Corona Viruses and the Chemical Senses: Past, Present, and Future

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Abstract

A wealth of rapidly evolving reports suggests that olfaction and taste disturbances may be manifestations of the novel COVID-19 pandemic. While otolaryngological societies worldwide have started to consider chemosensory evaluation as a screening tool for COVID-19 infection, the true nature of the relationship between the changes in chemosensory ability and COVID-19 is unclear. Our goal with this review is to provide a brief overview of published and archived literature, as well as the anecdotal reports and social trends related to this topic up to April 29, 2020. We also aim to draw parallels between the clinical/chemosensory symptomology reported in association to past coronavirus pandemics (such as SARS and MERS) and the novel COVID-19. This review also highlights current evidence on persistent chemosensory disturbances after the infection has resolved. Overall, our analysis pinpoints the need for further studies: 1) to better quantify olfaction and taste disturbances associated with SARS-CoV-2 infection, compared to those of other viral and respiratory infections, 2) to understand the relation between smell, taste, and chemesthesis disturbances in COVID-19, and 3) to understand how persistent are these disturbances after the infection has resolved.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, SARS-CoV, MERS- CoV, Smell, Hyposmia, Hypogeusia, Dysgeusia, Anosmia Taste, Loss, Gustatory, Olfactory, Olfaction, Infection, Chemosensory, Chemesthesis, Post-viral olfactory dysfunction, Pandemic

Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by the new Severe Acute Respiratory Syndrome SARS-CoV-2 coronavirus strain (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). The World Health Organization has so far reported more than 3 million confirmed cases of COVID-19 with more than 200,000 deaths by April 29, 2020. COVID-19 quickly became a pandemic that has now rapidly spread across 213 countries, areas or territories worldwide (WHO, 2020). The first clinical reports describing the major symptoms associated with COVID-19 included fever, coughing, fatigue and shortness of breath (Chan et al., 2020; Guan and Zhong, 2020; Huang et al., 2020; Wang et al., 2020). Yet, over the course of the past month, other clinical manifestations have been indicated as possible ancillary symptoms of COVID-19. Among those is the sudden appearance of olfaction and taste disturbances (OTDs) associated with diagnosed or suspected COVID-19 positive patients, even in absence of other symptoms. For instance, Gane et al. have recently (March 26, 2020) reported about a 48-year-old UK patient who tested positive to the SARSCoV-2 infection, yet did not present symptoms other than olfactory disturbances (Gane et al., 2020). Evidently, and pointed out in a previous report (Walker et al., 2020), a surge in the Google searches for smell and taste loss became evident both in one of the first COVID-19 hotspots (Italy) between March 15 and 21 (Google Trend, 2020b), and subsequently in the United States, a current hotspot, around March 23 (Google Trend, 2020c) in parallel to the COVID-19 pandemic in those countries.

Based on these reports, as well as on onsite clinical evaluations, different ENT societies including the UK (Hopkins and Kumar, 2020) and the US (AAO-HNS, 2020a), have advised as a precaution to treat the loss of sense of smell as a putative marker of SARS-CoV-2 infection. The American Academy of Otolaryngology (AAO) called for anosmia, hyposmia, and dysgeusia to be added to the list of screening tools for COVID-19 in asymptomatic individuals (AAO-HNS, 2020a), as of April 17, 2020, the US Centers for Disease Control and Prevention officially added them to as an important COVID-19 symptom

(Center for Disease Control and Prevention, 2020). The World Health Organization has them listed as less common symptoms.

At present, it is still unclear whether COVID-19 represents a special case of viral infection attacking the olfactory system. Additionally, it is also unknown whether the taste disturbances reported are a misrepresentation of olfactory disturbances (ODs) rather than reflect the direct impact of SARS-CoV-2 on taste and chemesthesis pathways. This review aims to summarize the reports available up to April 29, 2020 to gather insights on the nature of the relationship between the changes in chemosensory ability and COVID-19. We will then highlight the similarities and differences with the symptomatology reported in other human coronaviruses and viral infections known to cause OTDs.

Olfaction and Taste Disturbances associated with COVID-19

The first documented report of OTDs in COVID-19 dates back to February 2020 from China, when Mao et al. reported a retrospective study of 214 laboratory-confirmed COVID-19 patients (Mao et al., 2020). Data were extracted from electronic medical records of patients hospitalized at the Union Hospital of Huazhong University of Science and Technology in Wuhan from January 16, 2020 to February 19, 2020. Of this group of patients, the records show that 78 patients (36.4%) presented some forms of neurological manifestations. Of those, 11 patients (5.1%) complained specifically of hyposmia and 12 patients (5.6%) reported hypogeusia. Although the stage of the disease at which these data were collected is unclear in the records, the group included patients with comorbidities known to affect the chemical senses, e.g., diabetes (Naka et al., 2010) and anorexia (Aschenbrenner et al., 2008). Even though this early report started to underline the association between chemosensory disturbances and COVID-19, the interpretation of these data warrant caution in light of the methodology used. Indeed, all data were derived from electronic medical records, and minor neurological symptoms, such as OTDs, might not have been adequately captured.

The observation of increasing cases of ODs in concomitance with the COVID-19 spread in Iran motivated Iranian researchers to perform an extended cross-sectional study between March 12 and March

17, 2020 in order to evaluate this correlation (Bagheri et al., 2020). The results of this study are archived in medrxiv.org and include responses from more than 10,000 volunteers (mean ± sd: 32.5 ± 8.6 years old, range: 7-78 years; 71.1% female; 81.7% non-smoker) who reported to have anosmia/hyposmia. About only 1% of participants reported to be hospitalized and no direct information about COVID-19 diagnosis is available. The inclusion criteria for the study responders was experiencing ODs in the 4 weeks prior to the beginning of the study, but 83.4% of these volunteers also reported taste disturbances (TDs). The onset of anosmia was reported to be sudden in 76.2% of the sample. At the time of the response to the survey, 60.9% of respondents reported persistent ODs that lasted for a median of 10 days (range of duration of anosmia onset 0 to 30 days), with 17.3% reporting no sense of smell on a categorical scale from 0 (no sense of smell) to 10 (full sense of smell), and approximately 48% reporting a sense of smell of 3 or below. More than 85% of respondents reported that they were not currently being treated for anosmia. Additionally, the high incidence of smell loss across family members (48.2%) suggests that the ODs reported may be post-viral in nature. Despite the large sample tested, the combination of lack of information on the status of the COVID-19 diagnosis in these patients as well as the correlational analyses conducted do not allow us to conclude whether COVID-19 has a causal role in development of OTDs. Nevertheless, Bagheri and colleagues (2020) highlight a striking increase in the association of patients experiencing OTDs and flu-like symptoms.

In order to evaluate the prevalence of OTDs in the context of COVID-19, a cross-sectional survey was then performed on March 19, 2020 at the Infectious Disease Department of L. Sacco Hospital in Milan, Italy (Giacomelli et al., 2020). In this letter to the Editor published in the journal *Clinical Infectious Diseases*, the authors reported the answers of 59 SARS-CoV-2-positive hospitalized patients to a simple verbal interview including questions about the presence or absence of OTDs, their type and time of onset with respect to the time of hospitalization. Twenty patients (33.9%) reported taste or olfactory disorders, and 11 (18.6%) both. Twelve patients (20.3%) reported having experienced their chemosensory symptoms before the hospitalization, suggesting that OTDs may anticipate the major COVID-19 clinical symptoms. Similarly, 17% of 2428 individuals reported new onset anosmia was not accompanied with

other symptoms thought to be associated with COVID-19 (Hopkins et al., 2020). A meta-analysis published April 24, 2020 in the Otolaryngology-Head and Neck Surgery Journal reported the prevalence of olfactory dysfunction up to 52.7% and gustatory dysfunction about 43.9% for COVID-19 patients (Tong et al., 2020), suggesting olfactory and gustatory dysfunctions as common symptoms of COVID-19.

These results have also been confirmed on a larger sample of 417 mild-to-moderate laboratory-confirmed COVID-19 patients (mean ± sd: 36.9 ± 11.4 years old, range: 19–77 years, 63.1% female, Lechien et al., 2020). This recent study conducted by the Young-Otolaryngologists of the International Federation of Oto-rhino-laryngological Societies (YO-IFOS) includes patients from 12 European hospitals who completed questionnaires based on the smell and taste component of the National Health and Nutrition Examination Survey (Bhattacharyya and Kepnes, 2015) and a short version of the Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS, Mattos et al., 2019). Of those patients, 34.5% were in the acute phase of the infection, whereas the rest of the patients did not yet have general symptoms. ODs were reported by 85.6% of patients, of which 79.6% reported anosmia and 20.4% hyposmia; 11.8% of patients reported ODs before other symptoms, 65.4% after and 22.8% at the same time. This study also indicates cases of phantosmia and parosmia in 12.6% and 32.4% of patients, respectively. TDs were reported by 88.0% of the patients. Also, the role of other symptoms present during the infection (e.g., cough, loss of appetite, fever, and headache) and of pre-existing conditions (e.g., allergic rhinitis, asthma, high blood pressure, and hypothyroidism) confounds the interpretation of the relationship between OTDs and COVID-19. OTDs persisted after the resolution of other symptoms in 63.0% of the resolved cases (247 patients). When the final analyses were performed, 25.5% of patients reported to have recovered both olfactory and gustatory functions within 2 weeks after the resolution of the general symptoms.

More recently, Kaye et al. 2020 have published the first results obtained from the COVID-19 Anosmia Reporting Tool for Clinicians promoted by the American Academy of Otolaryngology–Head and Neck Surgery (AA-HNS), whose aim is to allow clinicians to anonymously track cases of anosmia and dysgeusia related to COVID-19 (Kaye et al., 2020). Among the first 237 responses, anosmia was

indicated in 73% of cases prior to the COVID-19 diagnosis and was reported as the initial symptom in 26.6% of cases. Improvement of OTDs was recorded in 27% of patients 7.2 days post response on average and in 85% within 10 days.

Olfaction and taste loss appeared also as a symptom collected from the COVID Symptom Tracker application, developed by a team at King's College London (https://covid.joinzoe.com/us). Fifty nine percent of 579 UK patients with laboratory-confirmed diagnosis of COVID-19 declared to experience loss of smell and taste, whereas among the 1123 COVID-19 negative patients only 18% of cases were associated with smell and taste loss (Menni et al., 2020). Importantly, the results on the correlation between loss of taste and smell and COVID-19 were adjusted for age, sex and body mass index. As the title of the pre-print by Menni et al. (2020) well summarizes, the "loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection". Indeed, considering a combination of loss of OTDs, fever, fatigue, persistent cough, diarrhoea, abdominal pain and loss of appetite produced the best predictor of COVID-19 diagnosis (sensitivity: 0.54 [0.44; 0.63], specificity of 0.86 [0.80; 0.90] (Menni et al., 2020). Analogous numbers by Yan et al. (2020) showed 68% smell and 71% taste impairment for Covid- 19- positive subjects compared to a respective 16% and 17% for Covid- 19- negative patients (Yan et al., 2020).

All in all, the preliminary data, which have so far been reported from areas where COVID-19 has been highly monitored, suggest that between 5.1% (Mao et al., 2020) to 98.0% (Moein et al., 2020) of individuals with symptoms compatible with COVID-19 show some sort of OTDs. In hospitalized patients with confirmed COVID-19, this percentage ranges between 33.9% (Giacomelli et al., 2020) and 98.0% (Moein et al., 2020), while in a general population, 59% showed mild-to-moderate COVID-19 symptoms (Menni et al., 2020). As evident from this brief review, the data have been primarily collected via self-reports, mostly without differentiation between olfactory and taste symptoms, and neglecting altogether chemesthetic phenomena. Even when considering the most studied olfactory loss in combination with other symptoms, the identification of true COVID-19 negative cases is maximized, whereas the

identification of true positives is around chance level (0.54; Menni et al., 2020). Whether the reported taste disturbance is olfactory-dependent or instead reflects true taste loss in COVID-19 is to date unclear.

Although functional anosmia is generally seen in conjunction with other COVID-19 symptoms, anosmia/hyposmia has also been reported as an isolated symptom (Eliezer et al., 2020; Gane et al., 2020; Marchese-Ragona et al., 2020; Villalba et al., 2020) or early symptoms in mild symptomatic patients (Spinato et al., 2020; Yan et al., 2020), and may be heritable (Williams et al., 2020). One recent controlled study even shows evidence that OTDs are more frequent in COVID-19 (39.2%) than other viruses such as influenza (12.5%) (Beltrán-Corbellini et al., 2020). However, exploring OTDs in infections caused by other coronavirus as well as on other non-corona viruses may help us understand whether the spontaneous reports of anosmia and taste disturbances in COVID-19 can fall in the general symptomatology of coronavirus illnesses or are indeed special to COVID-19.

Human Coronaviruses and Chemosensory Clinical Manifestations

In addition to SARS-CoV-2, the coronavirus family includes six other human pathogens named HCoV-OC43, HCoV-HKU1, HCoV-229E, HCoV-NL63, MERS-CoV, and SARS-CoV that trigger respiratory infection in humans (Su et al., 2016). While four of these endemic CoVs found in humans worldwide (HCoV-OC43, HCoV-HKU1, HCoV-229E, HCoV-NL63) present themselves as mild upper respiratory infection symptoms resembling common cold (Su et al., 2016; Corman et al., 2018), highly infectious MERS-CoV and SARS-CoV viruses may cause fatal respiratory disease in humans (Gralinski and Baric, 2015). MERS-CoV, SARS-CoV, and SARS-CoV-2 are all positive-sense single-stranded enveloped RNA viruses that can be transmitted from animal to animal, animal to human, and human to animal. Intriguingly, SARS-CoV shares 70-80% of its genetic information with novel SARS-CoV-2 and enters a target using the same receptors (Lu et al., 2020), which may provide important comparative insights into the symptoms and comorbidities of this novel virus.

Both SARS-CoV and MERS-CoV became emerging worldwide health concerns after their first outbreak in Taipei City in 2003 affecting 32 countries (Zhong et al., 2003), and in the Middle East in

2012 affecting 27 countries (Nassar et al., 2018a, 2018b). These infections caused a significant number of casualties (SARS-CoV: 8422 cases and 916 casualties; MERS-CoV: 2492 cases and 868 casualties; Meo et al., 2020). As with SARS-CoV-2, both these viruses are transmitted through the upper respiratory tract by contaminated mucus droplets (Meo et al., 2020). The patterns of SARS-CoV and MERS-CoV infections have seasonal variations, with SARS-CoV predominantly active during winter while MERS-CoV active during the summer months. Most importantly, like SARS-CoV-2 (Lechien et al., 2020), studies have reported that SARS-CoV and MERS-CoV infections characterize a wide spectrum, ranging from no clinical symptoms (asymptomatic), or mild to severe respiratory illness symptoms, to death (Meo et al., 2020). Most of the patients with SARS-CoV and MERS-CoV report clinical symptoms of fever with rigor, dry cough, dyspnea, general myalgia, shortness of breath, pneumonia, and even acute respiratory failure. Patients also present abdominal pain and disturbances, nausea, vomiting, diarrhoea, and acute renal failure. While rare, one study showed that some patients infected with SARS-CoV also developed neuromuscular problems 3 weeks after the onset. These neuromuscular problems are considered to be concomitant polyneuropathy and/or myopathy (Tsai et al., 2004). Most MERS-CoV hospitalized patients have also reported central nervous system involvement and cardiovascular symptoms (Arabi et al., 2015; Zegarra-Valdivia et al., 2020). Emerging new reports also suggest that COVID-19 patients are at a high risk of thrombocytopenia, elevated D-dimer, prolonged prothrombin time, and disseminated intravascular coagulation (Giannis et al., 2020; Klok et al., 2020). A similar dysregulation of coagulation cascade and the subsequent formation of intra-alveolar or systemic fibrin clots have also been reported in both SARS-CoV and MERS-CoV patients, and in animal models (Giannis et al., 2020). Most recently, skin lesions, commonly reported as “COVID toes” have also been added to the long list of COVID-19 manifestation (Marzano et al., 2020). Overall, there is an overlap in the clinical characteristics of all three viruses, yet this may not *tout court* translate to similarities in OTDs.

Data on the contribution of coronaviruses on olfactory acuity and perception are quite rare. For instance, experimental nasal inoculation with endemic HCoV-229E in healthy adults increased the threshold at which odors can be detected (Åkerlund et al., 1995). These olfactory impairments were

correlated with nasal congestion (Åkerlund et al., 1995). Olfactory loss or distortion was reported in patients with rhinosinusitis, typically caused by an endemic coronavirus (Rombaux et al., 2016). In the case of SARS-CoV and MERS-CoV, olfactory functioning has been rarely studied. To the best of our knowledge, only one publication has reported an olfactory connection with SARS-CoV. In particular, a young woman reported an acute onset of anosmia 3 weeks after the beginning of the first SARS-CoV specific symptoms (Hwang, 2006). This anosmia time course is compatible with the onset of SARS-CoV-related peripheral neuropathy as described above (Tsai et al., 2004), suggesting that acute anosmia may occur due to coronavirus-related olfactory nerve damage. It is evident from this sparse information on olfactory function was not routinely examined by clinicians during the SARS-CoV outbreak. Information related to taste and chemesthesis is even less explored and reported. With a large number of SARS-CoV-2 infected patients reporting acute anosmia, it is imperative to use chemosensory performance measures to support diagnosis and/or prognosis of any SARS virus during the acute and convalescent stages.

On the basis of the available observational data, it seems that olfactory disturbances may not be as prominent in SARS and MERS as they have been reported in COVID-19. No experimental nor anecdotal information seems to be available with respect to taste and chemesthetic experiences. This evidence can be the consequence of i) the lack of routine testing for chemical senses in clinical settings not directly specialized in chemosensation (Harris et al., 2006; Hummel et al., 2017b), ii) the larger scale at which COVID-19 has been spreading as compared to SARS and MERS, iii) unpopularity of anosmia as a significant health concern during SARS and MERS outbreak, iv) having been primed by the media reporting on the possibility of experiencing OTDs in association with COVID-19, v) a particular susceptibility of the chemical senses to SARS-CoV-2 or even a combination of all of the above is to date unknown. A non-exhaustive analysis of OTDs following viral infections at large could further provide insights on these questions.

Postviral Chemosensory Clinical Manifestations

Post-viral chemosensory loss is characterized by a sudden loss of olfactory function or reports of disturbance in taste changes after upper respiratory infection (URI) with over 200 viruses causing upper respiratory tract infection leading to a decrease in chemosensation (Mäkelä et al., 1998; Dalton, 2004). Post-viral olfactory dysfunction (PVOD) is primarily caused by four families of viruses: rhinoviruses, influenza, coronaviruses, and parainfluenza. PVOD shows different levels of persistent sensory loss after the infection has resolved, leading to anosmia or hyposmia. Hyposmia often emerges during the late symptomatic phase of viral illnesses in concomitance with nasal discharge and congestion, following symptoms such as headaches, sneezing, chillness, and malaise (Eccles, 2005). In particular, inflammatory mediators such as bradykinins (Proud et al., 1988; Shibayama et al., 1996) increase mucus production and its drainage as well as swelling of the blood vessels in the nostril leading to a restriction in airflow (Bende et al., 1989; Åkerlund et al., 1995). Typically, these intranasal changes account for the majority of smell loss during the infection (Dalton, 2004). However, there are some experimental accounts for olfactory decline independent of nasal discharge (Åkerlund et al., 1995) and congestion (Hummel et al., 1998a, 1998b) – implying direct damage to the olfactory sensory neurons (OSNs) during infection is possible. Similarly, asymptomatic smell loss for SARS-CoV-2 has been reported in recent case reports (Gane et al., 2020; Marchese-Ragona et al., 2020; Villalba et al., 2020). As viral symptoms resolve, chemosensations usually return to normal; however, some disturbances may persist (Welge-Lüssen and Wolfensberger, 2006).

PVOD is considered a sensorineural disorder as the mechanisms of dysfunction are generally attributed to peripheral damage to the olfactory epithelium (OE), which harbors OSNs (Jafek et al., 1990; Yamagishi et al., 1994). Clinical biopsy studies of the OE have revealed large areas of cicatrization (or scarring), decreased number of cilia on the olfactory receptor neuron, and replacement of sensory epithelium with respiratory epithelium (Yamagishi et al., 1994; Jafek et al., 2002; Seiden, 2004). Meanwhile, PVOD models on parainfluenza show the virus persists in OE and olfactory bulb (OB) tissue, reduces regenerative ability, and impairs the physiological function of OSNs (Tian et al., 2016). Indeed, central processing pathways related to smell may be damaged through direct transmission of the virus to

the brain through the olfactory or trigeminal nerves (Charles et al., 1995; Reiss et al., 1998; Doty, 2003; van Riel et al., 2015). Additionally, paresis/paralysis of the cranial nerves and history of neurological disease are associated with PVOD more than other olfactory disorders such as chronic rhinosinusitis (Jitaroon et al., 2020). Nevertheless, the decrease in sensory input leads to shrinkage of central olfactory areas such as the olfactory bulb that has both upstream and downstream effects (Mueller et al., 2005; Rombaux et al., 2006; Yao et al., 2018).

Spontaneous recovery in PVOD happens in a third of patients within three years from initial loss (Duncan and Seiden, 1995; Reden et al., 2006; Rombaux et al., 2012) with higher percentages of recovery in the first year (Hummel et al., 2017a), yet a significant portion of patients recovering from PVOD will still experience parosmia, or a distorted sense of smell (Portier et al., 2000; Frasnelli et al., 2004; Bonfils et al., 2005) and phantosmia (Rombaux et al., 2009). The large number of parosmic cases from post-viral loss further substantiates that damage to the peripheral rather than central nervous systems are at play. Additionally, regenerative capacity of OSNs decreases with age (Wysocki and Gilbert, 1989; Loo et al., 1996; Mobley et al., 2014), which explains why most PVOD happens in the fourth decade of life and age has a negative relationship with recovery (Konstantinidis et al., 2006; Reden et al., 2006).

A patient's symptom may not always precisely reveal which chemosensation is altered. While most patients may report taste and smell loss, the loss of taste may be reflected by some degree of olfactory impairment. There is less evidence that taste sensations are affected directly from the infection (Pellegrino et al., 2017) while drugs prescribed for viral illness might impact taste (e.g. protease inhibitors, Doty et al., 2008). Intranasal touch sensation, although limited in studies, has been reported to decrease in sensitivity (Ren et al., 2012; de Haro-Licer et al., 2013; Pellegrino et al., 2017). Importantly, the intranasal trigeminal system functions to release immediate protective mucosal responses and provides afferent connections to brainstem reflexes such as coughing, sneezing, gagging, and vomiting (Baraniuk and Merck, 2009). Whether this reduction in sensitivity is associated with reduced ability to promote the clearing of pathogenic agents from the nasal cavities is currently a speculation.

Conclusions and Future Perspectives

Although some aspects of COVID-19 manifestations are closely related to those reported in the epidemics of SARS and MERS diseases (e.g., Zegarra-Valdivia et al., 2020), this does not seem to be the case for OTDs. The available evidence, which has mostly been collected quickly with the goal of either describing or predicting COVID-19 new diagnoses, has prioritized estimates of OTDs that are focused on olfactory complaints. These reports lack the level of detail that can explain the association between clinical manifestations and chemosensory mechanisms. Indeed, while loss of taste is reported as a manifestation of COVID-19 in recent literature, currently available self-reports do not always address taste and never chemesthesis independent of olfactory complaints. Studies using validated psychophysical methods are needed to corroborate the extent of effects of smell and taste loss with COVID-19. To date, only one study (Moein et al., 2020) has taken objective measurements of smell loss, reporting the highest number of compromised patients. There have been no studies objectively measuring taste ("taste strips", (Landis et al., 2009)) nor trigeminal ("intranasal lateralized test", (Frasnelli et al., 2011)) function in Covid-19 patients. Understanding the contribution of the different chemosensory modalities - taste, smell, chemesthesis - to COVID-19 may help identify clusters of patients, informing patterns of prognosis for post-COVID-19 anosmia. To this end, to fully understand whether COVID-19 anosmia is unique, it is paramount to compare its chemosensory manifestations against those reported in patients diagnosed with other types of respiratory illness.

Our current report highlights important gaps in the literature needed to be addressed to understand the prevalence of chemosensory reports and potential mechanisms for these symptoms with COVID-19. For instance, there is a need to understand the mechanisms of COVID-19 chemosensory changes related to conductive and sensorineural issues (Butowt and Bilinska, 2020). In particular, distinguishing each aspect of chemosensation in patients with confirmed and suspected COVID-19 diagnosis as well as with other respiratory illnesses is needed to determine whether the chemical senses are uniquely affected by

the SARS-CoV-2 infection. Case studies have reported asymptomatic OTD with COVID-19; however, its clinical usefulness as a biomarker of the disease needs normative data. A hyperinflammatory response may lead to varying levels of congestion and damage to the OE while viral proliferation within the olfactory mucosa may provide a blood-independent pathway into the brain (Baig et al., 2020). Reports show an abundance of nasal epithelial cells expressing cellular receptors and proteases needed for viral entry, i.e. angiotensin-converting enzyme 2 (ACE-2) and transmembrane serine protease 2 (TMPRSS2) ((Brann et al., 2020; Chen et al., 2020; Gupta et al., 2020; Hoffmann et al., 2020; Sungnak et al., 2020) along with patients having neurological conditions to SARS-CoV-2 (Mao et al., 2020) and other infections leading to PVOD (Jitaroon et al., 2020). Although reports on OTDs in COVID-19 are being published or archived every day, the lack of follow-up studies to determine the dynamics of chemosensory changes in the disease and its reversibility over time are not currently available. Moreover, recent reports indicate that adults with obesity and diabetes - whose chemosensory abilities are often compromised - are at high risk for SARS-CoV-2 infection (Lighter et al, 2020); however, none of the reports to date have analyzed OTD's in these sensitive groups. Given the worldwide magnitude of this pandemic and the relevance of smell and taste loss as symptoms of COVID-19, understanding chemosensory changes should be performed on a global scale to account for possible confounds that would limit the interpretability of this association and to reach the numerous people that may not be in the position to receive a formal diagnosis.

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