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Review Article
Published: 25 Aug, 2020

SF Journal of Clinical Neurology and Brain

Covid-19: Anosmia and Ageusia Might be Initial or Unique Symptoms

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Abstract

SARS-CoV-2 (CoV-2) is a coronavirus which is causing the actual COVID-19 pandemic. The disease caused by 2019 new coronavirus (2019-nCoV) was named coronavirus disease-19 (COVID-19) by the World Health Organization in February 2020. Primary non-specific reported symptoms of 2019-nCoV infection at the prodromal phase are malaise, fever, and dry cough. The most commonly reported signs and symptoms are fever (98%), cough (76%), dyspnea (55%), and myalgia or fatigue (44%). Nonetheless, recent reports suggest an association between COVID-19 and altered olfactory and taste functions, although smell seems to be more affected than taste. These associations of smell and taste dysfunctions and CoV-2 are consistent with case reports describing a patient with SARS with long term anosmia after recovery from respiratory distress, with the observation that olfactory function is commonly altered after infection with endemic coronaviruses, and with data demonstrating that intentional experimental infection of humans with CoV-2 99 raises the thresholds at which odors can be detected. Post-viral anosmia and is one of the leading causes of loss of sense of smell in adults, accounting for up to 40% cases of anosmia. Viruses that give rise to the common cold are well known to cause post-infectious loss, and over 200 different viruses are known to cause upper respiratory tract infections. I reviewed the possible mechanisms of smell and taste loss in COVID-19. I concluded that since the existence of such a relationship is likely, it is highly recommended that those patients who experience complications such as smell and/or taste loss, even as unique symptoms, should be considered as potential SARS-CoV-2 virus carriers.

Keywords: SARS-CoV-2 (CoV-2); COVID-19; Coronavirus; Pandemic; Smell; Anosmia; Taste; Ageusia

Introduction

SARS-CoV-2 (CoV-2) is a coronavirus which is causing the COVID-19 pandemic [1-5]. The disease caused by 2019 new coronavirus (2019-nCoV) was named coronavirus disease-19 (COVID-19) by the World Health Organization in February 2020 [6-10].

The 2019-nCoV is phylogenetically related to severe acute respiratory syndrome-coronavirus (SARS-CoV) [1,11,12]. It has been shown that 2019-nCov enters the cell through the ACE2 cell receptor in the same way as the Severe Acute Respiratory Syndrome (SARS) coronavirus. 2019-nCoV effectively uses Angiotensin Converting Enzyme 2 receptor (ACE2) as a receptor for cell invasion [13-19].

The current knowledge on SARS-CoV-2 is relative scarce, and most of it comes from deductions than actual data analysis [3,20-23]. Coronaviruses are known as enveloped viruses with a positive-sense single-stranded RNA genome, and their helical symmetry nucleocapsid is about 26-32 kilobases in size, making it the largest investigated genome among RNA viruses [23-25]. SARS-CoV-2 is a beta coronavirus belonging to the 2B group [26-30]. It shares around 70-80% of its genome with SARS-CoV virus, but it shows to have the uppermost level of likeness with a horseshoe bat coronavirus [2,31-33]. Therefore, it is considered to be a recombinant virus transmitted from bats to human hosts by the mean of an intermediate host [34,35]. Being an RNA-virus with an RNA-dependent RNA Polymerase (RNRP)-based replication, mutation and recombination are frequent events. Moreover, in spite of the name and genetic similarities, SARS-CoV-2 shows genetic and clinical differences with SARS-CoV [36-40].

Initial reports stated that primary non-specific reported symptoms of 2019-nCoV infection at the prodromal phase are malaise, fever, and dry cough. The most frequently described signs and

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Received Date: *26 Jul 2020*
Accepted Date: *16 Aug 2020*
Published Date: *25 Aug 2020*

Citation: *Machado C, DeFina PA. Covid-19: Anosmia and Ageusia Might be Initial or Unique Symptoms. SF J Clin Neurol Brain. 2020; 1(1): 1002.*

symptoms are fever (98%), cough (76%), dyspnea (55%), and myalgia or fatigue (44%) [5,41-46].

Nonetheless, recent reports suggest an association between COVID-19 and altered olfactory and taste functions, although smell seems to be more affected than taste [47]. These associations of smell and taste dysfunctions and CoV-2 are reliable with case reports relating a patient with SARS with long term anosmia after recovery from respiratory distress, with the observation that olfactory function is usually altered after infection with endemic coronaviruses, and with data indicating that deliberate experimental infection of humans with CoV-2 raises the thresholds at which smells can be sensed [48-52]. Highly published news on this issue came when National Basketball Association player Rudy Gobert trapped the coronavirus, and complained loss of smell and taste [51].

Post-viral anosmia and is one of the leading causes of loss of sense of smell in adults, accounting for up to 40% cases of anostmia. Viruses responsible of the common cold are well known to cause post-infectious loss of smell, and over 200 different viruses are known to cause upper respiratory tract infections. Previously descriptions of coronaviruses are supposed to account for 10-15% cases [26]. Hence, it is therefore conceivably to suppose that the novel SARS-CoV-2 virus would also cause anosmia in infected patients [52].

Anosmia

Anosmia is the loss of the capability to detect one or more smells. Anosmia may be temporary or permanent. Full anosmia is reasonably rare related to hyposmia (a partial loss of smell), and dysosmia (a distortion or alteration of smell). Anosmia has different etiologies, such as inflammation of the nasal mucosa, blockage of nasal passages or a destruction of one temporal lobe. Inflammation is due to chronic mucosa changes in the lining of the paranasal sinus and in the middle and superior turbinates [47,52-61].

Ageusia

Ageusia is the loss of taste functions of the tongue, principally the incapability to sense sweetness, sourness, bitterness, saltiness, and umami, which means pleasant/savory taste. Ageusia is frequently confused with anosmia because the tongue can only indicate texture and distinguish between sweet, sour, bitter, salty, and umami, most of what is perceived as the sense of taste is certainly derivative from smell. Full ageusia is comparatively rare related to hypogeusia (a partial loss of taste), and dysgeusia (a distortion or alteration of taste). The foremost causes of taste disorders are head trauma, infections of upper respiratory tract, exposure to toxic substances, iatrogenic causes, medicines, and glossodynia (burning mouth syndrome). Head trauma can cause lesions in regions of the Central Nervous System (CNS) involved in processing taste stimuli, including thalamus, brain stem, and temporal lobes; it can also cause injury to neurological pathways involved in transmission of taste stimuli [52,56,59-63].

Nervous pathways of smell

The pathway of olfactory conduction begins with the olfactory receptors, which are small, slender nerve cells embedded in large numbers (about 100 million in the rabbit) in the epithelium of the mucous membrane lining the upper part of the nasal cavity. Each olfactory receptor cell emits two processes (projections). One of these is a short peripheral dendrite, which spreads to the surface of the epithelium, where it ends in a knob carrying a number of fine radially placed filaments, the olfactory hairs. The other process is a long and extremely thin axon, the olfactory nerve fiber, which reaches the cranial cavity by passing through one of the intros in the bony roof of the nasal cavity and arrives the olfactory bulb of the forebrain. Sensations of smell are experienced when certain chemical substances become dissolved in the thin layer of fluid covering the surface of the mucous membrane and then come in contact with the olfactory hairs. The receptor cells differ among themselves in their sensitivities to various odorous substances [64-74].

The olfactory epithelium, found within the nasal cavity, contains olfactory receptor cells, which have specialized cilia extensions. The cilia trap odor molecules as they pass across the epithelial surface. Information about the molecules is then transmitted from the receptors to the olfactory bulb in the brain. In the olfactory bulb, the olfactory nerve fibers end in contact with the antenna-shaped dendrites of the large mitral cells, which represent the second main link in the chain of olfactory conduction. Each mitral cell emits a long axon, many of which enter into the formation of the olfactory tract, a white fiber band extending back from the bulb over the basal surface of the forebrain. The olfactory tract distributes its fibers mainly to the cortex of the pyriform lobe, which constitutes the final cortical receiving area of the olfactory pathway. In humans this region corresponds to the uncus of the hippocampal gyrus. A smaller number of fibers of the olfactory tract end in two further olfactory structures; the olfactory tubercle and the medial part of the amygdaloid complex (the latter lies deep to the olfactory cortex). In the nasal passage lies the olfactory epithelium (mucous membrane) lined by olfactory receptors. These olfactory receptors contain Golf protein, which are stimulated by odor molecules. Upon stimulation, the Golf protein stimulates the release of a cyclic AMP catalyzing enzyme. When catalyzed, this cyclic AMP serves as a transmitter that signals the opening of sodium ion channels, leading to depolarization of the receptor cells [53,71,75-79].

Olfactory sensory input travels from the axons through the cribiform plate holes and mitral cell synapses. These mitral cells, found in the olfactory bulbs, comprise the olfactory tract. The information travels through the olfactory tract towards the primary olfactory cortex in the limbic system. This cortex transfers the information to three areas: the hypothalamus, the thalamus and the orbitofrontal cortex. The reception of olfactory input in the orbitofrontal cortex explains why we may perceive smell and taste at the same time [71,75,80-82].

Taste

The tongue contains small bumps called papillae, within or near which taste buds are situated. In the tongue's taste buds, the taste receptors receive sensory input via two important mechanisms: depolarization and neurotransmitter release. Intake of salty foods leads more sodium ions to enter the receptor, causing the said mechanisms. The same is true with intake of sour foods (hydrogen ions) and sweet foods (sugar molecules), both of which result to the closing of K^+ channels upon their entry. From the axons of the taste receptors, the sensory information is transferred to the three taste pathways via the branches of cranial nerves VII, IX and X. The chorda tympani of CN VII (facial nerve) carries the taste sensory input from the tongue's anterior two-thirds. Then, the rest of the taste sensations from the throat, palate and posterior tongue are transmitted by the branches of CN IX (glossopharyngeal nerve) and CN X (vagus nerve). From these cranial nerves, taste sensory input travels through the nerve fiber synapses to the solitary tract, the ventral posteromedial thalamic nuclei, and the thalamus. In these three locations, there

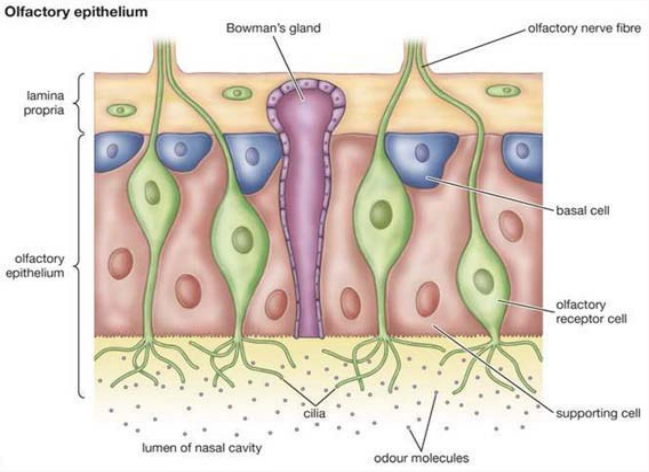

Figure 1: Smell mechanisms: Olfactory epithelium.

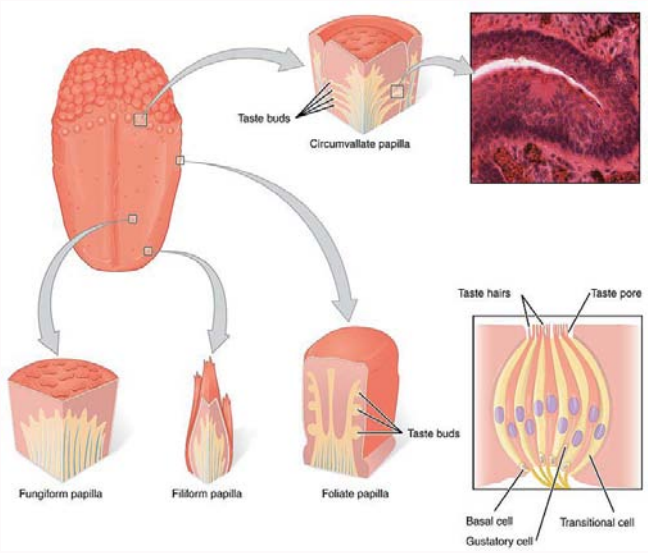

Figure 2: Taste mechanisms: Taste buds and papillae of the tongue.

are clustered neurons which respond to the same taste (sweet, sour, salty or bitter).The thalamus relays the information to the primary gustatory cortex located in the somatosensory cortex. The primary gustatory cortex is where the perception of a particular taste is processed [64,66,71,76,83-92].

Diagnosis of smell and taste loss

Anosmia can be diagnosed by doctors by using acetylcysteine tests. Doctors will begin with a detailed clinical history about particularities of smell and taste loss. Then the doctor will ask for any related injuries in relation to anosmia which could include upper respiratory infections or head injury.

Ageusia is assessed by measuring the lowest concentration of a taste quality that the subject can detect or recognize. The subject is also asked to compare the tastes of different substances or to note how the intensity of a taste grows when a substance's concentration is increased. Scientists have developed taste testing in which the patient responds to different chemical concentrations. This may involve a simple "sip, spit, and rinse" test, or chemicals may be applied directly to specific areas of the tongue [26,55,68,78,93-104].

Mechanisms leading to smell and taste sense loss by SARS-Cov-2

Smell loss can be caused by many things, including swelling in the nose and sinuses (such as chronic sinusitis), head injury, and nerve disorders (such as Parkinson's disease). In some cases, no cause is found. The olfactory system is part of the upper respiratory tract in mammals and therefore, pathogens can reach other parts of the respiratory system once they effectively invade the olfactory mucosa. Known respiratory pathogens which infect the human olfactory organ include influenza virus, respiratory syncytial virus, rhinovirus, *Staphylococcus aureus, S. pneumoniae*. The upper respiratory system is also connected to the gastrointestinal tract *via* the esophagus and therefore it is possible for pathogens that cause gastric infection can produce nasal diseases. Although this route is less well studied, some examples may include human bocavirus, human rotavirus, Epstein-Barr virus and Salmonella enteric [26,50,105,106].

Loss of smell because of a viral infection, such as the common cold, is the second most common cause of smell loss and accounts for about 12% of all cases of anosmia. These episodes typically happen when the virus infects the nose, giving rise to the usual cold symptoms, including a blocked or runny nose. Sense of smell usually recovers once symptoms diminish. But sometimes even when other symptoms disappear, sense of smell doesn't subside, or in some cases it's reduced (hyposmia), or is distorted (parosmia).

In these cases, the virus has damaged the smell receptors causing them to lose the fine, hair-like endings that allow them to pick up smell molecules from the nasal mucus. Preceding studies have looked at which viruses cause this condition, and many have been implicated, with the coronavirus family of which COVID-19 is a member [26,49, 50,52,105,106].

The anatomical organization of the human olfactory system makes it an attractive site for pathogens to get into the host. The olfactory system is directly connected to the CNS via the olfactory bulb and consequently frequent neurotropic agents including parasites, bacteria and viruses can reach the CNS via transport lengthways to the olfactory nerve [54,71,75,76,107-110].

Several reports have evaluated coronavirus's effects on the CNS. These studies suggest that the human CNS may be vulnerable to coronavirus infection. The routes for CNS infection with coronaviruses are peripheral trigeminal or olfactory nerves following intranasal inoculation. Studies on rodents demonstrate that these viruses cause demyelination and stimulate T cell-mediated autoimmune reactions against CNS antigens. This fact has raised the question about the relationship between coronaviruses, particularly the 2019-nCoV, and neurologic disorder in humans. Considering that the peripheral trigeminal or olfactory nerves are pathways of penetration of the coronaviruses into the CNS, and based on animal studies, it may be theorized that complications, such as demyelination and stimulation of T cell-mediated autoimmune reactions, may happen in the path of the infection dispersion, so the incidence of dyssomnia and dysgeusia can be painstaking potential consequences of these nerve injuries [26,49-52,105,106].

A virus typically arrives the body by imbedding itself and infecting host cells thru the body, such as in the airways or the gut, and then replicating. During the acute phase of a viral cold a patient may experience nasal congestion and blockage caused by nasal obstruction, membrane edema and excess nasal secretions. This congestion may

cause momentary loss of smell and taste but with recovery from the cold, over time, these nasal symptoms vanish, ease of nasal breathing is recommenced and smell and taste function usually recur as they did prior to the onset of the viral cold [26,50,103,105,106,111-113].

SARS-CoV-2 is believed to enter the nasal and mouth tissues through the Angiotensin Converting Enzyme 2 (ACE2) receptor, although more research is needed to approve whether this is the case. This protein is copious in the nose, although its function is not clear. By entering the nose and mouth through this protein, it may cause temporary damage to the smell and taste nerves. However, this damage appears to get better within one to two weeks after the onset of the disease [13-15,17,19]. Stem cells have probably a role on smell and taste recovering [49].

It has been hypothesized that a viral replication process is present in the protein secreting glands in the nose and the mouth which is sustained by a dynamic process involving nonstop rounds of *de novo* virus infection and replication. Hence, the initial systemic viral infection the viral RNA arrives into specific protein secreting glands in the nose and mouth, replicating their genomes. These are usually single stranded RNAs which may produce viral factories that can direct the products of proteins and construction of new viral particles which can infect these glands. Whereas the systemic viral infection is eliminated this local process can endure to generate viral RNA, which is toxic to the protein secretions generated by these protein secreting glands. This toxicity can constrain secretion of some of the endogenously secreted proteins, so-called growth factors, produced by these glands. These endogenous proteins consist of multiple chemical moieties including cAMP, cGMP and sonic hedgehog. Stem cells, which maintain the receptors of both olfactory epithelial cells for smell and taste bud receptor cells for taste, necessitate continual stimulation by these secreted proteins for these receptors to function. As these receptors turnover as rapidly as every 24 hours, inhibition of these secretions inhibits receptor growth causing loss of smell and taste [24,49,52,55,114-118].

Reports in both mouse and human datasets demonstrate that olfactory sensory neurons do not express two key genes involved in CoV-2 entry, ACE2 and TMPRSS2. In contrast, olfactory epithelial support cells and stem cells express both of these genes, as do cells in the nasal respiratory epithelium. These findings suggest possible mechanisms through which CoV-2 infection could lead to anosmia or other forms of olfactory dysfunction [14,15,17,19,49,52].

Conclusion

Although definitive reports of pervasive CoV-2-associated anosmia have not yet been finally proved, these findings raise the question of how CoV-2 might affect processing mechanisms to change smell and taste perception in COVID-19 patients [26,48-52].

Since the existence of such a relationship is likely, it also seems likely that during the COVID-2019 outbreak, those who experience complications such as smell and/or taste loss, even as unique symptoms, should be considered as potential SARS-CoV-2 virus carriers.

References

1. Ahn DG, Shin HJ, Kim MH, Lee S, Kim HS, Myoung J, et al. Current Status of Epidemiology, Diagnosis, Therapeutics, and Vaccines for Novel Coronavirus Disease 2019 (COVID-19). J Microbiol Biotechnol. 2020; 30: 313-324.
2. Caly L, Druce J, Roberts J, Bond K, Tran T, Kostecki R, et al. Isolation and rapid sharing of the 2019 novel coronavirus (SAR-CoV-2) from the first patient diagnosed with COVID-19 in Australia. Med J Aust. 2020; 212: 45-462.
3. Chatterjee P, Nagi N, Agarwal A, Das B, Bnerjee S, Sarkar S, et al. The 2019 novel coronavirus disease (COVID-19) pandemic: A review of the current evidence. Indian J Med Res. 2020; 151: 147-149.
4. de Lusignan S, Lopez Bernal J, Zambon M, Akinyemi O, Amrithalingam G, Andrews N, et al. Emergence of a Novel Coronavirus (COVID-19): Protocol for Extending Surveillance Used by the Royal College of General Practitioners Research and Surveillance Centre and Public Health England. JMIR Public Health Surveill 2020; 6: e18606.
5. Kim ES, Chin BS, Kang CK, Kim NJ, Kang YM, Choi JP, et al. Clinical Course and Outcomes of Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection: a Preliminary Report of the First 28 Patients from the Korean Cohort Study on COVID-19. J Korean Med Sci. 2020; 35: e142.
6. Ludwig S, Zarbock A. Coronaviruses and SARS-CoV-2: A Brief Overview. Anesth Analg. 2020; 131: 93-96.
7. Park SE. Epidemiology, virology, and clinical features of severe acute respiratory syndrome -coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19). Clin Exp Pediatr. 2020.
8. Shah SGS, Farrow A. A commentary on "World Health Organization declares global emergency: A review of the 2019 novel Coronavirus (COVID-19)". Int J Surg. 2020; 76: 128-129.
9. Purcell LN, Charles AG. An Invited Commentary on "World Health Organization declares global emergency: A review of the 2019 novel Coronavirus (COVID-19)": Emergency or new reality? Int J Surg. 2020; 76: 111.
10. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwn A, Al-Jabir A, et al. World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). Int J Surg. 2020; 76: 71-76.
11. Saghazadeh A, Rezaei N. Immune-epidemiological parameters of the novel coronavirus - a perspective. Expert Rev Clin Immunol. 2020; 16: 465-470.
12. Carletti F, Lalle E, Messina F, Ippolito G, Capobianchi MR. About the origin of the first two Sars-CoV-2 infections in Italy: inference not supported by appropriate sequence analysis. J Med Virol. 2020.
13. Brake SJ, Barnsley K, Lu W, McAlinden KD, Eapen MS, Sohal SS. Smoking Upregulates Angiotensin-Converting Enzyme-2 Receptor: A Potential Adhesion Site for Novel Coronavirus SARS-CoV-2 (Covid-19). J Clin Med. 2020; 9: 841.
14. Lukassen S, Lorenz Chua R, Trefzer T, Kahn NC, Schneider MA, Muley T, et al. SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells. EMBO J. 2020; 39: e105114.
15. Guzzi PH, Mercatelli D, Ceraolo C, Giorgi FM. Master Regulator Analysis of the SARS-CoV-2/Human Interactome. J Clin Med. 2020; 9: 82.
16. Luan J, Jin X, Lu Y, Zhang L. SARS-CoV-2 spike protein favors ACE2 from Bovidae and Cricetidae. J Med Virol. 2020.
17. Hussain M, Jabeen N, Raza F, Shabbir S, Baig AA, Amanullah A, et al. Structural Variations in Human ACE2 may Influence its Binding with SARS-CoV-2 Spike Protein. J Med Virol. 2020.
18. Bavishi C, Maddox TM, Messerli FH. Coronavirus Disease 2019 (COVID-19) Infection and Renin Angiotensin System Blockers. JAMA Cardiol. 2020.
19. Sommerstein R, Kochen MM, Messerli FH, Grani C. Coronavirus Disease 2019 (COVID-19): Do Angiotensin-Converting Enzyme Inhibitors/ Angiotensin Receptor Blockers Have a Biphasic Effect? J Am Heart Assoc. 2020; 9: e016509.

20. Calton B, Abedini N, Fratkin M. Telemedicine in the Time of Coronavirus. J Pain Symptom Manage 2020; 60: e12-e14.

21. Cagliani R, Forni D, Clerici M, Sironi M. Computational inference of selection underlying the evolution of the novel coronavirus, SARS-CoV-2. J Virol. 2020; 94: e00411-e00420.

22. Cao Y, Liu X, Xiong L, Cai K. Imaging and Clinical Features of Patients With 2019 Novel Coronavirus SARS-CoV-2: A systematic review and meta-analysis. J Med Virol. 2020.

23. Chang L, Zhao L, Gong H, Wang L, Wang L. Severe Acute Respiratory Syndrome Coronavirus 2 RNA Detected in Blood Donations. Emerg Infect Dis. 2020; 26: 1631-1633.

24. Chen Y, Chen L, Deng Q, Zhang G, Wu K, Ni L, et al. The Presence of SARS-CoV-2 RNA in Feces of COVID-19 Patients. J Med Virol. 2020; 92: 833-840.

25. Parra B, Hinton DR, Lin MT, Cua DJ, Stohlman SA. Kinetics of cytokine mRNA expression in the central nervous system following lethal and nonlethal coronavirus-induced acute encephalomyelitis. Virology. 1997; 233: 260-270.

26. Ceccarelli M, Berretta M, Venanzi Rullo E, Nunnari G, Cacopardo B. Differences and similarities between Severe Acute Respiratory Syndrome (SARS)-CoronaVirus (CoV) and SARS-CoV-2. Would a rose by another name smell as sweet? Eur Rev Med Pharmacol Sci. 2020; 24: 2781-2783.

27. Trilla A. One world, one health: The novel coronavirus COVID-19 epidemic. Med Clin. 2020; 154: 175-177.

28. Wu P, Duan F, Luo C, Liu Q, Qu X, Liang L, et al. Characteristics of Ocular Findings of Patients With Coronavirus Disease 2019 (COVID-19) in Hubei Province, China. JAMA Ophthalmol. 2020; 138: 575-578.

29. Zhou M, Zhang X, Qu J. Coronavirus disease 2019 (COVID-19): a clinical update. Front Med 2020; 14: 126-135.

30. Kim S, Kim YJ, Peck KR, Jung E. School Opening Delay Effect on Transmission Dynamics of Coronavirus Disease 2019 in Korea: Based on Mathematical Modeling and Simulation Study. J Korean Med Sci. 2020; 35: e143.

31. Xie M, Chen Q. Insight into 2019 novel coronavirus - an updated intrim review and lessons from SARS-CoV and MERS-CoV. Int J Infect Dis. 2020; 4: 119-124.

32. Licastro D, Rajasekharan S, Dal Monego S, Segat L, D'Agaro P, Marcello A. Isolation and full-length genome characterization of SARS-CoV-2 from COVID-19 cases in Northern Italy. J Virol. 2020; 94: e00543.

33. Caly L, Druce J, Roberts J, Bond K, Tran T, Kostecki R, et al. Isolation and rapid sharing of the 2019 novel coronavirus (SARS-CoV-2) from the first patient diagnosed with COVID-19 in Australia. Med J Aust. 2020; 212: 459-462.

34. Yan Y, Shin WI, Pang YX, Meng Y, Lai J, You C, et al. The First 75 Days of Novel Coronavirus (SARS-CoV-2) Outbreak: Recent Advances, Prevention, and Treatment. Int J Environ Res Public Health. 2020; 17: 2323.

35. Zhao H, Xu D, Zhang S, Zhang J. Genomic and genetic evidence for the loss of umami taste in bats. Genome Biol Evol. 2012; 4: 73-79.

36. Tsai JC, de Groot L, Pinon JD, Lacono KT, Phillips J, Seo S, et al. Amino acid substitutions within the heptad repeat domain 1 of murine coronavirus spike protein restrict viral antigen spread in the central nervous system. Virology. 2003; 312: 369-380.

37. Jensen JD, Lynch M. Considering mutational meltdown as a potential SARS-CoV-2 treatment strategy. Heredity (Edinb). 2020.

38. Wei X, Ghosh SK, Taylor ME, Johnson VA, Emini EA, Deutsch P, et al. Viral dynamics in human immunodeficiency virus type 1 infection. Nature. 1995; 373: 117-122.

39. Das Sarma J, Scheen E, Seo SH, Koval M, Weiss SR. Enhanced green fluorescent protein expression may be used to monitor murine coronavirus spread in vitro and in the mouse central nervous system. J Neurovirol. 2002; 8: 381-391.

40. Chen BP, Kuziel WA, Lane TE. Lack of CCR2 results in increased mortality and impaired leukocyte activation and trafficking following infection of the central nervous system with a neurotropic coronavirus. J Immunol. 2001; 167: 4585-4592.

41. Kimball A, Hatfield KM, Arons M, James A, Taylor J, Spicer K, et al. Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020. MMWR Morb Mortal Wkly Rep. 2020; 69: 377-381.

42. Lovato A, Rossettini G, de Filippis C. Sore throat in COVID-19: comment on "Clinical characteristics of hospitalized patients with SARS-CoV-2 infection: A single arm meta-analysis". J Med Virol. 2020.

43. Xie H, Zhao J, Lian N, Lin S, Xie Q, Zhuo H. Clinical characteristics of Non-ICU hospitalized patients with coronavirus disease 2019 and liver injuryA Retrospective study. Liver Int. 2020; 40: 1321-1326.

44. Sundaram M, Ravikumar N, Bansal A, Nallasamy K, Basawaraja GV, et al. Novel Coronavirus 2019 (2019-nCoV) Infection: Part II - Respiratory Support in the Pediatric Intensive Care Unit in Resource-limited Settings. Indian Pediatr. 2020; 57: 335-342.

45. Gennaro S. 2020: The Year of the Nurse as Seen Through a Coronavirus Lens. J Nurs Scholarsh. 2020; 52: 231-232.

46. Zhang T, Sun LX, Feng RE. Comparison of clinical and pathological features between severe acute respiratory syndrome and coronavirus disease 2019. Zhonghua Jie He He Hu Xi Za Zhi. 2020; 43: E040.

47. Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome? Rhinology. 2020; 58: 299-301.

48. Gautier JF, Ravussin Y. A New Symptom of COVID-19: Loss of Taste and Smell. Obesity (Silver Spring). 2020; 28: 848.

49. Brann DH, Tsukahara T, Weinreb C, Logan DW, Datta SR. Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients. BioRxiv. 2020.

50. Bienkov A. If you've lost your sense of smell or taste, you could be a 'hidden carrier' of the coronavirus. 2020.

51. Gale J. NBA Player's Loss of Smell Highlights Unusual Marker of Covid-19. 2020.

52. Keyhan SO, Fallahi HR, Cheshmi B. Dysosmia and dysgeusia due the novel 2019 novel Coronavirus: a hypothesis that needs further investigation. Maxyllofacial Plastic and Resonsctructive Surgery. 2020.

53. Ogle W. Anosmia, or Cases illustrating the Physiology and Pathology of the Sense of Smell. Med Chir Trans. 1870; 53: 263-290.

54. Callahan CD, Hinkebein JH. Assessment of anosmia after traumatic brain injury: performance characteristics of the University of Pennsylvania Smell Identification Test. J Head Trauma Rehabil. 2002; 17: 251-256.

55. Henkin RI, Velicu I. Decreased parotid salivary cyclic nucleotides related to smell loss severity in patients with taste and smell dysfunction. Metabolism. 2009; 58: 1717-1723.

56. Welge-Lussen A. Impaired sense of smell and taste. Therapy options in anosmia and dysgeusia. Laryngorhinootologie. 2005; 84: S92-S100.

57. Nordin S, Blomqvist EH, Olsson P, Stjarne P, Ehnhage A, Group NSS. Effects of smell loss on daily life and adopted coping strategies in patients with nasal polyposis with asthma. Acta Otolaryngol. 2011; 131: 826-832.

58. Toledano A, Rodriguez G, Martin AM, Onrubia T, Galindo N. Quality of life in patients with smell loss due to upper respiratory tract infections. Am J Otolaryngol. 2011; 32: 504-510.

59. Fujikura K. Multiple loss-of-function variants of taste receptors in modern humans. Sci Rep. 2015; 5: 12349.

60. Jin S, Lu Q, Jin S, Zhang L, Cui H, Li H. Relationship between subjective taste alteration and weight loss in head and neck cancer patients treated with radiotherapy: A longitudinal study. Eur J Oncol Nurs. 2018; 37: 43-50.

61. Chabwine JN, Tschirren MV, Zekeridou A, Landis BN, Kuntzer T. Sweet taste loss in myasthenia gravis: more than a coincidence? Orphanet J Rare Dis. 2014; 9: 50.

62. Czupryniak L, Loba J. Loss of taste-induced hypertension--caveat for taste modulation as a therapeutic option in obesity. Eat Weight Disord. 2007; 12: e11-13.

63. Kumari A, Ermilov AN, Grachtchouk M, Dlugosz AA, Allen BL, Bradley RM, et al. Recovery of taste organs and sensory function after severe loss from Hedgehog/Smoothened inhibition with cancer drug sonidegib. Proc Natl Acad Sci USA. 2017; 114: E10369-E10378.

64. Gu QD, Joe DS, Gilbert CA. Activation of bitter taste receptors in pulmonary nociceptors sensitizes TRPV1 channels through the PLC and PKC signaling pathway. Am J Physiol Lung Cell Mol Physiol. 2017; 312: L326-L333.

65. Moine F, Brechbuhl J, Nenniger Tosato M, Beaumann M, Broillet MC. Alarm pheromone and kairomone detection via bitter taste receptors in the mouse Grueneberg ganglion. BMC Biol. 2018; 16: 12.

66. Lazutkaite G, Solda A, Lossow K, Meyerhof W, Dale N. Amino acid sensing in hypothalamic tanycytes via umami taste receptors. Mol Metab. 2017; 6: 1480-1492.

67. Jaggupilli A, Singh N, Upadhyaya J, Sikarwar AS, Arakawa M, Dakshinamurti S, et al. Analysis of the expression of human bitter taste receptors in extraoral tissues. Mol Cell Biochem. 2017; 426: 137-147.

68. Miras AD, le Roux CW. Bariatric surgery and taste: novel mechanisms of weight loss. Curr Opin Gastroenterol. 2010; 26: 140-145.

69. Gopallawa I, Freund JR, Lee RJ. Bitter taste receptors stimulate phagocytosis in human macrophages through calcium, nitric oxide, and cyclic-GMP signaling. Cell Mol Life Sci. 2020.

70. Welcome MO. The bitterness of genitourinary infections: Properties, ligands of genitourinary bitter taste receptors and mechanisms linking taste sensing to inflammatory processes in the genitourinary tract. Eur J Obstet Gynecol Reprod Biol. 2020; 247: 101-110.

71. Hummel C, Frasnelli J, Gerber J, Hummel T. Cerebral processing of gustatory stimuli in patients with taste loss. Behav Brain Res. 2007; 185: 59-64.

72. Behrens M, Briand L, de March CA, Matsunami H, Yamashita A, Meyerhof W, et al. Structure-Function Relationships of Olfactory and Taste Receptors. Chem Senses. 2018; 43: 81-87.

73. Lee AA, Owyang C. Sugars, Sweet Taste Receptors, and Brain Responses. Nutrients. 2017; 9: 653.

74. Park JH, Song DK. Sweet taste receptors as a tool for an amplifying pathway of glucose-stimulated insulin secretion in pancreatic beta cells. Pflugers Arch. 2019; 471: 655-657.

75. Burbach JP. The 2004 Nobel Prize for Physiology or Medicine for research into smell receptors and the organization of the olfactory system. Ned Tijdschr Geneeskd. 2004; 148: 2576-2579.

76. Levy LM, Degnan AJ, Sethi I, Henkin RI. Anatomic olfactory structural abnormalities in congenital smell loss: magnetic resonance imaging evaluation of olfactory bulb, groove, sulcal, and hippocampal morphology. J Comput Assist Tomogr. 2013; 37: 650-657.

77. Lafreniere D, Mann N. Anosmia: loss of smell in the elderly. Otolaryngol Clin North Am. 2009; 42: 123-131.

78. Henkin RI, Velicu I. cAMP and cGMP in nasal mucus related to severity of smell loss in patients with smell dysfunction. Clin Invest Med. 2008; 31: E78-E84.

79. Haehner A, Hummel T, Reichmann H. A clinical approach towards smell loss in Parkinson's disease. J Parkinsons Dis. 2014; 4: 189-195.

80. Levy LM, Henkin RI, Hutter A, Lin CS, Schellinger D. Mapping brain activation to odorants in patients with smell loss by functional MRI. J Comput Assist Tomogr. 1998; 22: 96-103.

81. Liu JF, You H, Ni DF, Zhu YY, Jin ZY. Olfactory event-related functional magnetic resonance imaging in young adults with normal sense of smell and anosmia patients. Zhonghua Yi Xue Za Zhi. 2008; 88: 1543-1546.

82. Invitto S, Montinaro R, Ciccarese V, Venturella I, Fronda G, Balconi M. Smell and 3D Haptic Representation: A Common Pathway to Understand Brain Dynamics in a Cross-Modal Task. A Pilot OERP and fNIRS Study. Front Behav Neurosci. 2019; 13: 226.

83. Belelovsky K, Kaphzan H, Elkobi A, Rosenblum K. Biphasic activation of the mTOR pathway in the gustatory cortex is correlated with and necessary for taste learning. J Neurosci. 2009; 29: 7424-7431.

84. Duarte AC, Santos J, Costa AR, Ferreira C, Tomas J, Quintela T, et al. Bitter taste receptors profiling in the human blood-cerebrospinal fluid-barrier. Biochem Pharmacol. 2020; 177: 113954.

85. Lee BC, Hwang SH, Rison R, Chang GY. Central pathway of taste: clinical and MRI study. Eur Neurol. 1998; 39: 200-203.

86. Gutierrez R, Simon SA. Chemosensory processing in the taste - reward pathway. Flavour Fragr J. 2011; 26: 231-238.

87. Dehkordi O, Rose JE, Balan KV, Millis RM, Bhatti B, Jayam-Trouth A. Co-expression of nAChRs and molecules of the bitter taste transduction pathway by epithelial cells of intrapulmonary airways. Life Sci. 2010; 86: 281-288.

88. Cheron JB, Soohoo A, Wang Y, Golebiowski J, Antonczak S, Jiang P, et al. Conserved Residues Control the T1R3-Specific Allosteric Signaling Pathway of the Mammalian Sweet-Taste Receptor. Chem Senses. 2019; 44: 303-310.

89. Park JH, Song DK. Correction to: Sweet taste receptors as a tool for an amplifying pathway of glucose-stimulated insulin secretion in pancreatic beta cells. Pflugers Arch. 2019; 471: 1041.

90. Jacobson A, Green E, Haase L, Szajer J, Murphy C. Age-Related Changes in Gustatory, Homeostatic, Reward, and Memory Processing of Sweet Taste in the Metabolic Syndrome: An fMRI Study. Perception. 2017; 46: 283-306.

91. Oberndorfer TA, Frank GK, Simmons AN, Wagner A, McCurdy D, Fudge JL, et al. Altered insula response to sweet taste processing after recovery from anorexia and bulimia nervosa. Am J Psychiatry. 2013; 170: 1143-1151.

92. Maia GH, Soares JI, Andrade PA, Leite J, Luz LL, Andrade JP, et al. Altered taste preference and loss of limbic-projecting serotonergic neurons in the dorsal raphe nucleus of chronically epileptic rats. Behav Brain Res. 2016; 297: 28-36.

93. Jette M, Anderson C, Ramakrishnan V. Case Report: Diagnosis of hypogeusia after oral exposure to commercial cleaning agent and considerations for clinical taste testing. F1000Res. 2017; 6: 373.

94. Mott AE, Grushka M, Sessle BJ. Diagnosis and management of taste disorders and burning mouth syndrome. Dent Clin North Am. 1993; 37: 33-71.

95. Schiffman SS. Diagnosis and treatment of smell and taste disorders. West J Med. 1987; 146: 471-473.

96. Tremblay KA, Bona JM, Kranzler HR. Effects of a diagnosis or family history of alcoholism on the taste intensity and hedonic value of sucrose. Am J Addict. 2009; 18: 494-499.

97. Hunt JD, Reiter ER, Costanzo RM. Etiology of subjective taste loss. Int Forum Allergy Rhinol. 2019; 9: 409-412.

98. Mundt B, Krakowsky G, Roder H, Werner E. Loss of smell and taste within the scope of vitamin B 12 deficiency. Psychiatr Neurol Med Psychol (Leipz). 1987; 39: 356-361.

99. Coucke PA. Are you able to smell a diagnosis ?. Rev Med Liege. 2019; 74: 611-615.

100. Deeb J, Shah M, Muhammed N, Gannon K, Findley LJ, Hawkes CH. A basic smell test is as sensitive as a dopamine transporter scan: comparison of olfaction, taste and DaTSCAN in the diagnosis of Parkinson's disease. QJM. 2010; 103: 941-952.

101. Lukas T, Berner ES, Kanakis C. Diagnosis by smell? J Med Educ. 1977; 52: 349-350.

102. Engel C. Diagnosis by the sense of smell. Med J Aust. 1953; 2: 254-258.

103. Poulton J, Tarlow MJ. Diagnosis of rotavirus gastroenteritis by smell. Arch Dis Child. 1987; 62: 851-852.

104. Jamshidi A, Murnick J, Reilly BK. Diminished Smell in a Teenaged Girl. Isolated anosmia. JAMA Otolaryngol Head Neck Surg. 2016; 142: 97-98.

105. Rabin R. Lost of sense of smell may be peculiar clue to coronavirus infection. 2020.

106. Stone J. There's An Unexpected Loss of Smell and Taste in Coronavirus Patients. 2020.

107. Han P, Mohebbi M, Unrath M, Hummel C, Hummel T. Different Neural Processing of Umami and Salty Taste Determined by Umami Identification Ability Independent of Repeated Umami Exposure. Neuroscience. 2018; 383: 74-83.

108. Kurtz P, Schuurman T, Prinz H. Loss of smell leads to dementia in mice: is Alzheimer's disease a degenerative disorder of the olfactory system? J Protein Chem. 1989; 8: 448-451.

109. Bennetto L, Kuschner ES, Hyman SL. Olfaction and taste processing in autism. Biol Psychiatry. 2007; 62: 1015-1021.

110. Schmidt FA, Goktas O, Harms L, Bohner G, Erb K, Dahlslett B, et al. Structural correlates of taste and smell loss in encephalitis disseminata. PLoS One. 2011; 6: e19702.

111. Myers LJ, Nusbaum KE, Swango LJ, Hanrahan LN, Sartin E. Dysfunction of sense of smell caused by canine parainfluenza virus infection in dogs. Am J Vet Res. 1988; 49: 188-190.

112. Mayet AY. Loss of smell (anosmia) and taste (ageusia) in a patient treated with pegylated interferon alfa and ribavirin. Curr Ther Res Clin Exp. 2007; 68: 271-277.

113. Gordon CB. Practical approach to the loss of smell. Am Fam Physician. 1982; 26: 191-193.

114. Guan WJ, Ni ZY, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020; 382: 1708-1720.

115. Guan W, Liu J, Yu C. CT Findings of Coronavirus Disease (COVID-19) Severe Pneumonia. AJR Am J Roentgenol. 2020; 214: W85-W86.

116. Wang Q, Li C, Zhang Q, Wang T, Li J, Guan W, et al. Interactions of SARS coronavirus nucleocapsid protein with the host cell proteasome subunit p42. Virol J. 2010; 7: 99.

117. Sun T, Guan J. Novel coronavirus and central nervous system. Eur J Neurol. 2020.

118. Abreu MS, Giacomini AC, Kalueff AV, Barcellos LJ. The smell of "anxiety": Behavioral modulation by experimental anosmia in zebrafish. Physiol Behav. 2016; 157: 67-71.