Role of inflammation in non-allergic rhinitis*

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Summary

Objective: To investigate the role of inflammation in non-allergic rhinitis (NAR) patients in a large series to establish the prevalence of different NAR-subtypes, clinical features and the role of nasal cytology in the diagnostic algorithm.

Methodology: Patients were selected out of 3650 individuals who spontaneously presented at our institution. We consecutively enrolled 519 NAR-patients in an analytical cross-sectional study between November 2007 and June 2013 (level of evidence: 3b). All patients underwent rhinological evaluation including symptoms questionnaire, endoscopy, CT scan, allergy tests and nasal cytology.

Results: The inflammatory cell infiltrate affects the severity of symptoms differently, allowing for identification of different phenotypes of NAR. We distinguished two groups: "NAR without inflammation"(NAR-) and "NAR with inflammation"(NAR+), in addition to different NAR-subtypes with inflammation. A significant difference was observed in terms of clinical symptoms and association with comorbidities (previously diagnosed asthma and aspirin intolerance) between NAR–, NAR+ and between different NAR+ subtypes.

Conclusion: Our data suggest that NAR- and NAR with neutrophils behave similarly, showing lower symptom score values and a lower risk of association with comorbidities compared to NAR with eosinophils and mast cells (singularly or mixed). In our belief it is very important to establish the presence and type of inflammation in non-allergic rhinitis patients and nasal cytology is a very useful test in correct differential diagnosis.

Key words: non-allergic rhinitis, nasal cytology, aspirin intolerance, asthma, inflammatory cells

Introduction

Although non-allergic rhinitis is a well-known entity, its prevalence, diagnosis, classification and therapy have not been clearly defined. Nasal symptoms induced by non-allergic rhinitis (NAR) are a cause of wide spread morbidity, even though the actual impact of this pathology is extremely underestimated, and NAR is often not identified or classified adequately [1-11]. Several studies have reported that rhinitis symptoms significantly affect the quality of life, and that NAR patients frequently refer to medical specialists (2-4 times more than asthma sufferers, 6-8 times more than those affected by acute rhino-sinusitis and more than twice as often compared to all patients)[12,13]. Nevertheless, there is a lack of epidemiological studies on the prevalence of NAR. Based on the available data, the prevalence varies from 14-23% of the general population in industrialized nations (19-20 million in the USA and about 50 million in Europe)[9-11,14,15].

Abbreviations: NAR: non-allergic rhinitis; NAR+: non-allergic rhinitis with inflammation; NAR-: non-allergic rhinitis without inflammation; NARNE: non-allergic rhinitis with neutrophils; NARES: non-allergic rhinitis with eosinophils; NARMA: non-allergic rhinitis with mast cells; NARESMA: non-allergic rhinitis with eosinophils and mast cells; VAS: visual analogue scale

The differential diagnosis of NAR is extensive. The term "non-allergic rhinitis" suggests several diseases, in which the aetiology and physiopathology are poorly understood and established only for few forms. The prevalence and classification of different syndromes that comprise this disorder is poorly defined, and in fact very few studies have provided specific data on this aspect. Several terms have been used to describe these patients including: non-allergic non-infectious perennial rhinitis (NANIPER), idiopathic rhinitis, intrinsic rhinitis and vasomotor rhinitis[4,5]. However, the lack of universal terminology of NAR and, in particular its phenotype using objective criteria, remain the most striking gaps in our knowledge at present[16].

NAR has commonly been defined as chronic rhinitis characterized by nasal congestion, rhinorrhea and sneezing in the absence of identifiable specific allergic sensitivities, infection, or other causes of rhinitis [6,7,9,10]. In December 2008, a round-table conference was convened to establish a consensus on the clinical definition of NAR. From this Consensus Panel Proceedings, there are at least 8 subtypes that fulfill criteria for NAR[17]. Nevertheless, there is still a general difference in opinion amongst clinicians and researchers regarding terminology and classification, and there is no agreement about the criteria that should be used to classify these conditions. In fact, NAR may be sub-classified on the basis of various characteristics including frequency of occurrence, immunological and cytological features, and aetiologic and systemic disease association[18].

Although it is controversial on how to best subdivide NAR, several studies have recently demonstrated that a cytological approach may be useful not only to establish involvement of inflammation, but also to improve classification [19-21]. There is debate regarding the role of inflammation in NAR. Indeed, some authors have suggested that there is a large subgroup of patients with symptomatic NAR in the absence of any inflammatory changes in the nasal mucosa. In these patients, it is not possible to identify an inflammatory cell infiltrate such us in hormonal rhinitis, damage to sympathetic nerves as in Horner's syndrome or overuse of topical-adrenergic agonists/nasal decongestants ("rhinitis medicamentosa")[22]. On the other hand, several authors have demonstrated that most patients with NAR have some degree of inflammation suggesting that nasal cytological evaluation may aid in identifying forms of NAR in which inflammation is involved and in classifying this latter according to the inflammatory cell type [3]. Nevertheless, there is a lack of expert consensus about whether nasal cytology should be routinely performed in the evaluation of rhinitis.

The first aim of our study was to examine the cellular profile in a large series of NAR to establish the prevalence of different NAR-subtypes and their clinical features. The second objective was to establish the role of nasal cytology in the diagnostic algorithm of patients with NAR.

Materials and methods

Study design

The study was performed at the Department of Head and Neck Surgery - Otorhinolaryngology of Catholic University of the Sacred Heart in Rome. Patients were selected from a population of 3650 persons (1798 males, 1852 females, mean age of 39.3 years) that spontaneously presented to our rhinology clinic. In this large population, 519 patients (192 males and 327 females; mean age 40.3 years) were diagnosed affected by non-allergic rhinitis (aged >18 years and with a minimum duration of 12 weeks of nasal symptoms) and were enrolled in the study. The patients were randomly enrolled at our institution in the period between November 2007 and June 2013. All patients affected by allergic rhinitis, pharmacologic rhinitis, acute infective rhinosinusitis, chronic rhinosinusitis with or without polyposis, were excluded from the study. Other exclusion criteria were use of systemic or inhaled drugs within the previous 3 months (sodium chromoglycate or nedocromil sodium, antihistamines, cortisone, leukotriene, etc.), inability of the patient to stop taking medication affecting nasal function, serious and/or unstable disease, abnormality of white blood cell counts such as neutropenia, nasal surgery within the previous 6 weeks, pregnancy or lactation or significant anatomical abnormalities affecting nasal function. The protocol was approved by our institutional board and all subjects gave written informed consent. Healthy subjects (n = 88) with normal nasal function and without any nasal symptoms were enrolled as controls.

NAR Diagnosis

Diagnosis of NAR was based on thorough clinical history and mainly achieved by a process of exclusion in a stepwise fashion. To exclude an allergic aetiology, all patients were tested by allergy tests including: total serum IgE (PRIST), skin prick test for common inhalant allergens (at least 18 inhalant allergens including house dust mites, major Italian pollens, mold, dogs and cats), determination of allergen-specific IgE (RAST) and intranasal allergen provocation test. All patients were tested by nasal endoscopy to exclude the presence of pathological purulent secretions (to exclude an infective aetiology) and/or naso-sinusal polyposis and by CT facial scan.

Cytology

All patients underwent nasal cytology. Samples were taken by scraping of the third medium of the inferior turbinate bilaterally using a rhinoprobe (Farmark s.n.c., Milan, Italy). Samples were delicately spread on glass slides and immediately fixed in 95% ethyl alcohol and stained with May-Grunwald-Giemsa. Cell counts were performed on scraped nasal tissue by microscopic

examination. Slides were examined under oil immersion by light microscopy at a magnification of x400. Samples were examined blindly by an experienced cytologist who was unaware about the clinical status of patients. Cells were counted and categorized as neutrophils, eosinophils, mast cells, basophils, lymphocytes, epithelial cells and goblet cells. Cells counts were expressed as percentage of cells of the granulocytic or mononuclear cells, excluding nasal epithelial cells, at high power field, as the mean of at least 10 fields observed. The mean percentage of the cell type per 100 cells is reported.

Symptom score determination

To evaluate the total severity of symptoms of rhinitis, the patient was asked to indicate on a VAS the answer to the question: "How troublesome are your symptoms of rhinitis?". The score was considered suggestive of mild symptoms for value inferior to 3, moderate between 3-7 and severe over 7. In addition, all patients were asked to complete a rhinological questionnaire about different symptoms such as rhinorrhoea, nasal obstruction, facial pain, sneezing, loss of smell, nasal itching, difficulty falling asleep, lacrimation and nocturnal awakening. To evaluate nasal symptoms, we used a visual analogue scale (VAS). Each symptom was scored from 0 to 10, and patients were told that 0 indicated 'nasal symptoms not at all bothersome' and that 10 indicated 'nasal symptoms extremely bothersome'. For each patient, we calculated the "total score" (adding scores of each symptom analyzed on the basis of the VAS) and the "partial score" (adding scores on the basis of the VAS exclusively for irritating nasal symptoms: sneezing, nasal itching, lachrymation, rhinorrhoea). Finally, for each class of NAR we calculated the "mean score for each analyzed symptom" (average of the values assigned to each patient on the symptom on the basis of the VAS); the "mean total score" (average of the total scores of patients for each group); "mean partial score" (average of the partial scores of patients for each group).

Based on the results of clinical evaluation and nasal cytology, we divided patients in two groups: patients without inflammation (symptomatic patients without evidence for nasal cytology with a cellular inflammatory infiltrate); patients with inflammation (symptomatic patients with evidence for nasal cytology with a cellular inflammatory infiltrate). We named the first group NAR- and the second NAR+. The latter group was further subdivided into 4 subgroups according to the results of the cytological nasal smear:

- NAR with eosinophils (NARES): eosinophils > 20% of total cells.
- NAR with neutrophils (NARNE): neutrophils > 50% of total cells.
- NAR with mast cells (NARMA): mast cells > 10% of total cells.
- Mixed NAR with eosinophils and mast cells (NARESMA): eosinophils > 20% and mast cells > 10% of total cells.

We did not find any significant selective infiltration of nasal mucosa by basophils in our patients, confirming the lack of allergy in these NAR patients.

Table 1. Prevalence of different sub-categories of non-allergic rhinitis.

Type of non-allergic rhinitis	Number of patients	% of non allergic rhinitis patients (n=519)	% of total studied patients (N=3650)
Non-allergic rhinitis without inflammation (NAR-)	231	44.51	6.33
Non-allergic rhinitis with inflammation (NAR +)	288	55.49	7.89
Non-allergic neutrophil rhinitis (NARNE)	171	32.95	4.68
Non-allergic rhinitis with eosinophilia syndrome	81	15.61	2.22
Non-allergic mast cell rhinitis (NARMA)	19	3.66	0.52
Non-allergic eosinophilic-mast cells rhinitis (NARESMA)	17	3.28	0.47

Statistical methods

Statistical analysis was performed using the SPSS package (version 13.0). Continuous variables were expressed as mean ± standard deviation. Demographic and clinical data were expressed as percentages. Comparisons between groups were performed using a Mann-Whitney U-test and student's t-test. The strength of the correlation between two parameters was obtained by Spearman's rank correlation test. A $p < 0.05$ was considered statistically significant.

Results

In our series, the prevalence of NAR was 14% (519 of 3650 patients) of the total population of patients with rhinological disorders that spontaneously presented to the division of rhinology at our institution. Based on the results of nasal cytology, it was possible to establish the prevalence of inflammation in NAR. Inflammation was demonstrated in 55.49% of NAR patients (288 of 519). In the remaining 44.51%, nasal cytology revealed the lack of inflammatory cells (231 of 519). Finally, the prevalence of different sub-categories of non-allergic rhinitis was established (Table 1). All healthy subjects tested as control were negative for nasal inflammation. In all control subjects, a normal subset of cells, which commonly characterize the pseudo-stratified

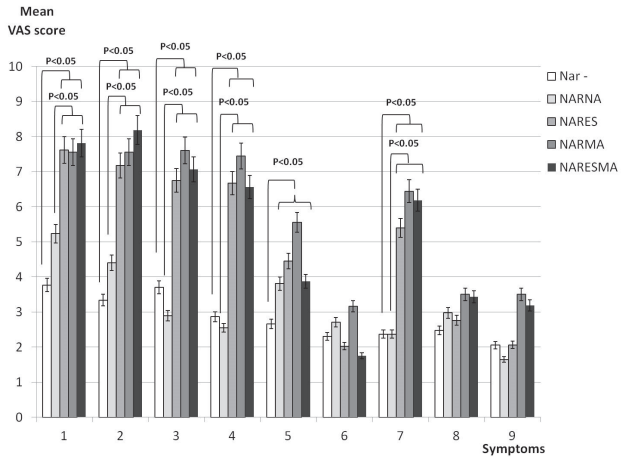

Figure 1. Distribution of the mean VAS scores for each symptom in the different studied subgroups of NAR. Each symptom was expressed as an mean value of the scores of all patients, based on a visual-analogue scale ranging from 0-10. The inter groups significant statistical differences have been indicated in the figure.

Symptoms: 1) nasal obstruction 2) runny nose 3) sneezing 4) nasal itching 5) dysosmia 6) cranio-facial pains 7) lacrimation 8) nocturnal awakenings 9) insomnia.

Abbreviations: Non-allergic rhinitis with negative cytology (NAR-), Non-allergic neutrophil rhinitis (NARNA), Non-allergic rhinitis with eosinophilia syndrome (NARES), Non-allergic mast cell rhinitis (NARMA), Non-allergic eosinophilic-mast cells rhinitis (NARESMA).

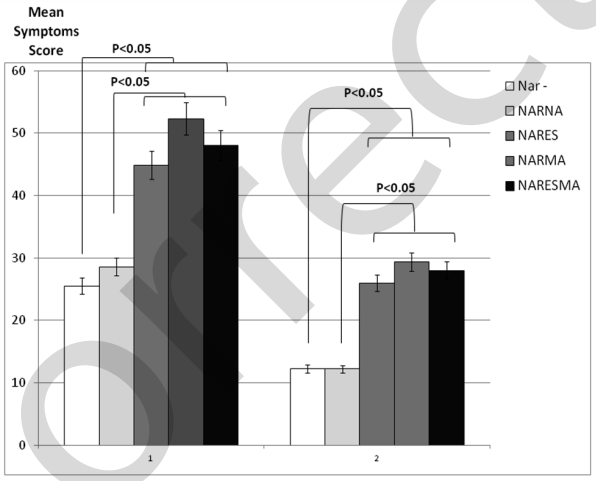

Figure 2. Comparison of mean total scores (1) and mean partial scores (2) in the different categories of NAR. The inter groups significant statistical differences have been indicated in the figure.

Abbreviations: Non-allergic rhinitis with negative cytology (NAR-), Non-allergic neutrophil rhinitis (NARNA), Non-allergic rhinitis with eosinophilia syndrome (NARES), Non-allergic mast cell rhinitis (NARMA), Non-allergic eosinophilic-mast cells rhinitis (NARESMA).

epithelium, was found; besides neutrophils (under 50% of total cells), no other cells were detected in healthy individuals. Casuistry's epidemiological data of the different sub-categories of NAR are reported in Table 2. We observed that NAR+ patients with an eosinophilic and/or mast cell infiltrate had a higher association with comorbidities compared to NAR– and NAR+ with a neutrophilic infiltrate, and in particular considering previously diagnosed asthma [respectively, 14% (17/117) vs. 5.22% (21/402)] and previously documented aspirin intolerance [respectively, 10.25% (12/117) vs. 2.7% (11/402)] with a significant difference for both ($p < 0.05$). Furthermore, a significant difference ($p < 0.05$) was also found for family history of disease [respectively, 27.35% (32/117) vs. 16% (66/402)] (Table 2).

The distribution of the mean score for each symptom analyzed in patients with and without inflammation is shown in Figure 1. The NAR+ and NAR– groups presented, respectively, a mean total score of 39.51 ± 11.1 and 25.53 ± 9.1 and a mean partial score of 21.08 ± 2.9 and 12.27 ± 8.1 with statistically significant difference for both ($p < 0.01$).

A statistically significant difference was observed between the mean total score of NAR– and the different subgroups of NAR+, and in particular with NARES [25.5 ± 12.2 vs. 44.91 ± 11.2 ($p < 0.01$)], NARMA [25.5 ± 11.2 vs. 52.33 ± 13.1 ($p < 0.01$)] and NARESMA [25.5 ± 11.2 vs. 48.09 ± 9.6 ($p < 0.01$)]. Finally, the differences between the average total score of NAR- and NARNE did not reach statistical significance [25.5 ± 11.2 vs. 28.5 ± 12.2 ($p > 0.01$)] (Figure 2).

A statistically significant difference was also observed between the mean partial score of NAR- and NARES, [12.27 ± 3.2 vs. 26.11 ± 8.2 ($p < 0.01$)], and NARMA [12.27 ± 3.2 vs. 29.05 ± 9.1 ($p < 0.01$)] and NARESMA [12.27 ± 3.2 vs. 28.08 ± 8.6 ($p < 0.01$)]. The difference between the mean partial score of NAR- and NARNE did not reach statistical significance [12.27 ± 3.2 vs. 12.20 ± 6.2] (Figure 2).

Table 3 shows the prevalence of different subcategories of NAR based on the severity of symptoms measured by total severity VAS score. The total score was considered suggestive of mild symptoms for value inferior to 3, moderate between 3-7 and severe over 7. The number of patients affected by NAR- and NARNE was very high for total scores < 3, while the number of patients of NARES, NARMA and NARESMA was higher for values of total scores > 7.

Discussion

Although NAR is a condition most common in both clinical outpatient primary care and in ENT specialist practice, its epidemiology, classification, diagnosis, clinical profile and treatment are still a matter of discussion[23,24]. The current study defined the

Table 2. Epidemiological data of the different sub-categories of NAR.

	Mean age	Gender	Familiarity	Current Smokers	Previously documented Aspirin intolerance	Previously diagnosed Asthma
(NAR -)	41.86	M:64 F:167	47 (20.35%)	30 (12.99%)	6 (2.60%)	13 (5.63%)
(NAR +)	39.30	M:128 F:160	47 (16.32%)	25 (8.68%)	14 (4.86%)	23 (7.99%)
(NARNE)	39.13	M:74 F:97	19 (11.11%)	12 (7.02%)	5 (2.92%)	8 (4.68%)
(NARES)	38.40	M:38 F:43	21 (25.92%)	10 (12.35%)	10 (12.35%)	12 (14.81%)
(NARMA)	44.00	M:9 F:10	5 (26.3%)	1 (5.26%)	2 (10.3%)	2 (10.53%)
(NARESMA)	39.80	M:7 F:10	6 (35.29%)	2 (11.76%)	0 (0%)	3 (17.65%)

Non-allergic rhinitis without inflammation (NAR-), Non-allergic rhinitis with inflammation (NAR +), Non-allergic neutrophil rhinitis (NARNE), Non-allergic rhinitis with eosinophilia syndrome (NARES), Non-allergic mast cell rhinitis (NARMA), Non-allergic eosinophilic-mast cells rhinitis (NARESMA).

prevalence, cellular profile and clinical features of NAR, and in particular its subcategories based on cellular profile, in a large series of patients with rhinological disorders who spontaneously presented to our institution.

There is a significant diagnostic problem in patients with NAR. For many years, NAR has been a diagnosis of exclusion, with no generally accepted definition or diagnostic criteria, and for this reason NAR- subcategories have been undetected or overlapped for a long time. A careful and thorough case history is undoubtedly the most important step towards diagnosis, and there is general agreement that complete evaluation of the patient should include currently anterior rhinoscopy, nasal endoscopy and tests to exclude specific sensitivities (skin prick test, specific IgE analysis and nasal provocation). However, no diagnostic tests had been specifically developed to directly identify the presence of inflammation. For these reasons, in recent years the interest of many authors toward nasal cytology has increased. Nasal cytology is also easy to perform and provides relevant information about the predominant cellular infiltration[19,25].

In 14% of patients who spontaneously referred to the rhinology centre of our hospital, it was possible to diagnose NAR. Nasal cytology established that in 55.49% of the cases an inflammatory infiltrate of selective cells of the immune system could be demonstrated by rhinocytogram, while in the remaining 44.51% of the cases there did not appear to be any significant immune system involvement. We strongly encourage dividing NAR patients into two main groups: those with inflammation and those without, because our data suggest that quality of life, based on severity of symptoms, significantly varies in the two categories with a significant difference between NAR– and NAR+ mean total scores. Furthermore, epidemiological data confirm that patients with NAR+ presented a higher association

Table 3. Prevalence of different sub-categories of NAR based on the severity of the symptoms.

	n	Mild symptoms	Moderate symptoms	Severe symptoms
NAR –	231	143 (61.90%)	64 (27.71%)	24 (10.39%)
NARNE	171	123 (71.93%)	35 (20.47%)	13 (7.6%)
NARES	81	1 (1.23%)	13 (16.05%)	67 (82.72%)
NARMA	19	0	2 (10.53%)	17 (89.47%)
NARESMA	17	0	2 (11.75%)	15 (88.24%)

The disease has been divided into MILD, MODERATE and SEVERE based on total severity visual analogue scale (VAS) score (0 10cm): MILD = VAS 0-3; MODERATE = VAS >3-7; SEVERE = VAS >7-10

Abbreviations: Non-allergic rhinitis with negative cytology (NAR-), Non-allergic rhinitis with positive cytology (NAR +), Non-allergic neutrophil rhinitis (NARNE), Non-allergic rhinitis with eosinophilia syndrome (NARES), Non-allergic mast cell rhinitis (NARMA), Non-allergic eosinophilic-mast cells rhinitis (NARESMA).

with comorbidities, and in particular with previously diagnosed asthma and aspirin intolerance with a significant difference in both cases ($p < 0.05$).

In addition, we believe that it is very important to identify the cell predominance of inflammation through cytological investigation. In fact, according to several studies in the literature [19-21], we demonstrated that the type of inflammatory cell population is crucial in determining the severity of nasal symptoms assessed by different symptom scores. In our series, based on nasal cytology, we identified four main subgroups of NAR+ patients according to the selective cellular infiltrate. We demonstrated

that NARNE is the most prevalent form of NAR with inflammation. In fact, we found neutrophils in 32.9% of cases, eosinophils in 15.61%, mast cells in 3.66 % and finally mixed cells (eosinophils and mast cells) in 3.28% of cases. Furthermore, our data confirm that these forms differ from a clinical point of view and, in particular in terms of quality of life[20,26-28]. In fact, our results show that the inflammatory cell infiltrate affects the severity of symptoms, allowing for identification of different phenotypes of NAR. Firstly, we observed that the mean total and partial scores of NARNE and NAR- patients were quite similar without any statistical difference ($p > 0.05$). However, a significant difference ($p < 0.05$) in terms of mean total score was found between the NAR– and NARNE subtypes compared to NARES, NARMA and NARESMA, and in particular for the following symptoms: nasal obstruction, sneezing, rhinorrhoea, itching and lacrimation. In addition, a significant difference was observed for the mean partial score between these same groups indicating that cellular movement affects principally irritating symptoms such as sneezing, nasal itching, lacrimation and rhinorrhoea. Secondly, epidemiological analysis demonstrated that NARES, NARMA and NARESMA presented a higher association with comorbidities than all other groups ($p < 0.05$), and in particular with previously diagnosed asthma and aspirin intolerance. It appears evident that eosinophilic and mast-cells infiltrates in isolated and mixed variants induces a high level of inflammation that causes the most severe symptoms, thus affecting the severity of the disease in a decisive manner[17,30]. Concluding our data also suggest that NARNE and NAR- behave similarly in terms of symptom severity. Whereas NARES, NARMA and NARESMA behave similarly, not only in terms of symptom severity, but also considering associated comorbidities.

The data on the family history of NAR was interesting. In fact, we demonstrated that patients with an eosinophilic and/or mast cells infiltrate had a higher prevalence of familiarity of NAR (27.35% vs. 16%). Our data support previously suggested hypotheses of genetic susceptibility of rhinitis associated with a certain type of cellular infiltrate[29,30]. Future studies should investigate this preliminary suggestion to improve our understanding about the trans-endothelial cellular migration in nasal mucosa.

Cytology allows for correct diagnosis of the different sub-types of NAR. However, when performing this test, the considerable inter-and intra-individual variability in results must be taken into consideration. These variables are partly due to intrinsic variations (environmental exposure to irritants, the presence of subclinical infections, etc.), and partly related to technical factors such as operator experience and sampling technique (mucosal scraping, blown secretions, nasal smears and nasal brushing), counting method and scoring system, which may be completely dissimilar. Sensitivity and specificity of the nasal cytological methods, in fact, differ in the literature[25]. For these reasons, the risk of false negatives for NAR+ is quite high, and this is confirmed by the low sensitivity generally observed in routine clinical practice. The risk of false negatives is even higher if it is considered that NAR+ is characterized by selective migration of immune cells for which the exact pathophysiological basis is unknown, and for this reason are poorly predictable.
Several studies have shown that a good statistically significant correlation exists between the cellular infiltrate and severity of symptoms in some forms of NAR+[14,31]. For this reason, we hypothesized that the symptoms can be collected in a standardized predictive manner. Our data confirmed that NAR subtypes can be differently predicted on the basis of severity of symptoms. By scoring symptoms by a total severity VAS [score (0-10) mild = VAS 0-3; moderate = VAS >3-7; severe = VAS >7-10], we demonstrated that the prevalence of NARNE and NAR- is very high in patients with mild and moderate symptoms. In contrast, the prevalence of NARMA, NARESMA and NARES was higher in patients with severe symptoms.

From a practical point of view, to avoid the risk of false negatives, it is always advisable to carry out the examination at a time in which the patient manifests symptoms more clearly. In our institution, to avoid false negative tests, we suggest to negative patients with a suggestive history of NAR+ to repeat the exam on a day when symptoms are worse. Furthermore, based on our experience, we suggest that useful information may be obtained by colleagues who need to interpret the results of a rhinocytogram if it is always associated with the score results of a questionnaire collected at the time of sampling. In particular, for diagnosis of NARES, NARESMA and NARMA it must be considered that a negative test associated with a low symptom score in a patient with suggestive clinical history and/or a pathognomonic mucosa features may yield a false negative result. In this particular situation, it is useful repeat the test when symptoms manifest more clearly.

Conclusion

In conclusion, we very strongly suggest to determine the presence of inflammation in non-allergic rhinitis patients. Our data confirm that the type of inflammation influences the clinical features, and in particular the severity of symptoms and risk of comorbidities. In our opinion, nasal cytology is a very useful test in outpatient clinical rhinological evaluation, allowing for correct differential diagnosis of various forms of NAR[31-35]. Its impact on differential diagnosis is valuable as it allows identification of patients with NAR who have a significantly reduced quality of life. However, in our opinion, the interpretation of these results can be facilitated if integrated with a symptom score collected at the same time of nasal cytology. Our data support the hypothesis that the type of cellular infiltration might be related to

poor outcome, and for this reason we believe that future studies should clarify the relationship between different mucosal cellular infiltrates and other clinical parameters related to the severity of the disease such us exacerbation rate, need of medication, control of asthma, etc. The most important challenge remains therapy. Nowadays, there are no specific treatment protocols for different types of NAR firstly due to the lack of a correct differential diagnosis, which does not allow to verify the different response of the different NAR subgroups to known drugs, and secondly to the lack of information on the pathogenesis of specific NAR-subtypes essential to identify new specific drugs. We believe that our considerations provide a good foundation for further research to improve the diagnostic and therapeutic approach towards the various subgroups of non-allergic rhinitis.

Authorship contribution

Authorship credit has been assigned based on criteria established by an international committee of medical journal editors (http://www.icmje.org/ethical_1author.html):
EDC: substantial contributions to conception and design, experienced cytologist, writing and drafting the article;
MB, MP, LL, MR: processing of samples and acquisition and collection of data in the very large series of patients;
BS, WDN: analysis and interpretation of data;
GCP, ARF, SB: critical revision of the article for important intellectual content;
GP: final approval of the version to be published.
All authors approved the final version of the manuscript.

Conflict of interest

All authors declare that they have no financial involvement (employment by an industrial concern, consultancies, honoraria, speakers bureau, stock ownership or options, expert testimony, grants received or pending, membership on a standing advisory council or committee, a seat on the board of directors, or being publicly associated with a company or its products, royalties, donation of medical equipment, etc.) with any organization that to any author's knowledge has a direct interest, particularly a financial interest, in the subject matter or materials discussed.

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