Trigeminal impairment in treatment-refractory chronic nasal obstruction*

Chloé Migneault-Bouchard[1], Franciscus J. M. Boselie[2], Marianne Hugentobler[3], Basile N. Landis[3,#], Johannes Frasnelli[1,4,#]

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[1] Department of Anatomy, Université du Québec à Trois-Rivières (UQTR), Trois-Rivières, QC, Canada
[2] Head and Neck Surgery Unit, Department of Otorhinolaryngology – Head and Neck Surgery, Geneva University Hospitals (HUG), Geneva, Switzerland
[3] Rhinology-Olfactology Unit, Department of Otorhinolaryngology – Head and Neck Surgery, Geneva University Hospitals (HUG), Geneva, Switzerland
[4] Research Center of the Sacré-Coeur Hospital, Montréal, QC, Canada

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[#]These authors contributed equally

Abstract

Background: Patients with anatomically unexplained, chronic nasal obstruction (CNO) that is refractory to medical treatment pose a challenge for clinicians. A surgical solution, addressing mechanical obstacles, is unsuited for these patients. CNO may result from disrupted airflow perception due to activation of the intranasal trigeminal system; therefore, aim of this study is to evaluate if intranasal trigeminal function of these CNO patients is decreased.

Methods: In this retrospective cross-sectional study, we compared 143 CNO patients and 58 healthy volunteers, between 18 to 80 years old. We assessed nasal patency by means of rhinomanometry (RM) and measured susceptibility of intranasal trigeminal system by the trigeminal lateralization task (TLT).

Results: TLT scores were significantly lower in CNO patients compared to controls ($p<0.001$), but RM scores were not different between groups. Accordingly, TLT allowed to identify CNO patients with an accuracy of the area under the curve (AUC) of 0.78, while the value for RM was at chance (AUC=0.47). CNO patients showed normal reaction to vasoconstrictive agents with significantly lower RM values after Xylomethazoline application.

Conclusion: Results suggest that reported nasal obstruction in CNO patients without any obvious anatomical obstacle and resistant to medical treatment may be linked to decreased perception of nasal airflow rather than physical obstruction. In this subset of CNO patients, trigeminal testing more adequately reflects the reported obstruction than nasal resistance assessment does. In future studies, the relation of the trigeminal status and the subjective sensation of nasal obstruction needs to be addressed with validated patient rated outcome measures (PROMs).

Key words: airflow perception, nasal obstruction, rhinomanometry, trigeminal system

Introduction

Chronic nasal obstruction (CNO) is one of the most common complaints in ENT practice [(1)]. For clinicians, the evaluation of CNO is therefore of considerable importance but can present a challenge. There are several aetiologies for CNO, including structural deformities, such as septal deviation, and chronic infection or inflammation, such as chronic rhinosinusitis [(2, 3)]. To complicate things, nasal obstruction can also be the results of a combination of causes (i.e. anatomical variations in combination with chronic inflammation) [(3, 4)]. Depending on the cause, CNO can be treated using surgical, medical (e.g., decongestants or nasal steroids) or combined approaches. Nevertheless, in some cases, no major anatomical deformity or obstructive mucosal inflammation is present to explain the reported CNO, and most empirical treatment attempts with topical agents and surgery fail to solve the CNO. As a result, patients continue to complain about CNO [5, 6], which is frustrating for patients and caregivers alike. Some of these patients undergo multiple surgeries with an increasing risk of developing empty nose syndrome [7]. It has been suggested that an altered perception of nasal patency in CNO may be caused by altered afferent neural pathways responsible for airflow perception [4]. Low intranasal trigeminal function seems to predict poor postoperative satisfaction after septal surgery [8], underling the implication of airflow perception in nasal obstruction.

Nasal patency is perceived via the activation of multimodal receptors on the trigeminal nerve, which respond to temperature changes as well as mechanical or chemical stimulation, such as menthol or eucalyptol. Thus, exposure to menthol causes the same sensation of cooling as does increased airflow [9]. The trigeminal system is not limited to the perception of cooling, but also allows for the perception of warmth, burning, stinging, or tickling by volatile substances [10, 11]. In other words, perceptions from the nasal mucosa are possible through a specific interaction of chemical substances with receptors of the trigeminal nerve in the nasal cavity, which also respond to temperature changes [12, 13].

Whereas nasal resistance, measured by means of rhinomanometry [14], is suitable in assessing mechanical obstruction, such as caused by anatomical deformity or inflammation, it may, however, not be appropriate in the evaluation of refractory CNO. Since no obvious mechanical or inflammatory obstruction is present in these treatment refractory CNO patients, their complaints may rather be caused by an impairment of the afferences of the trigeminal system [9]. If this is so for that particular subset of CNO patients, it would be important to identify decreased trigeminal function in order to avoid further surgeries and turn away the focus of endless seeking for a mechanical explanation. This may also open the way for a more suitable patient counseling in these particular patients by giving a sensory explanation to their complaint.

Currently, the best method to assess sensitivity of the trigeminal system is the trigeminal lateralization task (TLT) [15]. In this test, participants need to identify the nostril stimulated with a trigeminal stimulus such as menthol or eucalyptol in a monorhinal stimulation paradigm. The task is based on the fact that the localization of an odorant is possible only if it simultaneously stimulates the trigeminal nerve [16]. In fact, patients with subjectively reduced nasal patency due to chronic rhinosinusitis, with no anatomical obstruction, exhibit reduced scores in the TLT while showing normal RM scores [17]. The measurement of intranasal trigeminal function remains however a clinically unsatisfactorily solved issue. Many valid methods have been proposed but unfortunately have not yet found their way into routing clinical practice for diverse reasons [13, 18, 19]. We therefore set out to compare nasal patency (RM) and trigeminal susceptibility (TLT) in a subset of CNO patients without an anatomical deformity, refractory to topical treatments, that were referred to our tertiary center for further treatment. Specifically, the aims of the study were 1) to compare scores of these CNO patients and healthy controls for RM and TLT, 2) to assess the efficiency of each method to correctly classify CNO patients and 3) to validate RM measurements by comparing scores before and after application of decongestant nasal spray.

Materials and methods

We carried out this retrospective cross-sectional study in the department of Otolaryngology of Geneva University Hospitals. The study was conducted according to the guidelines of Helsinki on Biomedical Research Involving Human Subjects. The study was approved by the institutional ethics review board (IRB approval No: 2019-00601).

Participants

The study involved 154 patients with a single and main complaint of chronic nasal obstruction (CNO) without any other rhinological symptom and 62 healthy controls. After exclusion of 15 outliers (11 patients, 4 controls) in either rhinomanometry or the measurements of trigeminal sensitivity, the overall sample consisted of 143 patients (51 women, mean age of 44 ± 14; 92 men, mean age of 43 ± 14) and 58 controls (38 women, mean age of 39 ± 10; 20 men, mean age of 42 ± 11). Another common complaint was that all patients were either referred or previously treated at our tertiary center with topical treatments (steroids, ointments, salt water, etc.) and sometimes oral systemic treatment (mainly steroids) without any satisfactory outcome. Most CNO patients had undergone previous surgery for CNO (0 operations, n=36; 1 operation, n=66; 2 operations, n=36; 3 operations and more, n=5) – which had been unsuccessful in solving their complaints – and were referred for further treatment for their ongoing complaint of nasal obstruction. No CNO patient had any signs or symptoms of sinusitis as assessed by endoscopy or CT. Since there is no general agreement in the community on the standard of diagnostic tools, rather than following a uniform algorithm, the diagnostic tools were chosen for each patient individually by the ENT-surgeon (BNL) based on clinical criteria. Specifically, all patients, had full ENT examination including nasal endoscopy that ruled out any anatomical deformity or mucosal inflammation that could explain the CNO. Healthy controls were recruited by investigators in the ENT department. All healthy controls had full ENT evaluation including nasal endoscopy to exclude nasal diseases. Nevertheless, we did not exclude participants with a slight septum deviation. Of the 143 included patients with CNO, full data set for RM and TLT was available for 139 (RM, n=139; TLT, n=140).

Methods

Rhinomanometry (RM): We assessed nasal airway resistance

using RM (Rhinomanometer 300, ATMOS Medizin Technik, Germany), according to methods described previously [20]. It consists of measuring the difference in pressure and airflow between the posterior and anterior part of the nose during inspiration and expiration. Participants were seated, with a face mask that covered their mouth and nose. A tube taped to one of the nostrils was used to measure the anterior nasal pressure. Resistance in each of the nasal passages is measured separately. Nasal resistance was measured with a pressure difference of 150 Pa. We performed 2 measurements of RM; one measurement before and one measurement 15 minutes after administration of vasoconstrictor decongestant nasal spray (Xylometazoline HCl 1mg/ml).
Although RM is well established [14, 20, 21], we compared patients with and derived normative values from an age and gender matched control group. We therefore derived normative values from the control group. The 90e percentile of the control group was used to classify each case as pathological or non-pathological for each nostril separately. We considered a patient's score to be pathological if one of the two values was above the 90e percentile of the control group (cut off scores left nostril: 0.75 Pa*sec/mL; right nostril: 0.87 Pa*sec/mL).

Trigeminal lateralization task: We assessed trigeminal function using the trigeminal lateralization task, according to methods described previously [15]. It consists of assessing a participant's ability to detect unilateral stimuli presented to the left or the right nostril. Two identical squeeze bottles (total volume 250 ml) were presented to the participants at the same time, one to each nostril. One of them contained the target odor (30 mL of liquid pure eucalyptol, Sigma-Aldrich, Switzerland); the other bottle contained clean air. A puff of air was delivered by pressing the two bottles at the same time. A total of 40 stimuli of the same concentration, pseudo-randomized and counterbalanced, were applied at an interval of 30-40 seconds between each stimulation. Each nostril was stimulated 20 times. The participants were blindfolded to have no visual cues. After each stimulation, participants were asked to identify the nostril to which the target was presented (forced choice). The sum of correct identifications was used to estimate trigeminal sensitivity; scores could range between 0 and 20 for each nostril.
Although the trigeminal lateralization task is well established [15, 22, 23], there are no normative values available. We therefore derived normative values from the control group the same way as for RM. The 10e percentile of the control group was used to classify each case as pathological or non-pathological for each nostril separately. We considered a patient's score to be pathological if one of the two scores was below the 10e percentile of the control group (cut off scores left nostril: 12.8; right nostril: 13.8).

Statistical analysis
Data analyses were carried out using SPSS 27.0 (SPSS Inc., Chicago, IL, USA).
First, we analyzed data for potential outliers in RM or TLT scores. We defined outliers as scores that differed more than 3 standard deviations from the group average. If we detected an outlier, we excluded the participant from further analysis. We detected a total of 15 outliers (11 patients – RM, TLT, 4 controls – RM, TLT) which led to the exclusion of 15 participants. Therefore we included data from 143 patients (51 women, mean age of 44 ± 14; 92 men, mean age of 43 ± 14) and 58 controls (38 women, mean age of 39 ± 10; 20 men, mean age of 42 ± 11).
Then, we analyzed if there was any group difference on average scores for RM and TLT. To do so, we performed two separate repeated measures ANOVA, one for each technique (RM, TLT), with group (2 levels: patients, healthy controls) as between subject factor and side (2 levels: left nostril, right nostril) as within subject factors. Since data was not normally distributed, we ran Mann-Whitney tests for post-hoc comparisons.
Next, we determined which technique allowed to distinguish between patients and healthy controls. A perfect detector yields pathological values for all patients, and non-pathological ones for all controls. We counted for each technique (RM, TLT) the number of pathological cases in both groups, patients, and heathy controls. We first compared the ratio of pathological/non pathological cases in patients vs healthy controls when using RM or the TLT, by computing separate chi-square tests. Then we compared the ratio of pathological/non pathological cases in the patient group when using RM vs TLT, by means of an additional chi-square test.
Next, we created, for each technique (RM, TLT), Receiver Operating Characteristics (ROC) curves in order to assess the efficiency of both techniques to correctly classify CNO patients. True positive rate (sensitivity) as a function of the false positive rate (1-specificity) are represented by the ROC curve. The Area Under the Curve (AUC) represents the capacity of the test to distinguish the two groups (pathological vs non pathological). An AUC of 0.5 represents an absence of discrimination of the test, i.e., an inability to distinguish patients with and without disease based on the test while an AUC of 0 has a perfect discrimination, but in the wrong direction. It gives information on the efficacity of the diagnostic tool (nearest to 1 is the best) and allows to quantify the difference in sensitivity and specificity between the two tests.
Finally, we carried out an additional analysis to confirm the validity of the RM measurement. Specifically, we compared, in the CNO patients' group, RM measurements before and after decongestion. To do so, we performed a repeated measures ANOVA on RM scores with side (2 levels: left, right) and congestion status (2 levels: before and after nasal decongestant) as within subject factors.

Figure 1. Details of the surgical procedures performed on CNO group.

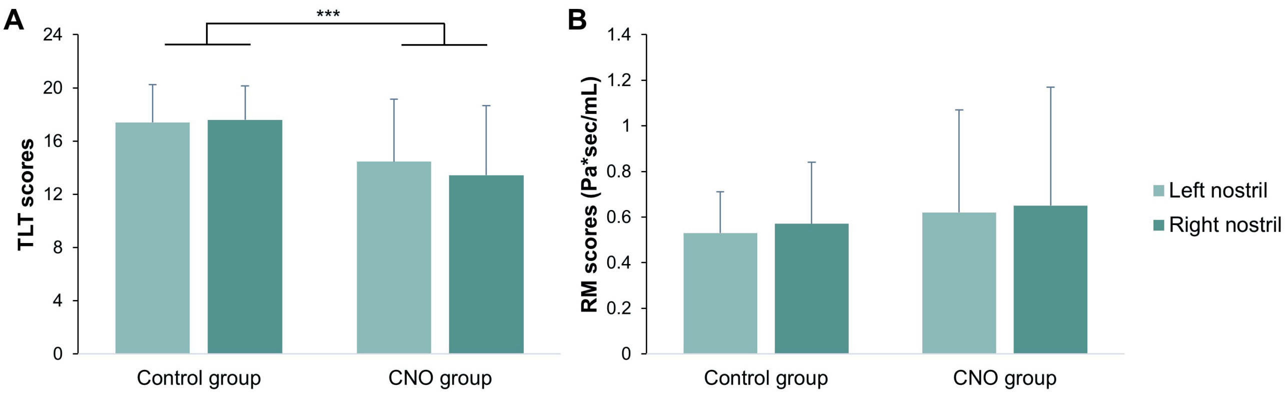

Figure 2. Chemosensory tests results of tests according to the groups: A) Means of trigeminal lateralization task for control group and CNO group; and B) Means of rhinomanometry for control group and CNO group. *** Indicate significant difference of trigeminal lateralization task between control group and CNO group for the left and the right nostril.

We set the alpha value at 0.05 and used a Bonferroni correction for multiple comparisons.

Results

Most CNO patients had undergone previous surgery for CNO (0 operations, n=36; 1 operation, n=66; 2 operations, n=36; 3 operations and more, n=5). The surgeries performed are septoplasty (n=89), turbinoplasty (n=54), turbinectomy (n=28), rhinoplasty (n=24), reposition (n=6), polypectomy (n=2), functional endoscopic sinus surgery (FESS; n=20) and other (n=1). In a surgery more than one type of intervention could be combined (Figure 1).

Average scores, standard deviation, percentile scores and cut off scores for RM (left, right nostril) and TLT (left, right nostril) are presented in Table 1.

The ANOVA on RM scores revealed no effect of group, side, or any interaction (all $p \geq 0.131$). When we carried out the same analysis with TLT scores as dependent variable, we observed a significant main effect of group ($F(1.196) = 44.338$; $p<0.001$), but no effect of side or any interaction. Post-hoc Mann-Whitney tests indicated that patients scored significantly lower TLT scores than healthy controls for both the left ($U=2475$; $p<0.001$) and the right nostril ($U=2093$; $p<0.001$); Figure 2).

Next, we counted the number of cases determined pathological and non pathological in both groups (Table 2). For both methods, significantly more patients than controls were considered to have pathological scores (chi-square; RM: $p=0.003$; TLT: $p<0.001$). Next, when comparing the distribution of pathological/ non-pathological cases for both techniques within the patient population, significantly more patients were considered to have pathological values when TLT was used than when RM was used (chi square; $p<0.001$).

We then proceeded to the ROC analysis. For RM, the AUC was 0.47; with a cut-off value of 0.54 it yielded a sensitivity of 0.74 and a specificity of 0.41. For TLT the AUC was 0.78; at a cut-off value of 32.5 the sensitivity was 0.78 and the specificity 0.66 (Figure 3).

Finally, we evaluated the validity of RM by comparing scores before and after decongestion. RM scores revealed a significant

Table 1. Average scores (standard deviation) for rhinomanometry (RM) and the trigeminal lateralization (TLT) in healthy controls and CNO patients, as well as cut off scores (90th percentile of healthy controls).

	RM (Pa*sec/ml) at 150Pa		TLT (number of correct answers)	
	Left	Right	Left	Right
Healthy (n=58)	0.53 (0.18)	0.57 (0.27)	17.4 (2.83)	17.59 (2.55)
CNO patients (n=140; *: n=139)	0.62* (0.45)	0.65* (0.52)	14.45 (4.71)	13.44 (5.22)
Cut off scores from healthy participants	0.75	0.87	12.8	13.8

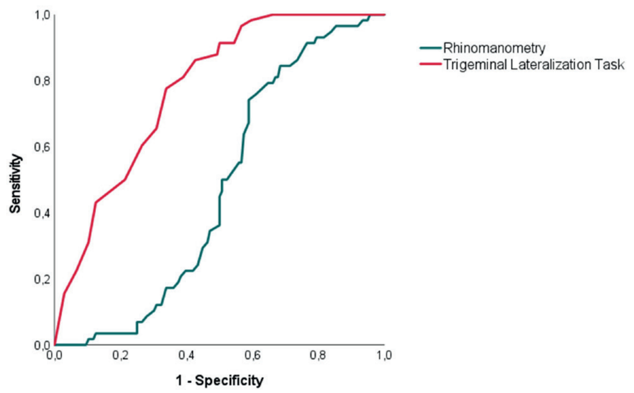

Figure 3. Receiver Operating Characteristics curve for the trigeminal lateralization task compared to rhinomanometry.

effect of congestion status (F(1.135)=31.651; p<0.001). Decongestion increased nasal patency significantly, as RM average scores before vasoconstriction (left: 0.62 (0.45); right: 0.65 (0.52) Pa*sec/mL) were significantly larger than after vasoconstriction (left: 0.48 (0.37); right: 0.43 (0.23) Pa*sec/mL.

There was no effect of gender in either the patient or control group.

Discussion

The present data suggest that in a subset of patients with CNO that do not have any obvious anatomical deformity, who did not improve with prior surgery or repeated medical treatments, there is a decreased intranasal trigeminal function. The present study does not give a causal answer, but it raises the question to which extent impaired intranasal trigeminal function may contribute to chronic nasal obstruction in this particular subset of patients which all rhinologists are exposed to. Although the analyzed sample was heterogeneous in terms of previous treatments, the included patients were homogenous in their clinical presentation. Anatomically unexplained, refractory CNO and referral for further treatment was the common denominator. As the biggest danger in such patients is to perform another, often unsuccessful, surgery, our goal was to further investigate several aspects of the complaint in these patients in order to better understand the so far mysterious CNO. With the present results we suggest that clinicians, who are faced with such particular CNO patients, should consider trigeminal testing, besides the other, traditional, physical resistance and flow measurements. The trigeminal lateralization task thus may be a clinically helpful tool to identify patients suspected to suffer from an atomically unexplained CNO refractory to medical treatment.

Table 2. Number of pathological and non pathological cases for control group and CNO group.

	CNO group		Control group	
	Pathological cases	Non-pathological cases	Pathological cases	Non-pathological cases
RM	51 (37%)	88 (63%)	9 (16%)	49 (84%)
TLT	80 (57%)	60 (43%)	10 (17%)	48 (83%)

In the CNO patients of the present study, the sensitivity/specificity of TLT for this condition was higher than for RM suggesting that CNO is more associated to airflow sensitivity than to mechanical obstruction. The AUC of the tests highlight the better capacity to distinguish the two groups (pathological vs non pathological) using the TLT (AUC=0.78) compared to the RM which is not able to discriminate the two groups (AUC=0.47).

The normative values obtained in controls were used to classify each case as pathological or non-pathological for each nostril separately in CNO group. A patient is pathological if one of the two values is not in the range of the normative values, i.e., above the 90e percentile for RM and below the 10th percentile for TLT of the control group. By using RM only 37% of CNO patients are correctly classified as pathological, whereas the trigeminal lateralization task allowed to correctly identify 57% of CNO patients as pathological.

The sensation of nasal obstruction is multifactorial. Many parameters can influence nasal airflow, such as anatomical obstruction or reduced nasal patency due to inflammation. For the diagnosis of CNO, these factors must be excluded, and no major obstruction should be observed with nasal endoscopy. The RM results presented here, within a normal range, reflect the lack of anatomical or inflammatory obstruction very well. This typical finding is often frustrating for patients and ENT surgeons alike. However, in the absence of objective obstruction, such as in CNO, the sensation of a blocked nose may instead be caused by disrupted receptive structures, i.e., an impairment of the structures that convey the information on airflow. Indeed, our results support this alternative explanation. In other words, our

results suggest that the trigeminal system, which is known to be involved in airflow perception [17], plays a role in the pathogenesis of CNO. Our results further support previous observations that underline the importance of identifying patients with poor intranasal trigeminal sensitivity prior to nasal surgery [8, 24].
The present results are in line with previous reports on trigeminal perception of the trigeminal stimulus menthol [17, 25]. As is widely known, inhalation of menthol causes the sensation of nasal decongestion. However, this effect is purely subjective, as there is no effect of menthol administration on nasal airflow resistance (when measured by RM). In other words, administration of menthol increases the sensation of nasal airflow, but leads to no change in objective airflow, i.e., no decongestion [9]. Our study extends these elements by comparing the trigeminal lateralization test to RM in a large sample size in the aim of determining the best modality to objectify the subjective complaints in CNO.
The nasal division of the trigeminal nerve conveys sensations such as warmth, burning, cooling, stinging, or tickling by odorous stimuli, but also about the perception of nasal airflow during breathing [6, 12, 26]. By being the afferent structures of respiratory reflexes, the trigeminal system plays a role in the protection of the organism from harmful stimuli. It is unclear how the trigeminal system is involved in the pathogenesis of CNO. First, trigeminal sensitivity is not independent from anatomy, but is rather also determined by nasal anatomy; i.e. sensitivity for trigeminal stimuli increases with the size of the nasal cavity [27]. Therefore, small intranasal anatomical differences including slight septum deviation or mucosal inflammation may influence trigeminal sensitivity without being detectable through significant changes in RM. Secondly, subliminal inflammation, invisible with common instruments, may impair the function of trigeminal receptors or fibers and therefore cause reduced susceptibility [5, 28]. Thirdly, an unknow cause may reduce susceptibility of trigeminal receptors and thus cause diminution of trigeminal sensitivity [29].
As a result of all these potential patho-mechanisms, perception of nasal patency is reduced, and the patient has the sensation of a blocked nose. Our data suggests that this can be best assessed by means of the TLT. Future studies should investigate to what extent the perception of reduced nasal patency is associated with alterations on a microscopic and cellular level in the nasal mucosa. By doing so the neurobiological underpinning of CNO could be unveiled.
Recent studies suggest that the subjective feeling of nasal obstruction could be caused by an alteration of a chemoreceptors, such as TRPM8, of the trigeminal nerve, located in the epithelium of the nasal cavity and the oral cavity [12]. These receptors respond to a modification of intranasal temperature caused by inhaled air as well as chemicals. It is for this reason that inhaling odorants such as menthol or eucalyptus, e.g., in lozenges, gives the impression of increasing the airflow, and therefore, of reducing nasal congestion in the case of a cold, although objectively there is no change in the degree of nasal congestion [9]. The perception of sensations such as the freshness evoked by menthol is possible by a specific interaction of odor molecules with these chemoreceptors. Furthermore, a study examined the distribution of trigeminal receptors on participants underwent septorhinoplasty for functional and esthetic reasons. It has been show that TRPM8 receptors are in low concentration in this subset of patients with a feeling of nasal obstruction (30). In future studies, it will be interesting to investigate the possible avenues to increase the responsiveness of TRPM8 in order to increase the airflow perception.
A limitation of the study is the absence of use of validated patient rated outcome measures (PROMs) such as the Nasal Obstruction Symptom Evaluation (NOSE), in the patient and healthy subject groups, which is due to the retrospective cross-sectional study character. This evaluation would have allowed comparing the trigeminal status with the subjective sensation of nasal obstruction experienced by the participants. A second limitation is the inclusion, due to the retrospective cross-sectional study character of our study, of a group of 20 CNO patients which had previous functional endoscopic sinus surgery for various indications. Retrospective analysis of their case files showed an operative indication of chronic rhinosinusitis in 10 of these patients. It is known that there is an effect of chronic rhinosinusitis on the trigeminal testing which we performed. However, at the moment of the performed testing on these patients, they did not fulfill the criteria to be considered as suffering from CRS, which is why we did not exclude them from our statistical analysis.

Conclusion

Here we show that reported nasal obstruction in CNO patients without any obvious anatomical obstacle and resistant to medical treatment could be linked to an impairment of trigeminal function which may explain their sensation of nasal obstruction rather than physical obstruction. In this subset of patients, assessment of trigeminal sensitivity (TLT) is more adequate to objectify the reported obstruction than nasal resistance assessment (RM) does. Trigeminal testing should be performed, despite normal nasal resistance, if no obvious anatomical deformity explains CNO and medical treatment failed.

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Authorship contribution

Conception or design of the work (CMB, BNL, JF); data acquisition (FJMB, MH, BNL), data analysis (CMB, BNL, JF), drafting work (CMB, FJMB, BNL, JF); final approval (all authors).

Conflict of interest

No conflict of interest.

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Johannes Frasnelli
Department of Anatomy
Université du Québec à Trois-Rivières (UQTR)
3351, Boul. des Forges
Trois-Rivières (Québec)
Canada, G9A 5H7