J Neuromonit Neurophysiol 2025;5(2):152–159
ISSN 2799–5496 eISSN 3058–5449 https://doi.org/10.54441/jnn.2025.5.2.152

JNN
Review article

Neurophysiological mechanisms of anosmia: shared pathways in traumatic brain injury, chronic rhinosinusitis, COVID–19, and neurodegenerative disease

Reiza Ventura[1], Ji–Hun Mo[1,2]
[1]Beckman Laser Institute Korea, Cheonan, Republic of Korea
[2]Department of Otorhinolaryngology, Dankook University College of Medicine, Cheonan, Republic of Korea

Anosmia, the loss or alteration of the sense of smell, is a condition with multifactorial causes and consequences for patient safety, nutrition, and mental health. This review explores the neurophysiological mechanisms underlying anosmia, focusing on both peripheral and central components of olfactory dysfunction. In traumatic brain injury, anosmia occurs due to direct mechanical damage to the olfactory nerve fibers or olfactory bulb, with experimental models revealing sustained inflammation, microglial activation, and oxidative stress that disrupt olfactory signaling. Chronic rhinosinusitis–induced anosmia, attributed to mechanical obstruction, and inflammatory changes within the olfactory mucosa that impair neurogenesis and sensory function. COVID–19–related anosmia is prevalent and involves multiple mechanisms: local epithelial inflammation due to angiotensin–converting enzyme 2 receptor–mediated viral entry, damage to sustentacular cells, disruption of olfactory cilia, cytokine release, and olfactory bulb. These diverse etiologies share overlapping pathological features including neuroinflammation, impaired neuronal regeneration, and altered olfactory processing. Anosmia is not only a symptom but may also serve as an early biomarker of neurological decline, particularly in neurodegenerative disorders. Accurate diagnosis requires objective olfactory testing, and management may include pharmacological, rehabilitative, and supportive strategies. Understanding the shared neurophysiological underpinnings of anosmia can enhance early detection of systemic disease and guide targeted therapeutic interventions.

Key words Anosmia, Olfactory dysfunction, COVID–19, Chronic rhinosinusitis, Neurodegenerative diseases

Introduction

Anosmia, the loss or change in the sense of smell [1], is a significant health issue with various causes and considerable impact on patients' lives. It is a well–established consequence of head injury [2], affecting a substantial percentage of individuals who experience traumatic brain injury (TBI) [3]. Reports suggest that approximately 20%–68% of TBI patients exhibit trauma–associated olfactory deficits (OD) [3]. Even patients with mild TBI can experience persistent OD, with prevalence reported in up to 20% of cases [4].

Beyond TBI, other causes of acquired smell loss include upper respiratory infections (such as the common cold or flu) [5], and notably, it is a common symptom of COVID–19, experienced by almost 53% of those affected [1]. Upper airway inflammation, including rhinitis, rhinosinusitis, and nasal polyps, is also a frequent cause of gradual olfactory dysfunction. Neurodegenerative diseases, intracranial/sinonasal tumors, certain drugs, exposure to toxic substances, irradiation, or iatrogenic factors can also lead to anosmia [5].

Globally, a large number of people are affected;

Received: May 21, 2025. **Revised:** June 9, 2025. **Accepted:** June 13, 2025

Corresponding to Ji–Hun Mo
E–mail. jihunmo@gmail.com **ORCID.** https://orcid.org/0000–0003–1331–364X

© Korean Intraoperative Neural Monitoring Society

recent reports suggest approximately 20.5 million adults over forty in the United States suffer from olfactory dysfunction [6]. Head trauma accounts for about 5%–17% of acquired chemosensory dysfunction cases [7–9].

The significance of olfactory dysfunction is often underestimated, but it has a significant negative impact on patients' quality of life and ability to accomplish daily activities [2,6]. OD can compromise not only the quality of life but also cognitive and neuropsychiatric functions [6], and can lead to issues like food poisoning, a reduction in appetite, malnutrition, and reduced immunity. Furthermore, olfactory function plays a crucial role in safety. Patients with olfactory impairment are at increased risk for personal injury, such as being unable to detect gas leaks, smoke, or spoiled foods. Studies show that a high percentage of patients with olfactory impairment have experienced hazardous events attributable to their loss of smell. Anosmia has also been associated with diminished satisfaction with life and an increased likelihood of depression [10,11].

Interestingly, anosmia can sometimes serve as an early clinical sign, potentially heralding the progression to dementia in TBI survivors, or serving as an early biomarker for the diagnosis and progression of neurodegenerative diseases like Parkinson's disease (PD) and Alzheimer's disease (AD) [12,13].

The diagnosis of anosmia requires objective olfactory testing, as self-assessment is often unreliable. Management often includes counseling regarding compensatory strategies to avoid safety risks and maximize quality of life [14].

1. Mechanisms of olfactory dysfunction

Post-traumatic OD can be classified as either conductive or neurosensory, depending on the injury location. Conductive deficits occur when odorants cannot reach the olfactory neuroepithelium, often due to physical obstruction like nasal bone fractures, septal deviation, mucosal edema, or hematoma [15]. Neurosensory deficits involve direct damage to the olfactory neuroepithelium or central olfactory pathways, including injury to the olfactory bulb. This can result from shearing of fibers at the cribriform plate or injury to the olfactory bulb itself. The prognosis for neurosensory deficits is generally poor, with many patients not recovering [16,17].

Beyond Physical Damage, Inflammation Plays a Significant Role in Olfactory Dysfunction Associated with Various Conditions

1. Post-traumatic anosmia

Trauma-associated OD are common in TBI patients. Neuroanatomical and kinetic factors make the central olfactory structures, including the olfactory bulb, highly vulnerable to TBI-related damage [13]. Damage to the central components of olfactory pathways, such as the olfactory bulb, can cause post-traumatic olfactory dysfunction [18]. This can result from mechanisms like the shearing or stretching of olfactory nerve fibers at the cribriform plate, which directly affects the connection to the olfactory bulb, or from focal contusion or hemorrhage within the olfactory bulb itself [18]. Neurosensory deficits, in general, involve direct damage to the olfactory neuroepithelium or central olfactory pathways, including the olfactory bulb [19]. The prognosis for neurosensory deficits is often poor, with many patients not recovering. Experimental TBI studies in mice highlight significant inflammatory changes and neuronal dysfunction in the olfactory bulb. TBI in mice causes a rapid and sustained inflammatory response in the olfactory bulb, including elevated levels of pro-inflammatory cyto-

kines, increased numbers of microglia and infiltrating by myeloid cells, and increased interleukin (IL)-1β and IL-6 production [20,21]. This neuroinflammation is accompanied by increased production of reactive oxygen species and upregulation of microglia/macrophages [22,23]. These changes are linked to neuronal dysfunction in the olfactory bulb, including early hyperexcitation and later hypo-neuronal activity, and contribute to OD [21].

2. Chronic rhinosinusitis

Historically, OD in patients with sinusitis were primarily attributed to mechanical obstruction caused by nasal obstruction, respiratory mucosal edema, and decreased airflow to the olfactory cleft [19]. The assumption was that the olfactory mucosa remained histologically normal despite the aggressive inflammatory process in the respiratory regions of the nose. This view considered anosmia secondary to chronic rhinosinusitis (CRS) mainly as a "transport" disorder, where odorant molecules simply couldn't reach the intact olfactory mucosa [24]. However, clinical studies have shown little correlation between nasal resistance and the degree of olfactory dysfunction, challenging the idea that obstruction is the sole cause [25]. Furthermore, surgical treatment for sinusitis and anosmia often has only limited effects on olfactory sensation despite successful resolution of other symptoms.

More recent studies, particularly a histological examination of olfactory biopsies from patients with chronic sinus disease, provide direct evidence for pathological changes within the olfactory mucosa itself [24]. This indicates that the pathological processes observed in the respiratory regions of the nose can also involve the olfactory mucosa. This suggests that olfactory loss with sinonasal inflammatory disease is a more complex process involving both transport and sensory pathology. Anosmia secondary to sinonasal disease involves direct effects on the olfactory mucosa (sensory disorder) in addition to any gross changes in airflow (transport disorder) [24]. Studies show inflammatory changes in the olfactory mucosa of patients with CRS, including infiltration of lymphocytes, macrophages, and eosinophils [26]. Moderate or severe inflammatory changes in the olfactory mucosa were observed in patients with decreased olfactory function [24]. This inflammation is likely to inhibit olfactory neurogenesis [27].

3. COVID-19

COVID-19, caused by the SARS-CoV-2 virus, is a global pandemic that originated in Wuhan, China, in December 2019 [28]. It is a positive-sense single-stranded RNA virus [29]. One of the most common symptoms reported by patients with COVID-19 infection is olfactory dysfunction or anosmia [30]. The SARS-CoV-2 virus utilizes the angiotensin-converting enzyme 2 (ACE2) receptor and the priming protease (transmembrane protease, serine 2) TMPRSS2 for entry into host cells. ACE2 receptors are found in various organs, including the respiratory cells and the central nervous system (CNS) [31]. The epithelium of the respiratory system is considered the primary site for initial coronavirus attachment [32]. Several mechanisms have been proposed to explain anosmia in COVID-19 patients:

1) Olfactory cleft obstruction

Nasal mucosal swelling and secretions can physically obstruct the olfactory cleft, preventing odor molecules from reaching the olfactory epithelium (OE) [33]. This is a "conductive" loss. However, anosmia can occur suddenly without nasal discharge or congestion, suggesting other mechanisms are involved. High expression of ACE2 receptors has been detected in the olfactory cleft region, and anosmic COVID-19 patients have shown significantly greater

volume and area in the olfactory cleft compared to healthy controls [34].

2) Local inflammation in the olfactory epithelium

High levels of ACE2 receptor expression are found on OE cells, particularly sustentacular cells [34,35]. The binding of the virus to these cells triggers the release of cytokines, promoting inflammation in the OE. Increased levels of pro-inflammatory cytokines like tumor necrosis factor (TNF)-α and IL-1β have been reported in OE biopsies from COVID-19 patients [36]. This inflammation in the OE is considered a probable mechanism for the quick recovery observed in many COVID-19-related anosmia cases. Since ACE2 is highly expressed in non-neuronal supporting cells rather than directly on olfactory neurons (ONs), the virus may primarily target these supporting cells, indirectly disrupting ON function.

3) Role of interleukins

IL-6 is thought to play a significant role in anosmia, potentially activating apoptotic pathways or directly inhibiting the sense of smell [37]. Studies have found significant correlations between decreased levels of IL-6 and the time taken for recovery from anosmia in COVID-19 [38]. Viral infections, including influenza, have been associated with increased levels of IL-6, IL-12, IL-15, and TNF-α [39].

4) Changes in olfactory cilia

Olfactory sensory neurons (OSNs) have cilia with receptors that detect odors. Viral infections, including COVID-19, may disrupt the structure and function of these cilia [40]. COVID-19 antigens have been found in ciliated nasal epithelial cells, and transmission electron microscopy showed absorption sites on cilia for viral entry. The Nsp13 protein of SARS-CoV-2 can bind to the centrosome of cilia, potentially disrupting their structure and leading to deciliation [41].

5) Effect on olfactory bulbs

Some studies have investigated the impact of COVID-19 infection on the olfactory bulb as a potential mechanism for anosmia. It is hypothesized that the virus can enter the CNS by traveling along OSNs and crossing the cribriform plate to reach the olfactory bulbs [42]. MRI studies have identified instances of olfactory bulb injury secondary to COVID-19 infection [43].

6) Damage to olfactory stem cells

In cases of persistent anosmia lasting for more than two months, damage to olfactory stem cells is considered a likely cause, delaying the regenerative capacity of the OE. Inflammation in the olfactory system is a critical factor for anosmia, and stem cell apoptosis can occur at sites of inflammation [44].

The prevalence and characteristics of COVID-19-related anosmia can vary based on several factors [1,45,46]:

7) Age

Anosmia occurs less frequently at the extreme ends of age ranges and is most common in the 40- to 50-year age bracket. This difference might be related to age-related changes in sustentacular cells (which have high ACE2 expression) in older individuals and varying levels of nasal ACE2 gene expression with age [47].

8) Disease severity

Patients with moderate to severe COVID-19 infections tend to report less olfactory involvement compared to those with mild infections. It is suggested that patients with mild disease might have

a stronger local immune response in the nasal and olfactory mucosa and bulb, leading to a more pronounced otolaryngological symptom pattern. The upper airway has higher ACE2 expression than the lower airway and is thought to be the initial site of infection [48].

9) Sex

Epidemiological data indicates that females are more likely to experience COVID-19-related olfactory dysfunction, although they are less likely to have severe infections. This difference may be linked to variations in ACE2 expression, innate immunity, steroid hormones, and factors related to sex chromosomes. The ACE2 gene is located on the X chromosome. Estrogen in females might reduce ACE2 expression compared to males, potentially resulting in lower viral load and reduced risk of severe disease. Women's potentially stronger immune responses might lead to a more significant local inflammatory reaction in the OE, contributing to olfactory dysfunction [49].

4. Neurodegenerative diseases

Olfactory dysfunction is an early symptom of many neurodegenerative diseases, particularly PD and AD, and may serve as an early biomarker [50]. In TBI survivors, OD may be an early sign of progression to dementia. The olfactory bulb is intricately connected to downstream olfactory centers, such as the piriform cortex and hippocampus. The hippocampus and entorhinal cortex are brain regions affected in the very early stages of AD [51]. The entorhinal cortex directly receives olfactory information and is part of a connection loop with the hippocampus and cortex, which is a main hub of network dysfunction in AD [52]. Studies in older adults free from dementia found that impaired olfactory identification was associated with lower volumes of the hippocampus and entorhinal cortex [53]. Post-mortem studies linked impaired odor identification with increased density of neurofibrillary tangles in the hippocampus and entorhinal cortex [53]. Olfactory identification impairment was also correlated with higher plasma total tau (t-tau) and neurofilament light chain concentrations, but not with plasma amyloid-beta [54]. This suggests that impaired odor identification may signify neurodegenerative processes and tau pathology in the brain, with negligible effects from amyloid pathology among dementia-free older adults [54]. Furthermore, impaired odor identification was associated with higher volumes of white matter hyperintensities (WMH) and periventricular WMH [55], markers of cerebral microvascular lesions [56]. These findings suggest that olfactory impairment and cognitive impairment may share common neuropathological bases related to neurodegeneration and vascular brain pathology.

Conclusion

Anosmia is a complex clinical symptom with diverse etiologies, including TBI, CRS, viral infections such as COVID-19, and neurodegenerative diseases. Despite differences in initial triggers, these conditions converge on shared neurophysiological mechanisms, particularly neuroinflammation, disruption of olfactory epithelial and bulb integrity, impaired neuronal regeneration, and central olfactory network dysfunction. Inflammatory cytokines, oxidative stress, and structural damage to olfactory pathways are recurring features that underlie olfactory dysfunction across these diseases. Importantly, anosmia not only affects quality of life and safety but may also serve as an early biomarker of neurodegeneration. Understanding these overlapping mechanisms enhances our ability to develop targeted diagnostic tools and therapeutic

strategies, emphasizing the need for interdisciplinary research bridging otolaryngology, neurology, and immunology.

Funding

This research was supported by the Bio&Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MSIT) (RS-2023-00220408), Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (RS-2025-00554060), and Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (RS-2020-NR049585).

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

None.

Author Contributions

Conceptualization: JHM; Writing-original draft: RV; Writing-review & editing: all authors.

ORCID

Reiza Ventura https://orcid.org/0000-0002-8693-8352
Ji-Hun Mo https://orcid.org/0000-0003-1331-364X

References

1. Najafloo R, Majidi J, Asghari A, Aleemardani M, Kamrava SK, Simorgh S, et al. Mechanism of anosmia caused by symptoms of COVID-19 and emerging treatments. ACS Chem Neurosci 2021;12:3795-805. doi: 10.1021/acschemneuro.1c00477
2. Howell J, Costanzo RM, Reiter ER. Head trauma and olfactory function. World J Otorhinolaryngol Head Neck Surg 2018;4:39-45. doi: 10.1016/j.wjorl.2018.02.001
3. Liu X, Lei Z, Gilhooly D, He J, Li Y, Ritzel RM, et al. Traumatic brain injury-induced inflammatory changes in the olfactory bulb disrupt neuronal networks leading to olfactory dysfunction. Brain Behav Immun 2023;114:22-45. doi: 10.1016/j.bbi.2023.08.004
4. Proskynitopoulos PJ, Stippler M, Kasper EM. Posttraumatic anosmia in patients with mild traumatic brain injury (mTBI): a systematic and illustrated review. Surg Neurol Int 2016;7:S263-75. doi: 10.4103/2152-7806.181981
5. Mullol J, Mariño-Sánchez F, Valls M, Alobid I, Marin C. The sense of smell in chronic rhinosinusitis. J Allergy Clin Immunol 2020;145:773-6. doi: 10.1016/j.jaci.2020.01.024
6. Liu G, Zong G, Doty RL, Sun Q. Prevalence and risk factors of taste and smell impairment in a nationwide representative sample of the US population: a cross-sectional study. BMJ Open 2016;6:e013246. doi: 10.1136/bmjopen-2016-013246
7. Duncan HJ, Seiden AM. Long-term follow-up of olfactory loss secondary to head trauma and upper respiratory tract infection. Arch Otolaryngol Head Neck Surg 1995;121:1183-7. doi: 10.1001/archotol.1995.01890100087015
8. Schriever VA, Studt F, Smitka M, Grosser K, Hummel T. Olfactory function after mild head injury in children. Chem Senses 2014;39:343-7. doi: 10.1093/chemse/bju005
9. Temmel AF, Quint C, Schickinger-Fischer B, Klimek L, Stoller E, Hummel T. Characteristics of olfactory disorders in relation to major causes of olfactory loss. Arch Otolaryngol Head Neck Surg 2002;128:635-41. doi: 10.1001/archotol.128.6.635
10. Liu DT, Prem B, Sharma G, Kaiser J, Besser G, Mueller CA. Depression symptoms and olfactory-related quality of life. Laryngoscope 2022;132:1829-34. doi: 10.1002/lary.30122
11. Gopinath B, Anstey KJ, Sue CM, Kifley A, Mitchell P. Olfactory impairment in older adults is associated with depressive symptoms and poorer qual-

ity of life scores. Am J Geriatr Psychiatry 2011;19:830-4. doi: 10.1097/JGP.0b013e318211c205
12. Schofield PW, Moore TM, Gardner A. Traumatic brain injury and olfaction: a systematic review. Front Neurol 2014;5:5. doi: 10.3389/fneur.2014.00005
13. Marin C, Langdon C, Alobid I, Mullol J. Olfactory dysfunction in traumatic brain injury: the role of neurogenesis. Curr Allergy Asthma Rep 2020;20:55. doi: 10.1007/s11882-020-00949-x
14. Scangas GA, Bleier BS. Anosmia: differential diagnosis, evaluation, and management. Am J Rhinol Allergy 2017;31:3-7. doi: 10.2500/ajra.2017.31.4403
15. Hummel T, Liu DT, Müller CA, Stuck BA, Welge-Lüssen A, Hähner A. Olfactory dysfunction: etiology, diagnosis, and treatment. Dtsch Arztebl Int 2023;120:146-54. doi: 10.3238/arztebl.m2022.0411
16. Mehkri Y, Hanna C, Sriram S, Reddy R, Hernandez J, Valisno JA, et al. Overview of neurotrauma and sensory loss. J Neurol Res Rev Rep 2022;4:1-7. doi: 10.47363/JNRRR/2022(4)158
17. De Luca R, Bonanno M, Rifici C, Quartarone A, Calabrò RS. Post-traumatic olfactory dysfunction: a scoping review of assessment and rehabilitation approaches. Front Neurol 2023;14:1193406. doi: 10.3389/fneur.2023.1193406
18. Coelho DH, Costanzo RM. Posttraumatic olfactory dysfunction. Auris Nasus Larynx 2016;43:137-43. doi: 10.1016/j.anl.2015.08.006
19. Goncalves S, Goldstein BJ. Pathophysiology of olfactory disorders and potential treatment strategies. Curr Otorhinolaryngol Rep 2016;4:115-21. doi: 10.1007/s40136-016-0113-5
20. LaFever BJ, Kawasawa YI, Ito A, Imamura F. Pathological consequences of chronic olfactory inflammation on neurite morphology of olfactory bulb projection neurons. Brain Behav Immun Health 2022;21:100451. doi: 10.1016/j.bbih.2022.100451
21. LaFever BJ, Imamura F. Effects of nasal inflammation on the olfactory bulb. J Neuroinflammation 2022;19:294. doi: 10.1186/s12974-022-02657-x
22. Seo Y, Kim HS, Kang KS. Microglial involvement in the development of olfactory dysfunction. J Vet Sci 2018;19:319-30. doi: 10.4142/jvs.2018.19.3.319
23. Yu Y, Yu Z, Xie M, Wang W, Luo X. Hv1 proton channel facilitates production of ROS and pro-inflammatory cytokines in microglia and enhances oligodendrocyte progenitor cells damage from oxygen-glucose deprivation in vitro. Biochem Biophys Res Commun 2018;498:1-8. doi: 10.1016/j.bbrc.2017.06.197
24. Yee KK, Pribitkin EA, Cowart BJ, Vainius AA, Klock CT, Rosen D, et al. Neuropathology of the olfactory mucosa in chronic rhinosinusitis. Am J Rhinol Allergy 2010;24:110-20. doi: 10.2500/ajra.2010.24.3435
25. Kern RC. Chronic sinusitis and anosmia: pathologic changes in the olfactory mucosa. Laryngoscope 2000;110:1071-7. doi: 10.1097/00005537-200007000-00001
26. Kohli P, Naik AN, Harruff EE, Nguyen SA, Schlosser RJ, Soler ZM. The prevalence of olfactory dysfunction in chronic rhinosinusitis. Laryngoscope 2017;127:309-20. doi: 10.1002/lary.26316
27. Yan X, Whitcroft KL, Hummel T. Olfaction: sensitive indicator of inflammatory burden in chronic rhinosinusitis. Laryngoscope Investig Otolaryngol 2020;5:992-1002. doi: 10.1002/lio2.485
28. Adil MT, Rahman R, Whitelaw D, Jain V, Al-Taan O, Rashid F, et al. SARS-CoV-2 and the pandemic of COVID-19. Postgrad Med J 2021;97:110-6. doi: 10.1136/postgradmedj-2020-138386
29. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol 2021;19:155-70. doi: 10.1038/s41579-020-00468-6
30. Sedaghat AR, Gengler I, Speth MM. Olfactory dysfunction: a highly prevalent symptom of COVID-19 with public health significance. Otolaryngol Head Neck Surg 2020;163:12-5. doi: 10.1177/0194599820926464
31. Barrantes FJ. Central nervous system targets and routes for SARS-CoV-2: current views and new hypotheses. ACS Chem Neurosci 2020;11:2793-803. doi: 10.1021/acschemneuro.0c00434
32. Leštarević S, Savić S, Vitković L, Mandić P, Mijović M, Dejanović M, et al. Respiratory epithelium: place of entry and / or defense against SARS-CoV-2 virus. Prax Med 2021;50:35-43. doi: 10.5937/pramed2102035L
33. Trotier D, Bensimon JL, Herman P, Tran Ba Huy P, Døving KB, Eloit C. Inflammatory obstruction of the olfactory clefts and olfactory loss in humans: a new syndrome? Chem Senses 2007;32:285-92. doi: 10.1093/chemse/bjl057
34. Chen M, Shen W, Rowan NR, Kulaga H, Hillel A, Ramanathan M Jr, et al. Elevated ACE-2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication. Eur Respir J 2020;56:2001948. doi: 10.1183/13993003.01948-2020
35. Klingenstein M, Klingenstein S, Neckel PH, Mack AF, Wagner AP, Kleger A, et al. Evidence of SARS-CoV2 entry protein ACE2 in the human nose and olfactory bulb. Cells Tissues Organs 2020;209:155-64. doi: 10.1159/000513040
36. Fara A, Mitrev Z, Rosalia RA, Assas BM. Cytokine storm and COVID-19: a chronicle of pro-inflammatory

cytokines. Open Biol 2020;10:200160. doi: 10.1098/rsob.200160
37. Cazzolla AP, Lovero R, Lo Muzio L, Testa NF, Schirinzi A, Palmieri G, et al. Taste and smell disorders in COVID-19 patients: role of interleukin-6. ACS Chem Neurosci 2020;11:2774-81. doi: 10.1021/acschemneuro.0c00447
38. Arulkumaran N, Snow TAC, Kulkarni A, Brealey D, Rickman HM, Rees-Spear C, et al. Influence of IL-6 levels on patient survival in COVID-19. J Crit Care 2021;66:123-5. doi: 10.1016/j.jcrc.2021.08.013
39. Brydon EW, Morris SJ, Sweet C. Role of apoptosis and cytokines in influenza virus morbidity. FEMS Microbiol Rev 2005;29:837-50. doi: 10.1016/j.femsre.2004.12.003
40. Dai X, Xu R, Li N. The interplay between airway cilia and coronavirus infection, implications for prevention and control of airway viral infections. Cells 2024;13:1353. doi: 10.3390/cells13161353
41. Li W, Li M, Ou G. COVID-19, cilia, and smell. FEBS J 2020;287:3672-6. doi: 10.1111/febs.15491
42. Bauer L, Laksono BM, de Vrij FMS, Kushner SA, Harschnitz O, van Riel D. The neuroinvasiveness, neurotropism, and neurovirulence of SARS-CoV-2. Trends Neurosci 2022;45:358-68. doi: 10.1016/j.tins.2022.02.006
43. Aragão MFVV, Leal MC, Cartaxo Filho OQ, Fonseca TM, Valença MM. Anosmia in COVID-19 associated with injury to the olfactory bulbs evident on MRI. AJNR Am J Neuroradiol 2020;41:1703-6. doi: 10.3174/ajnr.A6675
44. Verma AK, Zheng J, Meyerholz DK, Perlman S. SARS-CoV-2 infection of sustentacular cells disrupts olfactory signaling pathways. JCI Insight 2022;7:e160277. doi: 10.1172/jci.insight.160277
45. Kumar AA, Lee SWY, Lock C, Keong NC. Geographical variations in host predisposition to COVID-19 related anosmia, ageusia, and neurological syndromes. Front Med (Lausanne) 2021;8:661359. doi: 10.3389/fmed.2021.661359
46. Karamali K, Elliott M, Hopkins C. COVID-19 related olfactory dysfunction. Curr Opin Otolaryngol Head Neck Surg 2022;30:19-25. doi: 10.1097/MOO.0000000000000783
47. Brechbühl J, Lopes AC, Wood D, Bouteiller S, de Vallière A, Verdumo C, et al. Age-dependent appearance of SARS-CoV-2 entry sites in mouse chemosensory systems reflects COVID-19 anosmia-ageusia symptoms. Commun Biol 2021;4:880. doi: 10.1038/s42003-021-02410-9
48. Lee IT, Nakayama T, Wu CT, Goltsev Y, Jiang S, Gall PA, et al. ACE2 localizes to the respiratory cilia and is not increased by ACE inhibitors or ARBs. Nat Commun 2020;11:5453. doi: 10.1038/s41467-020-19145-6
49. Mele D, Calastri A, Maiorano E, Cerino A, Sachs M, Oliviero B, et al. High frequencies of functional virus-specific CD4+ T cells in SARS-CoV-2 subjects with olfactory and taste disorders. Front Immunol 2021;12:748881. doi: 10.3389/fimmu.2021.748881
50. Bhatia-Dey N, Heinbockel T. The olfactory system as marker of neurodegeneration in aging, neurological and neuropsychiatric disorders. Int J Environ Res Public Health 2021;18:6976. doi: 10.3390/ijerph18136976
51. Slabik D, Garaschuk O. Olfactory dysfunction as a common biomarker for neurodegenerative and neuropsychiatric disorders. Neural Regen Res 2023;18:1029-30. doi: 10.4103/1673-5374.355756
52. Scharfman HE, Chao MV. The entorhinal cortex and neurotrophin signaling in Alzheimer's disease and other disorders. Cogn Neurosci 2013;4:123-35. doi: 10.1080/17588928.2013.826184
53. Kubota S, Masaoka Y, Sugiyama H, Yoshida M, Yoshikawa A, Koiwa N, et al. Hippocampus and parahippocampus volume reduction associated with impaired olfactory abilities in subjects without evidence of cognitive decline. Front Hum Neurosci 2020;14:556519. doi: 10.3389/fnhum.2020.556519
54. Abed SS, Hamdan FB, Hussein MM, Al-Mayah QS. Plasma tau and neurofilament light chain as biomarkers of Alzheimer's disease and their relation to cognitive functions. J Med Life 2023;16:284-9. doi: 10.25122/jml-2022-0251
55. Ham JH, Lee JJ, Sunwoo MK, Hong JY, Sohn YH, Lee PH. Effect of olfactory impairment and white matter hyperintensities on cognition in Parkinson's disease. Parkinsonism Relat Disord 2016;24:95-9. doi: 10.1016/j.parkreldis.2015.12.017
56. Ryu SY, Lee DC, Lee SB, Kim TW, Lee TJ, Yang PS, et al. Olfactory identification and white matter integrity in amnestic mild cognitive impairment: a preliminary study. Int J Imaging Syst Technol 2016;26:270-6. doi: 10.1002/ima.22198