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Chemosensory Dysfunction in Coronavirus Disease 2019 (COVID-19)

Dent Update 2020; 47: 682–684

'Smell and taste are in fact but a single composite sense, whose laboratory is the mouth and its chimney is the nose'
Jean Anthelms Brillat-Savarin (18th century French Writer)
Coronavirus disease 19 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has affected virtually all organ systems of the body, including the chemosensory system which dictates our ability to taste and smell. In the third part of this COVID-19 Commentary we address in some detail what is currently known of the sensori-neuronal deficits consequential to SARS-CoV-2 infection, in particular the loss of taste.

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The agent of COVID-19, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), characterized as a respiratory virus, has a predilection to invade the host by penetrating the various epithelial barriers of the body. It is known that the angiotensin-converting-enzyme 2 (ACE2), abundantly present in the epithelia, including the oral and nasal mucosa and several human organs, are the crucial, functional host cell receptor for SARS-CoV-2, and hence the primary access route of the virus.

Nevertheless, in addition to being epitheliotropic, coronaviruses, are also known to be neurotropic and neuro-invasive in nature. Hence, it is not surprising that the neurosensory manifestations of the disease, including those due to impairment of chemosensory neuronal receptors, are now clinically recognizable. Recent data from several international studies indicate that the loss of smell (dysgeusia) and taste (anosmia) are notable early, presenting symptoms of such chemosensory dysfunction in COVID-19 patients. Due to the strength of such data, US Centers for Disease Control and Prevention (CDC) have included 'sudden loss of taste (dysgeusia/ageusia) and smell (anosmia/hyposmia)' into the growing list of symptoms of the pandemic disease.

Various neuronal tissues of the body are targeted by the neurovirulent SARS-CoV-2 and the resultant disease entities have been divided into three major categories:[1]
1. Central nervous system diseases (such as headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy);
2. Peripheral nervous system diseases (ageusia, hypogeusia, dysgeusia, hyposmia, and neuralgias);
3. Skeletal muscle injury associated diseases with neurological damage.

The purview of this commentary, however, is to focus on the loss of taste (dysgeusia) and smell (anosmia) in COVID-19, due to SARS-CoV-2, targeting the gustatory and the olfactory systems, respectively. However, it is important to note that dysgeusia could arise due to a number of other pathological conditions, ranging from upper respiratory viral infection; diabetes mellitus; malignancies; heart disease; candidiasis; zinc deficiency; Alzheimer's disease; asthma; liver and kidney diseases; chronic hepatitis C virus infection; hypothyroidism; Parkinson disease; or depression, or indeed various

medications.[2]

Although throughout this article we use the term dysgeusia as a general descriptor for altered taste sensation, the spectrum of taste disorders could vary from mild to severe, and is defined as follows: *ageusia* – total absence of taste; *hypogeusia* – diminished taste acuity; and *dysgeusia* – unpleasant, obnoxious or perverted taste sensation. It is still unclear the extent to which the variations in the spectrum of taste dysfunction is present in COVID-19, and this is yet another reason for using a universal term, dysgeusia, for the condition. In a similar vein, the term anosmia is used here to indicate either total loss, ie *anosmia*, or partial loss of smell, termed *hyposmia*.

Prevalence of dysgeusia and anosmia

A number of reviews are currently available on the prevalence and related characteristics of both dysgeusia and anosmia in COVID-19, including a recent review of ours.[3] In general, from a review of the data from over a dozen studies done in various regions of the World, it appears that both dysgeusia and anosmia are present as prodromal sub-clinical/clinical manifestations in up to two-fifths to three-quarters of ambulatory COVID-19 patients. Several reviewers have paid particular attention to evaluate the association between olfactory and gustatory dysfunction in COVID-19 in terms of their temporality of presentation, ie whether the gustatory and olfactory symptoms occur simultaneously or sequentially and, if so, which precedes the other. It appears, in general, that anosmia and dysgeusia can present either in isolation or occur simultaneously. Whether anosmia precedes dysgeusia or *vice versa* is unclear from the available data. However, the current data are by no means complete due to methodological lapses, and the nature of studies that are retrospective in most reports, and poor response rates due to patient compliance issues.

If indeed dysgeusia and anosmia are present during the early prodrome of the disease, or in otherwise asymptomatic patients harbouring the virus, this raises the interesting possibility of identifying patients in the early prodromal and/or the pre-symptomatic phase of the disease either through self-assessment or through tele diagnosis. Depending on how early in the disease development phase (ie COVID-19 prodrome) dysgeusia/anosmia appear, dental practitioners will also be ideally placed to make an early diagnosis of COVID-19 in their patients. In the event, dentists will be in a position to forewarn of the possibility to the patient, and take necessary interventional measures to prevent further spread of disease, both among the patient's family members, and also the community.

Pathophysiology of dysgeusia and anosmia

Dysgeusia

Pathophysiology of dysgeusia is somewhat speculative at present. There appear to be three possible pathways that SARS-CoV-2 infection leads to dysgeusia, as outlined below:

1. It is known that ACE2 receptors are found in the epithelium of taste buds and salivary glands in humans.[4] Hence, it is likely that human salivary glands may be targeted in the pre-symptomatic phase of SARS-CoV-2 infection, resulting in salivary gland dysfunction. The resultant impairment of salivary flow, and the effect on both the quality and quantity of saliva, may be reflected as dysgeusia.
2. A neurologic pathway, where it has been hypothesized that, as dysgeusia and anosmia are closely linked, impairment of the olfactory system with an abundance of ACE2 receptors for the virus may have an indirect impact on taste sensation, leading to dysgeusia.
3. The infection could directly damage peripheral taste neurosensory chemoreceptors, through the cranial nerves responsible for gustation and, in particular, the chorda tympani (CN VII) nerve. It has been posited that the virus could access the chorda tympani, first by travelling from the nasopharynx to the eustachian tube, and then colonizing the middle ear from where it could access the chorda tympani, eventually causing dysgeusia.

Others have proposed another inflammatory response pathway wherein the SARS-CoV-2 virus enters ACE2-expressing epithelial cells of the taste buds, triggering an inflammatory response, which in turn may lead to cellular and genetic changes that could alter taste.

Anosmia

The pathophysiology of anosmia appears to be much less complex than dysgeusia. In short, ACE2 receptors for SARS-CoV-2 are well expressed in the olfactory epithelial cells. The latter is a specialized tissue in the roof of the nasal cavity responsible for odour detection that contains olfactory sensory neurons and other supporting cells. It is known that two specific cell types, particularly those supporting and enveloping the olfactory epithelium, express ACE2 receptors. The current opinion is that the temporary loss of functionality of *supporting cells* of the olfactory epithelium indirectly impacts the olfactory sensory neurons, precipitating COVID-19-related anosmia.

Recovery period

The recovery period for both dysgeusia and anosmia appears to be approximately 4–5 weeks, according to the currently available data, suggesting that the damage to the gustatory and olfactory function by SARS-CoV-2 is unlikely to be permanent. Nevertheless, further investigations with follow-up assessments of taste and smell function are needed to generate reliable data.

Future directions

There are a number of questions related to COVID-19-related dysgeusia, in particular, that need answers to gain a further understanding of the condition, as follows:

- What other confounding demographic factors, such as the age, sex, ethnicity, geographic region of the COVID-19 patients contribute to dysgeusia?
- Do the underlying systemic medical

conditions or use of medications by the COVID-19 patient modify the frequency and/or severity of dysgeusia?
- Is dysgeusia a prognostic marker for the severity of SARS-CoV-2 infection for progression to respiratory or gastrointestinal disease manifestation?
- What is the period of post disease persistence of the symptoms and management of the conditions, and also the quality of life of the patients with dysgeusia.
- What are the precise pathophysiological mechanisms by which taste dysfunction develops in SARS-CoV-2 infection?

Conclusions

The current data indicate a wide prevalence of acute onset, impaired olfactory and gustatory symptoms in patients with COVID-19. Summarized evidence from all over the World strongly supports the view that sudden, acute onset of anosmia or dysgeusia could possibly be identified and recognized as harbingers of SARS-CoV-2 infection. Additionally, the loss of smell and taste appear be a pathognomonic feature of COVID-19 that distinguishes it from other viral upper respiratory tract infections. If indeed, these early symptoms of COVID-19 are confirmed as highly prevalent, as it seems to be, then it could save many a life in the future by early diagnosis and intervention. This may also indirectly impact the economies of many societies by mitigating the effect of the current pandemic and forestalling the predicted waves of the disease.

References

1. Mao L, Jin H, Wang M *et al*. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020; **77**: 683–690.
2. Lozada-Nur F, Chainani-Wu N, Fortuna G, Sroussi H. Dysgeusia in COVID-19: possible mechanisms and implications (published online ahead of print, 2020 Jun 27). *Oral Surg Oral Med Oral Pathol Oral Radiol* 2020; S2212-4403(20)31075-0. doi: 10.1016/j.oooo.2020.06.016.
3. Samaranayake LP, Fakhruddin KS, Panduwawala C. Sudden onset, acute loss of taste and smell in coronavirus disease 2019 (COVID-19): a systematic review. *Acta Odontol Scand* 2020; doi: 10.1080/00016357.2020.1787505.
4. Xu H, Zhong L, Deng J *et al*. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci* 2020; **12**: 8.