Olfactory dysfunction in the COVID-19 outbreak

Running title: COVID-19 and olfactory dysfunction

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Abstract

The first cases of coronavirus 2019 (COVID-19) occurred in Wuhan, China, and rapidly become a public health emergency of international proportions. The disease may cause mild-to-severe acute respiratory syndrome (SARS) and is caused by a SARS-CoV-2 coronavirus infection. The clinical manifestations of COVID-19 include fever, dry cough, fatigue, sputum production, shortness of breath, sore throat, and headache. This article is a narrative review with the aim of analyzing the current literature on postviral olfactory dysfunction (OD) related to SARS-CoV-2 pandemics. Since the initial anecdotal reports from China, international reports on COVID-19 patients have been increasing, describing a 5% to 85% range of loss of smell. To date, the literature is widely heterogeneous regarding the loss of smell; therefore, we advise home isolation measures and/or social distancing, and to carry out diagnostic tests for SARS-CoV-2 when possible in those patients with sudden and severe loss of smell who cannot be promptly evaluated.

Key words: Coronavirus, COVID-19, Taste disorder, Smell loss, Anosmia, SARS-CoV-2.

Resumen

Los primeros casos de la enfermedad por coronavirus 2019 (COVID-19) ocurrieron en Wuhan, China, y se propagaron rápidamente para convertirse en una emergencia de salud pública y de preocupación internacional. La enfermedad puede manifestarse desde una forma leve a un síndrome respiratorio agudo grave (SARS) y es causada por el coronavirus SARS-CoV-2. Las manifestaciones clínicas de COVID-19 incluyen fiebre, tos seca, fatiga, expectoración, dificultad respiratoria, odinofagia y cefalea. El objetivo de este estudio es revisar la literatura actual sobre la disfunción olfatoria (DO) posviral en lo que respecta a la pandemia de SARS-CoV-2. Se han publicado un creciente número de estudios a nivel mundial desde los casos anecdoticos inicialies en China, en los que se ha demostrado una prevalencia variable de pérdida de olfato en pacientes COVID-19 que va desde un 5 a un 85%. Hasta la fecha, la literatura es ampliamente heterogénea respecto a la pérdida de olfato, por lo que podemos advertir y recomendar a aquellos pacientes con pérdida del olfato súbita y grave que no puedan ser evaluados rápidamente, seguir medidas de aislamiento domiciliario y/o distanciamiento interpersonal, así como realizar pruebas de diagnóstico para el SARS-CoV-2 cuando sea posible.

Palabras Claves: Coronavirus, COVID 19, Alteraciones del gusto, Pérdida del olfato, Anosmia, SARS-CoV-2.

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Introduction

It is now widely recognized that respiratory symptoms of COVID-19 are extremely heterogeneous, ranging from minimal to severe symptoms that could progress rapidly to hypoxia and severe acute respiratory distress. The disease is very contagious and might sometimes be fatal. It is of the utmost importance to provide early diagnosis focusing on alarming symptoms to avoid the spread of the virus. A sudden and severe olfactory dysfunction (OD), in the absence of other respiratory diseases should alert physicians to COVID-19 infection.

This is a narrative review aiming to update the current knowledge on anatomy and physiology of olfactory pathways and providing more details on etiology of smell disorders and smell tests. In addition, the role of OD as a diagnostic criterion and a possible treatment in the context of the COVID outbreak is discussed.

Smell anatomy and physiology

Human sensory processes are mostly well understood (sight, hearing, perhaps even taste and touch); however, we still do not fully understand smell, the elusive sense. To date, scientists have not been able to explain how the human body's odour can act as a scented fingerprint. Researchers from all fields are coming together to solve the mysteries of olfaction.

The perception of flavour is perhaps the most multisensory of our everyday experiences. Flavour involves the combination of gustatory and olfactory stimuli, while it interacts with other sensory modalities, such as trigeminal perception, sight, and hearing [1].

The perception of odour is composed of orthonasal smell due to sniffing (eg, food aroma or the bouquet of wine) and retronasal smell located within the oropharynx and caused by airflow via the nasopharynx during swallowing or nasal exhalation. Apart from noticeable deficiencies in the detection of

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chemical gustometry (sweet, sour/acidic, bitter, salty, and savory/umami), “taste” disorders most commonly reflect inadequate stimulation of the olfactory receptors in the retronasal route [2].

The human olfactory neuroepithelium constitutes 1.25% of the nasal mucosa and covers an 8-10cm^2 area composed of the cribriform plate, the upper part of the nasal septum, and the middle/upper turbinates (Figure 1). About 10 million of the dendrites of olfactory receptor neurons in the olfactory bulb project to the mucosa. The odorants reaching the olfactory epithelium dissolve in the mucus layer and bind/activate olfactory receptors by a complex interaction often requiring odorant-binding proteins. One odour is capable of activating multiple receptor types to varying degrees [3].

Olfactory sensory neurons transduce the chemical message into nerve impulse emission frequencies and send them to olfactory glomeruli. Olfactory information is processed and integrated into the olfactory bulb. The axons of the olfactory bulb mitral cells successively cross the olfactory peduncle and olfactory tract before projecting onto the primary olfactory cortex. The information processed in the piriform cortex then projects to various brain areas: the orbitofrontal cortex, amygdala, hypothalamus, insula, entorhinal cortex, and hippocampus [4,5]. In humans, approximately 350 functional odorant genes encode specific protein receptors that interact with their own subset of chemicals or substances, leading to the complex mechanism of smell identification [6].

Furthermore, it is very important to know that neither the olfactory sensory neurons nor the olfactory bulb neurons express specific genes that are instead expressed in support cells, stem cells, and perivascular cells. These findings suggest that infection of non-neuronal cell types leads to anosmia and related disturbances in odour perception in patients [7,8]

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Loss of smell etiology

OD can be classified as either quantitative, involving strength alteration, or qualitative, in which case the quality of odours is changed. Normal olfactory function is defined as normosmia; quantitative disorders are classified into hyposmia (decrease in smell), functional anosmia (has no useful function in daily life), and anosmia (total lack of smell) [9,10]. Physiologically, our perception of smell changes with age. Although smell detection increases and peaks up to the fourth decade of life, smell recognition and identification significantly decline after the sixth decade [11].

OD plays an important role in daily living: it influences food selection and nutrient intake, enjoyment of food, socialization, overall quality of life (QoL), and detection of safety hazards from food poisoning and toxic agents [9]. Several studies have shown that olfactory impairment can affect QoL and may lead to depression [12]. Following that line, the improvement in sense of smell may be expected to be a potential antidepressant therapy [13].

Many disease states are associated with OD; among them are congenital causes, postinfectious disorders, sinonasal diseases, traumatic brain injuries, and neurodegenerative disorders.

- Regarding congenital anosmia (olfactory bulb hypoplasia or aplasia), it is highly recommended that Kallmann (hypogonadotropic hypogonadism) and Turner (absence of all or part of one X chromosome) syndromes be ruled out [14,15].
- Postviral upper respiratory infection could be due to a combined conductive and sensorineural/inflammatory disorder [16].
- Sinonasal diseases, such as allergic rhinitis or rhinosinusitis, can cause conductive and inflammatory disorders to arise from anatomic barriers that prevent odorants from reaching the olfactory epithelium and receptors [5,17].
- Neurodegenerative diseases, such as Alzheimer's and Parkinson's, are sensorineural disorders that arise from deficient reception or processing of a stimulus by the olfactory receptors, olfactory neurons, or central pathways to central nervous system centers of olfaction [18-20].

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- Traumatic head injuries are sensorineural disorders often overlooked by patients and their caregivers due to focus on initial stabilization and treatment of the patient [21-23].

The association between OD and smoking remains a controversy. Prior studies have found negative and positive effects of tobacco [24]. However, smoking cessation seems to improve both rated and measured olfactory function. A recent study included 3,900 patients with olfactory loss; 521 were current smokers and 316 former smokers. They concluded that patients with a history of smoking did not have a significantly lower olfactory function [25].

Additionally, multiple pharmacological treatments are related to DO. A study by Lötsch and co-workers [26] with a large sample identified an association between antagonistic targeting of the adrenoceptor α 1A (ADRA1A) and higher olfactory scores. It has been demonstrated that ADRA1A is the most common target among all those affected by the drugs reportedly influencing human olfaction, and it has been suggested that adrenergic activation enhances inhibitory transmission in the olfactory system. In addition, long-term treatments with aminoglycosides or tetracycline, and any use of opioids, cannabinoids, or sildenafil are known to affect olfaction [26].

Other types of medication that influence olfaction are potassium-sparing diuretics, antiplatelet drugs, α- and ß-blockers, and calcium channel blockers. It may be that potassium-sparing diuretics interfere with olfactory receptor activity because they comprise a large class of G-protein-coupled receptors that, once activated, are capable of triggering neuronal activity [27].

Ottaviano et al. found that the number of drugs taken (polypharmacotherapy) was demonstrated to be significantly correlated with greater olfactory loss in elderly patients [28].

Smell tests

Several techniques and tools are available to explore the olfactory capacity, each having its own advantages and disadvantages. It is important to note

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that of all these methods (subjective reporting, psychophysical, neurophysiological, and neuroimaging techniques), primarily subjective olfactometries and visual analogue scale (VAS) are complementary because they do not measure the same olfactory parameters, functions, and processes. Psychophysical testing for odour identification, discrimination, or threshold applied by a trained specialist is highly recommended to detect the severity of OD and to follow up on the progression/reversal of the loss of smell (Table 1).

Particularly in the research setting, combined psychophysical and electrophysiological tests have been developed to quantify olfactory ability with functional magnetic resonance imaging [29] and electro-olfactogram [30]. The limitations of these tests are that they cannot discriminate reliably between OD causes, and provide no information about the site-of-lesions.

COVID Pandemic

In the past two decades, humans have experienced two fatal coronavirus infections: the outbreaks of Severe Acute Respiratory Syndrome (SARS) in 2002, and Middle East Respiratory Syndrome (MERS) in 2012. Recently, a novel coronavirus has been introduced, SARS-CoV-2. The World Health Organization (WHO) named the disease coronavirus disease 2019 (COVID-19). The emergency pandemic of COVID-19 has swept across countries worldwide. More than two million (2,471,136 as April 22, 2020) have been diagnosed and almost 170,000 deaths have been reported [31].

The primary method of transmission is thought to occur from the spread of large droplets that carry virus particles. However, under certain circumstances, such as coughing, the virus particles can become aerosolized or airborne, which increases the risk of spread. Also, body fluids, direct and possible fecal-oral contact, have been proposed [32].

Transmission is mainly produced by symptomatic patients; however, a larger incubation period (which can last longer than 14 days) and asymptomatic

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shedding can exacerbate the infectivity of the virus, resulting in a large number of carriers [33]. This combination of being highly transmissible and asymptomatic carrier's contributes to its rapid spread [30-36].

As a newly emerging infectious disease, it is critical to understand and identify the key clinical characteristics of COVID-19 patients to aid in its early detection, isolation of infected individuals, and to minimize the spread of the disease. Based on a recent meta-analysis (38 studies involving 3,062 COVID-19 patients in China), the most common symptoms were fever, fatigue, cough, dyspnea, and expectoration, and less often, rhinorrhea or sore throat. A relatively small percentage of patients were asymptomatic (11%) [33]. Common laboratory findings include lymphocytopenia and increased values of C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, and erythrocyte sedimentation rate (ESR). On chest X-ray or chest computed tomography, bilateral lung involvement was common [32,37]. Diagnosis of SARS-CoV-2 is currently performed with reverse transcription polymerase chain reaction (PCR-RT) testing for nucleic acid sequence homology in nasopharyngeal or throat swabs [38].

A considerable age dependency has been described in symptomatic infection (susceptibility) and outcome (fatality). Compared with those aged 30-59 years, the populations aged below 30 and above 59 years were 0.6 and 5.1 times more likely to die after developing symptoms, revealing that the risks of symptomatic infection increased with age (eg, at ~4% per year among adults aged 30-60 years) [39]. Patients' comorbidities, such as circulatory diseases including hypertension and coronary heart diseases or diabetes, yielded poorer clinical outcomes [40].

COVID 19 and olfactory dysfunction

The occurrence of smell dysfunction in viral infections is not new. Many viruses may lead to OD through an inflammatory reaction of the nasal mucosa and further development of rhinorrhea; the most familiar agents are rhinovirus, parainfluenza, Epstein-Barr virus, and some coronaviruses. Overall,

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spontaneous improvement rates in patients after upper respiratory infection have been reported between 35-67%. Follow-up of postviral olfactory loss revealed that over 80% of the patients reported subjective recovery after one year [41]. The exact pathophysiology of postviral OD is not well understood. No specific upper respiratory symptoms allow COVID-19 to be reliably distinguished from other types of viral respiratory infections.

Because the respiratory epithelium is the primary site of SARS-CoV-2 attachment and infection, as with many other respiratory viruses, it may not be surprising for COVID-19 to affect the olfactory neuro-epithelium having an impact on smell and flavour [42]. Recently, our team has demonstrated that two out of three patients with the common cold or postviral acute rhinosinusitis have impaired smell, this being associated with disease severity [16].

In January 2020, angiotensin-converting enzyme 2 (ACE2) was identified as the functional receptor for SARS-CoV-2, which is present in multiple human organs, including the central nervous system (CNS) and skeletal muscles. The expression and distribution of ACE2 remind us that the SARS-CoV-2 may cause some neurologic manifestations through direct or indirect mechanisms. Autopsy results of patients with COVID-19 showed that the brain tissue was hyperemic and edematous, and some neurons were degenerated [43].

Neurologic injury has been confirmed in the infection of other CoVs, such as in SARS-CoV and MERS-CoV. Researchers detected SARS-CoV-2 nucleic acid in the cerebrospinal fluid of patients and also in their brain tissue on autopsy. The virus may enter the CNS through a hematogenous or retrograde neuronal route [44] (Figure 2). Previous studies have shown the ability of SARS-CoV to cause neuronal death in mice by invading the brain via the nose close to the olfactory epithelium [45].

Since the initial anecdotal reports from China, an increasing number of international reports of COVID-19 patients describe a 5% to 85% range of smell loss (Table 2). A study from Iran based on online surveys showed a significant increase in new-onset anosmia since the COVID-19 outbreak [42].

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Researchers found a strong correlation between the number of self-reported anosmia/hyposmia cases and COVID-19 cases. Later, a survey in confirmed COVID-19 patients reported an 87% prevalence of olfactory impairment [42].

Vaira et al. reported, in 320 COVID-19 patients, 19.4% anosmia. However, the study does not report the method used to determine how the smell loss was measured [46].
A study from China reported that the ratio of hospitalized patients complaining of smell loss and taste loss was only 5.1% and 5.6%, respectively [44]. Three categories for neurological manifestations were described: CNS (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system (taste impairment, smell impairment, vision impairment, and nerve pain), and skeletal muscle injury. However, the data were retrospectively collected from medical files, which might have led to an underestimation of the real prevalence, because these symptoms might not be spontaneously reported if not searched for.

Another study from the United Kingdom included 579 positive and 1123 negative COVID-19 patients. The authors concluded that the loss of smell and taste (59.4%) is a strong predictor of having been infected by the COVID-19 virus [47].

Gane et al. correlated the number of diagnosed cases of COVID-19 in the United Kingdom with the increase in reported and referred to sudden anosmia in social media in the early days of the pandemic [48]. Later on, sudden complete loss of smell was reported in a patient without nasal obstruction. Sinus CT/MRI scans revealed bilateral inflammation of the olfactory clefts with normal olfactory bulbs and tracts [49]. Villalba et al. described two elderly patients evaluated at emergency departments for anosmia/dysgeusia in the absence of any other respiratory symptoms. Clinical and biological workups led to a diagnosis of COVID-19 infection [50].

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A case-series study (n=23) from Iran showed OD in 83% of patients [51]. Another study (n=42) from Israel reported OD in 35.7% [52].

The first European study included 59 hospitalized patients in Italy. Twenty of them (33.9%) reported at least taste or olfactory disorders, and 11 (18.6%) reported both symptoms. Twelve patients (20.3%) had the symptoms before hospital admission, whereas 8 (13.5%) experienced the symptoms during the hospital stay [53].

In a population-based study in Iceland, 528 (11.5%) COVID-19 patients demonstrated OD [54]. Moreover, Benezit et al. studied 68 COVID-19 patients in France and concluded that 45% had OD [55].

Yan et al. included a total of 1480 patients from the United States with influenza-like symptoms who underwent COVID-19 testing. Smell and taste loss were reported in 68% and 71% of COVID-19-positive subjects (n=59), respectively, compared with 16% and 17% of COVID-19-negative patients (n=203) ($p<0.001$) [56].

Klopfenstein et al. analyzed 114 confirmed COVID-19 patients from France, and reported anosmia in 47% of patients, together with dysgeusia in 85%. Anosmia was never the first or second symptom to develop, but the third in 38% of cases. Anosmia developed 4.4 days after onset of infection [57]. Similar results from Italy (n=202) reported 64.4% [58].

Wee et al. from Singapore concluded that self-reported OD had high specificity as a screening criterion for COVID-19 in an Asian cohort (154). Patients with COVID-19 appeared to have higher odds of OD (27.7%) compared with those positive for other respiratory viruses [59].

A total of 417 COVID-19 patients from 12 European hospitals were included in a multicentre study from France, Belgium, Italy, and Spain. Researchers reported that 85.6% had OD (79.6% anosmic and 20.4% hyposmic), with an

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impact on patients' QoL, and 88.8% had gustatory disorders. The OD appeared before (11.8%), after (65.4%), or at the same time as the appearance of general ear, nose, and throat (ENT) symptoms (22.8%). OD linked to COVID-19 infection attracts special interest because it is not associated with rhinorrhea [60].

Furthermore, an international cross-sectional study by Kaye et al. with 237 COVID-19 patients reported OD in 73% [61].

Currently, due to limitations related to the diffusivity of the disease and emergency contingencies, it is impossible to perform a structured questionnaire and validated smell tests. Future studies using well-validated instruments of olfaction will be important to corroborate these patient-reported subjective assessments of OD. To date, there is only one study using smell quantitative assessment (University of Pennsylvania Smell Identification Test), which demonstrated that 98% of COVID-19 patients (n=60) exhibited some smell dysfunction, 33% having severe hyposmia and 58% anosmia (Table 1) [62].

Nasal biopsies from patients with postviral anosmia are characterized by extensive cicatrization, decreased numbers of receptor cells, absent or fewer cilia on remaining receptor cells, and replacement of sensory epithelium with respiratory epithelium [63]. However, in the absence of complete olfactory assessment (smell test and nasal endoscopy), the precise aetiology of COVID-19 remains undetermined. Clinical outbreak response tasks require the adoption of strict infection control, as well as personal protective equipment (PPE) and practices to minimize the risk of infection [64]. Many of these PPE are rarely used in daily practice and can be cumbersome, uncomfortable, and stressful to wear.

Theoretically, procedures based on RT-PCR are able to detect even a small number of viral RNA particles in biological samples. However, in practice, due to several technical factors, there must be much more viral load in the

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biological material collected to achieve a reliable diagnosis. Olfactory epithelium biopsy may possibly serve as a tissue source for early virus detection to minimize false-negative test results [65].

Two possibilities seem likely: during an upper respiratory infection, it is common to experience some smell loss as a result of nasal inflammation, mucosal edema, and obstruction of airflow into the olfactory cleft, or a post-viral anosmia syndrome with direct infection and inflammation of the olfactory mucosa and neurodegeneration of the olfactory sensory neurons. Damage to the peripheral nervous system and its dysfunction, with anosmia or hyposmia, could be a relevant indicator of disease progression [66,67].

Postviral anosmia treatment

The medical community is rapidly accruing information, and standards are likely to change quickly with additional results. We must learn from one another as the disease crosses the globe to integrate the lessons into practice.

Postviral anosmia is the most common cause of OD. Several treatments have been presented in the literature. Overall, there is no strong evidence for any pharmacologic treatment of postviral anosmia [68]. Similarly, we could deal with OD during the COVID-19 era as though it were postviral anosmia, taking into account that there is no specific treatment and therefore we should follow the same recommendations and management.

Treatment strategies depend upon what regions of the olfactory pathways are negatively impacted. In cases where obvious oral, nasal, or intracranial pathology is involved, rational straightforward approaches to treatment are often available. In cases where damage to the sensory pathways is secondary to chronic inflammatory disease, trauma, viral invasion, toxic exposure, or unknown causes, the direction for therapy is more challenging [63].

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Corticosteroids

Corticosteroids (CSs), both topical and systemic, improve olfaction in patients suffering from chronic rhinosinusitis [69]. Ethmoid tissue eosinophilia is associated with OD in nasal polyps, independent of disease severity. These results suggest a possible role for eosinophils or eosinophil-associated cytokines in CRS-associated olfactory loss.

However, for OD unrelated to sinonasal disease and without overt evidence of nasal inflammation, the exact treatment options are not well studied. Studies testing the efficacy of therapies for postviral OD, including steroids, had conflicting evidence. The benefit of CSs is less clear, but physicians still commonly use them as first-line therapy. CSs are hypothesized to improve olfactory function through their anti-inflammatory effects and regulation of the sodium and potassium-adenosine triphosphate enzyme found in olfactory receptor neurons [70]. A recent systematic review suggests using CS rinses to improve olfactory outcomes in select patients, with weaker evidence supporting the use of oral CSs. Topical CSs sprays do not improve OD in this patient population and are not recommended [71]. On the other hand, reports have demonstrated that the use of CSs may escalate COVID-19 infection. Yang et al., conducted a systematic review and meta-analysis concluding that CS use is associated with increased lung injury or shock and mortality in patients with CoV-pneumonia [72]. Although intranasal CSs are not recommended for sudden and severe smell loss in COVID-19 patients, when they are receiving them for the treatment of sinonasal diseases, such as rhinitis or chronic rhinosinusitis, drug discontinuation is not recommended [73].

Olfactory Training

It is well known that in subjects without OD manifestation, threshold sensitivity improves as a result of odorant exposure and/or repeated testing. Some clinical studies report that systematic exposure to odorants or “olfactory

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training" (OT) may be beneficial to some persons with hyposmia or anosmia [74-76].

Damm et al. conducted a randomized, controlled, multicenter study. They concluded that OT is a safe procedure and appears to be particularly useful in patients who start within 12 months after the onset of the OD. OT improves OD, and the use of odors at higher concentrations is beneficial to improvement. Authors recommend OT as a first successful therapy regime in patients with postviral anosmia [77].

Vitamins

Vitamin A (b-carotene or retinol) is listed as a putative treatment for smell loss. The initial use of vitamin A in the chemical senses was based upon the idea that a pigmented epithelium is critical for olfactory transduction. Intranasal vitamin A at a dose of 10,000 IU per day for 2 months may be useful in the treatment of postinfectious olfactory loss [78].

Concluding Remarks and Recommendations

A sudden and severe olfactory or taste dysfunction, in the absence of other respiratory diseases like allergic rhinitis, acute rhinosinusitis, or chronic rhinosinusitis, should alert physicians to COVID-19 infection. Assessing the sense of smell in these patients may be helpful to identify who requires quarantine and/or early treatment. A fast-moving pandemic demands equally agile research techniques using real-time data collection. Assessing loss of smell with subjective self-reported or psychophysical tests could help the early detection of infected patients and reduce the number of carriers, avoiding the spread of the virus. To date, with widely heterogeneous studies in the literature since the COVID-19 outbreak, we advise home isolation measures and/or social distancing and carry out diagnostic tests for SARS-CoV-2 when possible in those patients with sudden and severe loss of smell. Olfactory

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training, as a treatment, may be beneficial for some patients with permanent loss of smell after COVID-19.

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Conflicts of Interest

- Isam Alobid: Consultant for Roche, Novartis, Mylan, Menarini, MSD
- Joaquim Mullol: member of national or international advisory boards, received speaker fees, or funding for clinical trials and research projects from ALK, AstraZeneca, Genentech, GlaxoSmithKline, Glenmark, Menarini, Mitsubishi-Tanabe, MSD, Mylan-MEDA Pharma, Novartis, Regeneron Pharmaceuticals, SANOFI-Genzyme, UCB Pharma, and Uriach Group.

The other authors declare that they have no conflicts of interest.

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Figure legends.

Figure 1. Human olfactory pathways. BG: Bowman gland, GC: granule cell, GBC: globose basal cell, Glom: glomerulus, HBC: horizontal basal cell, HC: hippocampus, CP: cribriform plate, LEC: lateral entorhinal cortex, LON: lateral olfactory nucleus, MC: mitral cell, OB: olfactory bulb, ORN: olfactory receptor neuron, PC: piriform cortex, TC: tufted cell, SC: sustentacular cell

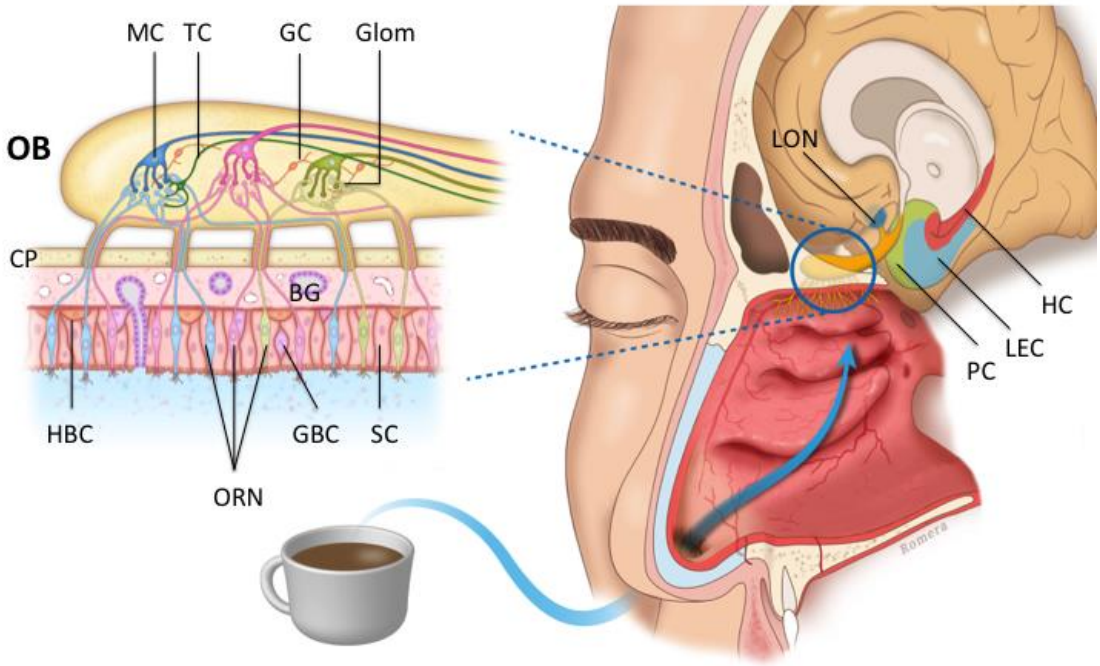

Figure 2. Potential mechanism of induced neuro-degenerative effects of SARS-CoV-2 coronavirus in human olfactory pathways. OB: olfactory bulb, ONE: olfactory neuroepithelium.

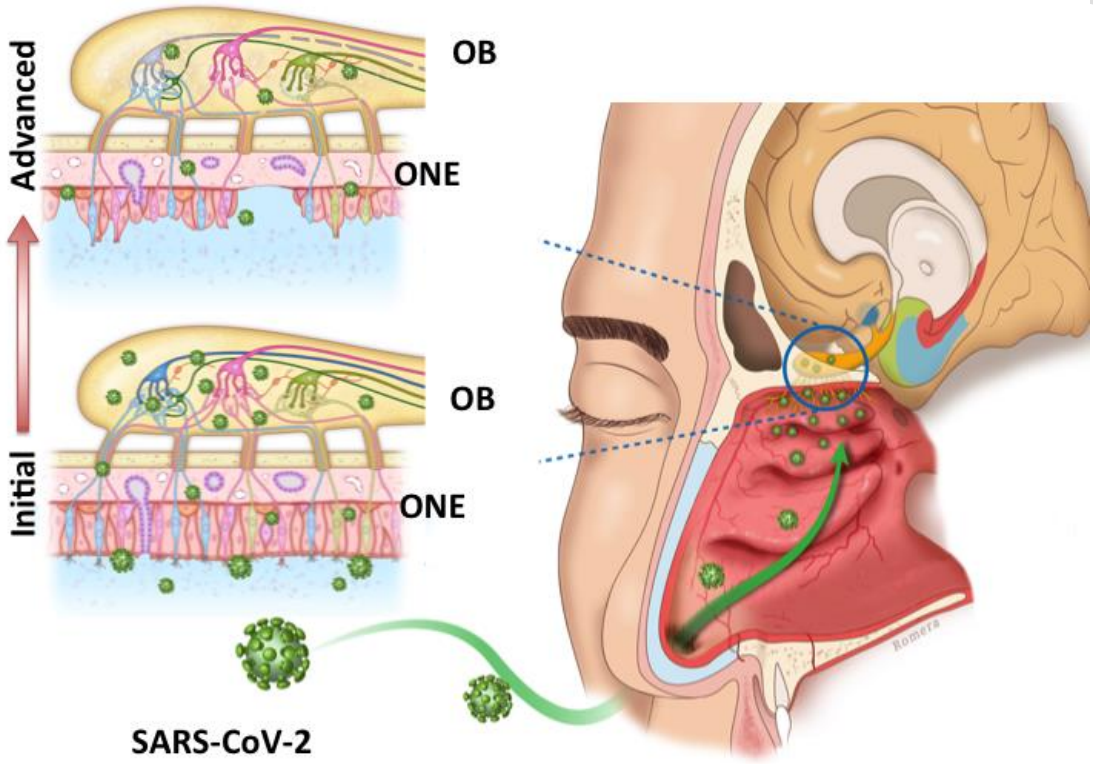

Table 1. List of validated subjective olfactory diagnosis tests.

University of Pennsylvania Smell Identification Test (UPSIT)
Connecticut Chemosensory Clinical Research Center Test (CCCRC)
Smell diskettes test (SDT)
Odorant confusion matrix (OCM)
Dutch odour identification test (GITU)
YN-odour Identification Test (YN-OIT)
T&T Olfactometer
San Diego Odor Identification Test (SDOIT)
Cross-Cultural Smell Identification Test (CC-SIT)
Combined olfactory test (COT)
Sniffin'-Sticks
Candy smell test (CST)
Alcohol Sniff Test (AST)
Identification Test (CA-UPSIT)
Kremer smell test (KST)
Scandinavian Odour-Identification Test (SOIT)
Pocket Smell Test (PST)
Eloit and Trotier Olfactory Test (ETOT)
Four-minute odour identification test
Ramdon Test
Barcelona Smell Test (BAST-24)
Nez du Vin smell test
Paediatric Barcelona Olfactory Test-6 (pBOT-6)
Universal Sniff Test (U-sniff), for children
Visual Analogue Scale (VAS, 0-10cm) for Loss of Smell or Taste

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Table 2. Summary of published data on olfactory and test dysfunction after SARS-CoV-2 infection.

Author	Country	Patient (N)	Female %	Age, years, mean (SD/range)	COVID-19 positive	Study design	Effect on Smell & Taste (%)
Bagheri, et al. [42]	Iran	10069	71.1	32.5 (8.6)	-	Cross-sectional study, Self-reported online checklist	Smell loss (87)
Mao, et al. [44]	China	214	59.3	52.7 (15.5)	214	Retrospective, observational case series. Electronic medical records, laboratory and radiologic findings	Smell loss (5.1) Taste loss (5.6)
Menni, et al. [47]	UK	1702	69	40.8	579	Cross-sectional study	Loss of smell and taste (59.4)
Heidari, et al. [51]	Iran	23	65	37.4	23	Case-series study	Smell loss (83)
Levinson, et al. [52]	Israel	45	45.2	Median 34 (15-82)	42	Cross-sectional study	Smell loss (35.7)
Giacomelli et	Italy	59	32.2	60 (50-74)	59	Cross-sectional study.	At least smell or

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al. [53]						Self-reported smell and taste loss (questionnaire)	taste loss (33.9) Both (18.6)
Gudbjartsson, et al. [54]	Iceland	4551	47.7	40.3±18.4	528	Population-based study	Smell loss (11.5)
Benezit, et al. [55]	France	259	-	-	68	Cross-sectional study	Smell loss (45) Taste loss (62)
Yan, et al. [56]	USA	1480	49	Stratified by decade (18-79)	102	Cross-sectional study, subjective olfaction score of 1-10	Smell loss (68) Taste loss (71)
Klopfenstein, et al. [57]	France	114	67	47 (16)	54	Retrospective observational study	Smell loss (47) Taste loss (85)
Spinato, et al. [58]	Italy	202	52	Median 56 (20-89)	202	Cross-sectional study, Sinonasal Outcome test 22 (SNOT-22)	Loss of smell and taste (64.4)
Wee, et al. [59]	Singapore	870	-	-	154	Cross-sectional study, Self-reported smell and taste loss	Loss of smell and taste (22.7)

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Lechien, et al. [60]	Belgium, Spain, Italy and France	417	63.1	36.9 (11.4)	417	Prospective multicentric study. Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS)	Smell loss (85) Taste loss (88)
Kaye, et al. [61]	US, Italy, Mexico, UK	240	54	39.6 ±14.6 (2-89)	237	Cross-sectional study	Smell loss (73)
Moein, et al. [62]	Iran	60	33	46.5 (12.2)	60	Case-control study Psychophysical test: University of Pennsylvania Smell Identification Test (UPSIT)	Smell loss (12) Taste loss (7) Both (17)

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