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Intranasal Trigeminal Function in Patients With Empty Nose Syndrome

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Objectives/Hypothesis: Trigeminal nerve mediates the perception of nasal airflow. This study examines whether impaired intranasal trigeminal function is a part of the paradoxical nasal obstruction sensation in patients with empty nose syndrome (ENS).

Study Design: Prospective case-control study in a tertiary hospital.

Methods: Three groups were examined: 1) ENS patients with previous bilateral near total inferior turbinectomy, 2) patients who underwent near total inferior turbinate removal (ITR) without ENS symptoms, and 3) control participants. All participants examined with active anterior rhinomanometry, olfactory testing (extended Sniffin' Sticks test), and trigeminal testing (lateralization task using menthol and odorless solvent).

Results: Seventy-one participants were included (21 ENS patients, 18 ITR patients, and 31 controls). Analyses revealed that ENS patients had significantly lower scores on trigeminal lateralization testing than the ITR group and controls. The ENS group had also significantly lower scores in olfactory testing than controls. No statistical differences were found in rhinomanometry between groups. The gender factor was not associated with the chemosensory testing; however, this was not the case with the age factor, as trigeminal test results were negatively correlated.

Conclusions: This study demonstrates significantly impaired intranasal trigeminal function in ENS patients when compared with ITR patients and controls. Further prospective studies are needed to clarify the role of preoperative trigeminal function of these patients and the contribution of surgery to this impairment.

Key Words: Trigeminal nerve, empty nose syndrome, turbinectomy, olfaction.

Level of Evidence: 3b.

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INTRODUCTION

The main complaint of empty nose syndrome (ENS) patients is the paradoxical nasal obstruction despite a widely patent nasal cavity in clinical examination. It is mainly a postoperative finding after inferior and/or middle turbinate resection and rarely can be a primary disorder. The pathophysiology of ENS remains unclear, involving impaired mechanisms of nasal resistance, humidification, and chemosensation.[1,2] However, not every patient having a wide resection of turbinates suffers from ENS.

There is evidence that trigeminal nerve endings, which are distributed within the whole nasal mucosa, mediate the sensation of nasal airflow.[3] Studies have shown that stimulation of intranasal trigeminal receptors with menthol produces a feeling of patent nose without changes in nasal resistance and the opposite feeling of a blocked nose when a local anesthetic is applied.[4,5]

The lack of objective methods to diagnose ENS results in a discrepancy between subjective symptoms and measurements from the available devices assessing nasal functions. Thus, measurements of trigeminal nerve function into the nose may help to better understand the pathophysiology of this disorder.

The objective of this study was to assess whether impaired intranasal trigeminal function contributes to the sensation of paradoxical nasal obstruction in ENS patients by comparing this group to patients with inferior turbinate removal (ITR) without ENS symptoms and healthy controls.

MATERIALS AND METHODS

Definition

Since the introduction of the term ENS by Eugene Kern in the 1990s, little has been explicitly stated about ENS, and quite often the term ENS and atrophic rhinitis are confused and overlapped in the literature.[1,2,6]

Thus, for the purposes of this study, the term ENS should be considered not as a form of atrophic rhinitis, but as a symptom complex in which the cardinal one is the paradoxical sense of nasal obstruction in the face of near total turbinate resection. We defined as ENS patients those with characteristic symptoms, such as sense of nasal obstruction, nasal or facial pain on inspiration, persistent crusting or discharge, and headache. The nasal obstruction was considered as intense, indicating ENS

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only if nasal patency scored <20 in a visual analogue scale from 0 to 100, where 0 represents total obstruction and 100 perfect nasal patency. ENS patients were also defined as having an endoscopic examination consistent with ENS, which revealed the near total absence of the inferior turbinate and abnormally wide nasal cavities, and a history of previous near total turbinectomy.

The term near total turbinectomy is used instead of total turbinectomy because in the vast majority of cases a small amount of inferior turbinate can be detected as a remnant, which is usually attached to the lateral wall and/or posteriorly as a small amount of tissue not larger than the 20% of the estimated initial turbinate volume in the endoscopy.[7]

A total nasal airway resistance of 0.3 Pa/cm^3/s, which is generally accepted as the upper limit of normal, was used as the criterion to exclude patients with highly subjective nasal obstruction due to high nasal resistance.[8]

Patients

A cohort of 21 patients (12 male/9 female) suffering from ENS after near total inferior turbinectomy with or without concomitant septoplasty was included in this study. The mean age was 47.4 years old (range, 21–57 years old). A second group of 18 patients (10 males, 8 females; mean age: 45.2 years, range, 25–51 years old) was included with similar age and gender after a telephonic survey between patients examined in our rhinology clinic with a previous history of total or near total inferior turbinectomy ± septoplasty without symptoms of ENS. Finally, a control group of 32 healthy individuals (18 males, 14 females; mean age: 44.5 years, range, 23–58 years old) with matched demographics to the other study groups completed the study.

All patients included in the study were either self-referrals or referred from another institution to the rhinology clinic, 2nd Department of Otorhinolaryngology, Aristotle University of Thessaloniki Medical School over a 3-year period. ENS patients were included in the study only if no legal claims existed or the legal process was completed to minimize biases.

All participants (patients and controls) first had to adapt to the rhinology clinic environment (average room temperature 22.5°C; relative humidity 33.8%) for 20 minutes before measurements while quietly breathing through their nose. During this time the study design was explained in details and then all provided signed informed consent. A full clinical examination including endoscopy without local drug application followed to remove any crusting and exclude other sources of obstruction (active inflammation with purulent secretions, exacerbation of allergic rhinitis, nasal polyps, and severe septal deviation). Patients with such findings in endoscopy were excluded from the study.

The study was carried out in accordance with the Declaration of Helsinki on biomedical research for human subjects[9] and was approved by the ethics committee of the Aristotle University of Thessaloniki Medical School.

Intranasal Trigeminal Testing

Trigeminal function was assessed by means of the so-called intranasal trigeminal lateralization test reported in previous studies.[10–12] In this test, patients are asked to lateralize stimuli presented to both nasal cavities, where one side is activated by one trigeminal stimulus and the other by an odorless solution. We used menthol as a trigeminal stimulus because when it activates the nerve, patients feel a cooling sensation in the nose.[4] Evidence now exists that the human nose is sensing patency via a mechanism involving localized peak nasal mucosal cooling.[13,14]

The participants were presented under blindfolded conditions with two polyethylene bottles (volume 250 mL) with a pop-up spout that was placed into either nostril. One bottle contained 15 mL of a menthol solution dissolved in propylene glycol (dilution: 50 g of menthol in 50 mL of propylene glycol) and the other 15 mL of odorless propylene glycol solvent. A puff of approximately 15 mL of air was delivered into the nasal cavities while pressing the two bottles simultaneously by means of a handheld squeezing device with the patient in a passive sniffing condition.[10,11]

After each trial, participants had to determine the side of the nose (left or right) where they felt the trigeminal stimulus (i.e., cooling sensation). A total of 40 stimuli were presented to the participants following a pseudorandomized sequence in which each nostril was stimulated 20 times. An interstimulus interval of 30 seconds was used to avoid habituation. As a total score of the test is considered the number of correct localizations.

Olfactory Testing

Olfactory function was tested by means of the Greek verbal version of the Sniffin' Sticks battery test.[15,16] Odors are presented to patients in felt-tip pens, which are placed approximately in front of both nostrils for a birhinal examination. This test includes three different subsets: 1) odor threshold (T), with n-butanol stepwise dilutions in a row of 16 felt- tip pens; 2) discrimination test (D), where patients are asked to discriminate odors 16 times, 3) identification test (I), with a row of 16 odors where the patient has to find the correct answer from a list of four verbal descriptors for each odor. The sum of the three subsets results provide a total TDI score.

A TDI score <16.5 corresponds to anosmia, a score between 16.5 and 30.5 orresponds to hyposmia, and a TDI score more than 30.5 is considered as normal olfactory function.[16]

Rhinomanometry

All participants had an active anterior rhinomanometry unilaterally. The device used was the Rhino 4000 M (Homoth Medizin Elektronik, Hamburg, Germany) at a reference pressure of 150 Pa for both nasal cavities. A minimum of five nasal breaths was required for each nasal cavity while participants were at a seated position breathing normally to average the results according to the congruence of the curves. One nostril was occluded with an adhesive patch connected to a pressure transducer to measure nasopharyngeal pressure.

Total flow was expressed in cm^3/s and total resistance (R) expressed in Pa/cm^3/s. Total resistance was calculated combining the resistances of the two nostrils according to the formula:

$$R\text{tot}=\frac{R\text{left}\times R\text{right}}{R\text{left}+R\text{right}}$$

The rhinomanometry was performed in accordance with the recommendations of the international standardization committee.[17]

Subjective Ratings

Subjective ratings of olfactory function and nasal obstruction were also recorded by means of a visual analogue scale, scoring from 0 to 100. In this scale 0 represents complete olfactory loss or total obstruction, and 100 represents perfect olfactory function or perfect nasal patency.

Statistical Analysis

All analyses were performed using Statistical Packages for Social Sciences version 20.0 (IBM, Armonk, NY). Descriptive

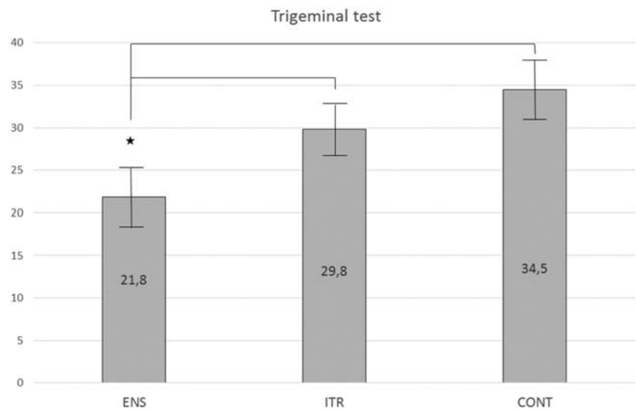

Fig. 1. Lateralization task test results. Comparison of mean ± standard deviation of the three study groups. The asterisk indicates significant difference between groups connected by the black line. CON = controls; ENS = empty nose syndrome; ITR = inferior turbinate removal.

statistics are presented as mean ± standard deviation or percentages. The significance level was set at $\alpha = .05$.

A t test for independent samples and χ^2 test were used to compare ENS patients to ITR and controls on all study variables. Correlation analyses were performed according to Pearson. Bonferroni tests were used for post hoc analyses.

In a previous study assessing lateralization test results, the limit of $\geq$25 correct answers was used as a significantly above chance level (pass) according to binomial distribution ($P < .05$).[18,19] Thus, 24 or fewer correct answers were considered as a test failure. Comparison of failure rates between groups was performed with the χ^2 test.

RESULTS

A total of 72 participants (mean age: 45.4 years; range, 21–58 years old) were included in the study without significant differences between the study groups in mean age and gender. Among the 40 patients in the ENS and ITR groups, 24 patients underwent a concomitant septoplasty (13 in the ENS group and 11 in the ITR group).

In all study groups, no differences were found in lateralization task test between right and left nasal cavities (all $P > .05$).

Lateralization task test showed a marked decrease of ENS group having significantly lower results in comparison with the ITR group and controls (Fig. 1). The ITR group, although presented to have significantly better results from the ENS group, had lower results from the control group with a tendency for significance ($P = .067$) (Table I).

The ENS group also demonstrated significantly higher failure rates on the lateralization task from both groups when analyzed according to criterion of pass/fail (failures: ENS 19/21, 90.4%; ITR 3/18, 16.6%; controls 1/32, 3.1%; χ^2 test all $P < .001$). Interestingly, the ITR group failure rate was also significantly higher than controls (χ^2 test $P = .042$).

However, the above differences were not reflected in participants' subjective ratings of nasal obstruction, with the IRT group scoring similarly as high as the controls and the ENS group presenting very low scoring (Table I).

Analysis of olfactory test results showed that TDI scores of ENS patients had significantly lower results than controls but not than the IRT group (Fig. 2). The later group presented a mean at the limit between hyposmia and normosmia. Again, subjective ratings were quite different, with the ENS group scoring significantly lower than the other two groups (Table I).

Comparison of trigeminal and olfactory test means between patients having only turbinectomy and patients having septal and turbinate surgery showed no significant difference (lateralization test (LT): $t = 0.78$, $P = .55$; TDI: $t = 0.82$, $P = .6$). In addition, when compared to subjective nasal patency and nasal resistance, no significant difference was noticed ($t = 0.31$, $P = .78$; $t = .73$, $P = .0482$, respectively).

The gender factor had no significant effect on trigeminal and olfactory function in both surgery groups and controls. Similarly, the age factor did not prove to have any significant effect on olfactory test results ($r = -0.24$, n = 70, $P = .2$). However, this was not the case with the trigeminal test results, where a negative correlation was found with aging ($r = -0.40$, n = 70, $P = .02$).

Rhinomanometry data analysis did not revealed significant differences between the means of bilateral inspiratory airflow and total resistance. All means are presented in detail in Table I.

DISCUSSION

The pathophysiology of ENS remains poorly understood, with several theories found in the current literature. The majority of them suggest that ENS has a multifactorial physiological mechanism involving structural changes of nasal resistance, reduced nasal air conditioning, and decreased sensory input. As the trigeminal nerve has a dominant role in the perception of nasal airflow, this study tried to clarify whether ENS is related to a decreased function of the intranasal portion of the nerve.

The present study had three main results. First, ENS patients had significantly lower results in the trigeminal and olfactory tests compared with controls and significantly lower results in the trigeminal test with ITR patients. Second, ITR patients had lower, though not significantly, trigeminal and olfactory results than controls accompanied by subjective ratings that are equal to healthy individuals. Third, concomitant septoplasty does not seem to play a significant role in trigeminal and olfactory impairment among ENS patients.

The reduced trigeminal sensitivity of ENS patients may be one of the reasons for the impaired sensation of nasal breathing despite the nonobstructed airway as confirmed by rhinomanometry. In a study assessing detection and pain threshold of trigeminal stimuli in different nasal sites, the inferior turbinate was clearly one of the sites of higher trigeminal sensitivity.[20] The rich trigeminal innervation of the inferior turbinate as seen also in experimental studies makes it a significant structure for the trigeminal sensation.[21] Trigeminal nerve endings are distributed within the nasal mucosa transmitting somatosensory (touch and temperature) and chemosensory sensations.[6] A near total resection of inferior turbinates may reduce critically the absolute number of these receptors and may contribute to the paradoxical feeling of obstruction.

TABLE I.
Chemosensory Tests Results, Subjective Symptoms Rates, and Rhinomanometric Results of the Study Groups.

	ENS	ITR	CON	Significance*
Lateralization test	21.8 ± 3.5	29.8 ± 3.2	34.5 ± 3.5	ENS vs. ITR P = .021* ENS vs. CON P = .004* ITR vs. CON P = .067
Sniffin' Sticks test (TDI)	28.1 ± 3.5	30.5 ± 4.1	35.5 ± 3.2	ENS vs ITR P = .62 ENS vs. CON P = .028* ITR vs. CON P = .1
Subjective olfaction	35.7 ± 6.3	72.2 ± 5.5	81.1 ± 4.9	ENS vs. ITR $P < .001$* ENS vs. CON $P < .001$* ITR vs. CON P = .08
Subjective nasal patency	10.1 ± 6.3	75.1 ± 5.8	79.8 ± 5.1	ENS vs. ITR $P < .001$* ENS vs. CON $P < .001$* ITR vs. CON P = .89
Rhinomanometry flow	485 ± 35	490 ± 28	468 ± 37	ENS vs. ITR P = .95 ENS vs. CON P = .91 ITR vs. CON P = .9
Rhinomanometry resistance	0.20 ± 0.04	0.21 ± 0.03	0.27 ± 0.05	ENS vs. ITR P = .97 ENS vs. CON P = .75 ITR vs. CON P = .79

*Statistical significance.
CON = controls; ENS = empty nose syndrome; ITR = inferior turbinate removal; TDI = odor threshold (T), discrimination (D), and identification test (I).

In a study by Zhao et al., the authors showed that air humidity significantly influences perceived patency, suggesting that mucosal cooling rather than air temperature alone provides the trigeminal sensation that results in perception of patency.[13] The same team by means of computational fluid dynamics demonstrated that the peak heat loss just posterior to the nasal vestibule correlates significantly with the subjective perception of nasal patency in normal healthy subjects.[14] As the cooling sensation is mediated by the activation of trigeminal cool afferents, any tissue removal in this area, such as turbinectomy, could significantly affect the nasal patency perception.

Evidence about reduced trigeminal sensitivity in ENS patients can be also found in a study by Huart et al., where in a smaller cohort of patients the authors reported that six out of nine had no trigeminal responses when assessed with event related potentials.[22]

ITR patients on the contrary presented no significantly lower trigeminal test results than controls. This fact may reflect what clinically happens, as not all patients with a gross resection of turbinates develop ENS. The interindividual variability of intranasal trigeminal function as seen in previous studies regarding the anatomy, nasal topography, and age indicates the need for further prospective studies on intranasal trigeminal function before and after surgery.[23–25] Thus, it will clarify the role of preoperative trigeminal function and the impact of surgery. One should be careful in the interpretation of our results, as a cause and effect relation cannot be established between decreased trigeminal sensitivity and ENS. It is most probably that impaired trigeminal function is just another contributing factor in a multifactorial syndrome.

The comparison between patients having concomitant septoplasty or not showed no difference in trigeminal function and subjective patency perception. Scheibe et al. studied the trigeminal function of patients before and after septoplasty and found a decreased trigeminal sensitivity in patients before surgery.[26] In the same study, septal surgery had no effect to the trigeminal sensitivity, a fact that is in agreement with our results. The authors hypothesized that some patients exhibited a decreased sensitivity for nasal airflow, which may also have contributed to the patients' impression of impaired nasal breathing, leading them to ask for medical consultation and maybe surgery. However,

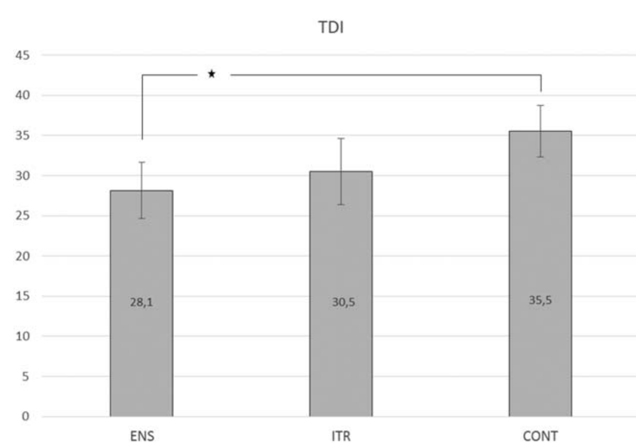

Fig. 2. Sniffin' Sticks test results. Comparison of mean ± standard deviation of the three study groups. The asterisk indicates significant difference between groups connected by the black line. CON = controls; ENS = empty nose syndrome; ITR = inferior turbinate removal; TDI = odor threshold (T), discrimination (D) and identification test (I).

the role of septoplasty and its impact in trigeminal sensitivity needs to be studied more extensively in a large number of patients.

The present study showed also an impairment of olfactory function in ENS patients. Olfactory function can be affected by interventions in inferior turbinates, as the nasal airflow toward the olfactory cleft can be significantly disturbed. In a study by Zhao et al., the authors, using numerical simulation airflow patterns, showed that relatively small changes in the anatomy of the nasal cavity at the nasal valve can induce large changes in the airflow and the odorant uptake on the olfactory mucosa.[27] In addition, the interactions between the olfactory and the trigeminal system in different levels from nasal mucosa to the central brain structures may explain why the two chemosensory systems presented fairly similar behavior in the ENS and ITR groups.[3]

Subjective symptoms of nasal obstruction, especially in ENS patients, did not correlate with the objective measurements of rhinomanometry. This fact suggests that measurements of physical resistance to airflow in the nasal cavity cannot adequately reflect their subjective sensation of nasal obstruction. A part of this missing information may be added by introducing a trigeminal nerve testing in clinical practice.

Finally, our study showed a correlation of age with the lateralization task results, a fact that is in agreement with previous studies. Specifically, Frasnelli and Hummel, by means of mucosal trigeminal potentials, showed that older subjects have higher thresholds for menthol when compared to younger subjects.[25] Further analysis indicated that the increase of response amplitudes to increasing stimulus concentrations was shallower in older subjects, indicating an age-related loss of intranasal trigeminal sensitivity also at the periphery of its system. This finding suggests that interventions for nasal obstruction in older patients should always take into account a potentially impaired trigeminal function.

CONCLUSION

The present study showed a significantly impaired intranasal trigeminal sensitivity in ENS patients after bilateral inferior near total turbinectomy. However, patients who underwent the same operation and did not develop ENS symptoms had significantly higher trigeminal function. Further studies are needed to clarify the role of preoperative trigeminal function and the contribution of surgery in trigeminal function impairment. Intranasal trigeminal sensitivity seems to be a less-investigated factor that can open new perspectives in the understanding of the subjective perception of nasal obstruction.

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