

## **Abstract**

Empty nose syndrome is a complication of nasal surgery wherein patients develop a persistent, debilitating sense of nasal obstruction and dyspnea despite clear nasal cavities. It is characterized by a discrepancy between prominent subjective symptoms and near total lack of objective findings, making it difficult to diagnose. The pathophysiology of empty nose syndrome is a complex mix of aerodynamic, physiologic, and neurological changes leading to altered airflow and diminished sensory function. Evolving treatment options consist of medical symptom control or surgical reconstruction.

## **Introduction**

Empty nose syndrome (ENS), first described in 1994 by Kern and Stenkvist, is a secondary form of atrophic rhinitis seen as a complication of sinonasal surgery. While ENS is considered rare, the incidence is unknown and some have suggested that it may be as high as 20%.<sup>1</sup> ENS is generally seen following turbinate resection—most commonly the inferior turbinate—but has also been reported following less destructive procedures such as submucosal cautery, laser therapy, and turbinate-sparing operations.<sup>2,3</sup> Although few patients develop ENS following nasal surgery, it remains greatly feared due to its debilitating effect on quality of life. In this review, we explore recent advances in the understanding and treatment of ENS.

## **Presentation and Diagnosis**

The diagnosis of ENS is challenging given the paucity of objective findings and the characteristic discrepancy between patients' subjective symptoms and clinician's findings on exam. Symptoms may begin months to years following nasal surgery and are categorized as nasal or extra-nasal symptoms.<sup>4</sup> The common nasal symptoms are a paradoxical sense of nasal obstruction—where the nasal cavities are widely patent but the patient reports severe

obstruction—nasal dryness and crusting, malodor from the nasal cavity, anosmia, mucopurulent rhinorrhea, and a persistent sense of dyspnea.<sup>3</sup> Extra-nasal symptoms include facial pain, headaches, sleep disturbances and psychological issues such as: fatigue, irritability, anger, anxiety and depression.<sup>3,5</sup> Perhaps the most debilitating psychological symptom is aprosexia nasalis: a chronic impairment of one's ability to concentrate due to extreme preoccupation with maintaining the sensation of nasal patency.<sup>3</sup> Although there is no predictive correlation between extent of surgery and occurrence of ENS, one study found that smaller residual turbinate volume was associated with increased severity of nasal symptoms.<sup>6</sup>

Given the lack of objective indicators, the diagnosis remains one of exclusion—based upon the patient's history. Currently, the main tool to assist in the diagnosis of ENS is the Sino-nasal Outcome Test-25 (SNOT-25) questionnaire. A recent six item ENS-specific questionnaire (ENS6Q) has also been shown to accurately differentiate ENS patients and to correlate with SNOT scores.<sup>7</sup>

Several objective findings have been proposed for use in distinguishing ENS from other causes of nasal dryness and perceived obstruction. The first is the placement of a saline-soaked cotton ball within the nasal cavity. Alleviation of symptoms within 20-30 minutes supports the diagnosis of ENS and predicts a favorable response to surgery.<sup>2</sup> Most recently Thamboo *et al* have proposed that patients with ENS have characteristically thicker central and posterior septal mucosa on CT when compared to control patients and patients with a history of inferior turbinate resection but no symptoms of ENS.<sup>8</sup> Additionally, they found that ENS patients had thicker nasal floor mucosa compared to control patients, but not patients having turbinate resection without ENS.<sup>8</sup> Until these tests are further validated though, the mainstays of diagnosis remain clinical history and the SNOT questionnaire.

## Pathophysiology

The mechanisms underlying ENS are complex and not yet fully elucidated. Current evidence suggests that anatomic changes from nasal surgery alter aerodynamics, pulmonary function, mucosal physiology, and CNS function to cause the aggregation of symptoms in ENS.

Turbinate resection alters airflow patterns through the nasal cavity. Decreased airflow velocity leads to reduced stimulation of nasal mechanoreceptors, likely contributing to the sensation of obstruction.<sup>9</sup> Subsequent decreases in shear stress along the mucosa lead to areas of higher temperature, with reduced activation of cool-sensing thermoreceptors—also important in the sense of nasal airflow and patency.<sup>3,9</sup> Loss of laminar airflow increases water vapor removal, likely contributing to increased nasal dryness.<sup>9</sup> Turbinate removal also moves airflow away from olfactory areas, decreasing sense of smell.<sup>9</sup>

Removal of the turbinates also decreases nasal resistance, which is known to be an important factor in opening peripheral bronchioles in the lungs.<sup>4,9-11</sup> Decreased lung aeration may explain the persistent dyspnea felt by ENS patients. Interestingly, changes in nasal aerodynamics were more prominent following inferior turbinate resection, except for increased airflow velocity around the sphenopalatine ganglion seen more with middle turbinate removal.<sup>9</sup> This may explain why ENS is more common with inferior turbinate surgery and why headache—thought to be due to sphenopalatine ganglion irritation—occurs most in ENS due to middle turbinate resection.<sup>9</sup>

Nasal surgery also modifies nasal mucosal physiology. Loss of glandular surface area contributes to decreased air humidification and is more prominent following inferior turbinate resection as the middle turbinate has smaller surface area and a lower density of erectile tissue.<sup>3,4,10</sup> Removal of mucosa also destroys sensory nerves, most notably the trigeminal cool thermoreceptor—TRPM8.<sup>3,10</sup> Dayal *et al* showed that aggregate stimulation of nasal TRPM8

thermoreceptors is important in generating sensation of airflow and thus, loss of receptor containing mucosa may contribute to the paradoxical sense of nasal obstruction in ENS.<sup>10</sup>

A still poorly explained feature of ENS is the alteration in CNS activation seen on fMRI. Increased temporal, cerebellar and amygdala activation, as well as marked limbic reactivity have been noted in patients with ENS, which may explain the common psychological symptoms.<sup>1,4,5</sup>

## **Treatment**

The mainstays of ENS treatment are prevention via minimally invasive nasal surgery and medical management with mucosal humidification, nasal irrigation, emollient application and even nasal lubricants with menthol—to increase activation of remaining TRPM8 receptors.<sup>2-4</sup> For those refractory to medical care, surgical recreation of turbinate mass becomes the goal. If enough turbinate mass remains this can be through reconstruction, otherwise augmentation of the lateral wall, septum, or floor is performed.<sup>3,11</sup> Medialization of remaining turbinate mass has been trialed, but has shown minimal results and has a risk of lacrimal duct obstruction.<sup>4</sup>

Many options for turbinate reconstruction have been evaluated and while it is difficult to accurately assess outcomes given the small sample size, some have shown promise. One review demonstrated that ENS symptoms improved post-surgery regardless of implant type.<sup>12</sup> Cartilage autograft has been assessed by multiple studies and has shown improvement in symptoms.<sup>13,14</sup> Costal cartilage appears to be superior to conchal cartilage given its better volume and ability to be shaped.<sup>14</sup> Medpor implants have also shown benefit in both subjective and objective measures and have been suggested given that their porous nature promotes fibrovascularization of the implant.<sup>15,16</sup> Acellular dermal grafts may be beneficial given their immunologic inertness and have been shown to be equal to silastic inserts for resolving symptoms;<sup>11</sup> however, they may undergo some shrinkage and resorption, requiring further augmentation.<sup>17</sup>  $\beta$ -Tricalcium

phosphate has also been tried, due to its compact, porous structure and slow resorption rate.<sup>17,18</sup> Xenograft transplant of porcine small intestine has also had good results, with minimal resorption, in a recent series.<sup>19</sup>

Injections have also been proposed for turbinate reconstruction. Hydroxyapatite and hyaluronic acid have been used, but have issues with excessive resorption requiring additional injections or procedures.<sup>12,15</sup> Recently, Xu *et al* described excellent results after trialing injection of autologous adipose-derived stem cells based upon the benefits of potential for differentiation into epithelial like cells, easy access, and low immunogenicity.<sup>20</sup>

Although most research on ENS treatment has focused on medical and surgical options, recently, Legmone *et al* have suggested that ENS patients should be managed as if they have a somatic symptom disorder.<sup>1</sup> This is predicated on similarities in extra-nasal ENS features to somatic symptom disorders and the evidence of abnormal neurologic function. It has been reported that treatment with cognitive therapy and an SSRI/SNRI dramatically improved patient function, although ENS specific symptoms did not decrease.<sup>1,5</sup>

## **Conclusion**

Empty nose syndrome is a complex condition that is difficult to anticipate and diagnose. ENS develops following nasal surgery due to alterations in nasal anatomy that affect airflow dynamics, mucosal physiology, and possibly even neurologic function. Although prevention is the best option, turbinate sparing procedures do not ensure that ENS will not develop and thus medical control and surgical reconstruction remain the most common treatment.

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