Olfactory-Disorders in Post-Acute COVID-19 Syndrome

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Altered smell is one of the most prevalent symptoms in acute COVID-19 infection. Although most patients recover normal neurosensory function in a few weeks, approximately one-tenth of patients report long-term smell dysfunction, including anosmia, hyposmia, parosmia and phantosmia, with a particularly notable impact on quality of life. In this complex scenario, inflammation and cellular damage may play a key role in the pathogenesis of olfactory dysfunctions and may affect olfactory signaling from the peripheral to the central nervous system.

Keywords: olfactory dysfunction ; anosmia ; post-acute COVID-19

1. Epidemiology

Accumulating evidence indicates that altered smell is one of the most prevalent symptoms in acute COVID-19 infection [1]. In self-report studies, the estimated prevalence of olfactory disorders in acute COVID-19 ranged from 5% to 85%, depending on disease severity, and seems to be higher than in other respiratory viral infections. Although most of the patients recover normal neurosensory function in a few weeks, approximately one-tenth of patients reported long-term smell dysfunction, including anosmia, hyposmia, parosmia, and phantosmia, with a particularly notable impact on quality of life [2].

Qualitative olfactory dysfunctions are often undervalued in the clinical management of COVID-19 infection and are generally underestimated in observational self-report studies. Individuals may experience a range of persistent and prolonged olfactory sequelae in PACS (**Table 1**). Continued loss of smell after several weeks was reported in 1.7–29% of patients with COVID-19 requiring hospitalization [3][4][5][6]. Disturbing taste and smell were also prevalent after 6 months in approximately one quarter of home-isolated young adults with a milder course of the disease [7]. In a cohort of 467 patients in the United Kingdom followed up at 4–6 weeks, participants with positive SARS-CoV-2 IgM/IgG antibodies reported a significantly higher prevalence of longstanding smell loss compared to participants with a negative antibody test, with rates of full resolution of olfactory impairment of 57.7% and 72.1%, respectively [8]. In addition, female individuals were almost 2.5 times more likely to experience persistent smell loss compared to participants of the male sex, and parosmia was also significantly associated with unresolved smell loss at 4 to 6 weeks follow-up [8].

Table 1. Prevalence of olfactory dysfunction in post-acute COVID-19 syndrome.

Author	Country	Setting	Time (Days)	Population	*n*	Prevalence of Olfactory/Gustatory Dysfunction
Garrigues 2020 [3]	France	Cross sectional, single center	110.9	Hospitalized	120	Anosmia (13.3%)
Chopra 2020 [4]	United States	Prospective cohort, multicenter	60	Hospitalized	488	Loss of taste and/or smell (28%)
Rosales-Castillo 2020 [5]	Spain	Retrospective cohort, single center	50.8	Hospitalized	118	Anosmia (1.7%)
Jacobs 2020 [6]	United States	Prospective cohort, single center	35	Hospitalized	183	Lack of smell (9.3%)
Daher 2020 [9]	Germany	Prospective cohort, single center	42	Hospitalized	33	Loss of smell (12%)
Klein 2020 [10]	Israel	Prospective cohort, single center	180	Hospitalized (5.5%) and home-isolated	112	Smell changes (9.8%)
Moreno-Pérez 2021 [11]	Spain	Prospective cohort, multicenter	112–126	Hospitalized (58.2%) and home-isolated	277	Anosmia-dysgeusia (21%)

Author	Country	Setting	Time (Days)	Population	*n*	Prevalence of Olfactory/Gustatory Dysfunction
Seessle 2021 [12]	Germany	Prospective cohort, single center	360	Hospitalized (32.3%) and home-isolated	96	Anosmia (20.8%)
Tenford 2020 [13]	United States	Cross sectional, multicenter	14–21	Home-isolated	270	Loss of smell (27%)
Boscolo-Rizzo 2020 [14]	Italy	Cross sectional, single center	28	Home-isolated	187	Altered sense of smell or taste (51.3%)
Paderno 2020 [15]	Italy	Prospective cohort, multicenter	30	Home-isolated	151	Olfactory dysfunction (17.7%)
Valiente-De Santis 2020 [16]	Spain	Prospective cohort, single center	84	Home-isolated	108	Anosmia (9.3%)
Otte 2020 [17]	Germany	Cross sectional, single center	56	Home-isolated	80	Hyposmia (45.1%)
Blomberg 2021 [7]	Norway	Prospective cohort, multicenter	168	Home-isolated	247	Disturbed taste/smell (27%)

COVID-19 indicates coronavirus disease 2019; Time, time to assessment in days; *n*, sample size.

2. Pathophysiogenesis of Olfactory Dysfunction

SARS-CoV-2's route of infection basically comprises two pathways: through cell entry factors such as angiotensin-converting enzyme 2 (ACE2), transmembrane protease serine 2 (TMPRSS2), and furin, or through an endosomal route that does not require previous cleavage of the spike protein (S). ACE2 can act as a primary receptor, and, after virus attachment, the spike protein in its surface is cleaved and dissociated by furin, after which the subunit S2 is cleaved by TMPRSS2, changing the structure of the S2 subunit, which ultimately leads to membrane fusion and viral RNA transferring to host cell cytoplasm. An alternative pathway can also be initiated by ACE2 binding and the internalization process involving clathrin and cathepsin L, and, in this case, the virus releases its genetic material directly after endocytosis, as an alternative independent from TMPRSS2 to invade cells [18].

After entering the mouth through salivary particles, the virus can infect cells in filiform and vallate papillae, lingual epithelium and taste buds, all cells that express ACE2, starting its replication, which in turn causes taste impairment [18]. Other potential targets for cell infection due to ACE2 are vascular endothelial cells and adipocytes in parotid and salivary glands. The damage in these cells affects both blood and nutritional supplies and, indirectly, it can change taste perception [18].

Upper airway mucosa has nasal goblet and ciliated cells expressing ACE2 and TMPRSS2, and these respiratory epithelium cell types may have a role in facilitating SARS-CoV-2 infection by storing viral particles [19].

High levels of ACE2 were found in sustentacular cells of the olfactory system, which are in intimate contact with dendrites of olfactory receptor neurons, and also other olfactory epithelium cells such as ductal cells of Bowman's gland, microvillar cells, globose and horizontal basal cells, and olfactory bulb pericytes [18][20]. It is hypothesized that infection of mesenchymal stromal and vascular cells in the nose and bulb and their subsequent inflammation affects the neuronal conduction, reduces nutritional and water supplies and, therefore, causes the death of olfactory sensory neurons (OSNs) and damage to olfactory bulb function [19] (**Figure 1**). Although OSNs are surprisingly not an ACE2 expressing tissue, it has already been described that the spike protein can bind to neural cell receptors, possibly due to cell-to-cell transmission through tunneling nanotubes (TNTs), filamentous cellular projections that form a communication and transportation net between cells [18].

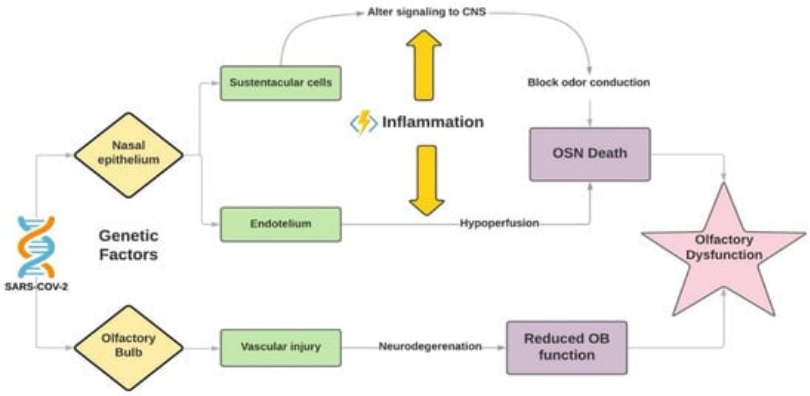

Figure 1. Pathogenesis of olfactory dysfunction. Infection of mesenchymal stromal and vascular cells in the nose and bulb and their subsequent inflammation affect the neuronal conduction, reduce nutritional and water supplies and, therefore, cause the death of olfactory sensory neurons (OSNs) and damage to olfactory bulb function. SARS-COV-2 indicates severe acute respiratory syndrome coronavirus 2; CNS, central nervous system; OB, olfactory bulb; OSN, olfactory sensory neurons.

3. Smell Dysfunction in PACS

Smell dysfunction can occur in the context of various infectious viral diseases [21]. Alteration of smell can be categorized into two distinct types: quantitative and qualitative, and subcategorized in total/complete or partial/incomplete, as well as in unilateral or bilateral [21]. Quantitative loss is seen in anosmia and hyposmia, while qualitative loss is noted in parosmia and phantosmia [22].

Hyposmia was reported in a study in Padua as an isolated or more prominent symptom of SARS-CoV-2 infection, often associated with hypogeusia [23]. Hyposmia and parosmia can be persistent olfactory dysfunctions in PACS [24].

Parosmia and phantosmia are distortions in smell perception. Parosmia is a disorder in which an odor is perceived as a different smell, either pleasant—euosmia—or unpleasant—troposmia [23]. Troposmia is often referred to as a burned, foul or rotten smell [25]. In an 18-FDG PET/CT study, the activity in the secondary olfactory cortex was preserved in a patient presenting parosmia post anosmia after COVID-19 infection [25]. In another study, reduced olfactory bulb activity was associated with parosmia [25]. Parosmia and anosmia can be related, and loss of smell can evolve into parosmia in the context of SARS-CoV-2 infection [8].

Parosmia can be related to peripheral and central injuries by SARS-CoV-2, since it can affect OSNs and olfactory centers in the bulb [25]. The growth of new olfactory axons can occur in a non-organized manner and, as a consequence, it prolongs parosmia [8]. Data concerning post-infectious parosmia point to a poorer prognostic value towards the recuperation of smell ability, although olfactory training can help in the recovery of smell [8].

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