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Perspective

Mechanisms and treatment of olfactory dysfunction in chronic rhinosinusitis

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Chronic rhinosinusitis (CRS) is one of the most common chronic conditions in North America. Patients with CRS experience discolored nasal drainage, facial pain, difficulty breathing, and decreased sense of smell.¹ CRS impairs quality of life, reduces productivity, and increases the risk of depression and sleep disorders.¹

One of the most debilitating aspects of CRS is its association with olfactory dysfunction (OD), which can affect up to 80% of patients with CRS.² OD in CRS has been associated with decreased quality of life and economic productivity. However, despite the high prevalence and effect of OD in CRS, the exact mechanisms of how OD develops in patients with CRS remains controversial and is an area of active investigation.

Traditional teachings of OD in CRS centered around nasal obstruction as the underlying cause. Edema of the sinonasal mucosa or nasal polyposis was thought to physically obstruct the delivery of odorants to the olfactory cleft (OC), leading to decreased olfaction.² Although this hypothesis appears logical, it has failed to be demonstrated in clinical studies. Instead, our current understanding of the pathophysiology of OD in CRS is focused on inflammation of the olfactory neuroepithelium in the sinonasal cavity.³ Olfactory neurons and their supporting cells reside within the epithelium of the nasal vault near the cribriform skull base and extend along the superior aspect of the nasal septum, middle turbinate, and superior turbinate. This area is known as the OC. Inflammation of the OC neuroepithelium leads to decreased odorant transport across the mucous layer and the epithelium, olfactory neurotoxicity as a result of inflammatory mediators, and an impaired neuroregeneration.²

Of particular interest for OD in CRS is eosinophilic inflammation, specifically at the level of the OC. Eosinophils release neurotoxic mediators, such as eosinophilic-derived neurotoxin, and may cause direct damage to the olfactory neurons. Patients with eosinophilic CRS have a higher likelihood of developing nasal polyps, but eosinophilic CRS is a continuum of disease that may not initially present with polyposis. Regardless, the degree of eosinophilic inflammation appears to be directly correlated with the severity of OD.² This observation raises the question of whether other diseases associated with hypereosinophilia, particularly in the nasal cavity, would then also lead to impaired olfaction. Allergic rhinitis (AR) is a highly prevalent condition, yet practitioners may not commonly associate OD and AR. However, OD is an important symptom in patients with AR, and as many as 40% of patients with AR have impaired olfaction.⁴ Research of OD in AR is limited by a relative lack of objective psychophysical testing in the relevant literature. Nonetheless, although OD can be present in AR, it is generally mild when compared with CRS. One possible explanation for this may be that patients with CRS have a more direct inflammatory and eosinophilic insult to the OC, whereas the inflammation in AR is perhaps more prevalent in the nasal cavity without as a great an effect on the olfactory neuroepithelium. However, the pathophysiology of OD in AR and its differences and commonalities with CRS is a subject that deserves further investigation.

Given our current understanding of the pathophysiology behind OD in CRS, the mainstay of treatment revolves around controlling sinonasal inflammation. Comprehensive medical management is the cornerstone of CRS treatment, with surgical treatment reserved for refractory cases. A similar treatment paradigm applies to managing OD in CRS. The first and most effective line of medical therapy to control sinonasal inflammation is accomplished with the use of corticosteroids. These can be delivered orally or topically. Oral corticosteroids can be highly effective in improving OD in some patients, but the results frequently dissipate after discontinuation of therapy, and prolonged oral corticosteroid use is not advisable if it can be avoided. Topical corticosteroid treatment can

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be effective, but the mode of delivery is important. Nasal sprays do not have notable efficacy for OD in CRS, likely given their inability to reach the OC. However, nebulized or high-volume irrigation techniques, which have greater penetration and higher likelihood of corticosteroid delivery to the OC, seem to improve olfactory function in CRS.² In addition, newer exhalation delivery systems for corticosteroids appear to have similar penetration levels as nebulization or irrigation and may be better tolerated by some patients. Recently, smell training therapy (STT) has been found to be of benefit in OD of a variety of etiologies. STT attempts to stimulate neuroplasticity and neurogenesis with frequent repeated exposures to a variety of odorants. Indeed, the combination STT and topical steroid irrigations has shown additive benefit over STT and saline irrigations alone.⁵

During the past few years, the development of biologic therapies has promised to transform our approach to refractory CRS. These medications appear to improve symptom control in patients in whom traditional treatment strategies have failed, and they also appear beneficial for smell function in patients with CRS. Sinus surgery also improves olfactory function in CRS, likely because of the greater disease and inflammation control that surgery provides in the recalcitrant patient. However, it is difficult to predict which patients will have OD improvement after biologics or sinus surgery, and biologics in particular are costly interventions. Consequently,

OD alone may not be an appropriate indication for these therapies except for selected situations.

The modern understanding of OD in CRS is centered around neuroepithelial inflammation. Specifically, the degree of eosinophilic inflammation seems to correlate with the extent of OD. CRS is not the only eosinophilic process of the sinonasal cavity, yet it appears to have a more significant effect on olfactory function than other forms eosinophilic inflammation, such as AR. However, OD in CRS and AR is a topic that deserves further investigation. Future diagnostic and management advances will rely on identifying and resolving inflammatory changes of the sinonasal mucosa.

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