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Review Article

Anosmia in COVID-19: Mechanisms and Significance

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Abstract

The global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains a challenge for prevention due to asymptomatic or paucisymptomatic patients. Anecdotal and preliminary evidence from multiple institutions shows that these patients present with a sudden onset of anosmia without rhinitis. We aim to review the pathophysiology of anosmia related to viral upper respiratory infections and the prognostic implications. Current evidence suggests that SARS-CoV-2-related anosmia may be a new viral syndrome specific to COVID-19 and can be mediated by intranasal inoculation of SARS-CoV-2 into the olfactory neural circuitry. The clinical course of neuroinvasion of SARS-CoV-2 is yet unclear; however, an extended follow-up of these patients to assess for neurological sequelae, including encephalitis, cerebrovascular accidents, and long-term neurodegenerative risk may be indicated.

Key words: anosmia, coronavirus, COVID-19, olfaction, postviral anosmia

Introduction

Coronavirus disease 2019 (COVID-19) is a multiorgan manifestation caused by an infection of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first discovered in Wuhan, China, in 2019. Although most patients infected with SARS-CoV-2 experience a mild disease, nearly 5% progress to disseminated viral pneumonia and multiorgan failure (Wu and McGoogan 2020). Over 2 million patients have been infected worldwide and the United States is now leading the number of infections and deaths by COVID-19 infection with unprecedented efforts to contain the viral spread (Dong et al. 2020). The nonspecific symptomatology of fever, cough, and fatigue makes early diagnosis of COVID-19 challenging (Huang et al. 2020). Insufficient PCR testing capability further hindered diagnosis and early containment within the United States.

Reports of olfactory dysfunction in otherwise asymptomatic persons have led to interest in this sign as a potential early indicator of SARS-CoV-2 infection (Hopkins et al. 2020). Furthermore, olfactory neurons could be at especially high risk of injury because of the high viral load within the nasal cavity (Zou et al. 2020). Olfactory dysfunction after SARS-CoV infection was also reported in the past (Hwang 2006). This paper reviews the olfactory physiology, summarizes the clinical reports of anosmia in current and previous viral outbreaks, and specifically discusses neurological implications of this syndrome. It is important to note that dysgeusia (lack of taste, also a chemical sense) has also been reported in COVID-19-infected patients (Hopkins et al. 2020); however, it can be difficult to distinguish the two symptoms without objective testing. Therefore, this review will be focused on the olfactory system.

Olfactory physiology

Olfactory function provides critical information about the environment, which is why substantial neural circuitry is dedicated to processing olfaction and multisensory integration. Initially, odorants enter the superior aspect of the nasal cavity, which is lined by the olfactory epithelium (OE; see Whitman and Greer 2009). At least

five cell types exist in this epithelial layer: olfactory sensory neurons (OSNs), sustentacular cells, microvillar cells, duct cells of the olfactory (Bowman's) glands, and basal cells (van Riel et al. 2015). Here, the odorants are detected by odorant receptors (ORs) on the cilia of the OSNs. ORs are G-protein-coupled receptors that activate Golf. Golf activation stimulates adenylyl cyclase, followed by the formation of cyclic adenosine monophosphate. This leads to the opening of chloride channels and an efflux of chloride ions, resulting in action potential (Attems et al. 2015). OSNs are bipolar neurons with axons that form synapses in the olfactory bulb, as well as dendrites that project out into the nasal cavity and are enwrapped by sustentacular cells (Liang 2018). From each dendritic knob of an OSN, 10–30 cilia protrude out into the mucus layer (Glezer and Malnic 2019). Each OSN expresses a unique OR type, and the axons of all OR-specific OSNs project to the glomeruli, where they synapse with mitral and tufted cells in the olfactory bulb.

The axons of the second-order olfactory neurons (mitral and tufted cells) subsequently project to diverse olfactory areas of the central nervous system (CNS). This includes the anterior olfactory nucleus (AON), the olfactory tubercle, the piriform cortex (area 51), the amygdala, and the entorhinal cortex (Attems et al. 2015; Diodato et al. 2016). Here, the neural circuit feeds into multimodal integration that is important for cognition and motor control. Recent studies have shown that the AON utilizes input from the hippocampus for storage of olfactory memory representations (Aqrabawi and Kim 2020).

OSNs in the OE undergo continuous turnover throughout a person's life. The basal cells (both globose and horizontal types) are pluripotent and can give rise to all subtypes of OE cells (Beites et al. 2005; Leung et al. 2007). Steroids inhibit this OSN regeneration as seen in murine models of OE injury from intranasal lipopolysaccharide administration (Crisafulli et al. 2018). Neurons in the olfactory bulb also undergo regeneration originating as neuroblasts from the subgranular zone of the dentate gyrus (Whitman and Greer 2009).

Current evidence regarding SARS-CoV-2-related anosmia

Preliminary evidence reveals that sudden anosmia might be the sole presenting symptom of COVID-19 patients (Gane et al. 2020; Hopkins et al. 2020). In 214 hospitalized COVID-19 patients in Wuhan, 5.1% and 5.6% of patients presented with hyposmia and hypogeusia, respectively (Mao et al. 2020). An anecdotal survey of patients in South Korea revealed that about 30% had anosmia as their major presenting symptom of COVID-19 (ENT UK 2020). Furthermore, these patients presented with anosmia and ageusia associated with fever (>37.5 °C) without nasal obstruction or rhinitis.

After these initial reports, the American Academy of Otolaryngology—Head and Neck Surgery, ENT UK, and the British Rhinological Society independently published guidelines that include anosmia, hyposmia, and dysgeusia in assessing patients suspected to have COVID-19 (ENT UK 2020). More recent olfactory surveys on COVID-19 patients showed olfactory dysfunction in 20–85% of patients (Giacomelli et al. 2020; Lechien et al. 2020; Spinato et al. 2020; Vaira et al. 2020). Magnetic resonance imaging of a patient with SARS-CoV-2-related isolated sudden anosmia revealed normal olfactory bulb volume and signal intensity (Galougahi et al. 2020). About 72.6% of these patients recovered olfactory function within the first 8 days, which suggests that the majority of anosmia is temporary in nature (Lechien et al. 2020). A similar finding was confirmed using the University of

Pennsylvania Smell Identification Test (Moein et al. 2020). It is possible that the apparently increasing incidence of olfactory dysfunction is due to greater awareness and more careful assessment of the symptom.

Molecular virology of SARS-CoV-2

SARS-CoV-2, part of the family Coronaviridae, is an enveloped, positive-sense single-stranded ribonucleotide acid (RNA) virus. Although data from this novel coronavirus is still emerging, more information is available on the related SARS-CoV that was studied in the wake of its outbreak in 2003. The mechanism of SARS-CoV entry into host cells has been well characterized and resembles that of the human immunodeficiency virus and the influenza virus. All of these viruses contain a viral spike protein (S protein) belonging to a group of class I viral fusion proteins. The N-terminal end of the spike protein (S1) contains the receptor-binding domain that binds to the host's angiotensin-converting enzyme 2 (ACE2), resulting in a conformational change of the S protein. This is followed by proteolytic cleavage of the S protein by TMPRSS2 (Chen and Subbarao 2007; Shulla et al. 2011). The C-terminal of the viral spike protein (S2) contains heptad repeat domains (HR1 and HR2) that form a six-helix bundle fusion core structure during fusion, enabling viral RNA entry into the cell (Du et al. 2009). SARS-CoV-2 is thought to enter the host cell in a similar way via priming of S protein subunits by TMPRSS2 and initiation of viral entry by their interaction with the host cell's ACE2 (Hoffmann et al. 2020).

Possible mechanisms of anosmia in SARS-CoV-2 patients

With few studies published yet, we can only speculate on the mechanism of anosmia symptoms in SARS-CoV-2 patients. We can glean understanding from other respiratory viral infections, including other coronaviruses in particular. Anosmia can be broadly categorized into conductive or sensorineural olfactory loss (Goncalves and Goldstein 2016). Conductive loss occurs due to impaired nasal airflow and is reversible when the obstruction clears; sensorineural loss implies dysfunction of the OE and can be permanent or have a longer time course to functional recovery. Several possible mechanisms are suggested for the SARS-CoV-2 anosmia that may cause anosmia alone or in concert.

Conductive or obstructive anosmia

Sinonasal conditions that affect airflow and impair the travel of odorants to the intact OE can result in a conductive loss. Indeed, nasal congestion or edema of the nasal respiratory epithelium from various causes can result in temporary anosmia. In the pre-COVID era, olfactory impairment resulting from sinonasal disease ranged from 14% to 30% of all patients presenting with anosmia (Cain et al. 1988; Miwa et al. 2001; Seiden and Duncan 2001; Temmel et al. 2002).

Infections resulting from the endemic strains of human coronavirus (HCoV), including NL63, OC43, and 229E, cause the common cold. A prospective study of hospitalized patients showed that patients with these endemic HCoV strains showed rhinitis, pharyngitis, and laryngitis, although less commonly than lower respiratory symptoms (Greenberg 2011). When healthy volunteers were inoculated with the HCoV-229E strain, patients began to report nasal obstruction and an impaired sense of smell. The recovery time was not assessed in this particular study, and it is not clear whether this was conductive or sensorineural olfactory dysfunction (Akerlund et al. 1995). Supporting evidence that SARS-CoV-2 causes conductive olfactory dysfunction comes from the time of onset of anosmia in

these patients: olfactory dysfunction after (26.7–65.4%) or at the same time (22.8%) as the general or ENT symptoms in COVID-19 patients (Lechien et al. 2020; Spinato et al. 2020). Furthermore, as mentioned before, the olfactory dysfunction was temporary with recovery within 8 days in the majority of COVID-19 patients (Lechien et al. 2020), again supportive of a conductive mechanism.

Disruption of olfactory epithelium following local infection

A viral infection of the nasal OE can result in injury to part or all of the nasal OE, including OSNs. In these patients, the "post-URI anosmia" or "postviral anosmia" persists for weeks to months after the clearance of rhinitis and associated upper respiratory infection (URI) symptoms until the damaged parts of the nasal OE regenerate. The pathophysiology of "postviral anosmia" and histological analyses have been described in the literature, mainly following rhinovirus infection. Upon infection of the nasal respiratory and OE, neutrophilic inflammation ensues, resulting in mucosal edema and rhinorrhea. As mentioned above, conductive olfactory loss is often associated with nasal obstruction; however, histologic analysis of the OE in these patients showed an absence of cilia and a decreased number of OSNs replaced by metaplastic squamous epithelium, indicating an additional sensorineural contribution (Jafek et al. 1990; Yamagishi et al. 1994).

Postviral anosmia has been reported after HCoV-229E infection, and the olfactory dysfunction lasted more than 6 months (Suzuki et al. 2007). Of note, HCoV-229E uses human aminopeptidase N as the receptor for host entry, which is different from SARS-CoV and SARS-CoV-2 that use ACE2 (Yeager et al. 1992; Hoffmann et al. 2020). In the patients with SARS-CoV, a high level of ACE2 expression was demonstrated in the nasal respiratory epithelium (Bertram et al. 2012), more specifically on the ciliated cells, consistent with intranasal viral entry into the human host (Sims et al. 2005). However, this result contradicted another study that identified ACE2 in the basal layer of the nasal respiratory epithelium (Hamming et al. 2004). Subsequent studies revealed that goblet cells of the nasal respiratory epithelium have a high level of ACE2 expression (Sungnak et al. 2020; Ziegler et al. 2020). The OE lacks goblet cells (Solbu and Holen 2012); however, recent preliminary data showed ACE2 expression in the OE, more specifically in the nonneuronal cells (supporting cells, stem cells, and perivascular cells) (Brann et al. 2020). The single-cell RNA-seq approach has been used to identify specific cells of the OE that coexpress ACE2 and TMPRSS2. Preliminary data from Fodoulian et al. identified sustentacular cells, facing the nasal cavity, and playing a critical role in maintenance in the neuroepithelium as the prime cellular targets for SARS-CoV-2 entry (Fodoulian et al. 2020). The high susceptibility of nasal tissues to coronavirus infection supports the concept that some of the olfactory dysfunction can be due to injury of the local environment. Those COVID-19 patients who do not rapidly recover olfactory function might have suffered greater intranasal injury. It is not yet known if prolonged olfactory disturbance correlates with the degree of symptoms generally.

Retrograde propagation to higher-order neurons in the olfactory pathway

Olfactory disorders can result from viral infections of the OSN and retrograde propagation to the higher-order neurons in the olfactory pathway. Indeed, in addition to anosmia and hyposmia, olfactory dysfunctions, such as phantosmia (distorted sense of smell) and olfactory hallucination (perceived distortion in the absence of an odorant), can occur in epilepsy, migraine, meningitis, and disorders of the CNS (Hong et al. 2012). Strictly speaking, olfactory dysfunction due to central causes would require involvement of the brain areas processing olfactory information.

Retrograde olfactory neuroinvasion as the underlying cause of anosmia is best studied in the case of the herpes virus. The herpes virus is an enveloped double-stranded deoxyribonucleic acid virus of the Herpesviridae family (Duarte et al. 2019). The human herpes virus spreads in a retrograde fashion via the olfactory and the trigeminal nerve, but the exact mechanism remains unknown. Neuroinvasion by the herpes virus can result in the rare, fatal sequelae of herpes simplex encephalitis (HSE), which has an incidence of 1–3 cases per million (Steiner et al. 2007). Approximately 70% of HSE cases are attributed to late viral reactivation (Duarte et al. 2019), supported by the detection of HSV-1 DNA in 1.9% of the asymptomatic general population (Olsson et al. 2016).

Permanent anosmia has been described in patients who recovered from HSE (Landis et al. 2010). Post-HSE anosmia often presents with other neurological sequelae, including epilepsy, amnesia, and cognitive deficits. In mouse models of HSE, necrotic debris was present in the olfactory bulb within 5 days postinfection, then within the cranial nerve tracts and nuclei with presence of neutrophils, macrophages, and lymphocytes by 7 days (Armien et al. 2010). Mice that survived the acute phase of the infection showed diffuse immune cell infiltration through the brain with profound atrophy of the piriform and entorhinal cortices and amygdala (Armien et al. 2010). Indeed, the degree and quality of olfactory deficit in post-HSE patients varies, suggesting that some patients might suffer from a more "central" pattern of olfactory impairment involving limbic areas (Landis et al. 2010). Evaluation of the OE of HSE patients revealed diffuse inflammation and ragged appearance due to vesicles between the cells. The perineural sheaths of olfactory nerves showed evidence of hemorrhage, indicating viral invasion (Twomey et al. 1979). Although the degree of CNS involvement in COVID-19 is unclear, it is anticipated that future studies would show patterns of necrosis and invasion similar to those of HSE if COVID-19-associated anosmia is due to retrograde propagation via the olfactory bulb. This may be an area for further investigation.

Growing evidence shows that coronavirus infection often is not confined to the nasal cavity and the upper respiratory tract but also enters into the CNS in unclear circumstances. The strongest evidence comes from mouse inoculation experiments, where it was confirmed that strains of coronavirus can invade the olfactory bulb (Perlman et al. 1990) as do other RNA viruses, such as rhabdoviruses (Christian et al. 1996), influenza A (Park et al. 2002), and flaviviruses (Goverdhan et al. 1992). Severe olfactory bulb degeneration and increased turnover of OSN were demonstrated within the OE with a high ratio of immature to mature neurons (Schwob et al. 2001). Intranasal inoculation of HCoV-OC43 in mice resulted in viral antigen detection in the olfactory bulb 3 days later and in the whole brain 7 days later (Perlman et al. 1989). The propagation of HCoV-OC43 viral particles is mediated by axonal transport in neuron-to-neuron transmission (Dubé et al. 2018). The viral spread can be prevented by the ablation of the olfactory bulb, confirming that neuroinvasion via intranasal inoculation is mediated by olfactory neural circuitry (Perlman et al. 1990).

Immune responses to local viral infection in the OE include upregulation of nitric oxide and major histocompatibility antigens I and II by infected OSNs (Bi et al. 1995; Lane et al. 1997; Durrant et al. 2016). Additional studies demonstrated

olfactory bulb expression of innate cytokines, including interleukin 1, interleukin 12, and tumor necrosis factor, which decrease viral titers within the olfactory bulb and are directly correlated with prompt recruitment of CD4+ and CD8+ T-cells, as well as natural killer cells (Pearce et al. 1994; Reiss et al. 1998). T-cells are especially crucial in clearing mouse hepatitis virus from olfactory neurons (Pearce et al. 1994). In the case of SARS-CoV, the direct infection of macrophages and T-lymphocytes alters the innate immune response and expression of inflammatory markers. SARS-CoV-infected immune cells are hypothesized to promote a pro-inflammatory state that contributes to severe disease, and a similar mechanism is implicated in SARS-CoV-2 (Perlman and Dandekar 2005; Mehta et al. 2020). A recent neuroimmunologic study revealed that microglia serve a critical role in limiting the replication of a mouse hepatitis virus via innate and virus-specific T-cell responses (Wheeler et al. 2018). Interestingly, administering cyclosporine to induce immune suppression during HCoV-OC43 inoculation did not prevent the formation of vacuolating lesions and neuronal death in mice, which suggests that some aspects of neurodegeneration are not immunologically mediated (Jacomy and Talbot 2003).

Human clinical and autopsy specimens further support the occasional neuroinvasion of coronaviruses. The endemic coronavirus strains HCoV-OC43 and -229E have been detected in postmortem specimens (Stewart et al. 1992; Arbour et al. 2000). SARS-CoV was also detected in cerebrospinal fluid (Hung et al. 2003) and postmortem specimens (Gu et al. 2005). In this case report, a 59-year-old male who had SARS-related respiratory symptoms experienced four-limb twitching and status epilepticus. The cerebrospinal fluid of this patient was found to have a high SARS-CoV viral load (6884 copies/mL). While SARS-CoV-2 has yet to be detected in the CNS, it is important to consider prolonged anosmia as part of COVID-19 symptomatology given the neuroinvasive potentials of previously studied coronavirus strains.

Hematologic spread to the CNS

Another plausible mechanism of viral entry to the CNS is by direct brain inoculation from epithelial disruption at the blood-brain barrier following hematologic seeding of SARS-CoV-2 from other organs. Indeed, a high prevalence of ACE2 was found in lung and intestinal epithelia, which provide possible hematologic routes of viral entry (Hamming et al. 2004). Recent evidence suggests that SARS-CoV-2 causes cardiac injury by targeting pericytes in the heart with high expression of ACE2 (Chen et al. 2020). It is likewise possible that hematologic spread of SARS-CoV-2 to endothelial cells of the blood-brain barrier injures pericytes and astrocytes. This would not only result in major ramifications on brain homeostasis but also cause central and peripheral olfactory disturbance (Kabbani and Olds 2020). Recent preliminary data showed ACE2 expression in perivascular cells of the OE, which supports the hypothesis of hematologic spread of SARS-CoV-2, although further studies are required to delineate the exact mechanism of pathogenesis (Brann et al. 2020).

Direct or indirect CNS injury causing demyelination

The neurodegenerative properties of latent HCoV infection emerged from a study that demonstrated a higher prevalence of HCoV-OC43 in postmortem brain specimens from multiple sclerosis (MS) patients compared to a control group (Arbour et al. 2000). MS is a disease of the CNS characterized by patches of demyelination and

autoimmune inflammation due to molecular mimicry. Although the etiology of MS remains disputed, it is postulated that genetic factors (Ebers and Sadovnick 1994) and viral pathogens, such as HCoV, induce CNS demyelination via chronic infection of oligodendrocytes (Perlman 1998; Arbour et al. 2000; Fazakerley and Walker 2003). Interestingly, recent studies have indicated that olfactory dysfunction is correlated with progressive cognitive impairment and physical disability in MS patients (Atalar et al. 2018; Carotenuto et al. 2019). Certainly, this hypothesis would require longitudinal patient studies to delineate and gather more evidence on the progressive decline of neurological function.

Conclusions

Viral URIs classically manifest as rhinorrhea and nasal obstruction, leading to conductive olfactory loss. Postviral anosmia may ensue in a subacute fashion after the acute symptoms of URI resolve. However, the preliminary data on COVID-19 patients identified a novel viral syndrome of acute anosmia without rhinitis or nasal obstruction. New data are being uncovered about the identity of cells responsible for viral entry into the olfactory neural system. Based on reviewing anosmia as a result of viral infection, specific mechanisms of anosmia can be postulated. Nasal congestion and obstruction similar to the common cold may contribute to a conductive olfactory loss. However, depending on the true distribution of ACE2, virulence potential, and resulting immune and inflammatory response, olfactory dysfunction may indicate a peripheral injury of the first cranial nerve and branches or a harbinger of a more global neurological manifestation of the disease. Long-term follow-up studies on patients with isolated sudden onset anosmia will be important because this symptom may indicate the onset of neuroinvasion that could result in chronic neurodegenerative disease. The rates of permanent anosmia post-COVID-19 infection and impact of viral treatment regimens should be assessed.

Disclaimer

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Conflict of interest

None

References

Akerlund A, Bende M, Murphy C. 1995. Olfactory threshold and nasal mucosal changes in experimentally induced common cold. *Acta Otolaryngol.* 115(1):88–92.

Aqrabawi AJ, Kim JC. 2020. Olfactory memory representations are stored in the anterior olfactory nucleus. *Nat Commun.* 11(1):1246.

Arbour N, Day R, Newcombe J, Talbot PJ. 2000. Neuroinvasion by human respiratory coronaviruses. *J Virol.* 74(19):8913–8921.

Armien AG, Hu S, Little MR, Robinson N, Lokensgard JR, Low WC, Cheeran MC. 2010. Chronic cortical and subcortical pathology with

associated neurological deficits ensuing experimental herpes encephalitis. *Brain Pathol*. 20(4):738–750.

Atalar AÇ, Erdal Y, Tekin B, Yıldız M, Akdoğan Ö, Emre U. 2018. Olfactory dysfunction in multiple sclerosis. *Mult Scler Relat Disord*. 21:92–96.

Attems J, Walker L, Jellinger KA. 2015. Olfaction and aging: a mini-review. *Gerontology*. 61(6):485–490.

Beites CL, Kawauchi S, Crocker CE, Calof AL. 2005. Identification and molecular regulation of neural stem cells in the olfactory epithelium. *Exp Cell Res*. 306(2):309–316.

Bertram S, Heurich A, Lavender H, Gierer S, Danisch S, Perin P, Lucas JM, Nelson PS, Pöhlmann S, Soilleux EJ. 2012. Influenza and SARS-coronavirus activating proteases TMPRSS2 and HAT are expressed at multiple sites in human respiratory and gastrointestinal tracts. *PLoS One*. 7(4):e35876.

Bi Z, Barna M, Komatsu T, Reiss CS. 1995. Vesicular stomatitis virus infection of the central nervous system activates both innate and acquired immunity. *J Virol*. 69(10):6466–6472.

Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B, Chance R, Macaulay IC, Chou H, Fletcher R, et al. 2020. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *bioRxiv*. doi: 10.1101/2020.03.25.009084.

Cain WS, Gent JF, Goodspeed RB, Leonard G. 1988. Evaluation of olfactory dysfunction in the Connecticut Chemosensory Clinical Research Center. *Laryngoscope*. 98(1):83–88.

Carotenuto A, Costabile T, Moccia M, Falco F, Scala MR, Russo CV, Saccà F, De Rosa A, Lanzillo R, Brescia Morra V. 2019. Olfactory function and cognition in relapsing-remitting and secondary-progressive multiple sclerosis. *Mult Scler Relat Disord*. 27:1–6.

Chen L, Li X, Chen M, Feng Y, Xiong C. 2020. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. *Cardiovasc Res*. 116(6):1097–1100.

Chen J, Subbarao K. 2007. The immunobiology of SARS*. *Annu Rev Immunol*. 25:443–472.

Christian AY, Barna M, Bi Z, Reiss CS. 1996. Host immune response to vesicular stomatitis virus infection of the central nervous system in C57BL/6 mice. *Viral Immunol*. 9(3):195–205.

Crisafulli U, Xavier AM, Dos Santos FB, Cambiaghi TD, Chang SY, Porcionatto M, Castilho BA, Malnic B, Glezer I. 2018. Topical dexamethasone administration impairs protein synthesis and neuronal regeneration in the olfactory epithelium. *Front Mol Neurosci*. 11:50.

Diodato A, Ruinart de Brimont M, Yim YS, Derian N, Perrin S, Pouch J, Klatzmann D, Garel S, Choi GB, Fleischmann A. 2016. Molecular signatures of neural connectivity in the olfactory cortex. *Nat Commun*. 7:12238.

Dong E, Du H, Gardner L. 2020. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 20(5):533–534.

Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. 2009. The spike protein of SARS-CoV–a target for vaccine and therapeutic development. *Nat Rev Microbiol*. 7(3):226–236.

Duarte LF, Farías MA, Álvarez DM, Bueno SM, Riedel CA, González PA. 2019. Herpes simplex virus type 1 infection of the central nervous system: insights into proposed interrelationships with neurodegenerative disorders. *Front Cell Neurosci*. 13:46.

Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. 2018. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J Virol*. 92(17): e00404–00418.

Durrant DM, Ghosh S, Klein RS. 2016. The olfactory bulb: an immunosensory effector organ during neurotropic viral infections. *ACS Chem Neurosci*. 7(4):464–469.

Ebers GC, Sadovnick AD. 1994. The role of genetic factors in multiple sclerosis susceptibility. *J Neuroimmunol*. 54(1-2):1–17.

ENT UK. 2020. Loss of sense of smell as marker of COVID-19 infection [press release]. Available from www.entuk.org/loss-sense-smell-marker-covid-19-infection (accessed March 30, 2020).

Fazakerley JK, Walker R. 2003. Virus demyelination. *J Neurovirol*. 9(2):148–164.

Fodoulian L, Tuberosa J, Rossier D, Landis BN, Carleton A, Rodriguez I. 2020. SARS-CoV-2 receptor and entry genes are expressed by sustentacular cells in the human olfactory neuroepithelium. *bioRxiv*: doi: 10.1101/2020.03.31.013268.

Galougahi MK, Ghorbani J, Bakhshayeshkaram M, Naeini AS, Haseli S. 2020. Olfactory bulb magnetic resonance imaging in SARS-CoV-2-induced anosmia: the first report. *Acad Radiol*. 27(6):892–893.

Gane SB, Kelly C, Hopkins C. 2020. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? *Rhinology*. 58(3):299–301.

Giacomelli A., Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, Rusconi S, Gervasoni C, Ridolfo AL, Rizzardini D, et al. 2020. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. *Clin Infect Dis*. doi: 10.1093/cid/ciaa330.

Glezer I, Malnic B. 2019. Olfactory receptor function. *Handb Clin Neurol*. 164:67–78.

Goncalves S, Goldstein BJ. 2016. Pathophysiology of olfactory disorders and potential treatment strategies. *Curr Otorhinolaryngol Rep*. 4(2):115–121.

Goverdhan MK, Kulkarni AB, Gupta AK, Tupe CD, Rodrigues JJ. 1992. Two-way cross-protection between West Nile and Japanese encephalitis viruses in bonnet macaques. *Acta Virol*. 36(3):277–283.

Greenberg SB. 2011. Update on rhinovirus and coronavirus infections. *Semin Respir Crit Care Med*. 32(4):433–446.

Gu J, Gong E, Zhang B, Zheng J, Gao Z, Zhong Y, Zou W, Zhan J, Wang S, Xie Z, et al. 2005. Multiple organ infection and the pathogenesis of SARS. *J Exp Med*. 202(3):415–424.

Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. 2004. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 203(2):631–637.

Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, et al. 2020. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 181(2):271–280.

Hong SC, Holbrook EH, Leopold DA, Hummel T. 2012. Distorted olfactory perception: a systematic review. *Acta Otolaryngol*. 132(Suppl 1):S27–S31.

Hopkins C, Surda P, Kumar N. 2020. Presentation of new onset anosmia during the COVID-19 pandemic. *Rhinology*. 58(3):295–298.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, et al. 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 395(10223):497–506.

Hung EC, Chim SS, Chan PK, Tong YK, Ng EK, Chiu RW, Leung CB, Sung JJ, Tam JS, Lo YM. 2003. Detection of SARS coronavirus RNA in the cerebrospinal fluid of a patient with severe acute respiratory syndrome. *Clin Chem*. 49(12):2108–2109.

Hwang CS. 2006. Olfactory neuropathy in severe acute respiratory syndrome: report of a case. *Acta Neurol Taiwan*. 15(1):26–28.

Jacomy H, Talbot PJ. 2003. Vacuolating encephalitis in mice infected by human coronavirus OC43. *Virology*. 315(1):20–33.

Jafek BW, Hartman D, Eller PM, Johnson EW, Strahan RC, Moran DT. 1990. Postviral olfactory dysfunction. *Am J Rhinol*. 4(3): 91–100.

Kabbani N, Olds JL. 2020. Does COVID19 infect the brain? If so, smokers might be at a higher risk. *Mol Pharmacol*. 97(5):351–353.

Landis BN, Vodicka J, Hummel T. 2010. Olfactory dysfunction following herpetic meningoencephalitis. *J Neurol*. 257(3):439–443.

Lane TE, Paoletti AD, Buchmeier MJ. 1997. Disassociation between the in vitro and in vivo effects of nitric oxide on a neurotropic murine coronavirus. *J Virol*. 71(3):2202–2210.

Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, Dequanter D, Blecic S, El Afia F, Distinguin L, et al. 2020. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. doi: 10.1007/500405-020.

Leung CT, Coulombe PA, Reed RR. 2007. Contribution of olfactory neural stem cells to tissue maintenance and regeneration. *Nat Neurosci*. 10(6):720–726.

Liang F. 2018. Olfactory receptor neuronal dendrites become mostly intra-sustentacularly enwrapped upon maturity. *J Anat*. 232(4):674–685.

Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, et al. 2020. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol*. 77(6):1–9.

Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. 2020. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 395(10229):1033–1034.

Miwa T, Furukawa M, Tsukatani T, Costanzo RM, DiNardo LJ, Reiter ER. 2001. Impact of olfactory impairment on quality of life and disability. *Arch Otolaryngol Head Neck Surg*. 127(5):497–503.

Moein ST, Hashemian SMR, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. 2020. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol*. doi: 10.1002/alr.22587.

Olsson J, Lövheim H, Honkala E, Karhunen PJ, Elgh F, Kok EH. 2016. HSV presence in brains of individuals without dementia: the TASTY brain series. *Dis Model Mech*. 9(11):1349–1355.

Park CH, Ishinaka M, Takada A, Kida H, Kimura T, Ochiai K, Umemura T. 2002. The invasion routes of neurovirulent A/Hong Kong/483/97 (H5N1) influenza virus into the central nervous system after respiratory infection in mice. *Arch Virol*. 147(7):1425–1436.

Pearce BD, Hobbs MV, McGraw TS, Buchmeier MJ. 1994. Cytokine induction during T-cell-mediated clearance of mouse hepatitis virus from neurons in vivo. *J Virol*. 68(9):5483–5495.

Perlman S. 1998. Pathogenesis of coronavirus-induced infections. Review of pathological and immunological aspects. *Adv Exp Med Biol*. 440:503–513.

Perlman S, Dandekar AA. 2005. Immunopathogenesis of coronavirus infections: implications for SARS. *Nat Rev Immunol*. 5(12):917–927.

Perlman S, Evans G, Afifi A. 1990. Effect of olfactory bulb ablation on spread of a neurotropic coronavirus into the mouse brain. *J Exp Med*. 172(4):1127–1132.

Perlman S, Jacobsen G, Afifi A. 1989. Spread of a neurotropic murine coronavirus into the CNS via the trigeminal and olfactory nerves. *Virology*. 170(2):556–560.

Reiss CS, Plakhov IV, Komatsu T. 1998. Viral replication in olfactory receptor neurons and entry into the olfactory bulb and brain. *Ann NY Acad Sci*. 855:751–761.

Schwob JE, Saha S, Youngentob SL, Jubelt B. 2001. Intranasal inoculation with the olfactory bulb line variant of mouse hepatitis virus causes extensive destruction of the olfactory bulb and accelerated turnover of neurons in the olfactory epithelium of mice. *Chem Senses*. 26(8):937–952.

Seiden AM, Duncan HJ. 2001. The diagnosis of a conductive olfactory loss. *Laryngoscope*. 111(1):9–14.

Shulla A, Heald-Sargent T, Subramanya G, Zhao J, Perlman S, Gallagher T. 2011. A transmembrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. *J Virol*. 85(2):873–882.

Sims AC, Baric RS, Yount B, Burkett SE, Collins PL, Pickles RJ. 2005. Severe acute respiratory syndrome coronavirus infection of human ciliated airway epithelia: role of ciliated cells in viral spread in the conducting airways of the lungs. *J Virol*. 79(24):15511–15524.

Solbu TT, Holen T. 2012. Aquaporin pathways and mucin secretion of Bowman's glands might protect the olfactory mucosa. *Chem Senses*. 37(1):35–46.

Spinato G, Fabbris C, Polesel J, Cazzador D, Borsetto D, Hopkins C, Boscolo-Rizzo P. 2020. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA*. 323(20): 2089–2090.

Steiner I, Kennedy PG, Pachner AR. 2007. The neurotropic herpes viruses: herpes simplex and varicella-zoster. *Lancet Neurol*. 6(11):1015–1028.

Stewart JN, Mounir S, Talbot PJ. 1992. Human coronavirus gene expression in the brains of multiple sclerosis patients. *Virology*. 191(1):502–505.

Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, Talavera-López C, Maatz H, Reichart D, Sampaziotis F, et al. HCA Lung Biological Network. 2020. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med*. 26(5):681–687.

Suzuki M, Saito K, Min WP, Vladau C, Toida K, Itoh H, Murakami S. 2007. Identification of viruses in patients with postviral olfactory dysfunction. *Laryngoscope*. 117(2):272–277.

Temmel AF, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. 2002. Characteristics of olfactory disorders in relation to major causes of olfactory loss. *Arch Otolaryngol Head Neck Surg*. 128(6):635–641.

Twomey JA, Barker CM, Robinson G, Howell DA. 1979. Olfactory mucosa in herpes simplex encephalitis. *J Neurol Neurosurg Psychiatry*. 42(11):983–987.

Vaira LA., G. Salzano, G. Deiana, De Riu G. 2020. Anosmia and ageusia: common findings in COVID-19 patients. *Laryngoscope*. doi: 1002/lary.28692.

van Riel D, Verdijk R, Kuiken T. 2015. The olfactory nerve: a shortcut for influenza and other viral diseases into the central nervous system. *J Pathol*. 235(2):277–287.

Wheeler DL, Sariol A, Meyerholz DK, Perlman S. 2018. Microglia are required for protection against lethal coronavirus encephalitis in mice. *J Clin Invest*. 128(3):931–943.

Whitman MC, Greer CA. 2009. Adult neurogenesis and the olfactory system. *Prog Neurobiol*. 89(2):162–175.

Wu Z, McGoogan JM. 2020. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. doi: 10.1001/jama.2020.26.

Yamagishi M, Fujiwara M, Nakamura H. 1994. Olfactory mucosal findings and clinical course in patients with olfactory disorders following upper respiratory viral infection. *Rhinology*. 32(3):113–118.

Yeager CL, Ashmun RA, Williams RK, Cardellichio CB, Shapiro LH, Look AT, Holmes KV. 1992. Human aminopeptidase N is a receptor for human coronavirus 229E. *Nature*. 357(6377):420–422.

Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, Cao Y, Yousif AS, Bals J, Hauser BM, et al. HCA Lung Biological Network. Electronic address: lung-network@humancellatlas.org; HCA Lung Biological Network. 2020. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell*. 181(5):1016–1035.e19.

Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, Yu J, Kang M, Song Y, Xia J, et al. 2020. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med*. 382(12):1177–1179.