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Patient-Reported Outcome Measures and Provocative Testing in the Workup of Empty Nose Syndrome—Advances in Diagnosis: A Systematic Review

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Abstract

Background: The last 5 years have seen a surge of both clinical and scientific interest in empty nose syndrome (ENS). Although ENS is still considered a controversial diagnosis plagued by a lack of standardized diagnostic criteria, ENS is increasingly becoming recognized as a legitimate, physiologic disease entity. As such, it is important for clinicians to understand the most up-to-date diagnostic tools to assess ENS, confirm the diagnosis, and create a more standardized means to counsel these complex patients.

Objective: Contemporary literature review to discuss diagnostic modalities in the evaluation of ENS, in order to introduce evidence-based diagnostic criteria.

Methods: A systematic review was conducted in PubMed and Embase (2013–2019) using the search term "empty nose syndrome" to identify peer-reviewed articles on the topic of ENS. Articles advancing contemporary methods of ENS diagnosis and testing were included. A quality assessment was conducted using The Rational Clinical Examination Levels of Evidence.

Results: The novel development of the Empty Nose Syndrome 6 Questionnaire (ENS6Q) offers the clinician a validated patient-reported outcome measure to supplement history and physical examination. The in-office cotton test, performed by placing an endoscopically directed cotton plug in the site of tissue loss, may help to identify patients who may benefit from turbinate augmentation. Tools such as the sinus computed tomography scan, computational fluid dynamics, and intranasal trigeminal nerve function testing currently have insufficient evidence to support routine use in the workup of ENS. Up to 66% of ENS patients present with comorbid anxiety or depression.

Conclusion: The ENS6Q and cotton test assist in creating a standardized approach to the evaluation of patients suspected of ENS. These instruments should be used as an adjunct, rather than the sole criteria, on which to ascertain the presumptive diagnosis. Patients suspected of ENS should be screened for comorbid psychological dysfunction.

Keywords

empty nose syndrome, systematic review, depression, anxiety, intranasal trigeminal function testing, nasal obstruction, diagnosis, cotton test, Empty Nose Syndrome 6 Questionnaire, computational fluid dynamics

Introduction

Empty nose syndrome (ENS) is rare disease entity associated with the upper airway, classically characterized by the unexpected development of paradoxical nasal obstruction, almost always in the setting of prior turbinate surgery.[1–3] Additional symptoms associated with this diagnosis include nasal dryness, nasal burning, and the feeling of dyspnea and/or the presence of hyperventilation.[1–3] In the most concerning presentations, patients cite new onset sleep disturbance, anxiety, and

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depression weeks-to-years after the performance of the nasal procedure. The severities of the latter symptoms, and their unexpected association with evolving psychological sequelae, have allowed ENS to be deemed by some practitioners as an uncloaked psychiatric issue rather than an otolaryngologic process. Historically, there has been a lack of standardized clinical tools to establish the diagnosis of ENS, and an inability to objectively identify this patient population in a manner that is both accurate and reproducible. This scenario presents a clinical challenge for practicing otolaryngologists and a source of frustration for the motivated and/or desperate symptomatic patient. Ultimately, the combination of these factors has created great unease among many otolaryngologists about the basis of this phenomenon. For the purposes of this review article, we assume that ENS is a true sinonasal disease with a physiologic foundation consistent with altered nasal airflow. We seek to review the evidence supporting more objective methods of substantiating a diagnosis of ENS and examine whether there is a role for the routine assessment of comorbid psychiatric disorders in these challenging patients.

Methods

A systematic review using the search term "empty nose syndrome" was conducted in PubMed and Embase from January 1, 2013 to December 31, 2018. Inclusion criteria were articles that addressed the diagnostic aspects of ENS including case reports, retrospective cohort studies, and systematic reviews. Narrative reviews, non-English language articles, articles solely describing surgical interventions for ENS, and articles that did not discriminate between ENS and rhinitis were excluded. After screening 91 titles and abstracts, a total of 14 studies met inclusion criteria (Figure 1). Titles, abstracts, and selected articles

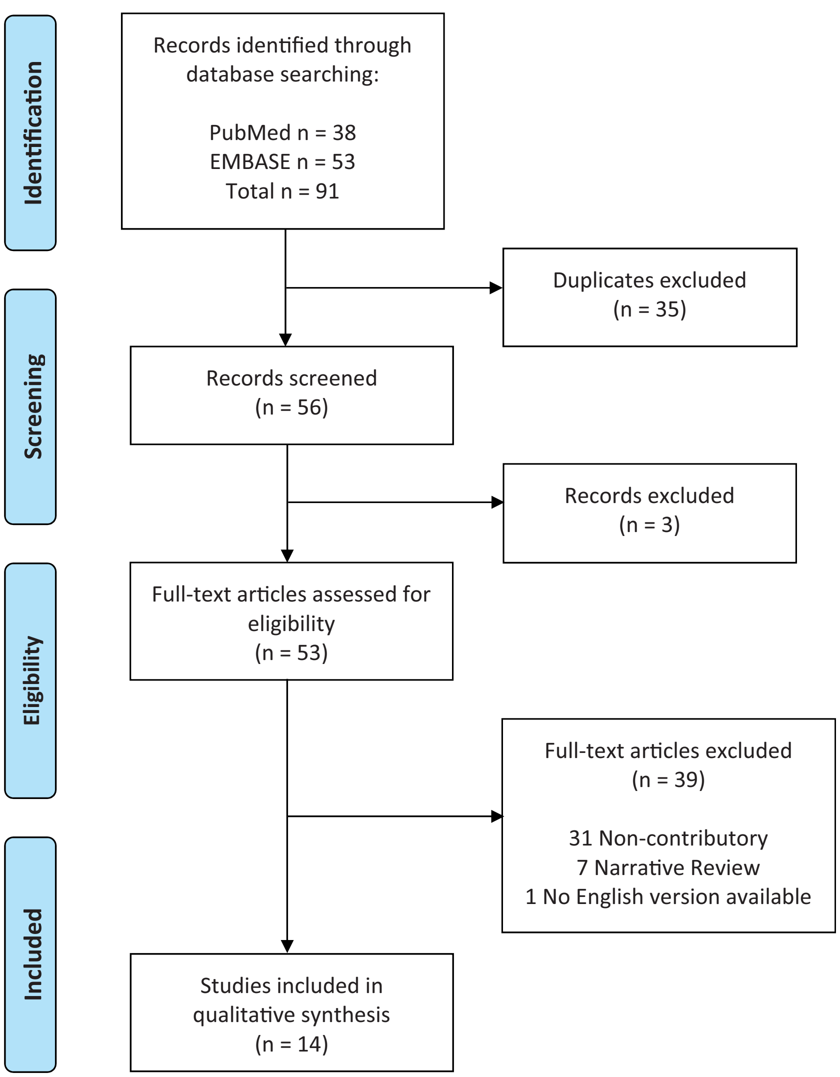

Figure 1. ENS article selection process.

were reviewed independently by 2 authors (A. S. G. and M. S.). Quality assessment was conducted using The Rational Clinical Examination Levels of Evidence.

Results

Major Diagnostic Advances

The last 5 years have seen a renewed vigor in the scientific evaluation of existing diagnostic modalities for ENS and the development of new diagnostic techniques and approaches (Table 1).[1,2] We review these diagnostic techniques as well as mental health comorbidities associated with ENS.

Patient-Reported Outcome Measures

Velasquez et al. published the first validated clinical tool to assess quality of life measures in patients with suspected ENS.[1] The ENS6Q was validated using the SNOT-22, but in addition presents 6 simple questions (with a score of 1–5 points each) that can be a helpful in screening/confirming the diagnosis of ENS. A score $\geq$11 (but especially >15) out of a maximum score of 30 suggests the presence of ENS in the appropriate clinical scenario. The authors divided 75 subjects into 3 groups: (1) normal control, (2) ENS, and (3) chronic rhinosinusitis without nasal polyposis (CRSsNP). Each patient filled out both the Sino-Nasal Outcome Test 22 (SNOT-22) and ENS6Q at 2 different time points within 48 hours. Analysis of the data demonstrated a strong internal consistency between patient responses for SNOT-22 and ENS6Q, respectively, as well as high test reproducibility across the 2 distinct time points. Moreover, the ENS6Q was able to discriminate differences in symptoms reported between patients with ENS, CRSsNP, and normal controls ($P < .05$).

The Cotton Test

Thamboo et al. then used the ENS6Q to validate an office-based physical examination maneuver, referred to as the cotton test, as another provocative adjunct helpful in confirming the diagnosis of ENS.[1] Eighteen controls and 15 patients with known ENS (confirmed by ENS6Q and history and physical examination) were asked to complete the ENS6Q both before and after the execution of the cotton test. The test itself was accomplished in the absence of any topical intranasal sprays, where a fashioned plug of cotton was placed in the patent inferior meatus space that was partially or completely devoid of inferior turbinate tissue for 20 to 30 minutes. Cotton was placed unilaterally or bilaterally depending on physical examination findings and laterality of symptoms. Patients with ENS due to inferior turbinate volume loss demonstrated a significant improvement in symptoms, with scores that unexpectedly overlapped with those of healthy controls. The majority of individual ENS6Q queries were markedly reduced as well. Control patients either had no change or worsening of nasal obstruction due to a feeling of nasal airway blockade via cotton placement. Subsequently, the authors concluded that patients with improvement in symptoms with the cotton test might benefit from potential inferior turbinate augmentation procedures.

The authors of the aforementioned 2 studies acknowledge limitations of their design, including the assumption, based on the majority of literature, that ENS is largely an iatrogenic disease primarily associated with prior sinonasal or turbinate surgery. All included study subjects had undergone prior surgical intervention on their turbinates. Moreover, the sample sizes were relatively limited (although large patient cohorts harboring ENS complaints are challenging to accumulate), with further studies recommended to increase power and confirm the major findings.

Computed Tomography Imaging

Several studies have examined the role of computed tomography (CT) in assessing mucosal thickness and nasal volume in patients suspected of ENS.[3,4] Hong and Jang compare CT estimated nasal volume to nasal symptoms, concluding that smaller inferior turbinate volume is associated with specific SNOT-25 symptoms. Thamboo et al. demonstrated that compared to normal controls, patients with ENS had a significantly greater soft tissue thickness of the central (>2.64 mm) and posterior (>1.32 mm) nasal septum, adjacent to areas of prominent inferior turbinate tissue loss.[4] Both studies were published prior to reporting of the ENS6Q or validation of the cotton test. Although the significance of these findings requires further research, CT imaging and the aforementioned findings, may help guide the clinician in the appropriate clinical setting.

Computational Fluid Dynamics

Recent studies have also evaluated the role of airflow in patients with ENS using computational fluid dynamics. Modeling has demonstrated significant disorganization in airflow distribution after surgical (or virtual) reduction of the inferior turbinate.[5–10] Of note, Dayal et al. observed that virtual/simulated total inferior turbinectomy in 10 patients appeared to have a greater impact on nasal aerodynamics compared to simulated total middle turbinectomy.[8] In addition, Maza et al. studied the use of computational fluid dynamics as a potential objective diagnostic tool for ENS.[7] In the study, patients with ENS (confirmed by ENS6Q scores >11) were grouped by surgical intervention: endoscopic endonasal approach (EEA) or non-EEA. The authors observed that 2 EEA patients with ENS and 27 non-EEA patients with ENS exhibited airflow favoring the middle turbinate region, compared to 42 normal subjects and 2 EEA patients without ENS complaints. This latter cohort demonstrated nasal airflow that was more evenly distributed across the middle turbinate and inferior turbinate, indicating that patients with ENS are more likely to exhibit an imbalanced nasal airflow that newly favors the middle turbinate region. Consequently, Maza et al. posited that computational fluid dynamics might be a useful objective diagnostic tool to confirm ENS in diagnostically challenging cases. The authors highlighted their study limitations, including the small study size and the need for additional confirmatory studies.

Intranasal Trigeminal Function Testing

Intranasal airflow leads to mucosal cooling and initiates a signaling cascade through the sensory limb of the trigeminal nerve (via the TRPM 8 menthol receptor), which communicates the presence/absence of adequate airflow to the central nervous system.[11–13] TRMP8 is the abbreviation for Transient Receptor Potential cation channel subfamily M member 8. A prospective case–control study by Saliba et al. found that 14 patients with chronic rhinosinusitis but no evidence of nasal airway obstruction had statistically significantly worse trigeminal nerve lateralization compared to 14 healthy controls. The authors highlighted that their findings may be related to nerve damage secondary to inflammatory processes associated with chronic rhinosinusitis.[14] Importantly, in a prospective case–control study, Konstantinidis et al. noted that 19 of 21 patients with ENS had a similar significant decrease in trigeminal lateralization when challenged with menthol compared to 3 of 18 inferior turbinate reduction patients without ENS complaints and 1 out of 32 healthy controls.[15] Furthermore, a case–control study by Li et al. found that patients with ENS ($n = 12$) had significantly worse methanol lateralization detection thresholds compared to a healthy control group.[6] It is important to consider these findings in conjunction with a 2012 study performed by Scheibe et al. that demonstrated a greater degree of trigeminal sensitization in the anterior portion of the nose compared to the posterior part in 50 healthy volunteers.[16] Thus, these discoveries may suggest the following: (1) impairment in trigeminal sensory innervation of the inferior turbinate may contribute to subjective nasal obstruction and (2) trigeminal function testing may be used as a preoperative and postoperative tool to delineate subjective nasal obstruction in ENS. However, given the improvement in patient symptoms with the cotton test or inferior turbinate augmentation, the role of trigeminal nerve function in the pathophysiology of ENS requires further investigation.[17]

Mental Health Comorbidities

Mental health comorbidities in patients with sinonasal disease have been shown to impact the patients' perception of the sinonasal disease process and may also exert an effect on postoperative outcome measures.[18] Manji et al. demonstrated a significant mental health burden of ENS, reporting that the incidence of concomitant anxiety/depression in this population to be as high as 66%.[19] There has also been interest in analyzing ENS as a somatic/mental health disorder, leading to the consideration of alternative therapies, such as cognitive behavioral therapy.[20]

Various validated screening tools (ie, Patient Health Questionnaire-2, Patient Health Questionnaire-9, Hospital Anxiety and Depression Scale, Becks Depression Inventory) are being used to help identify patients with rhinologic complaints who also have symptoms of depression and/or anxiety.[21–24] Lee et al. performed a prospective cohort study of 20 patients with ENS diagnosed by history and physical, undergoing endonasal submucosal implantation with high-density polyethylene or autologous bone grafts. The authors noted an improvement in the preoperative Beck's Depression Inventory II and Beck Anxiety Inventory scores from "moderate" to "normal" after surgical intervention.[25] Thus, the aforementioned studies demonstrate

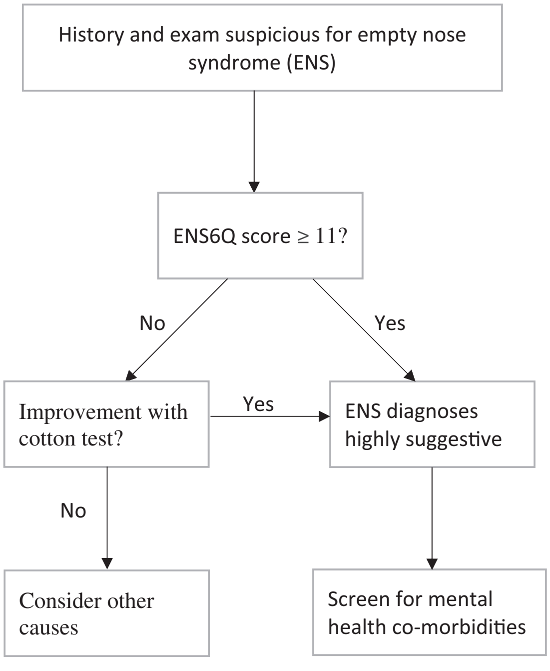

Figure 2. Diagnostic algorithm for suspected ENS. ENS, empty nose syndrome; ENS6Q, empty nose syndrome 6 questionnaire.

the benefit of preoperative and postoperative mental health screening in ENS.

Discussion

The ENS6Q and cotton test represent validated adjunctive tools that may help diagnose patients suspected of ENS in the appropriate clinical setting (Figure 2). There is insufficient evidence to confirm the reliability of CT imaging in identifying ENS patients. Computational fluid dynamics appears to be a promising technique for understanding the pathophysiology behind disturbed airflow in ENS. However, there is insufficient evidence to use computational fluid dynamics for confirmatory diagnosis of ENS. Similarly, intranasal trigeminal function testing has insufficient data to support clinical applicability. Finally, there is limited but impressive evidence that patients with ENS also have significantly high rates

Table 1. Major Diagnostic Advances in Empty Nose Syndrome.

Study	Level of Evidence	Diagnostic Management	Type of Evidence	No. of Patients With ENS (%)	Conclusion
Velasquez et al, 2017[1]	4	ENS6Q	Case-control	15 (20%)	ENS6Q is a validated questionnaire to assess patient reported outcomes in those with suspected ENS
Thamboo et al, 2017[2]	4	Cotton test	case-control	15 (45.5%)	The cotton test is a validated objective test to evaluate patienst with ENS who may benefit from surgical intervention.
Hong et al, 2016[3]	4	Computer Tomography	Case-control	34 (77.3%)	A reduced inferior turbinate volume is significantly associated with ENS symptoms.
Thamboo et al, 2016[4]	4	Computer Tomography	Case-control	18 (27.7%)	The mucosal thickness of the central and posterior segments of the septum after inferior turbinate reduction may distinguish patients with ENS.
Li et al, 2017[5]	4	Computational Fluid Dynamics; Intranasal Trigeminal function	case-control	6 (30%)	CFD is a useful tool to determine the aerodynamics associated with ENS. Trigeminal sensory testing can reveal concurrent neurosensory losses.
Li et al, 2018[6]	4	Computational Fluid Dynamics; Intranasal Trigeminal function	Case-control	27 (39.1%)	Airflow changes associated with ENS significantly correlate with ENS6Q scores, and patients with ENS have significantly worse trigeminal function compared to a healthy control group.
Maza et al, 2019[7]	4	Computational Fluid Dynamics	Case-control	29 (39.7%)	CFD may be a useful objective diagnostic tool to identify patient with ENS.
Dayal et al, 2016[8]	5	Computational Fluid Dynamics	Case-control	–	Total inferior turbinectomy significantly impairs nasal aerodynamics compared to total middle turbinectomy.
Balakin et al, 2017[9]	5	Computational Fluid Dynamics	Case report	1 (100%)	After development of ENS, CFD demonstrates nearly 50% reduction in airway resistance and significant redistribution of airflow.
Di et al, 2013[10]	5	Computational Fluid Dynamics	Case-control	–	Nasal aerodynamics contribute to the pathogenesis of ENS.
Konstantindis et al, 2017[15]	4	Intranasal Trigeminal function	Case-control	21 (29.6%)	Trigeminal sensory function is significantly impaired in patients who develop ENS after bilateral inferior near total turbinectomy.
Manji et al, 2018[19]	4	Mental Health Co-morbidities	Cross Sectional	53 (100%)	Depression and anxiety are highly prevalent in patients with ENS, and screening allows for multimodal treatment.
Lemogne et al, 2015[20]	5	Mental Health Co-morbidities	Case report	1 (100%)	Treating ENS as a somatic symptom leads to resolution of disease.
Lee et al, 2016[25]	4	Mental Health Co-morbidities	Cohort	20 (100%)	Depression and anxiety screening normalize after surgical intervention in ENS patients.

Abbreviations: CFD, computational fluid dynamics; ENS, empty nose syndrome; ENS6Q, Empty Nose Syndrome 6 Questionnaire.
Level of evidence determined via The Rational Clinical Examination Levels of Evidence.

of comorbid, dramatic rates of anxiety/depression. Consequently, clinicians should consider using validated mental health questionnaires and include a psychiatric history in their normal rhinologic workflow. Patients who are considered "at risk" of anxiety/depression may then be referred to their primary care physician for further evaluation. Moreover, limited evidence suggests that intervening on the underlying psychiatric disorders may positively influence prognosis and treatment of ENS.

Our review has several limitations. There is a clear lack of high-quality evidence in ENS literature and the overall level of evidence is weak. Moreover, the background controversy regarding the authenticity of an ENS diagnosis has limited the overall time and energy directed at studying this disease process, and the majority of data is contained within the last 3 to 5 years. Nevertheless, the rapid gains in our understanding of the pathophysiology following turbinate tissue loss and its contribution to ENS, as well as the development of novel diagnostic techniques, has led to novel therapeutic options. Thus, this is an exciting time to understand and track the clinical development of this entity. Finally, there are currently no guidelines for the diagnosis and management of ENS, which creates both clinical and research challenges in implementing a standardized approach to the evaluation of the disease, as well as conducting research that can be easily reproduced.

Conclusion

The ENS6Q and cotton test are 2 novel and validated diagnostic techniques that can assist in the evaluation of suspected ENS; they should be used as adjuncts, rather than sole criteria, on which to establish the diagnosis of ENS. Given the high incidence of comorbid anxiety/depression in patients with ENS, uniform screening for psychiatric illness during the outpatient workup in this vulnerable patient population should be considered.

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