

Allergic rhinitis and aspirin-exacerbated respiratory disease as predictors of the olfactory outcome after endoscopic sinus surgery

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ABSTRACT

Background: Unlike the functional outcomes of endoscopic sinus surgery, which have been thoroughly studied, the effect of the surgery on olfactory performance and the relative predictive factors have not been adequately assessed by literature. Allergic rhinitis and aspirin-exacerbated respiratory disease (AERD) are examined as potential confounding factors of the olfactory outcome in patients with extensive nasal polyposis and rhinosinusitis treated with functional endoscopic sinus surgery (FESS).

Methods: A population of 116 adults with severe nasal polyposis was subjected to FESS after failure of the appropriate medical treatment. The olfactory outcome was quantified by Sniffin' Sticks at the 1st, 3rd, and 6th postoperative month in relation to the concomitant presence of allergic rhinitis (n = 62) or AERD (n = 18).

Results: Allergic patients seemed to perform worse than nonallergic patients at all time frames. However, when patients with similar olfactory acuity, age, and medical history are compared, allergic rhinitis does not seem to affect the postoperative improvement of the composite threshold-discrimination-identification scores. The same seems to apply for the likelihood of acquiring normosmia after surgery. On the contrary, AERD significantly limits the recovery of olfactory function at all follow-up examinations and patients with AERD are unlikely to become normosmic.

Conclusion: The olfactory recovery after FESS for nasal polyposis is significantly affected by the concomitant presence of AERD. Although allergy seems to have a general negative effect on olfactory acuity, it was not found to affect the extent of the olfactory improvement, when patients with comparable preoperative characteristics are addressed.

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Key words: Allergic rhinitis, aspirin-exacerbated respiratory disease, endoscopic sinus surgery, nasal polyposis, olfactory, rhinosinusitis, Sniffin' Sticks

Functional endoscopic sinus surgery (FESS) has been for several years the gold standard for the restoration of nasal airflow and mucociliary recovery in cases of nasal polyposis and chronic rhinosinusitis that are resistant to medical treatment.^{1,2} Although defective olfactory performance is a common complaint, the information collected on the olfactory recovery has been rather limited. As a result, the pre- or postoperative counseling regarding the recovery of the olfactory impairment is often hypothetical or inadequate, especially in patients who present additional chronic inflammatory conditions, such as allergic rhinitis and aspirin-exacerbated respiratory disease (AERD; a combination of nasal polyposis, acetylsalicylic acid [ASA] intolerance, and asthma).

The aim of this study was to monitor the postoperative results of FESS on olfactory performance in a population with extensive nasal polyposis and evaluate the results with respect to the concomitant presence of persistent allergic rhinitis or AERD. The predictive value of each of these characteristics

on the postoperative outcome was specifically mentioned. The evaluation of the olfactory outcome was based on a quantitative and qualitative procedure (Sniffin' Sticks), unlike in previous reports.³⁻⁶

PATIENTS AND METHODS

Our population consisted of 116 patients, who were subjected to FESS, with the diagnosis of nasal polyposis stage III, according to the Malm classification.⁷ All patients considered to have persistent allergic rhinitis reported history of nasal congestion, rhinorrhea, postnasal drip, and sneezing and had at least one positive allergy skin test result that was relevant to their history (perennial antigen). A history of ASA sensitivity or positive oral ASA challenge (starting with 30 mg and advancing to 650 mg of aspirin) was present in all patients eligible for the AERD group and the diagnosis of asthma was made by a pneumonologist. All patients underwent preoperative CT scanning and scans were graded at a total score over 16 (average, 18; range, 18-24) according to the Lund-Mackay CT scoring system.⁸ All subjects completed the "Sniffin' Sticks" test (Burghardt, Wedel, Germany) once preoperatively and three times postoperatively (1, 3, and 6 months after surgery) as it has been described in detail in a previous study.⁹

The test battery consisted of three examinations, odor threshold (OT), suprathreshold odor discrimination (OD), and odor identification (OI), which were finally summed to

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form an overall score called "composite threshold-discrimination-identification score" (TDI). The TDI score ranged from 0 to 48 with values ≤ 15 considered consistent with functional anosmia. In the mild climate conditions of Greece, the TDI score at the 10th percentile, which defines the limit between normosmia and hyposmia, was 36.75 in subjects < 16 years, 38.75 for ages from 16 to 35 years, and 30.75 for subjects > 55 years.^{9,10}

AQ:3 Preoperatively, all patients received oral prednisolone for 10 days (40 mgr/day for 3 days, which was then gradually diminished by 5 mgr/day) and a nasal spray of budesonide for 1 month. Baseline examinations were performed before the initiation of oral therapy. All operations were performed by two experienced surgeons following the Messerklinger technique to the same extent (antroscopy, ethmoidectomy, sphenoidotomy, and opening of the frontal sinus) and with the use of a microdebrider device.^{11,12} All patients were administered postoperatively topical treatment with nasal corticosteroids (budesonide, 400 mgr twice daily) for 1 year and antibiotics (ciprofloxacin) for 2 weeks. No patient received postoperatively any corticosteroids systematically. All examinations were performed in accordance with the principles of the Declaration of Helsinki/Hong Kong.

Statistical analysis of the data was performed using the Statistical Package for the Social Sciences, version 13.0 (SPSS, Inc., Chicago, IL). The chi-square test was used to evaluate any potential association between categorical variables. Student's *t*-test was used to compare the indices of olfactory function between group of patients according to AERD and allergic rhinitis at each time frame. Repeated measures analysis of variance (ANOVA) was used to examine the changes of the indices of olfactory function throughout the follow-up time. One-way analysis of covariance (ANCOVA) was performed to investigate the effect of AERD and allergic rhinitis on the olfactory function 6 months after surgery, adjusting for baseline scores and other potential confounders (gender, age, duration of symptoms, smoking, previous surgery, and gustatory impairment). Odds ratio (OR) was estimated as the measure of association of AERD and allergic rhinitis with normal olfactory function. All tests were two tailed and statistical significance was considered for values of $p < 0.05$.

RESULTS

T1 The study population (Table 1) included 116 patients with mean age of 47.55 ± 13.08 years (range, 25–78; median age, 44 years). AERD was present in 18 patients (15.5%) and allergic rhinitis was diagnosed in 62 patients (53.4%). A statistically significant stepwise increment of TDI score over time was noted both in patients without allergic rhinitis ($p < 0.001$) and in patients with allergic rhinitis ($p < 0.001$). TDI score exhibited highly significant elevation of 97.6% in patients without allergic rhinitis and of 140.1% in patients with allergic rhinitis (both, $p < 0.001$) at the 1st postoperative month. Smaller but significant improvements of TDI score were observed at the 3rd (14.9% in patients without and 24.1% in patients with allergic rhinitis; both, $p < 0.001$) and 6th postoperative month (10.5% in patients without and 12.1% in patients with allergic rhinitis; both, $p < 0.001$; Table 2).

T2 In terms of TDI scores, allergic patients performed significantly worse than nonallergic patients in all time frames (all,

Table 1 Characteristics of the 116 patients who underwent endoscopic sinus surgery

	No of patients	Percentage (%)
Gender		
Male	45	38.8
Female	71	61.2
Age		
\leq yr	23	19.8
36–55 yr	59	50.9
> 55 yr	34	29.3
Duration of olfactory dysfunction		
≤ 10 yr	60	51.7
> 10 yr	56	48.3
Samter's disease		
No	98	84.5
Yes	18	15.5
Allergic rhinitis		
No	54	46.6
Yes	62	53.4
Smoking		
No	72	62.1
Yes	44	37.9
Previous surgeries		
No	78	67.2
Yes	38	32.8
Taste disorders		
No	96	82.8
Yes	20	17.2

$p < 0.001$); OT, OD, and OI scores showed a similar trend in these two groups of patients in all follow-up examinations (all, $p < 0.010$). However, the interaction between the presence of allergic rhinitis and the change over time was not statistically significant for OT ($p = 0.076$), OD ($p = 0.740$), OI ($p = 0.381$), or TDI scores ($p = 0.081$; Table 2). After adjustment for baseline TDI score and all other potential confounders, one-way ANCOVA failed to indicate a significant influence of allergic rhinitis on the postoperative improvement of olfaction. The postoperative OT and OI scores were not affected by the concomitant presence of allergic rhinitis ($p = 0.849$ and 0.233 , respectively), whereas regarding OD and TDI scores, significance levels were approached ($p = 0.053$ and 0.061 , respectively; Table 2).

Marginal homogeneity test showed a significant improvement of olfactory function from one measurement to another in both nonallergic (all, $p < 0.001$) and allergic patients (all, $p < 0.05$; Fig. 1). However, in the multivariate analysis, allergic rhinitis was not confirmed as an independent predictor of normal olfactory function, although statistical significance was approached (48.1% versus 30.6%; $p = 0.054$; OR = 2.10; 95% CI = 0.98–4.49).

TDI score exhibited a highly significant elevation of 110.3% in patients without AERD and of 191.9% in patients with AERD (both, $p < 0.001$) on the 1st postoperative month.

Table 2 Olfactory function (mean values ± SD) of the 116 patients who underwent functional endoscopic sinus surgery in relation to allergic rhinitis

	Preoperatively	Postoperatively			p Value
		1st mo	3rd mo	6th mo	
OT score					<0.001,* 0.076,# 0.849§
No allergic rhinitis	0.59 ± 0.94	4.24 ± 2.05	5.20 ± 1.74	6.08 ± 1.49	
Allergic rhinitis	0.24 ± 0.69	2.73 ± 2.36	3.79 ± 2.51	4.29 ± 2.79	
OD score					<0.001,* 0.740,# 0.053§
No allergic rhinitis	7.06 ± 3.25	11.61 ± 3.12	13.28 ± 2.14	14.46 ± 1.50	
Allergic rhinitis	4.10 ± 3.23	8.08 ± 5.19	9.98 ± 4.89	11.27 ± 4.94	
OI score					<0.001,* 0.381,# 0.233§
No allergic rhinitis	5.94 ± 3.18	11.00 ± 3.13	12.37 ± 2.61	13.56 ± 1.79	
Allergic rhinitis	3.40 ± 2.92	7.77 ± 4.99	9.29 ± 4.82	10.29 ± 4.91	
TDI score					<0.001,* 0.081,# 0.061§
No allergic rhinitis	13.59 ± 6.99	26.85 ± 7.88	30.85 ± 6.03	34.10 ± 4.45	
Allergic rhinitis	7.74 ± 6.60	18.58 ± 12.27	23.06 ± 11.90	25.86 ± 12.30	

*Statistical significance between the different time frames within each group (one-way repeated measures ANOVA).
 #Statistical significance for the interaction between allergic rhinitis and postoperative outcome (two-way mixed ANOVA).
 §Statistical significance for the interaction between allergic rhinitis and postoperative outcome after adjustment for potential confounding factors (ANCOVA).
 ANOVA = analysis of variance; ANCOVA = analysis of covariance; OT = odor threshold; OD = odor discrimination; OI = odor identification; TDI = threshold–discrimination–identification

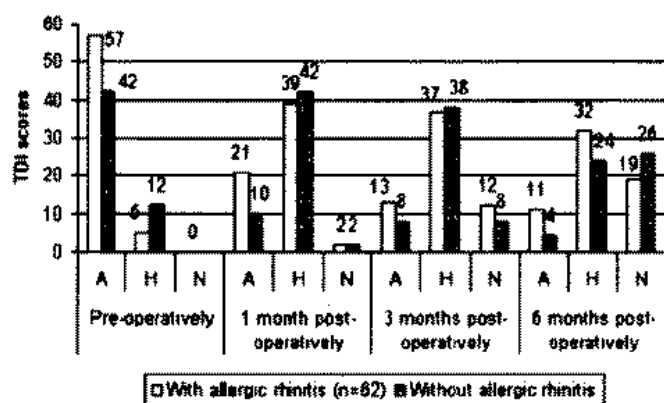


Figure 1. Olfactory function (anosmia = A, hyposmia = H, or normosmia = N) in patients with and without allergic rhinitis preoperatively and 1, 3, and 6 months after FESS.

Smaller but significant improvements of TDI score were observed on the 3rd postoperative month in both groups (16.7% in patients without AERD, $p < 0.001$; 50.9% in patients with AERD, $p = 0.012$). On the 6th postoperative month, while TDI score continued to increase in patients without AERD ($p < 0.001$), it remained approximately at the same level in patients with AERD ($p = 1.000$). Similar changes over time were observed for OT, OD, and OI scores. It is of note that in patients with AERD all indices of olfactory performance seemed to increase only during the first 3 postoperative months (Table 3).

In all four examinations, patients presenting with AERD performed significantly worse than patients without AERD in all tests (Table 3, $p \leq 0.001$). Patients with the AERD showed

a significantly smaller increase of the TDI score during the postoperative follow-up when compared with patients without AERD (12.81 ± 6.47 versus 20.41 ± 6.97 , $p = 0.003$). The negative effect of AERD on the course of the postoperative recovery was reflected on all olfactory examinations in a statistically significant extent (OT, $p < 0.001$; OD, $p = 0.009$; OI, $p = 0.001$). After adjustment for baseline scores and all other potential confounders, ANCOVA showed that all final olfactory scores (TDI, OT, OD, and OI) at the 6th postoperative month were significantly less satisfactory in the group of patients presenting the AERD (all, $p < 0.001$).

The olfactory function of patients with AERD improved significantly only during the 1st and 3rd postoperative month ($p = 0.046$ and $p = 0.005$, respectively). No significant change was observed during the time interval between the 3rd and 6th month ($p = 1.000$). The percentage of normal olfactory performance at the 6-month follow-up was higher for patients without the AERD (43.9% versus 11.1%, $p = 0.009$; OR = 6.24; 95% CI = 1.36–28.57; Fig. 2). Multivariate logistic regression analysis revealed that the absence of AERD remained a strong independent predictor of normal olfactory function; a successful outcome was approximately six times commoner in patients without the AERD than in patients with the AERD (OR = 6.04; 95% CI = 1.10–36.46).

DISCUSSION

Allergic rhinitis and nasal polyposis are common etiologic factors of conductive olfactory loss.^{13,14} However, the pathophysiology of olfactory dysfunction seems to expand beyond an obvious physical blockade of odorant molecules from reaching the olfactory mucosa in the nasal vault. Several studies report the absence of clear association between cleft

Table 3 Olfactory function (mean values \pm SD) of the 116 patients who underwent endoscopic sinus surgery in relation to aspirin-exacerbated respiratory disease (AERD)

	Preoperatively	Postoperatively			p Value
		1st mo	3rd mo	6th mo	
OT score					<0.001,* <0.001,# <0.001§
No AERD	0.48 \pm 0.88	3.85 \pm 2.20	4.86 \pm 2.05	5.65 \pm 2.09	
AERD	0.00 \pm 0.00	1.17 \pm 1.66	2.22 \pm 2.27	2.25 \pm 2.21	
OD score					<0.001,* 0.009,# <0.001§
No AERD	6.13 \pm 3.36	10.69 \pm 3.97	12.39 \pm 3.26	13.78 \pm 2.84	
AERD	1.89 \pm 2.14	4.44 \pm 4.80	6.78 \pm 5.44	7.22 \pm 5.24	
OI score					<0.001,* 0.001,# <0.001§
No AERD	5.16 \pm 3.16	10.22 \pm 3.81	11.65 \pm 3.36	12.76 \pm 3.12	
AERD	1.44 \pm 1.95	4.11 \pm 4.61	5.67 \pm 4.92	6.67 \pm 5.11	
TDI score					<0.001,* <0.001,# <0.001§
No AERD	11.78 \pm 7.09	24.77 \pm 9.62	28.90 \pm 8.22	32.18 \pm 7.69	
AERD	3.33 \pm 4.03	9.72 \pm 10.94	14.67 \pm 12.55	16.14 \pm 12.34	

*Statistical significance between the different time frames within each group (one-way repeated measures ANOVA).
 #Statistical significance for the interaction between AERD and the postoperative outcome (two-way mixed ANOVA).
 §Statistical significance for the interaction between AERD and the postoperative outcome after adjustment for potential confounding factors (ANCOVA). ANOVA = analysis of variance; ANCOVA = analysis of covariance; OT = odor threshold; OD = odor discrimination; OI = odor identification; TDI = threshold–discrimination–identification

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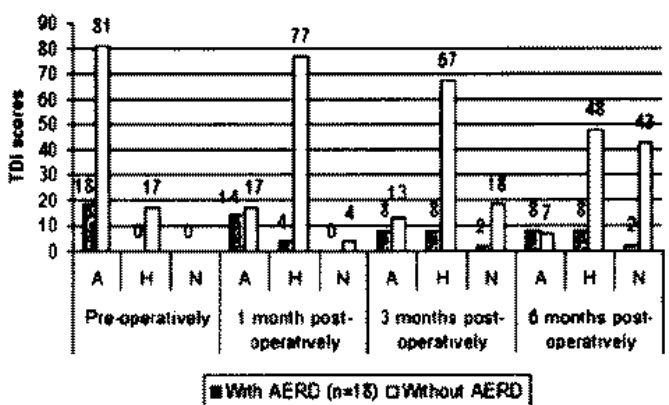


Figure 2. Olfactory function (anosmia = A, hyposmia = H, or normosmia = N) in patients with and without AERD preoperatively and 1, 3, and 6 months after FESS.

visibility or rhinomanometry measures and olfactory function.^{13,15,16} Hyposmia may also result from an inflammatory dysfunction of the neuroepithelium, inflammatory hypersecretion, or destruction of the mucosa.^{13,17} Allergic rhinitis patients, who are prone to nasal infections, demonstrate morphologic and functional changes on the olfactory cilia, dendrites, and neurons as well as changes in composition and function of the olfactory mucus.^{18–20} On the other hand, the olfactory receptor cells have some propensity to regenerate, and the olfactory bulb is one of the few central nervous system structures where cells are continually being replaced.²¹

The postoperative outcome of FESS on olfactory dysfunction seems, therefore, a multifactorial process. The potential prognostic factors have not been objectively established but

and the relative counseling remains mainly hypothetical. Neither the degree of preoperative obstruction nor the duration of olfactory loss seems to correlate directly with therapeutic success. The endoscopically monitored formation of normal mucosa may not be the only factor affecting the improvement of olfaction.^{3,22,23} Similarly, the predictive value of CT seems to be limited and controversial in terms of both olfactory and endoscopic examination.^{24–27} Most of the existing studies have used the patient's subjective evaluation of symptoms to assess the clinical outcomes after FESS with questionnaires on several patient-evaluated symptoms, without targeting olfactory performance.^{3,5,6} Individuals, however, seem to vary in their awareness of changes in olfactory sensitivity and only 84% of the patients with impaired sense of smell seem to be aware of their problem.^{28,29}

The prognostic value of allergic rhinitis and AERD for the acquisition of normal olfactory performance was estimated during the first 6 postoperative months. This time interval was selected as representative for the postoperative trends in olfactory recovery, because it correlates with the terminal phase of the healing process of main nasal tissues and is used as a standard in the study of the healing process after endoscopic nasal surgery.^{3,22,29} Ciliary beat frequency has been reported to reach normal values 6 months after operation.³⁰

Patients with allergic rhinitis seemed to benefit from FESS in all indices of olfactory performance. The recovery of the olfactory dysfunction is well extended in all of the first 6 postoperative months (TDI, OD, OI, and OT scores were found significantly elevated at the 1st, 3rd, and 6th postoperative month; all, $p < 0.001$). Allergic patients seemed to perform worse than nonallergic patients at all time frames. However, after statistical adjustment for other potential confounding factors (gender, age, duration of symptoms, smoking, previous surgery, and gustatory impairment), the

degree of postoperative improvement in olfactory function was not clearly affected by the concomitant allergic rhinitis, because no significant differences in the elevation of OD, OT, OI, or TDI scores was noted. OD and OI, which are considered to reflect disorders of the central nervous olfactory system, are not affected significantly, presumably indicating that the regeneration of the neuroepithelium and the olfactory neurons is not affected by allergic rhinitis.³¹ No significant differences were noted with respect to the acquisition of normal olfactory function after FESS between allergic and nonallergic patients either, but it is of note that significance failed only by a small extent ($p = 0.054$). When asked to evaluate by themselves the olfactory outcome, patients also seemed to report no influence of allergic rhinitis on the overall final postoperative result.^{3,32}

In all four examinations and after statistical adjustment for other potential confounding factors (gender, age, duration of symptoms, smoking, previous surgery, and gustatory impairment), patients presenting with AERD performed significantly worse than patients without AERD in all tests (Table 3). Although they seemed to significantly benefit from FESS, patients with AERD showed a significantly smaller increase of all four preoperative olfactory indices (OT, OD, OI, and TDI) 1, 3, or 6 months after surgery (all, $p < 0.001$), when compared with patients without AERD. An interesting observation is that the recovery of the olfactory dysfunction seemed to be confined in the first 3 postoperative months. On the 6th postoperative month, while TDI score continued to increase in patients without AERD ($p < 0.001$), it remained approximately at the same level in patients with AERD ($p = 1.000$). The same recovery time course was also observed for OT, OI, and OD scores, which seemed to ameliorate only during the first 3 postoperative months. The normosmic patients at the end of our follow-up period were significantly less among patients with AERD, as it has been reported by studies using patient-staged questionnaires.³

In patients presenting with AERD, the conductive impairment caused by nasal polyposis is much attenuated by pronounced inflammatory processes, which render the endoscopic outcome poorer.³³ Allergic rhinitis and aspirin-sensitive nasal polyp patients may share similar histopathological findings, such as enhanced nasal eosinophilia and production of chronic inflammatory mediators. However, in patients with nasal polyposis and coexisting allergic rhinitis the eosinophilic influx, which seems to result from the release of IL-5, is retained at the same levels as in nonatopic patients. On the contrary, in patients with AERD eosinophilic infiltration, mainly mediated by high concentrations of IgE, is significantly higher. This difference in eosinophilic influx may account for the more aggressive inflammatory response, which is, in turn, a possible reason for more extensive polyposis and poorer recovery of the olfactory neuroepithelium after surgery,^{34,35} as well as the significantly shorter amelioration period.

Conclusively, patients with allergic rhinitis and nasal polyposis benefit significantly from FESS. Allergic patients seem to perform worse than nonallergic patients at all time frames. Unlike what may be expected, the inflammation associated with allergic rhinitis does not significantly affect either the extent of the postoperative olfactory improvement or the time course of the postoperative recovery, at least during the first 6 months after surgery. On the contrary, patients with AERD

are not expected to regain normal function after FESS and AERD is a significant predictor of worse outcome. Moreover, the amelioration of the olfactory acuity seems to be restricted in the first 3 postoperative months.

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