

THE ROLE OF NASAL CYTOLOGY IN THE MANAGEMENT OF INFERIOR TURBINATE HYPERTROPHY

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Inferior turbinate hypertrophy (ITH) is the main cause of nasal obstruction symptom. This study aimed at investigating whether a particular cellular pattern could be a predictive factor for failure of medical treatment for ITH in patients with rhinitis. Globally, 258 patients with chronic nasal obstruction due to ITH were evaluated by: visual analogue scale assessment of symptoms, skin prick tests, fiberoendoscopy, active anterior rhinomanometry, and nasal cytology. All patients were treated with drugs for 3 months and then re-evaluated. The symptom improvement depended on the different cellular pattern. There was improvement in: 54 (51.4%) patients with allergic rhinitis, 72 (69.2%) with non-allergic rhinitis with neutrophils (NARNE), 15 (42.8%) with non-allergic rhinitis with eosinophils (NARES), and 9 (64.3%) with non-allergic rhinitis with mast cells/non-allergic rhinitis with eosinophils and mast cells (NARMA/NARESMA). The non-responders (108; 41.9%) were therefore directed towards surgical treatment. Both patients with allergic rhinitis and patients affected by NARES had a higher failure rate to medical treatment compared with NARMA and NARESMA groups ($p < 0.01$). In conclusion, elevated number of eosinophils, in the nasal secretion of both allergic (allergic rhinitis) and non-allergic (NARES) patients with ITH, can be associated to a higher medical treatment failure rate.

Chronic inferior turbinate hypertrophy (ITH) is a common cause of nasal obstruction. ITH is sustained by inflammation, which may be caused by allergic (AR) or non-allergic rhinitis (NAR). AR is characterized by an IgE-mediated reaction, documented by skin prick test positivity. On the other hand, NAR is diagnosed on the basis of: i) allergen-specific IgE absence, ii) chronic symptoms due to nasal hyper-reactivity, and iii) absence of nasal infection (1).

NAR is a heterogeneous disease whose etiology is largely unknown. In fact, NAR is classified as idiopathic or vasomotor rhinitis in about 75-80%

of patients. This high percentage of idiopathic etiology is, at least in part, due to the fact that nasal cytology is very rarely performed. Indeed, it has been previously highlighted that nasal cytology only allows to classify NAR on the basis of the particular cellular infiltrate pattern: i) NAR with eosinophils (NARES), characterized by predominant eosinophil infiltration; ii) NAR with neutrophils (NARNE), characterized by predominant neutrophil infiltration; iii) NAR with mast cells (NARMA), characterized by prevalent mast cell infiltrate; iv) NAR with eosinophils and mast cells (NARESMA), characterized by concomitant relevant eosinophil

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and mast cell infiltration (2).

The importance of distinguishing between AR and NAR is essential to choose the more appropriate treatment since the former optimally responds to allergen-specific immunotherapy as well as to the avoidance of the causal allergen, whilst the latter is refractory to specific treatments (3). Anyway, medical treatment is the first therapeutic step in both disorders. A graded approach has been suggested, using oral or intranasal antihistamines, intranasal corticosteroids, or a combination of both; some patients with leading watery nasal discharge may respond to anticholinergic drugs (e.g. ipratropium bromide) (4). However, it is to note that these medications provide only symptomatic relief, but not a permanent cure (5).

If medical treatment fails to relieve nasal obstruction because of relevant ITH, a surgical reduction could be performed to facilitate better functional nasal airflow and to achieve consequent improvement of obstruction symptom (6-8). The indication for nasal turbinate surgery is often based only upon a subjective clinical examination by otolaryngologists without objective assessment (9).

The subjective perception of nasal obstruction is of great importance for the patient and the surgeon because this is the symptom that leads the patient to investigation, treatment, and follow-up, but an objective measurement of nasal obstruction should be essential for selecting the patient candidate for surgery (10).

This study aimed to investigate whether a particular cellular pattern could be a predictive factor for failure of medical treatment for inferior turbinate hypertrophy (ITH) in a group of patients with rhinitis.

MATERIALS AND METHODS

Globally, 258 patients (140 males and 118 females, median age 34.8 years, range 17-83) with symptoms of chronic nasal obstruction were consecutively visited in the rhino-allergology ambulatory of the Department of Otorhinolaryngology of the University of Foggia from January 2009 to January 2011.

The patients underwent:

- Clinical history: nasal symptoms were evaluated using a visual analogue scale (VAS): 0 = no symptom and 10 = worst symptom.

- Anterior rhinoscopy and fiber-endoscopy: to evaluate the severity of turbinate enlargement, and the presence of associated sino-nasal disorder (e.g. septal deviation, septal perforation, sinusitis, nasal polyposis, etc.).

- Skin prick test: to identify allergic subjects. Allergy was assessed by the presence of sensitization to the most common classes of aeroallergens using a skin-prick test. It was performed as stated by the European Academy of Allergy and Clinical Immunology (11). The allergen panel consisted of the following: house-dust mites (*D. farinae* and *D. pteronyssinus*), cats, dogs, grasses mix, Compositae mix, *P. judaica*, birch, hazel trees, olive trees, cypress, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix. The concentration of allergen extracts was 100 immune reactivity/mL (Stallergenes, Milan, Italy). A histamine solution in distilled water (10 mg/mL) was used as positive control and the glycerol-buffer diluent of the allergen preparations was used as negative control. Each patient was skin tested on the volar surface of the forearm using 1-mm prick lancets (Stallergenes). The skin reaction was recorded after 15 min by evaluating the skin response in comparison with the wheal given by the positive and the negative control. A wheal diameter of at least 3 mm was considered as a positive reaction. The AR diagnosis was made if nasal symptom history was concordant with sensitization

- Active anterior rhinomanometry (AAR) performed with a rhinomanometer (Atmos 300, Atmos, Milan, Italy) to record partial nasal resistance at baseline and after 10 min from the administration of 2 puffs of naphazoline nasal spray into each nasal cavity (nasal decongestion test). A change of 120 mL/s in the nasal flow after decongestion test was considered clinically relevant to define reversibility. In this case the chronic obstruction proved to be caused by inferior turbinate enlargement. Total nasal resistance baseline at 150 Pa was taken as the reference value;

- Nasal cytology: performed by scraping the middle part of inferior turbinate with a Rhino-Probe. The sample was stratified on a slide, fixed with methanol for 4 min and colored using the May-Grunwald Giemsa staining method. Microscopic observation was performed at 400x magnification to check coloration quality and cell distribution, and at 1000x magnification in immersion to discriminate different cell types and to study the intracellular components. NARES was diagnosed if nasal eosinophils were >20% of total cells recovered on a slide, including both inflammatory and epithelial cells; NARMA was diagnosed if nasal mast cells were >10% of total cells. NARNE if neutrophils were > 50% of total cells and NARESMA when concurrent nasal eosinophils were >20% and mast cells were >10% of nasal cells (Fig.1).

Inclusion criteria were turbinate hypertrophy

enlargement with positive nasal decongestion test and without other nasal pathology causing nasal obstruction. Exclusion criteria were: concomitant septal deviation or perforation, endoscopic signs of additional sino-nasal disease (rhinosinusitis, nasal polyposis), previous nasal or sinus surgery.

All subjects with diagnosis of ITH were then submitted to a medical treatment with topical corticosteroids (furoate mometasone 50 µg, 2s puff for each nostrils once daily) and oral antihistamines (levo-cetirizine 5 mg, 1 tablet once daily) for at least 3 months. In patients with watery nasal discharge also anticholinergics (ipratropium bromide 4 mg nasal spray, 2 puffs for each nostril twice daily) were added.

A value of VAS post-treatment for nasal obstruction ≤ 4 was arbitrarily considered a sign of medical treatment success, while patients with VAS ≥ 5 were candidates for surgery.

Statistical analysis

Qualitative data (effectiveness of therapy) were analyzed by Pearson's *chi*-squared test (for $df=1$ the reported *chi*-square value is the Yates's correction for continuity) by multiple testing procedures. Bonferroni correction was applied to obtain P values adjusted for multiple comparisons.

To adjust for covariates, multiple logistic regression was used to examine the association between specific disease (or nasal cytology) and therapy failure. Covariates included family history, sex, age, ASA sensibility and asthma.

Pearson's test of linear correlation was used to compare pre-treatment rhinomanometric resistances with post-treatment values to evidence a possible correlation. A P value of <0.05 was considered statistically significant for all analyses. All analyses were performed using MedCalc® version 12.2.1.0 for Windows (MedCalc Software,

Broekstraat, Mariakerke, Belgium) and R version 2.3.1 for Linux (R Foundation for Statistical Computing, Vienna, Austria). Charts were obtained using SOFA Statistics version 1.1.6 for Linux (Paton-Simpson & Associates Ltd, Auckland, New Zealand).

RESULTS

The case history showed the presence of nasal obstruction in all the patients with a VAS median of 8.0 (min. 6; max 10) (Table I). Rhinorrhea was present in 78 patients (30.2%), itchiness in 110 (42.6%) and sneezing in 158 (61.2%).

The rhino-fibroscopic exam confirmed an ITH in all the patients without other causes of nasal obstruction.

The AAR showed average total resistances at 150 Pa equal to 2.29 (Std Dev: 0.74), which after the decongestion test reached an average of 1.69 (Std Dev: 0.62). The skin prick tests revealed an allergy in 105 (40.7%) of the patients. Of these, 35 (33.3%) were sensitive to *Dermatophagoides*, 11 (10.5%) to *Parietaria*, 18 (17.1%) to graminaceae plants, 8 (7.6%) to olive trees, 2 (1.9%) to cypress trees, 2 (1.9%) to animal dander, and 29 (27.6%) with more than one sensitization.

The remaining 153 (59.3%) patients were therefore affected by non-allergic rhinitis, that, according to nasal cytological assessment, were classified as: NARES in 35 (13.6%) cases, NARNE in 104 (40.3%), NARMA in 8 (3.1%), and NARESMA in 6 (2.3%). As the last two groups had such small numbers, they were considered together to be able to draw statistical conclusions.

Table I. Pre- and post-therapy symptom score of nasal obstruction in the different cytological groups.

Pre-therapy symptoms score						
		Nasal Cytology				
		ALLERGY	NARES	NARMA/NARESMA	NARNE	TOTAL
Nasal Obstruction	Median	8.0	8.0	8.0	8.0	8.0
	Min	7.0	7.0	7.0	6.0	6.0
	Max	9.0	9.0	10.0	10.0	10.0
Post-therapy symptoms score						
		ALLERGY	NARES	NARMA/NARESMA	NARNE	TOTAL
Nasal Obstruction	Median	6.0	6.0	6.0	5.0	6.0
	Min	0.0	4.0	4.0	0.0	0.0
	Max	8.0	8.0	8.0	8.0	8.0

Table II. OR of having therapeutic failure after three months of therapy. Multiple logistic regression analysis; ORs are expressed for NAR compared with ALLERGY, adjusted for family history, sex, age, ASA sensibility and asthma.

Diagnosis	OR	95% CI	P value
NARES	3.00	1.36-6.60	0.006
NARMA/NARESMA	0.59	0.18-1.87	0.37
NARNE	0.46	0.27-0.77	0.003

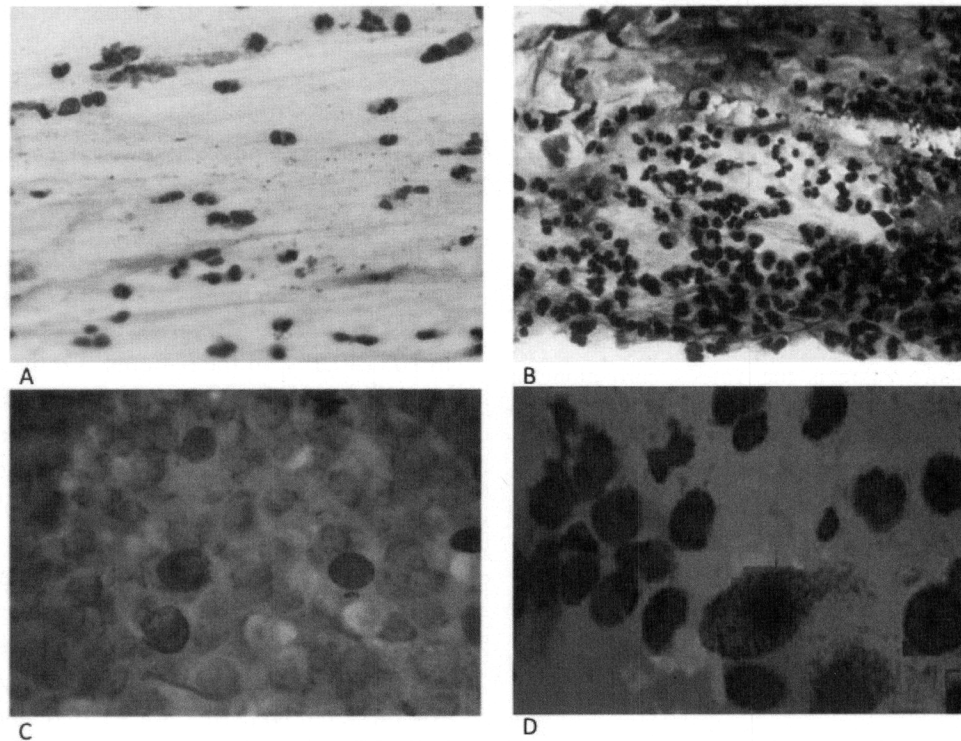


Fig. 1. Rhinocytogram of the sub-groups of non-allergic rhinitis: A) Non-allergic rhinitis with eosinophils (NARES); B) Non-allergic rhinitis with neutrophils (NARNE); C) Non-allergic rhinitis with mast-cells (NARMA); 4) Non-allergic rhinitis with eosinophils and mast-cells (NARESMA) (May Grunwald Giemsa. x 400).

The distribution of the nasal obstruction in the allergic patients and in the various subgroups of the non-allergic patients with the relative severity expressed by the VAS is shown in Table I, whereas the rhinomanometric resistances are shown in Fig. 2.

After medical treatment, an improvement in the nasal obstruction symptoms was evident in 150 (58.1%) patients with a median VAS of the entire sample reduced from 8 to 6 (min 0; max 8), as shown in Table I. The AAR showed, furthermore, a reduction of the basal resistances to 150 Pa up to an average value of 0.96 (SD: 0.77) (Fig. 2).

The symptomatic improvement was, however, different in the different cytological classes having occurred in 54 out of 105 (51.4%) of patients with allergic rhinitis, in 72 out of 104 (69.2%) with NARNE, in 15 out of 35 (42.8%) with NARES and in 9 out of 14 (64.3%) with NARMA/NARESMA. These differences were, however, less evident when we analyzed the VAS median (Table I).

The remaining 108 patients (41.9%) who did not benefit from the medical treatment were therefore directed towards surgical treatment. In this group, 51 (47.2%) patients suffered from allergic rhinitis,

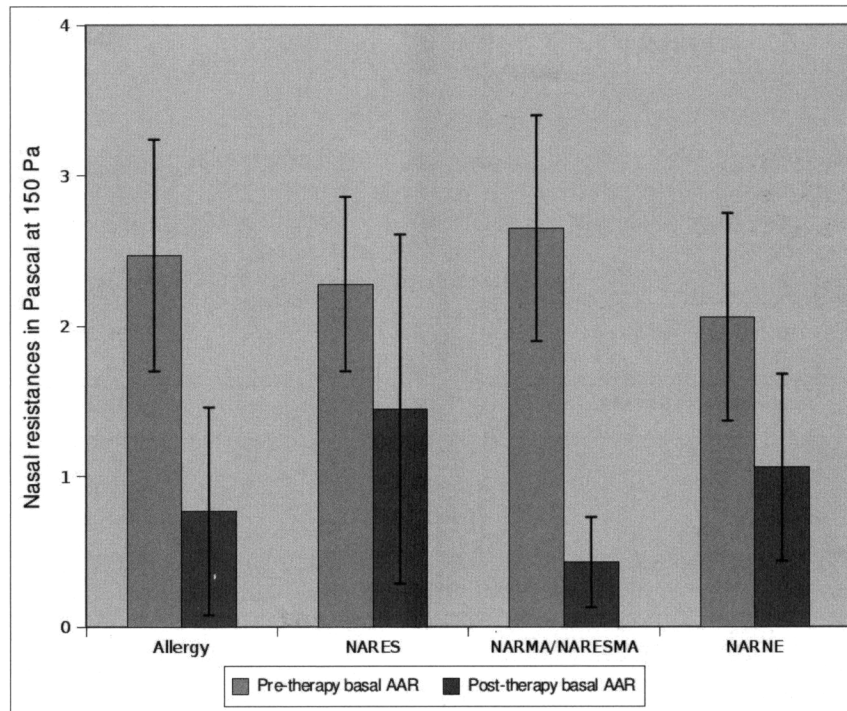


Fig. 2. Mean of nasal resistances at 150 Pascal calculated by active anterior rhinomanometry (AAR) before and after medical therapy.

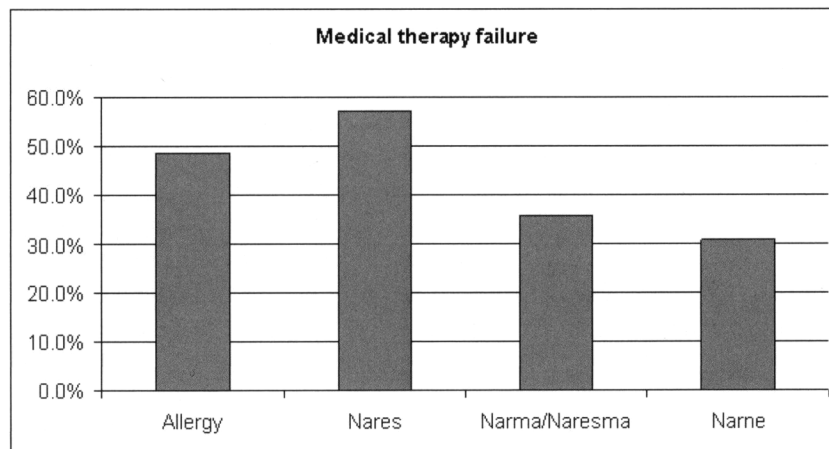


Fig. 3. Percentage of medical therapy failure in allergic and non-allergic rhinitis patients.

20 (18.5%) from NARES, 32 (29.6%) from NARNE and 5 (4.6%) from NARMA/NARESMA.

Hence, the failure of medical treatment was seen in 51 out of 105 allergic patients (48.6%), 20 out of 35 patients affected by NARES (57.1%), 5 out of 14 by NARMA/NARESMA (35.7%) and 32 out of 104 by NARNE (30.8%), as shown in Fig. 3.

The χ^2 test, with procedure for multiple

confrontations and relative corrections, was used to compare proportion of therapeutic failure between diagnosis groups. A significant statistical difference emerged between the various groups ($P = 0.012$).

Both the allergic and NARES groups ($P = 0.49$), just as the NARNE and NARMA/NARESMA groups ($P = 1$), did not differ from each other in the frequency with which they have shown a failure in

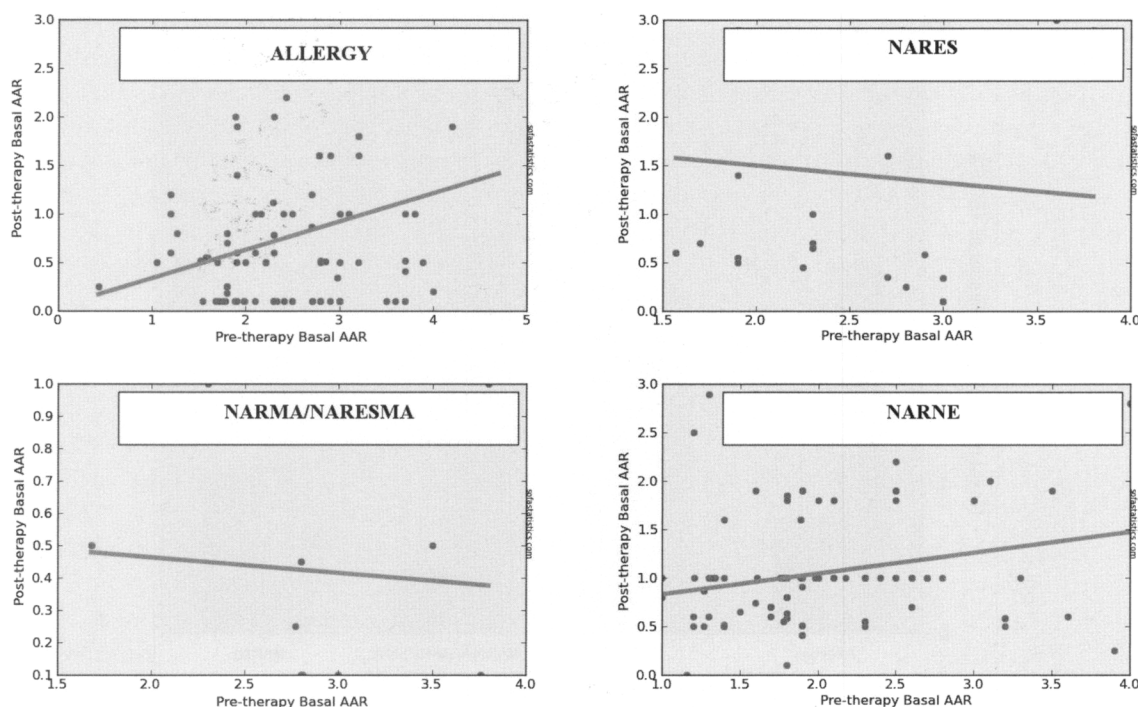


Fig. 4. Pearson's Test of Linear Correlation between pre-therapy and post-therapy resistances at active anterior rhinomanometry (AAR) in the "allergy" groups ($p < 0.001$; $r = +0.322$), NARNE ($p = 0.015$; $r = +0.237$), NARES ($p = 0.613$; $r = -0.089$) and NARMA/NARESMA ($p = 0.677$; $r = -0.122$).

medical treatment. Therefore, both patients with allergic rhinitis and patients affected by NARES had a higher failure rate with medical treatment (50.71% had to undergo surgery) compared to the NARMA and NARESMA groups (only 31.36% had to undergo surgery).

Hence, a logistic regression model was fit between the response to treatment and predictor variables. The significance value for the overall model fit statistic is $P = 0.0061$, therefore there is evidence that at least one of the independent variables contributes to the prediction of the outcome.

The OR of having therapeutic failure after adjusting for family history, sex, age, ASA sensibility, and asthma is shown in Table II.

After adjusting for covariates, Odds Ratios were calculated by regression coefficients between ALLERGY and other group outcomes. Compared with the ALLERGY group, the NARES group had significantly higher odds of having a therapeutic failure (OR, 3.00; 95% CI, 1.36-6.60; $P = 0.0063$); on the other hand, the NARNE group had significantly

lower odds of having therapeutic failure (OR, 0.46; 95% CI, 0.27-0.77; $P = 0.0032$); however, no significance was found with NARMA/NARESMA group ($P = 0.369$).

Furthermore, studying the difference in the resistance values in the AAR between the various groups, before and after a cycle of medical treatment using "Pearson's Test of Linear Correlation", a correlation was shown between the pre-therapy AAR and the post-therapy AAR in the "allergy" groups ($P < 0.001$; $r = +0.322$) and NARNE ($P = 0.015$; $r = +0.237$) whereas there was no correlation in the remaining two groups, NARES ($P = 0.613$; $r = -0.089$) and NARMA/NARESMA ($P = 0.677$; $r = -0.122$) (Fig. 4).

DISCUSSION

There is currently no consensus on patient selection for turbinate surgery. Most otolaryngologists offer surgery on the basis of patient's subjective complaint of nasal obstruction. Measuring nasal obstruction

is essential for both patient selection for surgery and the assessment of any surgical technique used to reduce the size of the turbinate (10). Subjective scores (VAS, symptom score) provide important information about how severely the patients feel the nasal obstruction (12, 13), but they cannot be used for patient selection. Thus, rhinomanometry remains the gold standard objective assessment of nasal airflow because it shows the degree of obstruction during nasal breathing measuring nasal airflow and resistance (14). Moreover, a reduction of nasal resistance on the AAR after a decongestion test is considered by many authors the main test to evaluate the role of mucosal or sub-mucosal tissue on turbinate hypertrophy and, consequently, an indication for turbinate surgery (15, 16).

Acoustic rhinometry gives an anatomical measure of cross-sectional area of volume of the nasal cavity, but it does not directly measure nasal breathing (17). However, the border between the presumed failure of the medical treatment and the indication for surgery remains quite subjective and varies between different specialists with numerous cases of overtreatment where the execution of an optimal medical treatment would have allowed to control the basic disease and therefore resolved the symptoms.

There are no objective parameters that show when the medical treatment should be considered inefficient or that recognize patients for whom such a treatment would most likely fail. Some authors have tried to verify the need to turbinate surgery based on the histological research of the inferior turbinate in patients who have already undergone a turbinectomy (9). However, the possibility of histologically verifying the probability of successful medical treatment (and consequently the eventual need for surgery) is not possible since it would mean that all patients would have to undergo an invasive exam, such as nasal mucosa biopsy.

We, therefore, hypothesized that the study of the nasal cytology would be able to give us a predictive factor for the failure of medical treatment, indicating the presence of a particular cytotype in patients with allergic or non-allergic rhinitis, both being tied to a higher probability of needing surgery.

Differentiating the various clinical-cytological subclasses in our sample, it emerged that the NARES patients presented the highest medical treatment

failure rate (57.1%), followed by the patients with allergic rhinitis (48.6%), the NARMA/NARESMA patients (35.7%), and NARNE patients (30.8%). From a statistical point of view, NARES group had significantly higher odds of having a therapeutic failure (OR 3.00) compared to the other groups, while the NARNE group had significantly lower odds of having therapeutic failure, indicating a higher percentage of improvement of nasal obstruction after medical therapy.

Such data were partially confirmed by the rhinomanometry results that showed an improvement in the resistance in all the groups, but with a statistical correlation between the pre- and post-operative rhinomanometric resistances in the NARNE group and the allergic group, indicating therefore, an absence in correlation with the NARES patients. The subjective evaluation of the nasal obstruction with VAS showed an improvement after treatment, however, it did not show significant difference in the various clinical-cytological subclasses.

In a previous study, Gelardi et al. showed that patients with NARESMA had the worst symptoms, QoL and rhinomanometric resistance, and the highest association with asthma and sleep apnea (2).

In our sample, the NARESMA group was small (only 6 cases – 2.3%) and no particularly severe symptoms emerged. The average rhinomanometric resistance resulted slightly higher compared to the other groups; however, they had a good response with the medical treatment.

The NARES group showed the worst results with medical treatment: only 42.9% of patients improved, with resistance values still elevated after treatment. A high failure rate was also found in the allergic group, even though the resistance values diminished after treatment. The poor results achieved by NARES and allergic patients could be explained by the presence of elevated amounts of eosinophils in the nose. In fact, the abundant presence of eosinophils would induce a more intense inflammation, responsible for the severity of the symptoms and refractoriness to medical therapy (18). The role of the eosinophils was underlined by Chawes, who found a nasal inflammation sustained by eosinophils in a pediatric population, especially in children with allergic rhinitis (19).

Therefore, the type of predominant infiltrating

cell is relevant, not only to differentiate the severity of the different NAR (20), but also to give a prognosis regarding medical therapy for turbinate hypertrophy. Therefore, the finding of an elevated number of eosinophils in the nasal secretion of both allergic (allergic rhinitis) and non-allergic (NARES) patients represents a negative prognostic index for medical treatment success. It does not mean that these patients will be directly oriented to surgical therapy without a period of medical therapy, but it will allow us to warn the patient on the possibility of medical treatment failure.

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