirms that modern medicine, which is increasingly characterized by advanced technologies (computed tomography [CT], magnetic resonance imaging [MRI], positron emission tomography [PET], nanotechnology, etc.) can never do without the basic aspects of medical arts, whose teachings, dictated by Hippocrates as early as 460 BC, are represented by the patient's medical history and physical examination. The clinician must always be ready and alert to seize new "signs" and "symptoms" that can occur with the use of new diagnostic tools, in order to achieve a more accurate diagnosis essential to establish a fair and rational therapeutic approach.

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