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Role of Olfaction in Human Health: A Focus on Coronaviruses

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The COVID-19 pandemic has been accompanied by increasing reports of smell and taste impairment in patients infected by its etiologic agent, SARS-CoV-2. An increasing number of studies and more recently a meta-analysis have supported these reports.[1–4] The Centers for Disease Control and Prevention (CDC) has recently added "new loss of taste or smell" to their list of symptoms of COVID-19.[5] These sensory changes may hold important implications for the diagnosis and management of COVID-19. Viral upper respiratory infections are among the most common causes of olfactory disorders, and viral etiology accounts for 19% to 43% of patients who present with olfactory dysfunction.[6]

SARS-CoV-2 belongs to the coronavirus family, which is associated with a mild to moderate upper respiratory tract infection widely known as the common cold.[7] Human coronavirus strains are often accompanied by temporary taste and smell (together henceforth referred to as "chemosensory") impairments such as diminished sense of smell (hyposmia) and taste (dysgeusia),[7] often attributed to a virus-induced sinonasal mucosal inflammatory response (rhinitis). More recently, 3 human coronaviruses—the Middle East Respiratory Syndrome,[8] Severe Acute Respiratory Syndrome (SARS), and SARS-CoV-2—have displayed more severe pathogenicity and symptomatology, potentially including more severe and persistent loss of smell (anosmia) or loss of taste (ageusia). Indeed, an unspecified human coronavirus strain was isolated from a patient with confirmed postviral olfactory dysfunction.[9]

In the case of COVID-19, health-care professionals and scientists around the world have noted a rise in reports of smell and taste impairments. A brief report of 88 patients hospitalized with SARS-CoV-2 infection in Italy found that 34% reported at least 1 olfactory or gustatory complaint.[2] Ninety percent of these chemosensory impairments occurred prior to hospitalization, and all participants reported that symptoms persisted to the time of the survey was conducted 10 to 21 days later (median of 15 days).[2] Studies in the United Sates and across Europe have also highlighted smell and taste dysfunction in COVID-19 patients.[1,3,4] In the United States, among an ambulatory population of 1,480 patients with influenza-like symptoms (including 102 COVID-19 positive patients), there was a strong correlation between chemosensory dysfunction and COVID-19.[4] Another study with 417 mild-to-moderate COVID-19 patients across twelve European hospitals found 86% and 89% of COVID-29 patients reported smell and taste dysfunction, respectively.[3] A recent meta-analysis of COVID-19 patients reported a 52.73% and 43.93% prevalence of olfactory and gustatory dysfunction, respectively.[1] Unlike coronaviruses responsible for the common cold, patients with COVID-19 have reported olfactory dysfunction in the absence of nasal obstruction or nasal discharge, suggesting SARS-CoV-2-related anosmia has a distinct etiology. A potential mechanism of SARS-CoV-2-related anosmia is viral-induced olfactory neuropathy (Figure 1), which has been shown in a murine model of SARS-CoV.[10] Notably, the novel strain of SARS-CoV-2 infection is not typically associated with rhinitis.

The COVID-19 pandemic serves as a poignant reminder of the relevance of the chemical senses to human health and stresses the need to include smell and taste in clinical assessments. Despite the critical importance of the chemical senses in daily life, they

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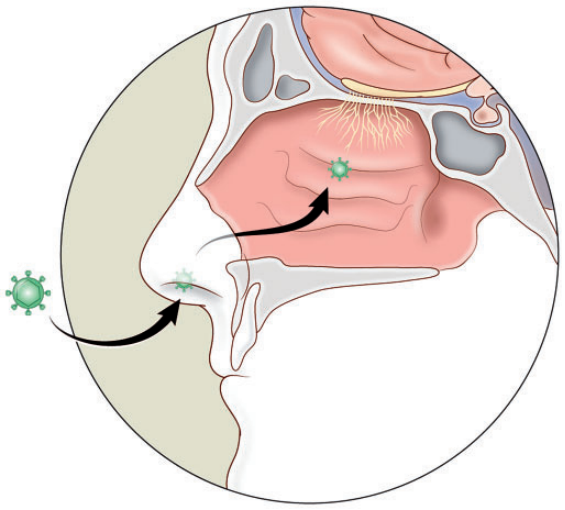

Figure 1. SARS-CoV-2 entering the nasal cavity: potential neurotropic mechanism. Green represents the virus. Salmon represents the sinus nasal mucosa (with green virus). Yellow are the olfactory neurons that are preferentially targeted by COVID-19 (seemingly without much inflammation) and cause smell loss.

remain understudied in the context of health and disease. Although in rare cases the preservation of smell is used in differential diagnoses (eg, Parkinson's disease vs vascular Parkinsonism), health professionals rarely incorporate examination of the chemical senses in the diagnostic process. Moreover, as evidenced by the limited literature on olfactory and taste science compared to that of visual and auditory science, the chemical senses remain among the more poorly understood special senses. In the absence of a more robust understanding of smell and taste, clinicians are limited in their assessment of chemical sensory dysfunction and may not recognize its significance or association to disease. However, smell and taste sensation are intimately intertwined with mammalian survival. They impact nutritional intake, mood, and serve as important mechanisms for detecting danger; they enable detection of contaminated foods and the presence of harmful and potentially life-threatening chemicals.

Although smell and taste have yet to be systematically evaluated in patients with COVID-19, emerging evidence suggests that chemosensory dysfunction is part of the COVID-19 and is now recognized by the CDC and health departments across the globe.[5,11] Given the complex interdependent relationship between smell and taste, anosmia may be reported as gustatory changes. With regard to taste, true ageusia (independent of smell) is rare, and discerning its prevalence in COVID-19 patients may be difficult. Nonetheless, data examining the prevalence of chemosensory dysfunction is only beginning to emerge and its prevalence in patients with COVID-19 remains largely understudied.

In the context of the COVID-19 pandemic, appreciating the potential effects on smell and taste may aid in early diagnosis and containment efforts. Importantly, currently available reports and emerging studies indicate that olfactory dysfunction presents early in infection.[1–3] If confirmed and highly prevalent, chemosensory changes could be included in the early COVID-19 symptom profile used to recommend isolation and prevent the spread of the virus. The establishment of hyposmia, anosmia, ageusia, and dysgeusia as COVID-19 symptoms can now improve diagnosis and disease containment. Early detection of chemosensory impairment may also serve to reduce the burden of potential complications related to anosmia and ageusia in patients with COVID-19; however, research is needed to establish this.

Many questions remain regarding the role of SARS-CoV-2 in chemosensory dysfunction. Does SARS-CoV-2 cause or is it merely correlated with chemosensory dysfunction? If it is indeed an etiologic agent, what is the penetrance of SARS-CoV-2-related chemosensory dysfunction? What clinicopathological factors are associated with SARS-CoV-2-related chemosensory dysfunction? Is SARS-CoV-2-related chemosensory dysfunction complete (anosmia or ageusia) or partial (hyposmia or hypogeusia)? How long does SARS-CoV-2-related chemosensory dysfunction persist or how much does the length of symptoms vary across populations? Can methods used to support olfactory function, such as smell training,[12,13] help in the recovery of COVID-19 chemosensory symptoms?

Further research is necessary to establish the prevalence, duration, and pathophysiology of SARS-CoV-2-related chemosensory dysfunction, and to identify which olfactory and/or gustatory patterns may be most helpful in the diagnosis and prognosis of COVID-19. To fully interrogate the occurrence of chesemosensory issues in this patient population, large-scale, natural history studies using validated psychophysical instruments to map over time olfactory (as in Moein et al.[14]) and gustatory changes (e.g., taste strips,[15] NIH Toolbox Sensation Measures and others[16,17]) are necessary.

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Statement of Human and Animal Rights

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