The Importance of Considering Olfactory Dysfunction During the COVID-19 Pandemic and in Clinical Practice

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The emergence of a worldwide pandemic due to coronavirus disease 2019 (COVID-19) and frequent reports of smell loss in COVID-19–infected patients have brought new attention to this very important sense. Data are emerging that smell impairment is a prominent symptom in COVID-19 and that this coronavirus behaves differently in causing olfactory dysfunction compared with other respiratory viruses. Anosmia and hyposmia, the complete and partial loss of smell, respectively, can result from many causes, most commonly from viral infections, sinonasal disease, and head trauma. Olfactory dysfunction negatively impacts quality of life, because sense of smell is important for flavor perception and the enjoyment of food. Olfaction is also important for the detection of warning smells, such as smoke, natural gas leaks, and spoiled food. Allergists and immunologists frequently encounter anosmia and hyposmia in patients with severe chronic rhinosinusitis with nasal polyps, and will likely see more infection-induced olfactory dysfunction in the era of COVID-19. Therefore, now more than ever, it is crucial that we understand this impairment, how to evaluate and how to measure it. In this review, we offer a clinically relevant primer for the allergist and immunologist on olfactory dysfunction subtypes, exploring the pathophysiology, appropriate clinical assessment, objective smell testing, and management of this condition. We will also focus on the emerging literature on COVID-19 olfactory dysfunction, its unique features, and its important implications for this pandemic. **(J Allergy Clin Immunol Pract 2021;9:7-12)**

Key words: *COVID-19; Coronavirus; Anosmia; Hyposmia; Olfactory dysfunction; Chronic rhinosinusitis; Nasal polyposis*

INTRODUCTION

Globally, as of December 4, 2020, more than 65 million confirmed cases of coronavirus disease 2019 (COVID-19) have been reported to the World Health Organization.[1] Early in the global pandemic, evidence emerged that many people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, present with loss of smell and/or taste. In response, the Centers for Disease Control and Prevention added new loss of smell or taste to its list of key symptoms of COVID-19, which includes cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, and sore throat.[2] Importantly, anosmia or hyposmia may be indicative of COVID-19 infection, even in the absence of other symptoms. Data are emerging that COVID-19 olfactory dysfunction (OD) has distinct features from typical viral-induced OD, in both its prevalence and clinical characteristics, and is an area of active investigation. For patients with complete anosmia, many of whom have never experienced loss of smell before, anosmia can be a disturbing symptom that disrupts their enjoyment of food, with many of them asking their physician "will I be able to smell again?"

Beyond COVID-19, allergists and immunologists see OD frequently in patients with chronic rhinosinusitis (CRS), and in particular, in patients with CRS with nasal polyps (CRSwNP). Treatment paradigms for CRSwNP have shifted with the approval of dupilumab for the treatment of refractory nasal polyps, and will likely expand given that several additional biologics are in the pipeline. With expansion of the treatment armamentarium, many patients who were previously primarily managed by ear, nose, and throat doctors are now being referred to allergists and immunologists for medical management and follow-up. Therefore, it is crucial that allergists and immunologists have a good working knowledge of OD; this will help them evaluate clinical symptoms and therapeutic efficacy when starting biologics and other treatments. We suspect this important sense is likely underappreciated by allergists, because the mechanics of olfaction, differential diagnosis, and quantitative smell testing are not routine parts of fellowship training curricula.

DEFINITIONS

OD is defined as the reduced or distorted ability to smell (orthonasal olfaction) or reduced or absent flavor perceptions

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Abbreviations used
COVID-19- Coronavirus disease 2019
CRS- Chronic rhinosinusitis
CRSwNP- Chronic rhinosinusitis with nasal polyps
NHANES- National Health and Nutrition Examination Survey
OD- Olfactory dysfunction
SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2
SNOT-22- 22-item Sino-Nasal Outcome Test
UPSIT- University of Pennsylvania Smell Identification Test
URTI- Upper respiratory tract infection

when eating (retronasal olfaction). Impairment may be sudden in onset or gradual, and may be temporary or permanent. Symptoms may be constant in nature, or fluctuate in severity; these characteristics can provide clues to the underlying etiology of disease. There may also be associated dysgeusia (also known as parageusia), which is distortion in the quality of taste. Table I provides a summary of commonly used terms when describing smell and taste disorders.

EPIDEMIOLOGY OF OD

OD is a prevalent condition; analysis of the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2012 found that 10.6% of adults (translating to an estimated 15.1 million) in the United States older than 40 years reported problems with sense of smell in the previous 12 months.[3] Altered smell (and taste) increases with age and is more prevalent in minority populations.[3,4] A 2016 cross-sectional study of data collected in the NHANES 2013-4 examined 3519 subjects 40 years and older using the NHANES Pocket Smell Test to define smell impairment.[4] The survey found that 14% had smell impairment, 17% had taste impairment, and 2% had both. Similarly, an NHANES-based study examining 1281 participants completing objective smell tests found OD in 12%.[5] Prevalence increased with age: 4% (40-49 years), 10% (50-59 years), 13% (60-69 years), 25% (70-79 years), and 39% (80+ years). Lower prevalence has been noted when based on self-report alone, suggesting that some patients may be poor perceivers of smell dysfunction.[3] In addition, it is not uncommon for patients to report a problem with taste, when actually their taste is intact and what they are experiencing is a loss of sense of smell that is impacting flavor perception. This is due to the complex experience of smell, taste, and flavor, and underscores the importance of objective testing, which will be discussed later in this review.

ANATOMY AND PHYSIOLOGY OF OLFACTION

Smell

Olfaction is one of the body's 5 basic senses (alongside sight, hearing, taste, and touch). These senses send information to the brain to help us perceive the world. Olfaction occurs via the sensory olfactory system, as shown in Figure 1. Most of the human nasal cavity is lined with nonsensory respiratory mucosa, except for the olfactory cleft, which is lined by olfactory neuroepithelium.[6] This neuroepithelium consists of bipolar olfactory receptor neurons. Special proteins called odorant-binding proteins bind odorant molecules and transport them to olfactory receptor neurons. Odorants bind specific sites on these neurons, which gets transduced into a neural signal that is transmitted to the olfactory bulb. The olfactory bulb is where sensory input begins to interact with parts of the brain. Olfactory neurons have a relatively short lifespan (weeks to months), and are replaced with new olfactory neurons from adult stem cells in the basal layers of the olfactory epithelium.[6]

Taste and flavor

OD may be accompanied by disturbances in taste. There are 4 classic taste qualities: sweet, sour, salty, and bitter. There is also a fifth taste, umami,[7] but it is more difficult to test for, due to its complexity. Taste mainly occurs through taste buds on the tongue while eating. Flavor perception is a complex, multisensory experience that involves the chemical senses of smell, taste, and chemical irritation. The aroma of foods is an important contributor to flavor. Retronasal smell, olfactory information that enters via the mouth through the oropharynx, is important in flavor determination (such as distinguishing the flavor of an apple and a peach).

PATHOPHYSIOLOGY OF OD

OD may be related to conductive or sensorineural processes, or both. In conductive disease, odorants are blocked from reaching the olfactory cleft in the nasal cavity. In sensorineural disease, the pathology occurs at the level of the olfactory receptor neurons and/or their projections, presumably due to direct damage of sensory neural structures. Viruses and head injury can cause sensorineural damage. CRSwNP is attributed to conductive or mixed (conductive and sensorineural) losses.[6]

SUBTYPES OF OD

The causes of OD include severe sinonasal disease, viral infection—induced (such as COVID-19 OD), posttraumatic, neurodegenerative diseases (Alzheimer disease, Parkinson disease), structural brain disease, medications, malignancy, normal aging, congenital anosmia, and more. A list of common diagnoses and typical presentations is presented in Table II. Nasal and paranasal sinus disease, postviral upper respiratory tract infections (URTIs), and posttraumatic injury account for approximately two-thirds of cases of OD.[8] We will discuss subtypes particularly relevant to the practicing allergist and immunologist below.

Sinonasal OD

Nasal and paranasal sinus disease is the most common cause of OD. Prevalence rates for OD have been reported to be as high as 60% to 80% in patients with CRS.[9] It is much more commonly seen in CRSwNP compared with CRS without nasal polyposis. It can also be seen in patients with allergic rhinitis. Mucosal inflammation causes a conductive olfactory loss due to blockage of odorants from reaching olfactory neurons. There is also evidence that the pathophysiological mechanism of OD may be mixed. A component of sensorineural loss may occur because of direct damaging effects of inflammatory cytokines on olfactory neurons.[6] Restoration of olfactory function is presumed to occur when inflammation resolves and basal stem cells produce new olfactory neurons.

Infectious and postinfectious OD

Hyposmia or anosmia in the setting of an acute viral URTI is common, and typically temporary. The pathophysiology is related to local mucosal effects and viral damage to peripheral

TABLE I. Definitions of smell and taste function and disorders

Smell disorders	Taste disorders
Normosmia: normal smell	Normogeusia: normal taste
Hyposmia: diminished smell function	Hypogeusia: diminished taste function
Anosmia: absent smell	Ageusia: absent taste function
Dysosmia (parosmia): general term describing distortions of smell sensations	Dysgeusia (parageusia): altered perception of taste (sweet, sour, salty, bitter, metallic) in response to stimulus
Phantosmia: unpleasant smell without odorant stimulus	Phantogeusia: unpleasant taste in absence of stimulus

olfactory receptors and central olfactory pathways.[10] Viruses can behave in a myriad of ways, having variable effects on olfactory pathways, clinical presentation, and course. In patients who develop persistent symptoms (postinfectious OD), most experience symptom improvement over time. In an observational study looking at long-term prognosis after postviral OD, more than 80% of patients reported improvement in symptoms after a year.[11] Self-reported recovery of smell to normal was 32%. This may be an underestimate given reliance on self-report.

COVID-19 OD

OD (anosmia, hyposmia) is emerging as a key symptom of COVID-19. Its prevalence is not yet known, but reports suggest it is common, and occurs across a spectrum of disease severity. Notably, it may be present in individuals who are otherwise minimally symptomatic or asymptomatic. It may also be the sole presenting symptom and is typically sudden in onset. Several medical organizations suggest that new-onset OD during the pandemic may be used as a warning flag to suggest appropriate testing and quarantine to prevent infectious spread, and use of appropriate personal protective equipment in health care workers evaluating these patients.[12]

It is too soon to fully elucidate the clinical features of COVID-19 OD. There is suggestion that it may be a subtype of OD different than the typical viral (common cold)-induced OD. Emerging literature suggests that patients with COVID-19 OD typically lack associated sinonasal complaints (such as nasal congestion, rhinorrhea, postnasal drip).[13] One small study by Huart et al[13] shows the impairment to be more severe in COVID-19 OD and that there may be a concomitant taste disturbance. This study compared 10 patients with COVID-19 with 10 patients with acute cold and 10 healthy controls using chemosensory testing.[13] Patients with COVID-19 had lower smell identification scores compared with patients with acute cold. Taste testing found that patients with COVID-19 appeared to have worse global, sweet and bitter gustatory scores. Emerging literature on COVID-19 OD prevalence, characterization, and pathophysiology will be discussed later in this article.

IMPACT ON QUALITY OF LIFE

OD is common in the general population, particularly in the elderly, and can impact quality of life, nutrition, and safety. Patients with OD demonstrate decreased quality of life and higher rates of depression than normosmic patients.[9] One study found olfactory status to be negatively correlated with the emotional status of patients, including stress and depression.[14] A complete or partial loss of smell can impact a person's interest and enjoyment in eating. This can lead to weight loss, poor nutrition, and oversalting of foods. Sense of smell is important for detection of dangers, such as spoiled food, fire, leaking natural gas, and other toxic exposures. In the NHANES study of 1281 participants, among adults 70 years and older, misidentification rates for smoke and natural gas were high, at 20% and 31%, respectively.[5]

CLINICAL ASSESSMENT OF OD

Subjective Evaluation

Obtaining a detailed medical history is the most important part of the clinical assessment of OD. Although the list of potential etiologies is broad, asking detailed questions (about the nature and degree of impairment, severity, symptom fluctuation, and time course) can help provide a likely diagnosis in most cases. Time should be spent inquiring about the common causes of OD (recent viral illness, CRS, history of head trauma) and associated symptoms. Asking about timing is important; as given in Table II, OD is typically sudden when related to URTI or trauma, and gradual in CRS and neurodegenerative disease. Further directed questioning about associated symptoms and exposures (chemical, toxic, medications) can provide clues to less common etiologies, some of which are presented in Table II. As mentioned previously, many patients incorrectly report a problem with taste when actually their smell is impaired. Asking the patient if they can detect salty or sweet foods can help determine whether there is a concurrent loss of taste.

Validated patient-reported scales may be used to track symptom intensity. The 22-item Sino-Nasal Outcome Test (SNOT-22) measures loss of smell or taste (using a 5-point Likert scale) and CRS consequences such as reduced productivity, concentration, and frustration. SNOT-22 is often used in tracking outcomes after surgical intervention. One limitation is that patients may not be able to reliably detect recovery of smell function. In fact, subjective assessments have been shown to have limited correlation with objective measures.[12,15] As such, objective evaluation of patient complaints is very important.

Objective evaluation

Objective evaluation of patients presenting with OD may include rhinoscopy, imaging, and/or chemosensory testing. It is important to note that in a pandemic situation, timing and safety of testing should be taken into consideration; in particular, any procedures that can be aerosol generating, such as endoscopy, require extra caution and use of personal protective equipment. Physical examination of a patient with OD typically includes full otolaryngologic examination including nasal endoscopy to evaluate for patency, structural abnormalities, and signs of malignancy or inflammatory disease. When head injury or neurodegenerative disease is suspected, a full neurological examination should be performed. A computed tomography of the paranasal sinuses may be warranted for evaluation of sinus disease. If an intracranial etiology is suspected, a magnetic resonance imaging of the olfactory tract and brain can be considered.

Chemosensory testing is used when more precise determination of the nature and degree of smell impairment is needed. Chemosensory tests quantify a patient's perception of olfactory stimuli. They can be divided into odor threshold tests, odor discrimination tests, and odor identification tests.[15] For odor threshold tests, various stimulus concentrations are presented to

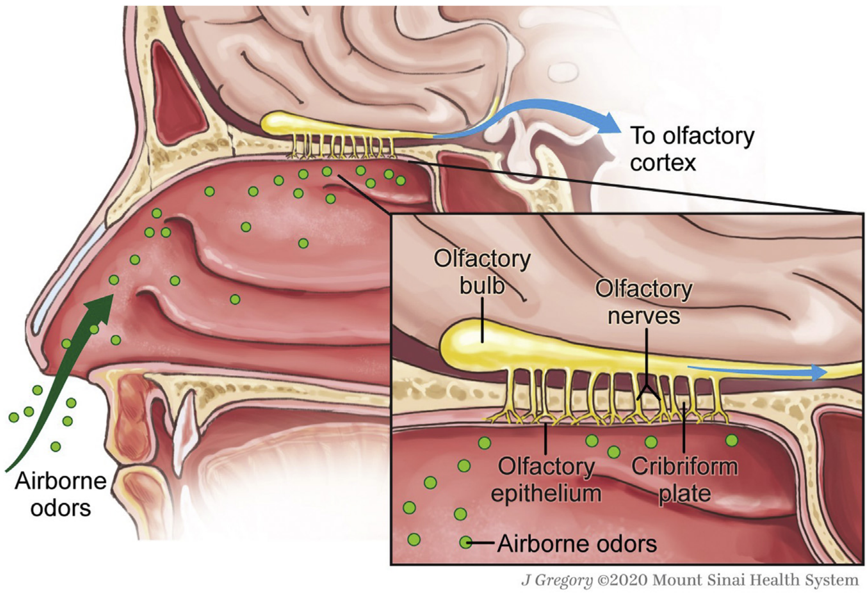

FIGURE 1. Anatomy of olfactory sensory system. Used with permission from © Mount Sinai Health System.

the subject for threshold detection, using sniffing "sticks" or "wands." Odor identification tests are widely used in clinical practice; typically, patients are asked to identify a series of odorants with multiple-choice options. One that is commonly used is the University of Pennsylvania Smell Identification Test (UPSIT), which is commercially known as the Smell Identification Test (Sensonics International, Haddon Heights, NJ).[15] UPSIT is a 40-item "scratch and sniff" test. Shorter versions of UPSIT are also available; NHANES used an 8-item version of this test. It can be performed in the office, or it can be self-administered and mailed to the subject to be performed at home. Retronasal testing can also be performed; this may involve application of foods (such as in powder form) to the oral cavity for identification. Clinical evaluation of taste function usually involves testing for the original 4 taste qualities (sweet, salty, bitter, and sour).

TREATMENTS OF OD

Management should begin with safety counseling; patients should be made aware of consequences of smell dysfunction (impaired detection of smoke and gas leaks in particular, spoiled foods). They should be advised to maintain smoke and natural gas detectors and monitor food expiration and nutritional intake.[12] Management also involves smell retraining, which consists of patients exposing themselves to specific intense odors in a structured way for a set period of time. One study of 40 subjects who underwent smell retraining with exposure twice daily to 4 intense odors (rose, eucalyptus, lemon, cloves) demonstrated improvement in olfactory function, as measured by objective odor testing, compared with the control group.[16] Investigational agents are also an active area of study, such as use of omega-3 supplementation in patients with OD following neurosurgery.[17] Small studies have also looked at intranasal theophylline for various forms of OD with positive results.[18]

A trial of nasal or oral corticosteroids may be considered if there is an inflammatory component; however, this is not recommended for postviral OD.[12] In patients with CRSwNP anosmia or hyposmia, smell improvement is frequently reported following a course of oral steroids or postoperatively. Recovery may be transient if polyp regrowth occurs. Treatment with biologics offers a new and promising therapeutic intervention for this troubling symptom. Currently, dupilumab is the only biologic that has federal Food and Drug Administration approval in the United States. Two phase 3 trials of dupilumab in patients with CRSwNP (LIBERTY NP SINUS-24 and SINUS-52) involving data on key end points from more than 700 patients found significant improvements in SNOT-22 and UPSIT smell test scores with dupilumab treatment compared with placebo.[19] Several additional biologics being studied for nasal polyps in phase 3 clinical trials include omalizumab (POLYP1, POLYP2; completed March 2019), mepolizumab (SYNAPSE; completed December 2019), benralizumab (ORCHID; underway), and fevipiprant (a prostaglandin D2 receptor 2 antagonist; THUNDER; underway).[20]

EMERGING LITERATURE ON COVID-19 OD

Early studies on prevalence

Two early reports from Italy indicated that OD is prevalent, to a surprising degree, in patients with COVID-19.[21,22] In a letter, authors describe a cross-sectional survey conducted in March 2020, during which hospitalized patients with COVID-19 were given a simple questionnaire through verbal interview.[21] A total of 59 hospitalized patients were interviewed; of these, 34% reported a taste or olfactory disorder and 19% reported both. Twenty percent experienced symptoms before hospitalization.

The second study of COVID-19 and OD from Italy, published in *JAMA*, found that alterations in smell or taste were frequently reported by mildly symptomatic patients with COVID-19, oftentimes as the first presenting symptom.[22] The cohort included patients who were contacted 5 to 6 days after positive PCR testing result and who had symptoms mild enough to be suitable for outpatient management. Any altered sense of

TABLE II. Common subtypes of OD

Infectious					
COVID-19	**Typical URTI**	**Inflammatory sinonasal disease**	**Posttraumatic**	**Neurodegenerative (Alzheimer, Parkinsons)**	**Examples of other causes**
• Anosmia sudden, severe • Typical lack of other nasal complaints (rhinorrhea, nasal obstruction) • ±COVID-19 symptoms • Potential true taste disturbance • May be temporary • Under investigation; not yet fully characterized	• ±URTI symptoms • Oftentimes temporary • Some develop persistent postinfectious OD	• Gradual onset • Associated nasal symptoms (nasal congestion, sinus pressure, discharge) • Fluctuates in severity • May respond to anti-inflammatory medications	• Sudden onset • Severe • Persistent • Head injury	• Gradual onset • Associated symptoms (memory loss, confusion, cognitive dysfunction for Alzheimer) • Persistent	• Intracranial or central nervous system disease • Multiple sclerosis • Sinonasal tumor • Environmental and chemical exposures • Hypothyroidism • Congenital anosmia • Medication related • Normal aging

smell or taste was reported by 130 of 202 (64%) patients completing the telephone survey, with a median SNOT-22 score of 4. Among all respondents, anosmia occurred before the onset of other symptoms in 24 (12%), at the same time in 46 (23%), and after other symptoms in 54 patients (27%), but this is likely an underestimate because it relied on self-report.

Olfactory testing in COVID-19

In a case-control Iranian study, researchers administered the Persian version of the 40-odorant UPSIT to 60 hospitalized patients with COVID-19 and 60 matched controls. Remarkably, they found that 59 of 60 (98%) patients hospitalized with COVID-19 demonstrated smell loss, with most having anosmia or severe hyposmia.[23] In the control group, 82% were normal and 18% had mild dysfunction. Of note in this study, researchers found that only 35% of patients with hyposmia were aware of the smell loss. This finding emphasizes the limitation of self-reports of dysfunction and potential benefits of smell testing in early identification of cases. This may be useful for self-quarantine instructions and early treatment.[12]

SARS-CoV-2, the nasal epithelium, and potential neurotropism

The pathophysiology of how SARS-CoV-2 causes OD in COVID-19 is not yet understood, but there is suspicion for neurological tropism. Neurological complications of COVID-19 have been identified, ranging from mild to catastrophic, in case reports and case series. It is suspected that SARS-CoV-2 may affect the nervous system, especially the central nervous system olfactory system areas, as seen on brain magnetic resonance imaging scans.[24] There appears to be high expression of SARS-CoV-2 entry receptor, angiotensin converting enzyme 2, in nasal goblet and ciliated cells.[25] In one article, the authors postulate that impairment of smell discrimination and identification and disturbance of taste pathways suggest involvement of central olfactory structures.[13] There is also emerging literature, however, that SARS-CoV-2 may indirectly impact olfaction, by entry through nonneural cells (support cells, stem cells, and perivascular cells) that express SARS-CoV-2 entry molecules.[26] Ongoing, intense investigation in this area is likely to elucidate the underlying pathophysiologic mechanisms further in the near future.

Natural history of COVID-19 OD

Preliminary analysis of a US-based COVID-19 Anosmia reporting tool, developed by the American Academy of Otolaryngology-Head and Neck Surgery, found that in the first 237 entries, anosmia was noted in more than 70% of patients before their COVID-19 diagnosis, and was the initial symptom in almost 30%.[27] Some symptom improvement was noted in the first 7 days, with the vast majority reporting symptom improvement within 10 days. High rates of recovery may be in line with those seen in OD induced by other viruses, but remain to be further studied. In the study by Huart et al[13] comparing COVID-19 OD to acute URTI OD, the authors found favorable recovery in both groups; all patients with COVID-19 reported improvement at a mean follow-up of 18 days, but only 30% reported complete recovery.

CONCLUSIONS

Smell is a key sense, important for flavor, enjoyment of food, and danger detection. Allergists and immunologists frequently encounter smell dysfunction in patients with CRSwNP and patients with acute viral infections. Subjective measures, such as validated questionnaires, can help to determine the impact of smell disturbance on the patient's quality of life, whereas chemosensory testing can help determine the degree of OD. OD is a striking feature of COVID-19, manifesting in both mild and severe forms of the disease. According to experts, acute onset of OD (either complete or partial loss of sense of smell) during the pandemic should prompt suspicion for COVID-19, and accordingly, testing, quarantine, and use of personal protective equipment.[12] OD can be very distressing for these patients, but early studies suggest rates of resolution similar to URTI-induced OD. OD in COVID-19 is an active area of investigation, and we expect more information to be forthcoming regarding underlying mechanisms, viral propensity for olfactory sensory structures, and recovery.

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