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Original Article

Regular CPAP utilization reduces nasal inflammation assessed by nasal cytology in obstructive sleep apnea syndrome

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ABSTRACT

Objectives: To analyze nasal inflammation in a group of patients with obstructive sleep apnea syndrome (OSAS) by means of nasal cytology and to describe the changes induced by continuous positive air pressure (CPAP) treatment.
Subjects and methods: Thirty-two consecutive patients affected by OSAS (mean age 46.9 years) and 13 control subjects (mean age 49.1 years) were enrolled. Detailed clinical, laboratory, and polysomnographic studies were obtained in all participants and, in particular, nasal cytology was performed; inflammatory cells (neutrophils, eosinophils, mast cells, lymphocytes), bacteria, and spores were counted. A subgroup of 19 OSAS patients underwent regular nasal CPAP for eight weeks while the remaining 13 were noncompliant. Nasal cytology was repeated after eight weeks in all patients and controls.
Results: All patients with OSAS were affected by some form of rhinopathy, mostly subclinical, which was not found to influence compliance to CPAP. Regular CPAP treatment induced a significant reduction of cell infiltration (neutrophils, eosinophils, lymphocytes, and muciparous cells), which was not seen in non-treated patients.
Conclusion: Nasal inflammation/infection is a very frequent finding in OSAS and can be reverted by the regular use of CPAP.

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1. Introduction

Multilevel anatomical obstruction contributes to the determinism of obstructive sleep apnea; in particular, even if conflicting results have been reported, several studies suggest that nasal obstruction contributes to its pathogenesis in many patients with obstructive sleep apnea syndrome (OSAS) [1,2]. Nasal obstruction leads to mouth breathing, which is thought to destabilize the upper airway and to aggravate OSAS [3].

It is important to note that the nasal airways represent an important factor for the current treatment of OSAS by means of continuous positive air pressure (CPAP) ventilation during sleep. Therefore, nose pathology might represent an important factor influencing CPAP treatment in OSAS and there is preliminary evidence that subclinical nasal inflammation that cannot be identified from clinical assessment, nasal symptom scores, or rhinomanometry might be frequent and may be a factor influencing patients' compliance to CPAP treatment [4].

The aim of this study was to analyze subclinical nasal inflammation in patients with OSAS by means of nasal cytology and to describe the changes induced by effective treatment by CPAP for a period of eight weeks.

2. Subjects and methods

2.1. Subjects

Thirty-two consecutive patients affected by OSAS (22 men and 10 women, mean age 46.9 ± 14.76 SD) and 13 control subjects (nine men and four women, mean age 49.1 ± 13.97 SD) were asked to participate in this study. Tobacco smoking was reported by five patients and two controls. The two groups showed no differences in age, sex ratio, or tobacco smoking.

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Careful otorhinolaryngological history and examination was carried out in all subjects admitted to this study who also underwent inhalation prick test and nasal cytology.

2.2. OSAS measurement

The patients affected by OSA were all diagnosed following standard clinical/laboratory criteria [5]. Nocturnal polysomnography was carried out with a portable device in-hospital. Light-out time was based on individual habitual bed time and ranged between 09:30 and 11:30 p.m. Subjects were allowed to sleep in until their spontaneous awakening in the morning. The sleep respiratory pattern of each patient was monitored using oral and nasal airflow thermistors or nasal pressure cannula, thoracic, and abdominal respiratory effort strain gauge, respiratory noise with a microphone, body position, oxygen saturation (pulse-oximetry), electrocardiography or heart rate. Apneas were defined as 10 s of absent airflow. Hypopneas were scored as 10-s decrements in airflow, chest, or abdominal movement followed by an arousal, awakening, or oxygen desaturation of at least four percentage points. Patients with an apnea/hypopnea index $\geqslant$15 were included and subjects with an apnea/hypopnea index <15 were excluded, as were subjects with a history of stroke, traumatic brain injury, or any other neurological condition.

The control subjects did not have any symptoms of OSA (excessive daytime sleepiness, habitual snoring reported by their bed partner, obesity, cranio-facial malformation, systemic hypertension, etc.), or any other neurological or otorhinolaryngological disease.

2.3. Otorhinolaryngological examination

Nasal endoscopy was carried out by means of a flexible device (Vision Science – ENT 2000, diameter 3.4 mm) in order to detect the eventual presence of endonasal anatomical structure changes (septal cartilage, turbinates, nasal secretions, polyps, etc.). None of the patients needed local anesthesia nor nasal decongestion. In this study we did not include patients with clearly obstructive septal deformities because these patients need surgical treatment before CPAP; for this reason, rhinomanometry was not performed in the patients admitted.

2.4. Skin prick test

Allergy was assessed by the presence of sensitization to the most common classes of aeroallergens by carrying out a skin prick test as stated by the European Academy of Allergy and Clinical Immunology: sensitization was considered when the wheal diameter was equal to or greater than three mm [6]. The allergen panel consisted of the following: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria judaica*, birch, hazel tree, olive tree, *Alternaria* tenuis, *Cladosporium*, and *Aspergilli* mix; the concentration of allergen extracts was 100 I.R./mL (Stallergenes, Milan, Italy).

2.5. Nasal cytology

Nasal cytology was performed by anterior rhinoscopy using a nasal speculum and good lighting. The collection technique consisted of collecting scrapings from the middle portion of the inferior turbinate using a Rhino-Probe® [7]. Anaesthesia was not necessary. Briefly, the cellular material was 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, since 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 by a Nikon E600 light microscope (Nikon, Canada) equipped with a digital camera (Nikon "Coolpix 990, 3.34 MP") 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 semi-quantitative grading, as proposed by Meltzer and Jalowayski [8]. 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 rhinopathy were subdivided on the basis of the prick test and of the nasal cytology into subjects with allergic rhinitis or with "cellular" nonallergic rhinitis [9–11]. Cellular forms were further subdivided based on their cytotype:

Non Allergic Rhinitis with neutrophils "NARNE" (neutrophils >50% with absent spores and bacteria);
Non Allergic Rhinitis with eosinophils "NARES" (eosinophils >20%);
Non Allergic Rhinitis with mast cells (mast cells >10%);
Non Allergic Rhinitis with eosinophils and mast cells "NARESMA" (eosinophils >20% and mast cells >10%).

2.6. Study protocol

CPAP titration was attempted, manually selecting, for each OSAS patient, the lowest pressure sufficient for preventing snoring, apneas, and hypopneas in all postures of sleep. The optimal CPAP pressure established during the titration night, which ranged between seven and 12 cm H_2O, was continued and monitored throughout the entire protocol period. However, based on the individual effective compliance to CPAP during the titration night and during the first week of study, patients were subdivided into two subgroups: the first was composed of subjects who were found to be compliant with the nasal CPAP ventilation, regularly applied every night for a minimum of five hours/night, for a period of eight weeks (19 patients, OSAS + CPAP); the second subgroup was composed of patients who did not adapt or accept CPAP ventilation and discontinued it during the titration night or during the first week of ventilation (13 patients, OSAS). Nasal cytology was performed at baseline (before the CPAP titration) and at follow-up after eight weeks in both subgroups of patients and in normal controls.

This study was approved by the local ethics committee and all subjects provided informed consent according to the Declaration of Helsinki before entering the study.

2.7. Statistical analysis

For the statistical analysis, all comparisons were performed by means of the nonparametric Mann–Whitney test for unpaired datasets, the Kruskal–Wallis ANOVA, or the Wilcoxon test for paired datasets, as appropriate. However, because of the relatively limited number of subjects available and to rule out possible type II errors, we also calculated effect sizes using the Cohen's *d* value [12]. Cohen's *d* is defined as the difference between two means divided by their pooled standard deviation. According to Cohen, 0.2

is indicative of a small effect, 0.5 of a medium, and 0.8 of a large effect size. The commercially available Statistica software package (StatSoft, Inc., 2001. STATISTICA data analysis software system, version 6, www.statsoft.com) was used. Differences were considered significant when they were below the $p < 0.05$ level.

3. Results

3.1. History

A family history for atopia/allergies was found in seven (21.8%) patients. Almost all patients reported nasal symptoms coherent with a possible vasomotor condition: 15 (46.8%) reported nasal obstruction, 11 (34.3%) reported rhinorroea, five (15.6%) reported nasal itching, and 16 (50%) reported sneezing. Three (9.3%) patients also reported a reduction of the olfactory function.

3.2. Nasal endoscopy

Twelve out of the 32 OSAS patients (37.5%) showed non-obstructive deformities of the septal cartilage, 15 (46.8%) had hypertrophic inferior turbinates, and in eight (25%) a mucous secretion from the middle meati was found (rhino-sinusitis). No polyps or rhinopharyngeal pathologies were found.

3.3. Skin prick test

Five out of the 32 patients examined (15.6%) were found to be allergic, three of them were monosensitive (*Dermatophagoides farinae* and *pteronyssinus*) and two were polysensitive (*Dermatophagoides pteronyssinus*, cat, dog, grasses mix, *Parietaria judaica*, olive tree, and *Alternaria tenuis*).

3.4. Nasal cytology

At cytologic analysis, nine patients (28.1%) had signs of NARNE, six (18.7%) of NARES, and four (12.5%) of NARESMA. Five (15.6%) patients showed the cellular signs of allergic rhinitis with numerous neutrophils and eosinophils, partially degranulated [13]; in eight (25%) the cytologic signs of rhinosinusitis where characterized by numerous neutrophils and bacteria [14]. Fig. 1 shows, as examples, the typical rhinocytograms of normal nasal mucosa, allergic rhinitis, and all forms of non allergic nasal conditions.

The comparison between BMI and nasal cytology results obtained from OSAS patients and normal controls at baseline is shown in Table 1. As expected, BMI was significantly higher in patients who also showed significantly increased eosinophil cell count and bacteria count grade than normal controls. Among the other parameters a trend of increase was also evident for neutrophils, mast cells, and muciparous cells in OSAS patients, which was supported by a moderate-to-high effect size.

3.5. Effects of CPAP treatment

As described above, only a subgroup of patients underwent effective and regular CPAP treatment; thus, patients were subdivided into two subgroups but nasal cytology did not differ significantly between them at baseline. Among OSAS + CPAP patients, seven had NARNE, three had NARES, two had NARESMA, three had allergic rhinitis, four had rhinosinusitis; among OSAS patients, two had NARNE, three had NARES, two had NARESMA, two had allergic rhinitis, four had rhinosinusitis.

Table 2 reports the detailed intra-group (OSAS + CPAP, OSAS, and controls) comparison of BMI and nasal cytology results obtained at baseline and at follow-up. The group of patients with OSAS + CPAP showed a significant reduction in neutrophil, eosinophil, lymphocyte, and muciparous cell counts while no significant changes were observed in the other two groups (OSAS patients and controls). Fig. 2 shows, as examples, the nasal cytology of two patients in the OSAS + CPAP subgroup before and after regular CPAP treatment for eight weeks.

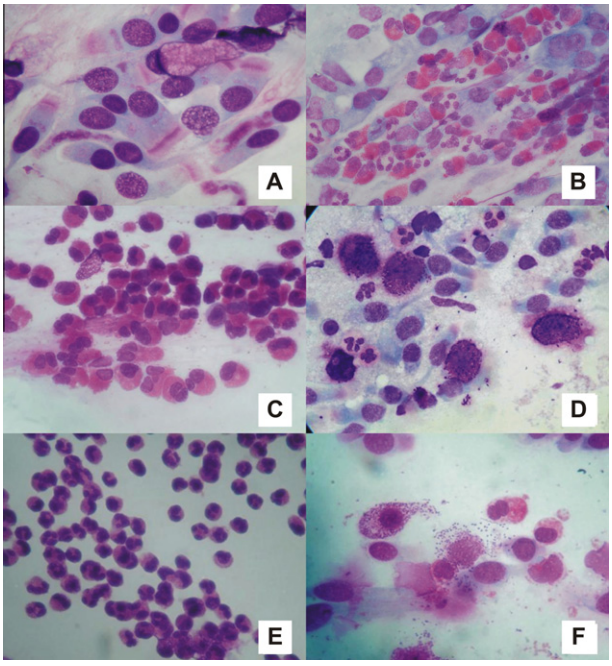

Fig. 1. (A) Normal nasal cytology with evident ciliate cells; (B) allergic rhinitis; (C) NARES; (D) NARMA; (E) NARNE; (F) NARESMA. Staining MGG, magnification ×1000.

The comparison of the BMI and of the nasal cytology results between patients with OSAS + CPAP and with OSAS at baseline did not show any significant difference between these two patient subgroups.

Finally, in Table 3, the intergroup differences in BMI and nasal cytology parameters between baseline and follow-up, obtained from OSAS patients (treated with CPAP or not) and normal controls are reported. In this table it is possible to see that the reduction in neutrophils, lymphocytes, and muciparous cells observed in OSAS + CPAP patients were significantly larger than the changes observed in the other two groups of subjects who did not undergo CPAP treatment.

4. Discussion

Several studies have been carried out on the relationship between OSAS and inflammation of the upper airways [15–17]; others have searched for the eventual presence of predictive factors of the compliance to nasal CPAP treatment by means of the evaluation of the cytologic aspects, the modifications of certain mediators, and the degree of nasal obstruction, and also by rhinomanometry [4,18–20].

The aim of this study was to analyze subclinical nasal inflammation in a group of patients with OSAS by means of nasal cytology and to describe the changes induced by an effective treatment with CPAP after a period of eight weeks. First of all, we have found that all patients with OSAS were affected by a form of rhinopathy, mostly subclinical. This is in partial agreement with the previous report by Shadan et al. [4] who found that 58% of their OSAS patients were affected by rhinitis. However, different from that study, we could not confirm that these factors significantly influence the

Table 1
Comparison between BMI and nasal cytology results obtained from OSAS patients and normal controls at baseline.

	OSAS (n = 32)		Controls (n = 13)		Mann–Whitney test	Effect size
	Mean	S.D.	Mean	S.D.	$p<$	Cohen's d
BMI	31.2	6.25	20.5	1.39	0.000001	2.363
Neutrophils, count	112.0	56.16	81.5	25.27	NS	0.700
Eosinophils, count	6.6	10.25	0.0	0.00	0.015	0.911
Mast cells, count	1.7	4.40	0.0	0.00	NS	0.546
Lymphocytes, count	6.5	11.39	3.5	3.99	NS	0.352
Muciparous cells, count	119.1	109.70	77.4	25.71	NS	0.523
Bacteria, count grade	1.2	1.20	0.0	0.00	0.0034	1.414
Spores, count grade	0.2	0.47	0.1	0.28	NS	0.259

Table 2
Comparison between BMI and nasal cytology results obtained from OSAS patients (treated with CPAP or not) and normal controls at baseline and at follow-up.

	Baseline		Follow-up		Wilcoxon test	Effect size
	Mean	S.D.	Mean	S.D.	$p<$	Cohen's d
OSAS + CPAP (n = 19)						
BMI	31.7	6.02	31.4	5.96	NS	0.053
Neutrophils, count	109.2	49.60	42.4	30.89	0.00013	1.615
Eosinophils, count	5.9	10.21	1.4	2.09	0.028	0.614
Mast cells, count	0.9	2.33	0.6	1.89	NS	0.124
Lymphocytes, count	8.4	12.88	2.3	2.91	0.017	0.654
Muciparous cells, count	116.8	121.15	35.3	37.47	0.002	0.910
Bacteria, count grade	0.9	1.22	0.8	2.32	NS	0.085
Spores, count grade	0.1	0.46	0.0	0.00	NS	0.324
OSAS (n = 13)						
BMI	30.5	6.75	30.4	6.85	NS	0.011
Neutrophils, count	116.2	66.53	118.5	57.42	NS	−0.037
Eosinophils, count	7.6	10.65	6.8	9.92	NS	0.075
Mast cells, count	2.8	6.29	2.5	5.95	NS	0.050
Lymphocytes, count	3.8	8.51	4.8	11.00	NS	−0.102
Muciparous cells, count	122.3	95.14	137.7	104.65	NS	−0.154
Bacteria, count grade	1.5	1.13	1.5	1.27	NS	0.000
Spores, count grade	0.3	0.48	0.6	0.77	NS	−0.480
Controls (n = 13)						
BMI	20.5	1.39	20.5	1.20	NS	0.000
Neutrophils, count	81.5	25.27	76.9	19.44	NS	0.201
Eosinophils, count	0.0	0.00	0.0	0.00	NS	0.000
Mast cells, count	0.0	0.00	0.0	0.00	NS	0.000
Lymphocytes, count	3.5	3.99	4.1	3.62	NS	−0.141
Muciparous cells, count	77.4	25.71	72.5	28.09	NS	0.180
Bacteria, count grade	0.0	0.00	0.0	0.00	NS	0.000
Spores, count grade	0.1	0.28	0.0	0.00	NS	0.392

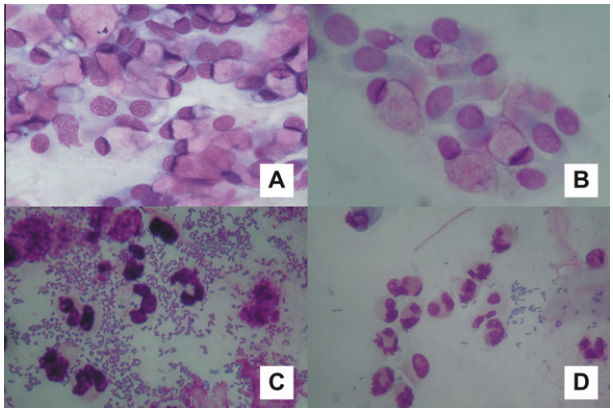

Fig. 2. (A) Muciparous metaplasia in one patient with OSAS before CPAP; (B) the same patient after CPAP treatment, note the significant reduction in muciparous cells; (C) bacterial rhinosinusitis in another patient with OSAS before CPAP with numerous bacteria and neutrophils; (D) the same patient after CPAP treatment, note the significant reduction of the infectious components. Staining MGG, magnification ×1000.

compliance to CPAP treatment, since they were equally present in compliant and noncompliant patients. However, the relatively small sample size of the patient groups in the study by Shadan et al. [4] and in our own does not allow for the derivation of definite statements on the eventual significance of the cytological abnormalities found for the CPAP compliance, but the results represent an important indication for the future assessment of this point in larger analyses.

The most interesting result of our study is the significant effect of CPAP treatment on cell infiltration (neutrophils, eosinophils, lymphocytes, and muciparous cells); this was observed exclusively in patients who regularly used CPAP during the study period. It is reasonable to assume that such a reduction in immune- and inflammation-related cell components might be determined by the better ventilation of the nasal airways that is possible with CPAP. Thus, a night-time under-ventilated nose (due to apnea) may have an increased risk for infections and inflammation that can, at least partially, be reverted by CPAP. It is possible to speculate that the mechanisms of this reversal might be based on the reduction in neutrophils and on a cascade of reductions in interleukins 1 and 8 that are also active for other inflammation-related

Table 3
Comparison between the differences in results of BMI and nasal cytology between baseline and follow-up, obtained from OSAS patients (treated with CPAP or not) and normal controls.

	OSAS + CPAP (n = 19)		OSAS (n = 13)		Controls (n = 13)		Kruskal–Wallis ANOVA	Post-hoc Mann–Whitney test		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	$p<$	1 vs. 2	1 vs. 3	2 vs. 3
BMI	−0.3	0.67	−0.1	0.64	0.0	0.58	NS			
Neutrophils, count	−66.7	44.91	2.3	27.13	−4.5	9.94	0.00001	0.00004	0.000034	NS
Eosinophils, count	−4.5	8.73	−0.8	1.48	0.0	0.00	NS			
Mast cells, count	−0.3	2.86	−0.3	0.85	0.0	0.00	NS			
Lymphocytes, count	−6.1	10.56	1.0	4.20	0.5	3.95	0.05000	0.046	NS	NS
Muciparous cells, count	−81.6	110.57	15.4	34.79	−4.8	14.64	0.0001	0.00025	0.0014	NS
Bacteria, count grade	−0.2	1.92	0.0	0.71	0.0	0.00	NS			
Spores, count grade	−0.1	0.46	0.3	0.85	−0.1	0.28	NS			

cells, such as eosinophils, lymphocytes, and mast cells. The reduction of the presence of these cells would positively influence the nasal mucosa by reducing the risk of chronicization or complications.

In particular, the reduction in neutrophils can induce a reduction in elastasis, a lysosomial enzyme that seems to be one of the main responsible factors for the production of free radicals, with subsequent cell damage. In addition, the reduction in eosinophils and, subsequently, of their intracellular mediators (major basic protein and eosinophil cationic protein) should protect from damages to the intercellular junction systems, which are responsible for the maintenance of the mucosal barrier and, therefore, should also avoid the stimulation of the trigeminal irritant receptors responsible for the classical vasomotor symptoms affecting patients with allergic or cellular rhinitis (NARES, NARESMA) [21–25].

Finally, the reduction of the muciparous cells can also be beneficial because muciparous metaplasia induces an increase of the mucous component with a subsequent reduction of the transport of cilial mucous, a predisposing condition for bacterial adhesion and formation of biofilm [26].

This study has some limitations due to the relatively limited number of patients analyzed and the relatively short CPAP usage compared to the usual years of use by patients. However, it might be hypothesized that a longer CPAP use might be followed by even more significant beneficial changes in nasal cytology. Moreover, all patients in this study used CPAP devices with an air humidifier; thus, we do not know if similar results can be obtained with devices without a humidifier and we cannot exclude a major role for this factor (air vs. water). Further studies are warranted in this field in order to better understand these mechanisms.

5. Financial disclosures of all authors

Raffaele Ferri has consulted for Merck & Co., Sanofi-Aventis, and Sapio Life; there are no financial interests that represent a potential conflict of interest for Matteo Gelardi, Giuseppe Carbonara, Enrico Maffezzoni, Maurizio Marvisi, or Nicola Quaranta.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi: 10.1016/j.sleep.2012.04.004.

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