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Managing Post-Viral Anosmia

Introduction

Olfactory dysfunctions (OD), characterized by reduced, absent, or distorted olfaction, are relatively common in the general population, and may affect approximately 20% of the adult population at some point in their lives1. OD dysfunction can be classified in either quantitative terms, involving the intensity of the alteration, or qualitative terms, in this case involving the altered odor quality. Normal olfactory function is defined as normosmia. Quantitatively, olfactory dysfunctions are classified as hyposmia (decrease in smell), functional anosmia (has no useful function in daily life), and anosmia (total lack of smell)2,3.

Physiologically, our olfactory perception changes with age, reaching the peak of perception in the fourth decade of life and significantly declining in odor recognition and identification after the age of 60 years4. Several diseases are associated with OD; among them are congenital causes, sinonasal diseases, traumatic brain injuries, neurodegenerative diseases, and post-infectious disorders4. Olfactory dysfunction, through loss (quantitative changes) or distortion (qualitative changes) of smell, is a debilitating condition with a variety of causes and has a significant impact on the patient's quality of life. There are also safety implications, due to the inability to detect odors that could signal potential danger situations (e.g. smoke, gas, or deteriorated food). Because of the close relationship of smell to the sense of taste, olfactory dysfunction can impair the ability to enjoy food, thus potentially causing/enhancing eating and weight disorders associated with social anxiety and depression.5.

Post-viral olfactory loss (PVOL)

Post-infectious olfactory dysfunction is one of the most common causes of olfactory dysfunction, representing approximately 20% of all cases seen in otorhinolaryngology clinics6. Knowledge about the occurrence of olfactory dysfunction in viral infections is not recent. Several viruses (e.g. rhinovirus, parainfluenza, Epstein-Barr virus, respiratory syncytial virus, adenovirus, and some coronaviruses such as SARS-CoV-2(COVID-19) can lead to OD through inflammatory reaction in the nasal mucosa and subsequent development of rhinorrhea4,7. For some patients, this condition is temporary and resolves benignly within two to four weeks. However, in a significant minority, the symptoms of OD persist. Loss of smell (hyposmia or anosmia) and taste (hypogeusia or ageusia) have been shown to be the most prevalent symptoms of COVID-19. About 10% of COVID patients have persistent anosmia9. Zayet and colleagues compared the features of COVID-19 with those of influenza and found a higher prevalence of anosmia (53 vs.17%) in patients with COVID-1910.

The prognosis for recovery from PVOL is better in younger individuals with no previous risk factors. The symptoms are generally acute, without fluctuation, and both quantitative and qualitative olfactory dysfunction may occur. However, in more subtle viral infectious conditions, OD may be misinterpreted as having an idiopathic cause8.

Pathophysiology of PVOL

The exact pathophysiology of PVOL is not fully understood. It may be caused by a combined conductive and sensorineural/inflammatory disorder. There appear to be two possible causes4:

(a) Loss of smell that occurs during upper respiratory infection as a result of nasal swelling, mucosal edema, and obstruction of airflow in the olfactory cleft, and/or

(b) PVOL caused by infection and direct swelling of the olfactory mucosa, leading to subsequent neurodegeneration of the olfactory neuroepithelium.

The mechanisms involved in OD in individuals with COVID-19 are also unclear. One possible hypothesis is based on the ability of the SARS-CoV-2 virus to cross the blood-brain barrier and reach the brain, or that the virus may reach the brain via the hematogenous route11. Otherwise, the route of entry of the coronavirus into the brain could be through: (1) the olfactory nerves; (2) the cribriform plate (from the Latin "cribrum" = perforated) which is located in the ethmoidal incisure of the frontal bone and forms the roof of the nasal cavity; (3) the trigeminal nerve. The trigeminal nerve and olfactory nerve involvement would result in olfaction and taste dysfunctions12. Another possible mechanism would be through a decrease in the sensitivity of the sensory neurons' reflexes. However, some recent studies investigating olfactory epithelial cells expressing ACE2 receptors and other viral entry genes have concluded that olfactory sensory neurons do not express ACE212.

Contrastingly, coexpression of ACE2 and TMPRSS2 was observed in key support cells (including sustentation cells, Bowman's gland, and microvilli cells) and in stem cells that reconstitute the epithelium after damage13. In addition, the inflammatory environment in the nasal cavity can potentially affect olfactory neuronal function. Anosmia and ageusia in patients with COVID-19 occur simultaneously with elevated levels of interleukin-6, an important pro-inflammatory cytokine14. Some studies have reported damage to the olfactory epithelium after SARS-CoV-2 infection, with case reports of olfactory neuropathy in patients with acute severe SARS-CoV2 infection with occurrence of anosmia. It is uncertain whether the inflammatory neuropathy resulted from direct viral damage or was mediated by damage to non-neural supporting cells15. One case report demonstrated significant damage to the olfactory epithelium evidenced in a biopsy performed on a patient with persistent anosmia for more than three months after infection16.

Possible treatments for post viral hyposmia and anosmia

The efficacy of available treatments for PVOL is not yet established. However, some recommended topical and systemic treatments with evidence in the scientific literature are listed in table 1.

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Possible mechanisms of action for some of the treatments

Olfactory training

Olfactory training is a potential therapy for OD caused by several factors, including PVOL. It is one of the therapies with the strongest scientific evidence to improve OD. The regeneration capacity of olfactory neurons and olfactory epithelium is well established. It is presumed that olfactory training can aid in regeneration. It may also play a central role in the influence of the olfactory central structure on the olfactory bulb and may promote a change in the connection with the brain12,31.

Zinc

Zinc deficiency is a well-known cause of anosmia and taste dysfunction. It has been proposed that a decrease in nasal zinc levels as a consequence of the immune response to viral infections (including SARS-CoV-2 infection) could play a role in the pathogenesis of anosmia due to decreased zinc-dependent carbonic anhydrase activity32. Carbonic anhydrase is involved in taste and smell perception. Furthermore, the drop in local zinc levels in response to SARS-CoV-2 could lead to a reduction in type 1 interferon and a shift toward Th2 immune responses. Nevertheless, RNA polymerase activity (involved in viral replication) is partially inhibited by zinc31,32. Zinc therapy showed a significant reduction in the time to recovery of olfactory ability in a clinical trial involving patients with COVID-1918.

Vitamin A

Intranasal vitamin A has been used as an adjuvant in the treatment of PVOL, based on its potential role in the regeneration of the olfactory epithelium and olfactory bulb. The vitamin A may promote olfactory neurogenesis through its ability to regenerate the neuroepithelium1,12.

a-lipoic acid (ALA)

Alpha lipoic acid is a fatty acid that stimulates the expression of nerve growth factors and appears to have antioxidant and neuroprotective effects. Alpha lipoic acid possibly reduces ACE2 activity after SARS-CoV-2 replication and could reduce NADPH oxidase activity, leading to suppression of inflammatory cytokines12, 21.

Sodium citrate

The perception of odors depends on both a functional olfactory neuroepithelium as well as intact superior cortical processing. It has been theorized that intranasal sodium citrate may improve olfactory function in patients with hyposmia by reducing free calcium in the nasal mucus layer. Calcium has an inhibitory role in the olfactory transduction signal that supposedly involves calcium-calmodulin-dependent interference with nucleotide gated channels and calcium-dependent phosphorylation and thus deactivation of adenylylcyclase. The reduction of the concentration of free calcium in the nasal mucus layer through the chelating action of sodium citrate could prevent the intracellular calcium influx required for inhibitory actions24.

Omega 3

Omega-3 polyunsaturated fatty acids are essential components of the phospholipid membrane with significant influence on gene expression. The role of omega-3 in anti-inflammatory mechanisms has been extensively demonstrated, and its ability to reduce pro-inflammatory cytokines (e.g. IL-6) has been evidenced. The beneficial omega-3 activity in the treatment of post-infection olfactory dysfunction could be explained through neuroregenerative or anti-inflammatory mechanisms, potentially aiding in the healing process of the olfactory nerve1,12,23 .

Theophylline

The mechanism of action of theophylline in the olfactory neuroepithelium is not completely understood, but it seems to aid in the regeneration of the olfactory neuroepithelium. It is suggested that theophylline inhibits the phosphodiesterase enzyme and increases secondary messengers, such as cAMP and cGMP, collaborating in the regeneration of the olfactory neuroepithelium28. Low levels of cAMP and cGMP are reported in patients with hyposmia and hypogeusia33,34,35,36.

Hyaluronic acid plus Mint

Hyaluronic acid (with high molecular weight and hydrophilic nature) can form viscous water solutions and has antiinflammatory properties, while mint oil is well-known to stimulate the olfactory and trigeminal nerve37.

Topical corticosteroids

Topical corticosteroids have been used in the therapy of olfactory dysfunction, especially in upper respiratory tract infections such as rhinosinusitis due to their anti-inflammatory activity. Its uses have also been considered in the elimination of the inflammatory component of olfactory dysfunction after infection. However, there are no conclusive data regarding its efficacy and studies with conflicting results have been published12.

Conclusion

Here, we presented the recent literature regarding treatment of post viral olfactory loss. Although in many individuals with PVOL the evolution occurs relatively quickly and spontaneously, in a significant number of patients the partial or total loss of the sense of smell has been shown to be persistent. In this context, it is necessary to resort to specific treatments in order to return quality of life to these individuals.

References

1. Whitcroft KL, Hummel T. Clinical Diagnosis and Current Management Strategies for for Olfactory Dysfunction: A Review. JAMA Otolaryngol Head Neck Surg. 2019 Sep 1;145(9):846-853 doi:10.1001/jamaoto.2019.1728.
2. Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, et al. Position paper on olfactory dysfunction. Rhinol Suppl 2017;54:1-30.
3. Boesveldt S, Postma EM, Boak D, Welge-Luessen A, Schöpf V, J Investig Allergol Clin Immunol 2020; Vol. 30(5) © 2020 Esmon Publicidad doi: 10.18176/jiaci.0567
4. Izquierdo-Domínguez A, Rojas-Lechuga MJ, Mullol J, Alobid I. Pérdida del sentido del olfato durante la pandemia COVID-19. Med Clin (Barc). 2020;155:403–408.

5. Whitcroft KL, Merkonidis C, Cuevas M, Haehner A, Philpott C, Hummel T. Intranasal sodium citrate solution improves olfaction in post-viral hyposmia. Rhinology 54:368-373, 2016.
6. Webster KE, O'Byrne L, MacKeith S, Philpott C, Hopkins C, Burton MJ.Interventions for the prevention of persistente post-COVID 19 olfactory dysfunction (Review). Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD013877.DOI: 10.1002/14651858.CD013877.pub2.
7. Potter MR, Chen JH, Lobban NS, Doty RL. Olfactory dysfunction from acute Upper respiratory infections: relationship to season of onset. Int Forum Allergy Rhinol. 2020;10(6).doi:10.1002/alr.22551.
8. Lin YT, Yeh TH. Studies on Clinical Features, Mechanisms and Management of Olfactory Dysfunction Secondary to Chronic Rhinosinusitis. Front. Allergy 3:835151.doi:10.3389/falgy.2022.835151
9. Wahid NW, MCLELLAND L. Running a post-COVID smell clinic. ENT and audiology News.2021;30(3).
10. Zayet, S., Kadiane-Oussou, N.J., Lepiller, Q., Zahra, H., Royer, P.Y., Toko, L., Gendrin, V., Klopfenstein, T., 2020. Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster. Microb. Infect. 22 (9), 481–488. https://doi.org/10.1016/j.micinf.2020.05.016.
11. Garg, R., Jain, R., Sodani, A., Chouksey, D., Dosi, R., Athale, S., Goyal, N., Rathi, P., Singh, H., Telang, K., 2020. Neurological symptoms as initial manifestation of covid-19 – an observational study. Ann. Indian Acad. Neurol. 23 (4), 482–486. https://doi.org/10.4103/aian.AIAN_560_20.
12. Neta FI, Fernandes ACL, Vale AJM et al. Pathophysiology and possible treatments for olfactory gustatory disorders in patients affected by COVID-19. Current Research in Pharmacology and Drug Discovery 2 (2021)100035.
13. Brann, David H., Tsukahara, Tatsuya, Weinreb, Caleb, Lipovsek, Marcela, Van den Berge, Koen, Gong, Boying, Chance, Rebecca, et al., 2020. Non-neuronal expression. of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Science Advances 6 (31), eabc5801. https://doi.org/10.1126/sciadv.abc5801.
14. Cazzolla, A.P., Lovero, R., Lo Muzio, L., Testa, N.F., Schirinzi, A., Palmieri, G.,Pozzessere, P., Procacci, V., Di Comite, M., Ciavarella, D., Pepe, M., De Ruvo, C., Crincoli, V., Di Serio, F., Santacroce, L., 2020. Taste and smell disorders in COVID-19 patients: role of interleukin-6. ACS Chem. Neurosci. 11 (17), 2774–2781. https://doi.org/10.1021/acschemneuro.0c00447.
15. Kirschenbaum, Daniel, et al., 2020. Inflammatory olfactory neuropathy in two patients with COVID-19. Lancet 396 (10245), 166. https://doi.org/10.1016/S0140-6736(20)31525-7.
16. Vaira, L.A., Hopkins, C., Sandison, A., Manca, A., Machouchas, N., Turilli, D.,Lechien, J.R., Barillari, M.R., Salzano, G., Cossu, A., Saussez, S., De Riu, G., 2020a. Olfactory epithelium histopathological findings in long-term coronavirus disease 2019 related anosmia. J. Laryngol. Otol. 134 (12), 1123–1127. https://doi.org/10.1017/S0022215120002455.
17. Damm M, Pikart LK, Reimann H, Burkert S, Göktas Ö, Haxel B, et al. Olfactory training is helpful in postinfectious olfactory loss: a randomized, controlled, multicenter study. Laryngoscope. 2014;124:826–31.
18. Abdelmaksoud, A.A., Ghweil, A.A., Hassan, M.H., Rashad, A., Khodeary, A., Aref, Z.F., Sayed, M., Elsamman, M.K., Bazeed, S., 2021. Olfactory disturbances as presenting manifestation among Egyptian patients with COVID-19: possible role of zinc. Biol.Trace Elem. Res. 1–8. https://doi.org/10.1007/s12011-020-02546-5. Advance online publication.
19. Hummel, T., Whitcroft, K.L., Rueter, G., Haehner, A., 2017. Intranasal vitamin A is beneficial in post-infectious olfactory loss. European archives of oto-rhinolaryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology. Head Neck Surg. 274 (7), 2819–2825. https://doi.org/10.1007/s00405-017-4576-x.
20. Romano F, Lima W, Fornazieri M. Olfato e Paladar: Da Anatomofisiologia Ao Diagnóstico e Tratamento. Vol 1. Thieme Revinter; 2021.
21. Hummel, T., Heilmann, S., Hüttenbriuk, K.B., 2002. Lipoic acid in the treatment of smell dysfunction following viral infection of the upper respiratory tract. Laryngoscope 112(11), 2076–2080. https://doi.org/10.1097/00005537-200211000-00031.
22. Hopkins, C., Alanin, M., Philpott, C., Harries, P., Whitcroft, K., Qureishi, A., Anari, S., Ramakrishnan, Y., Sama, A., Davies, E., Stew, B., Gane, S., Carrie, S., Hathorn, I., Bhalla, R., Kelly, C., Hill, N., Boak, D., Nirmal Kumar, B., 2021b. Management of new onset loss of sense of smell during the COVID-19 pandemic - BRS Consensus Guidelines. Clin. Otolaryngol. : official journal of ENT-UK ; official journal

of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 46 (1),16–https://doi.org/10.1111/coa.13636.

23. Whitcroft, K.L., Ezzat, M., Cuevas, M., Andrews, P., Hummel, T., 2017. The effect of intranasal sodium citrate on olfaction in post-infectious loss: results from a prospective, placebo-controlled trial in 49 patients. Clin. Otolaryngol. : oficial journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 42 (3), 557–563. https://doi.org/10.1111/coa.12789.
24. Whitcroft, K.L., Merkonidis, C., Cuevas, M., Haehner, A., Philpott, C., Hummel, T., 2016. Intranasal sodium citrate solution improves olfaction in post-viral hyposmia. Rhinology 54 (4), 368–374. https://doi.org/10.4193/Rhin16.054.
25. Philpott, C.M., Erskine, S.E., Clark, A., Leeper, A., Salam, M., Sharma, R., Murty, G.E., Hummel, T., 2017. A randomised controlled trial of sodium citrate spray for nonconductive olfactory disorders. Clin. Otolaryngol. : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-FacialSurgery 42 (6), 1295–1302. https://doi.org/10.1111/coa.12878.
26. Yan, C.H., Rathor, A., Krook, K., Ma, Y., Rotella, M.R., Dodd, R.L., Hwang, P.H.,Nayak, J.V., Oyesiku, N.M., DelGaudio, J.M., Levy, J.M., Wise, J., Wise, S.K.,Patel, Z.M., 2020b. Effect of omega-3 supplementation in patients with smelldysfunction following endoscopic sellar and parasellar tumor resection: a multicenter prospective randomized controlled trial. Neurosurgery 87 (2), E91–E98. https://doi.org/10.1093/neuros/nyz559.
27. Henkin, R., Abdelmeguid, M., 2019. Improved smell and taste dysfunction with intranasal theophylline. Am J Otolaryngol Head Neck Surg 2 (9), 1070, 2019.
28. Henkin RI, Schultz M, Minnick-Poppe L. intranasal Theophylline Treatment of Hyposmia and Hypogeusia. Arch Otolaryngol Head Neck Surg.2012;138(11):1064-1070.
29. Goldstein MF, Hilditch GJ, Frankel I, et al. Intra-Nasal Theophylline for the Treatmento of Chronic Anosmia and Hyposmia. The Journal of Allergy and Clinical Immunology.2017;139(2)SUPP.AB252.
30. Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, et al. Position paper on olfactory dysfunction. Rhinol Suppl. 2017;54:1–30.
31. Othman BA, Maulud SQ, Jalal PJ, et al. Olfactory dysfunction as a post-infectious symptom of SARS-CoV-2 infection. Annals of Medicine and Surgery 75 (2022) 103352.
32. Elquis O, Lekag K, Wu A, et al. Intra-nasal zinc level relationship to COVID-19 anosmia and type 1 interferon response: A proposal. Laryngoscope Investigative Otolaryngology 2021;6:21-24.
33. Henkin RI, Velicu I, Papathanassiu A. cAMP and cGMP in human parotid saliva: relationships to taste and smell dysfunction, gender, and age. Am J Med Sci. 2007;334(6):431-440.
34. Henkin RI, Velicu I. Decreased parotid salivary cyclic nucleotides related to smell loss severity in patients with taste and smell dysfunction. Metabolism. 2009; 58(12):1717-1723.
35. Henkin RI, Velicu I. cAMP and cGMP in nasal mucus: relationships to taste and smell dysfunction, gender and age. Clin Invest Med. 2008;31(2):E71-E77. http://cimonline.ca/index.php/cim/article/view/3366. Accessed March 10, 2011.
36. 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(2):E78-E84.
37. Terranova MG, Sica E, Castelnuovo PGM, Macchi A. Effectiveness of Therapy with Hyaluronic Acid and a Mint Olfactory Substance in the Treatment of Olfactory Dysfunctions in Patients with Post-Vital Hyposmia-Anosmia. J Clin Res Med.2022;5(3):1-4.
38. Allen Jr. LV. Sodium citrate 9% Nasal Spray for Olfactory Disorders. IJPC. 2018;22(1):57.
39. Allen Jr.LV. Theophylline 50µg/mL Intranasal Solution. 2021. International Journal of Pharmaceutical Compounding, Inc.: www.CompoundingToday.com

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