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LETTER TO THE EDITOR

Dysgeusia in COVID-19: Possible Mechanisms and Implications

To the Editor:

For the purpose of this letter to the editor, we will focus solely on new-onset dysgeusia as a potential early marker of COVID-19 infection and its implications.[1-3]

This is an interesting finding of practical significance, which may allow easier identification of presymptomatic or asymptomatic patients. This identification could play an important role in limiting transmission, particularly when testing is not widely available and/or reliable.

Recent publications on this topic have included anecdotal reports[4,5] and 2 epidemiologic studies,[6,7] with reported prevalence ranging from 68% to 85% for olfactory disturbances and 71% to 88.8% for taste disturbances in patients with COVID-19. These taste disturbances have included loss of taste (complete ageusia or partial hypogeusia) and altered taste (dysgeusia). For simplicity, we will use the term *dysgeusia* here to include ageusia and hypogeusia. The distribution of these symptoms in subgroups of patients (e.g., those with specific underlying medical conditions) has not been reported yet.

A European multicenter epidemiologic study[6] analyzing the prevalence of olfactory and gustatory dysfunctions as a clinical presentation in a cohort of 417 laboratory-confirmed cases of COVID-19 with mild-to-moderate disease presentation reported that 88.8% of patients had gustatory disorders. A number of patients also presented with several comorbidities, the most common of which included allergic rhinitis, asthma, hypertension, and hypothyroidism, but the percentage of patients with these conditions was low.

A cross-sectional online survey by Yan et al.[7] included 1480 patients with influenza-like symptoms, and of the 59 of 102 patients who tested positive for COVID-19, 40 (68%) reported loss of smell, and 42 (71%) reported loss or changes in taste. Unfortunately, medical and/or oral comorbidities were not reported. In a recent meta-analysis of 9 studies from Europe, North America, China, and the Middle East, Tong et al. reported gustatory dysfunction (n = 1390) in 43.93% (95% confidence interval 20.46%−68.95%) of patients with COVID-19.[8]

Chemosensory dysfunction is a common occurrence. We know that dysgeusia can be associated with numerous medical conditions (e.g., upper respiratory viral infection; diabetes mellitus; malignancies; heart disease; candidiasis; Alzheimer disease; asthma; liver and kidney diseases; chronic hepatitis C virus infection; hypothyroidism; Parkinson disease; or depression) and that various medications are known to interfere with the taste function.[9-11] In the National Health and Nutrition Survey in 2012, 5% of greater than 142 million U.S. respondents reported experiencing taste disorders, most notably those correlating with increasing age and institutionalization or acute hospitalization.[9] Also, a high prevalence of altered taste has been reported in a population of acute hospitalized German patients.[12]

Furthermore, chemosensory data on smell disorders collected by the National Health and Nutrition Survey between 2013 and 2014 identified a prevalence rate of 13.5% in persons age 40 years and older. In the same survey, several risk factors were associated with a higher prevalence of smell dysfunction, including racial background (African Americans, Latinos), lower income and educational level, older age, and a history of cancer or asthma, among other conditions.[13]

Early in the human immunodeficiency virus (HIV) epidemic, one of the authors of this letter (F.L.N.) was among the first to report on the oral manifestations of opportunistic infections and tumors in the HIV/AIDS population.[14-16] The reporting on these markers was clearly a major contribution toward alerting clinicians to the possibility of HIV carrier status in young people, otherwise healthy and without any known oral/dental and/or medical comorbidities.

Further understanding of dysgeusia in relation to COVID-19 is needed to answer the following questions, which may help in management of patients with COVID-19 during this pandemic and shed light on the pathophysiology of taste disturbances in general:

1. Is dysgeusia a prognostic marker for the severity of COVID-19 after SARS-CoV-2 infection[7] or for progression to primarily respiratory or gastrointestinal disease manifestation?[17]
2. Does the presence of any underlying medical conditions or use of medications modify the effect of SARS-CoV-2 infection on the occurrence or severity of dysgeusia?
3. Does the occurrence of dysgeusia in patients with COVID-19 vary by patient characteristics, such as age, sex, ethnicity, and severity of COVID-19?
4. What are the likely mechanisms by which taste dysfunction develops in SARS-CoV-2 infection?

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Although questions 1 through 3 will likely be answered by findings from future epidemiologic studies, we would like to share some hypotheses regarding potential mechanisms, which can be further investigated in future studies.

Angiotensin-converting enzyme 2 (ACE2) receptors have been found in the epithelium of taste buds and salivary glands, not only in rhesus macaques but also in humans.[18] Salivary glands in rhesus macaques have been demonstrated to be an early target for SARS-CoV,[19] and SARS-CoV RNA has been demonstrated to be present in saliva before pulmonary lesions.[20] It is, therefore, plausible that human salivary glands may be affected early on by SARS-CoV-2 infection, resulting in salivary gland dysfunction with subsequent salivary flow impairment, in both quality and quantity, and the resultant dysgeusia as an early symptom in asymptomatic patients with COVID-19.

A neurologic nature has been suggested as a possible mechanism for dysgeusia.[21] Indeed, gustatory and olfactory functions are closely linked[22]: An impairment of the olfactory system, resulting from direct damage to nonneuronal cells in the olfactory epithelium—where ACE2 receptors are highly expressed—via replication and accumulation of SARS-CoV-2 virus,[23] can also result in taste disturbance.[22] The viral lytic pathway could also directly affect the peripheral neuronal trajectory of the gustatory tract in 2 ways: (1) direct damage of ACE2-expressing cells of the taste buds and peripheral taste neurosensory chemoreceptors,[24] or (2) direct damage of any of the cranial nerves responsible for gustation (CN VII, IX, or X). Among these, damage to chorda tympani (CN VII) might be the most plausible explanation: Once the nasopharynx is colonized, SARS-CoV-2 virus could use the eustachian tube as a port of entry and colonize the middle ear, causing subsequent damage to the chorda tympani and the resultant dysgeusia. Involvement of the central nervous system seems less likely because the manifestations of such involvement (e.g., meningitis/encephalitis) in patients with COVID-19 usually last longer and are less frequent than dysgeusia.[24]

We would also like to propose an inflammatory response pathway. The oral mucosa is lined with ACE2 receptors, which are used by SARS-CoV-2 virus to enter epithelial cells.[18,19] It is quite plausible that SARS-CoV-2 virus binds to ACE2 receptors present in the oral mucosa, triggering an inflammatory response, which leads to cellular and genetic changes that could alter taste.[11] This response may be mediated by the interaction of Toll-like receptors upon contact with the virus leading to tissue damage, a similar pathway to acute respiratory distress. Wang et al.[11] demonstrated in mammalian tissue that "taste bud cells express cytokine signaling pathways and that inflammation may affect taste functions via these pathways. Inflammatory cytokines, such as IFN (interferon) can trigger apoptosis and therefore may cause abnormal turnover in taste buds, which may result in net losses of taste bud cells and/or skewing the representation of different types of taste cells and ultimately lead to the development of taste dysfunction." This could be another plausible mechanism for taste alteration resulting from SARS-CoV-2 infection.

It is also possible that the tissue hypoxia in patients with COVID-19 who are clinically conscious and in a functional state may result in tissue injury that leads to the reported disturbance in taste.[25] Anemia and presumably the poor oxygen transport that ensues has been shown to result in dysgeusia.[26] The unusual feature of a mild clinical picture in some patients with COVID-19 in spite of severe measured hypoxia may explain why dysgeusia is reported in some patients in the early stages of COVID-19.

Yet another possible mechanism may involve zinc, which is thought to play an important role in taste perception. It is possible that zinc chelation through immune mechanisms and molecules known to increase in concentration with inflammatory processes may result in acute hypozincemia[27] or a more localized change in cellular zinc homeostasis of oral gustatory cells as a result of infection by SARS-CoV-2 virus.[27] This may result in taste disturbances similar to what has been observed in association with other processes leading to zinc insufficiency.[28] Some randomized controlled trials have demonstrated benefit of zinc supplementation in patients with taste disturbances.[29] In addition, zinc has been shown to inhibit coronavirus RNA polymerase activity in vitro[30] and is thought to play a role in antiviral immune responses.[31]

Systematic reviews of randomized controlled trials have concluded that zinc lozenges at a dose 75 mg per day or greater may decrease the duration of common cold symptoms in healthy children and adults.[32] Common cold−like illnesses are caused by other coronaviruses, rhinoviruses, and adenoviruses, so there has been interest in using zinc supplements for prevention during the current pandemic.

It is of particular significance that dysgeusia (with or without olfactory symptoms) has been reported as an early or lone symptom of COVID-19 before involvement of the lungs or other organs. We hypothesize that changes in localized cellular zinc homeostasis in oral gustatory cells resulting from immune responses to SARS-CoV-2 viral replication may result in dysgeusia, which may or may not be accompanied by hypozincemia. If this is the case, the time of onset of dysgeusia may correspond with the time when zinc supplementation in the form of lozenges or syrups may be most effective because this localized delivery of zinc to oral

and oropharyngeal mucosae may help control COVID-19 replication at early replication sites.

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