



Olfactory Neuroepithelium in Olfactory Cleft Polyps: Do They Have Any Effect on Olfaction Results After Endoscopic Sinus Surgery?

Original Investigation

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Abstract

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Objective: How the presence of olfactory structures in olfactory cleft polyps (OCPs) affect olfaction function outcomes after surgical removal has not yet been investigated. In this study we aimed to assess the presence of olfactory structures in OCPs and correlate these findings with olfaction outcomes after endoscopic sinus surgery (ESS).

Methods: Twenty seven patients with OCP underwent preoperative topical and systemic steroid treatment and ESS. Biopsies from the middle meatal polyps (MMPs) and OCPs were immunohistochemically analyzed for olfactory marker protein (OMP). The smell diskettes olfaction test was applied to patients at baseline, after steroid treatment (AST) and after ESS.

Results: OCPs exhibited OMP staining more commonly and intensely compared to MMPs ($p=0.008$), however, there were no correlations between OMP staining scores and any of the olfaction scores ($p>0.05$). Steroid treatment increased smell function significantly ($p<0.001$), however, there were no significant differences between AST and after ESS smell scores ($p=0.17$). There were significant correlations between smell gains AST and final smell gains after ESS ($r=0.665$, $p<0.001$).

Conclusion: OCPs contain olfactory neuroepithelium more commonly and intensely than MMPs in nasal polyp patients. However, surgical importance of this finding is controversial because removal of these polyps did not decrease smell function postoperatively in our study. Nasal polyp patients who will take steroid treatment pre-operatively must be informed that the success of ESS on olfaction depends on the response of the steroid treatment and ESS AST might not have additional favorable effect on smell function.

Keywords: Chronic rhinosinusitis with nasal polyps, endoscopic sinus surgery, olfaction, olfactory neuroepithelium, olfactory cleft polyp

Introduction

Chronic rhinosinusitis with nasal polyps (CRS w/NP) is the inflammation of the nasal mucosa and the paranasal sinuses with symptoms of rhinitis and the presence of middle meatal polyps (1). It affects 1–4% of the population and the underlying pathogenesis has not been fully understood. Infections, genetic predisposition, mucociliary dysfunction, vasomotor imbalance and neurogenic inflammation have all been suggested as the possible mechanisms of NP formation (2-4). The symptoms of CRS w/NP include nasal obstruction, headache, rhinorrhea, and olfactory dysfunction (5). Olfactory dysfunction affects 65–80% of the patients with CRS w/NP patients are more commonly affected than CRS patients without NPs.

The etiology of the olfactory problems in CRS w/NP patients is multifactorial. In addition to the conductive olfactory dysfunction by the mass effect of NPs, epithelial erosion, inflammatory infiltration, and cytokine related sensorineural damage of the olfactory epithelium (OE) are also important factors that contribute to the hyposmia/anosmia pathogenesis for CRS w/NP patients (6-8). Surgical removal of middle meatal polyps (MMPs) is the main surgical step during endoscopic sinus surgery (ESS) to relieve the nasal obstruction and restoring the smell deficit. However, removal of olfactory cleft polyps (OCPs) is a surgical controversy as these polyps are located between the nasal septum and the middle/superior turbinate adjacent to the OE and the smell function may be impaired while OCPs are removed during ESS. On the other hand, leaving these polyps in place may continue to block the OE and decrease the chance of olfactory recovery. Recent studies demonstrated that surgical excision of OCPs does not impair and even restore smell function after ESS (9-11). The OE has been demonstrated to be more anteriorly distributed than it was supposed to be before, and middle turbinate may also contain OE (12-14). The relationship between the presence of olfactory neuroepithelium in these polyps and olfactory function results has not yet been properly investigated.

In this study, we aimed to investigate the smell function of CRS w/NP patients with OCPs using the smell diskettes olfaction test pre- and post-operatively. We also aimed to investigate the olfactory structures in both MMPs and OCPs by using immunohistochemical analysis of olfactory marker protein (OMP), which is a marker widely used for detecting OE and olfactory structures in the nasal cavity, and we also correlated the staining results with the smell scores of the patients (6, 13-15).

Methods

Local ethical committee approval (decision no: 2010/350, date: 14.05.2010) and written informed consent from the patients were obtained for the study. The study group consisted

of 27 CRS w/NP patients with OCPs. The diagnosis of CRS w/NP was made according to the recent European Position Paper on Rhinosinusitis and Nasal Polyps (1). All patients had presented with symptoms for more than 12 weeks before NPs were endoscopically visualized and diagnosed. Only CRS w/NP patients with OCP were included in the study. OCPs were diagnosed endoscopically and defined as a polyp between the nasal septum and the middle/superior turbinate (the ethmoid turbinate wall) (Figure 1) (10). All patients underwent detailed clinical examination including anterior rhinoscopy, nasal endoscopy with rigid telescopes (0 or 30°) and paranasal sinus computerized tomography. Lund-Mackay staging system was used to assess the extensiveness of the disease (16). Atopy of the patients were evaluated using skin prick test with a standardized allergen Prick test panel (Stallergenes®, Antony, France) (2). To eliminate the effect of allergic rhinitis on the study results, only patients whose skin Prick tests were negative were included. The exclusion criteria also included pediatric patients (age <18 years), patients who had aspirin intolerance, previous nasal surgeries, underwent septoplasty surgery during ESS, used topical or systemic steroid in the previous one month, or had mental and neurological disorders.

All patients received a three-week course of topical (mometasone furoate 0.05%, two sprays per nostril twice a day) steroid therapy. Additionally, systemic steroid therapy was given to all study patients. Oral methylprednisolone was started before the surgery, initially at a dose of 1 mg/kg and gradually tapered by ¼ of the initial dose every fourth day for a period of 16. All endoscopic sinus surgeries were performed by the same surgical team. Briefly, uncinectomy, maxillary antrostomy, total ethmoidectomy, sphenoidotomy, gentle excision of MMPs and OCPs were performed using through cutting forceps and microdebrider. Frontal sinusotomy was not performed in any of the patients. Biopsies were taken from both MMPs and OCPs. Topical steroid therapy was continued for three months after ESS.

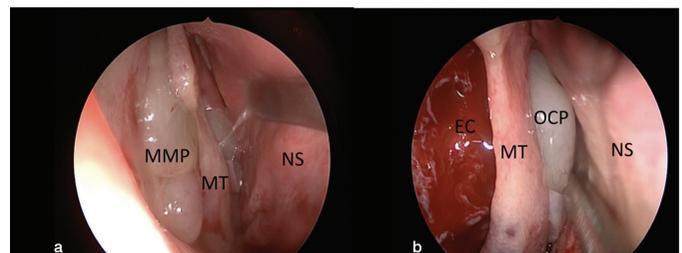


Figure 1. Intraoperative appearances of olfactory cleft polyps and middle meatal polyps were demonstrated: (a) Middle meatal polyp of the right nasal cavity; (b) Olfactory cleft polyp of the right nasal cavity

MMP: Middle meatal polyp, MT: Middle turbinate, OCP: Olfactory cleft polyp, NS: Nasal septum, EC: Ethmoid cavity

Smell Test

Smell diskettes olfaction test (Novimed, Dietikon, Switzerland) was used as the standardized and validated smell identification screening test. As previously described; eight odorants were used in a high suprathreshold concentration for the olfaction test. Patient were scored between 0 (no sense of smelling) and 8 (optimal sense of smelling) according to their olfaction performance (17). The smell test was performed three times for each patient: 1) Pre-treatment: at the initial evaluation of the patient, 2) after steroid treatment (AST), i.e., after topical and systemic steroid treatment before the surgery, and 3) after ESS, i.e., three months after the sinus surgery. To compare the effect of steroid treatment and ESS treatment on olfaction function; olfactory gains were also calculated. Olfactory gain AST was calculated by subtracting initial smell scores from AST smell scores. Final olfactory gain after ESS was calculated by subtracting initial smell scores from after ESS smell scores.

Immunohistochemistry

MMPs and OCPs were fixed in 10% formaldehyde, embedded in paraffin, and cut into 4 μ m sections. One section was systematically stained for routine hematoxylin-eosin pathological examination. Sections processed for immunohistochemistry were deparaffinized and blocked with 4% bovine serum phosphate-buffered saline (PBS) for immunohistochemical analysis. Sections were incubated with antibodies against OMP (OMP Antibody, Abcam, ab62144). After 20 minutes of pretreatment, the sections were cooled at room temperature for 20 minutes and washed with distilled water. After another rinse with PBS solution, peroxidase block solution was applied for 10 minutes. Protein block solution and another rinse with PBS solution was done, then the primary antibodies against OMP were applied. Another

rinse with PBS solution was done and sections were exposed to diaminobenzidine solution. Finally, counterstaining with hematoxylin was performed and sections were dehydrated in 96% alcohol and covered with Ultramount Labvision balsam for histopathological analysis (13).

All pathological specimens were evaluated by the same pathologist who was unaware of the group of the specimens during histopathological analysis. Briefly, the intensity of immunostaining was analyzed, and staining intensity was scored between 0 (no staining) and 4 (very intense staining) for each patient (18). The OE was regarded as positive control (score 4 staining) for OMP immunostaining. It was obtained from another CRS w/NP patient who was excluded from the study from the dorsoposterior part of the nasal cavity at the upper part of superior turbinate (Figure 2, 3) (6).

Statistical Analysis

Statistical analysis was performed using SPSS version 24.0 (IBM SPSS, New York, USA, 2016). Data were shown as mean \pm standard deviation for continuous variables and the number of cases was used for categorical ones. Data were controlled for normal distribution using the Shapiro-Wilk test. Paired sample t-test was used to compare the mean initial, AST and after ESS smell scores of the patients.

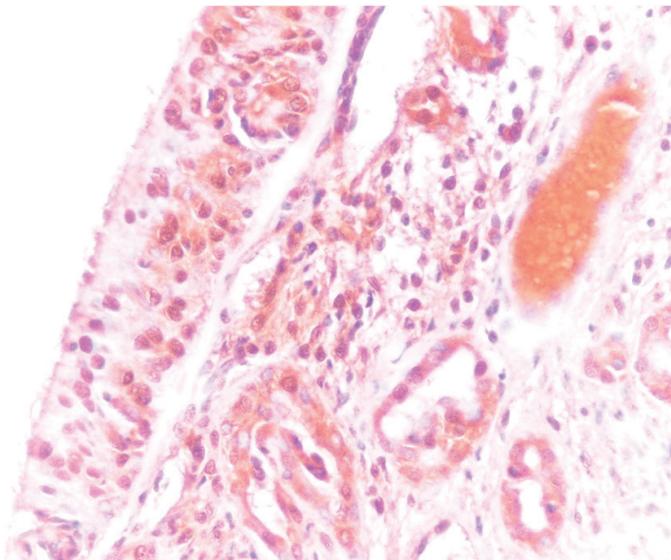


Figure 2. Very intense (+4) immunostaining of olfactory epithelium with olfactory marker protein (x400)

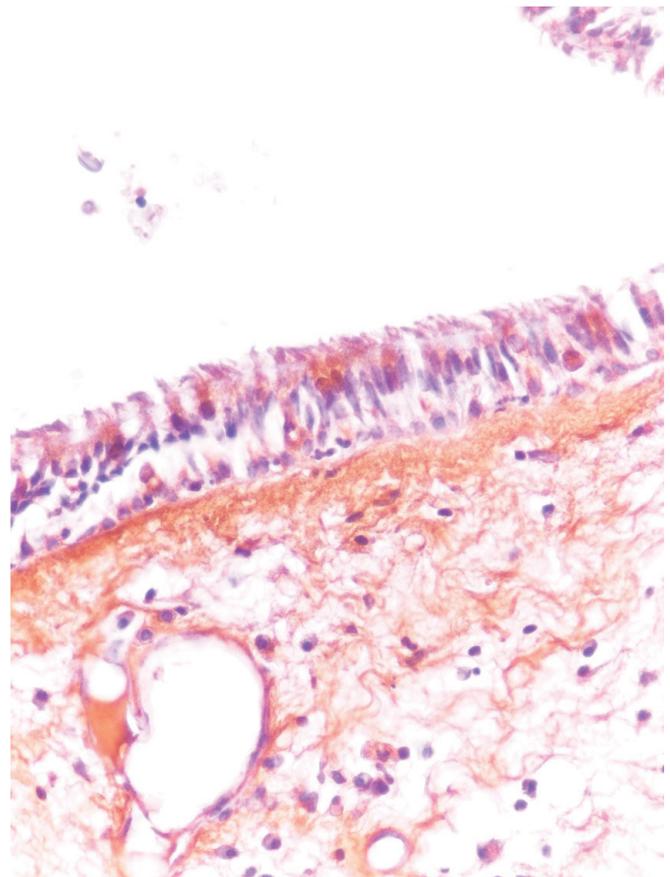


Figure 3. Very intense (+4) immunostaining of olfactory cleft polyp with olfactory marker protein (x400)

correlations between the Lund–Mackay scores and the initial, AST and after ESS smell scores ($p=0.585$, 0.555 and 0.791 , respectively).

There were no statistically significant correlations between the mean OMP staining scores of OCPs and the initial, AST and after ESS smell scores ($p=0.519$, 0.876 and 0.693 , respectively).

Similarly, there were also no statistically significant correlations between the mean OMP staining scores of MMPs and the initial, AST and after ESS smell scores ($p=0.76$, 0.752 and 0.362 , respectively).

Discussion

In this study, we found that steroid treatment significantly increased olfaction scores in CRS w/NP patients. Also, smell gains AST directly correlated with the final smell gains after ESS. Olfactory neuroepithelium in OCPs were observed to be more common and more intense compared to MMPs. However, this finding was not correlated with the preoperative and postoperative smell scores. Lund–Mackay scores of the patients were not related to olfactory outcomes.

The pathogenesis of olfactory dysfunction in patients with CRS w/NP is multifactorial. In addition to the obstructive smell loss by NPs, interleukin (IL) 2,5,6,10,13 related sensorineural loss, IL-5, eotaxin 1 and Charcot–Leiden crystal protein related inflammation by eosinophilic infiltration, inflammation related degeneration and disorganization in the OE were also demonstrated to increase the olfactory dysfunction (6, 8, 19). Thus, the effect of topical and systemic steroids on olfactory dysfunction were evaluated in patients with CRS w/NPs. Topical dexamethasone and fluticasone usage were proven to significantly improve smell function in patients with CRS w/NP (20, 21). Additionally, Bardaranfar et al. (22) reported that triamcinolone embedded gelatin coating application to the OC during ESS increased the smell scores significantly compared to the surgery alone in CRS w/NP patients. Decrease in smell function was demonstrated to be the most common improved symptom for CRS w/NP patients after systemic steroid treatment (23). Recently, two studies showed that the success of surgery on olfactory function was related to the response of the steroid treatment for CRS w/NP patients (24, 25). According to the results of Bogdanov et al. (24), ESS had no additional benefit on smell scores after steroid therapy. Similarly, in our study, significant smell gain was established after topical and systemic steroid treatment, however, surgery had no additional effect on the smell scores AST. Additionally, response to the steroid treatment directly correlated with the final smell gains after ESS in our study. Basing on our study results and the previous literature, it can be suggested that topical and systemic steroid treatment is effective in the recovery of the olfactory dysfunction for patients with CRS w/NP. Surgical

removal of the polyps may overwhelm conductive smell loss, however, for the treatment of the OE inflammation, topical and/or systemic steroid treatment seems to be more useful for the recovery of smell function. CRS w/NP patients who take steroid therapy before surgery should be informed that ESS might not provide any additional benefit on the smell function compared to steroid treatment. Similarly, our findings suggested that the final olfactory outcome after ESS should be related to the response of the patient to the steroid treatment.

The OC region is surrounded laterally by the attachment of the middle and/or superior turbinate, medially by the superior part of the nasal septum, and posteriorly by the anterior face of the sphenoid sinus. The roof is formed by the cribriform plate and the floor is an imaginary line drawn one centimeter below the cribriform plate (26). OCPs and REAHs are among the most common benign lesions that block the OC region, impair airflow to the OE, and thereby diminish the olfactory function (10). Surgical procedures to remove these lesions in this critical area may result in major complications such as CSF leakage and permanent olfactory loss due to the surgical trauma (9). In fact, few contemporary studies have focused on the effect of surgical excision of OCPs on the olfactory function outcomes (9-11). Particularly, they have shown that the surgical removal of OCPs without preoperative steroid treatment did not impair and even improved olfactory function. Similarly, we also determined a significant final olfactory gain after excision of OCPs when compared to the initial smell scores in our study. Additionally, we encountered a statistically insignificant olfactory decrease after the excision of OCPs compared to steroid treatment. According to our study results, we might say that topical and systemic steroid treatment has a major effect on olfactory function improvement in patients with OCPs and surgical excision of these polyps AST does not impair olfactory function. The main difference of our study from the aforementioned studies is that we determined the olfactory structures in OCPs and compared these findings with the olfactory function (9-11). We demonstrated that OCPs contain olfactory structures more commonly and intensely as compared to the MMPs. However, surgery of these polyps did not deteriorate smell function. Bhutta et al. (15) showed that none of the polyps originating from the superior turbinate region contained olfactory structures immunohistochemically. Its difference from our study may be explained by the anti-inflammatory effect of steroid treatment on the OCPs. Steroid treatment may have decreased the polyp size and may have increased the chance of OE sampling intraoperatively in our study. Additionally, both light microscopy and electron microscopy studies demonstrated that there is no clear boundary of OE and respiratory epithelium. OE is distributed among the respiratory epithelium near the cribriform plate region in a patchy manner (12). These gaps among the OE may have caused false negative sampling of olfactory structures

in the study of Bhutta et al. (15). Also, Sasaki and Nakahara (27) demonstrated that NPs might contain nerve fibers and respond to neurogenic stimulation. Moreover, it was proven that even the middle turbinate contained olfactory structures in most of the concha bullosa patients (13-14). Hence, based on our study findings, both OCPs and MMPs may contain olfactory neuroepithelium. However, the surgical importance of this issue is controversial since removal of these polyps did not impair smell function in our study.

The correlation between olfaction and extensiveness of the disease on CT findings in CRS w/NP patients was investigated in various studies. According to the results of our study and the previous literature postoperative smell function was not correlated with the preoperative LMS values (11, 28, 29). However, some studies reported a negative correlation between LMS and preoperative olfactory function (29, 30). LMS values were not correlated with the preoperative olfaction test results in our study and in the study of Paksoy et al. (28).

Limitations of this study were firstly, the small sample size of the group. Secondly, we did not have a control group of patients without preoperative systemic steroid treatment or without removal of the OCPs to compare the results of different ESS techniques and steroid treatment on the olfactory function results. Lastly, we did not classify NPs according to the genotyping results of the histopathological specimens. Hence, we could not analyze the difference of the histological types of the NPs regarding the presence and intensity of the OE. Despite the limitations, we believe that our study exhibits meaningful results regarding the relationship between olfactory structures in the OCPs and olfactory function outcomes after ESS.

Conclusion

In conclusion, OCPs contain olfactory neuroepithelium more commonly and intensely than MMPs for CRS w/NP patients. However, surgical importance of this finding may be controversial because removal of these polyps did not decrease smell function postoperatively in our study. Future studies with larger patient groups should also investigate the impact of the presence of olfactory structures on postoperative smell function results in patients with OCPs. CRS w/NP patients who will take topical and systemic steroid treatment pre-operatively must be informed that the success of ESS on olfaction function depends on the response of the steroid treatment, and ESS AST might not have additional favorable effect on smell function.

Ethics Committee Approval: Mersin University Clinical Researches Ethics Committee approval was acquired for the current study (decision no: 2010/350, date: 14.05.2010).

Informed Consent: Written informed consent was taken from all patients who participated in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Ö., O.İ., F.M., Y.V., K.G., Concept: C.Ö., O.İ., F.M., İ.G., Y.V., K.G., Design: C.Ö., O.İ., F.M., İ.G., Y.V., K.G., Data Collection and/or Processing: C.Ö., O.İ., F.M., İ.G., Y.V., K.G., Analysis and/or Interpretation: C.Ö., O.İ., F.M., İ.G., Y.V., K.G., Literature Search: C.Ö., O.İ., F.M., İ.G., Y.V., K.G., Writing: C.Ö., O.İ., F.M., İ.G., Y.V., K.G.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Main Points

- Olfactory cleft polyps (OCPs) contain olfactory neuroepithelium more commonly and intensely than middle meatal polyps (MMPs) in chronic rhinosinusitis with nasal polyp (CRS w/NP) patients.
- However, surgical removal of OCPs during endoscopic sinus surgery (ESS) does not decrease olfaction scores postoperatively, despite the existence of olfactory neuroepithelium in OCPs.
- The success of endoscopic sinus surgery on olfaction function depends on the response of the steroid treatment, and ESS after steroid treatment might not have additional favorable effect on smell function in CRS w/NP patients.

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