



Post Viral Olfactory Dysfunction After SARS-CoV-2 Infection: Anticipated Post-pandemic Clinical Challenge

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Abstract Persistent olfactory dysfunction (OD) is the second most common symptom of post coronavirus disease-19 (COVID-19) now being termed long-COVID. Its prevalence after recovery from COVID-19 is estimated to be 12% after nearly 6 months of follow-up. It thus becomes imperative for the treating clinicians to update themselves with the pathophysiology of this post COVID disability as well as the tools for diagnosis and the available treatment options. A systematic literature search was performed as per PRISMA guidelines in MEDLINE, Cochrane Library, LILACS, Google Scholar, *ClinicalTrials.gov*, and medRxiv databases. The keywords used were *covid-19*, *Olfactory Disorders*, *Smell*, *Anosmia*, *PVOD*, *Post Viral Olfactory Disorders*, *post-covid* and *post haul*. All articles were studied for definition, mechanism, diagnostic tests and treatment options for post COVID OD. 33 published articles and 8 ongoing trials were found relevant and included after full-text review. SARS-CoV-2 can cause conductive, neural and central OD. Olfactory evaluation can be done both subjectively (visual analogue scale) and objectively (Sniffin' sticks, Sinonasal Outcome Test, University of

Pennsylvania Smell Identification Test and modified Davidson's alcohol sniff test). They can be used to detect and follow-up patients. Despite several on-going clinical trials, the most reliable and advisable treatment option available till date is olfactory training.

Keywords COVID-19 · Olfaction disorders · Anosmia · Post COVID · PVOD · Long-COVID · Post viral

Introduction

New onset olfactory dysfunction (OD), in the form of hyposmia, anosmia or parosmia, was identified as a conspicuous feature of coronavirus disease 2019 (COVID-19), in the initial months of the pandemic. Albeit ODs in COVID-19 mostly improve within 7–20 days of symptom onset, a significant proportion of survivors (12–65% after about 1 month of symptom onset) are still left with a lasting debility despite viral clearance [1, 2]. With a major portion of world population already infected by SARS-CoV-2, there is an expected increase in the proportion of out-patients presenting with such post-viral olfactory disorder (PVOD) in coming months. This population will further be augmented with the advent of COVID-19 vaccine which shows decrease in the severity of disease, to forms which are known to have higher prevalence of OD [3].

The persisting effects of COVID-19 after initial illness are now being termed as long-COVID. In the long run, the treatment of PVOD will be important because it is a common symptom of long-COVID, second only to dyspnea [1]. Despite being regarded as an innocuous symptom, OD leads to a significant impediment in quality of life. This disability is associated with a higher chance of decrease in

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appetite leading to undernutrition, and even depression. Due to the inability to smell for dangerous odours, ODs also pose people at increased risk of injuries which can at times be life-threatening. It thus becomes imperative for treating clinicians to update themselves with the pathophysiology of the PVOD as well as the tools for diagnosis and the available treatment options.

Methods

A thorough literature search was conducted on the databases MEDLINE, Cochrane Library, LILACS, Google Scholar, *ClinicalTrials.gov*, and medRxiv between 12-12-2020 and 21-12-2020 using the MeSH terms covid-19 AND (Olfactory Disorders OR Smell OR Anosmia) and Keywords (covid-19 OR corona virus) AND (PVOD OR Post Viral Olfactory Disorders OR post-covid OR post haul). The search was further augmented by hand-searching of the relevant articles. A total of 1772 articles were found. After a preliminary filtering by titles, 325 articles were selected for abstract review. Finally, 147 articles were taken up for full text review. Of which 42 were eventually found relevant to the subject, which included 8 ongoing clinical trials (registered on *ClinicalTrials.gov*). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart is depicted in Fig. 1. All

included articles were studied for definition, mechanism, diagnostic tests and treatment of PVOD after COVID-19.

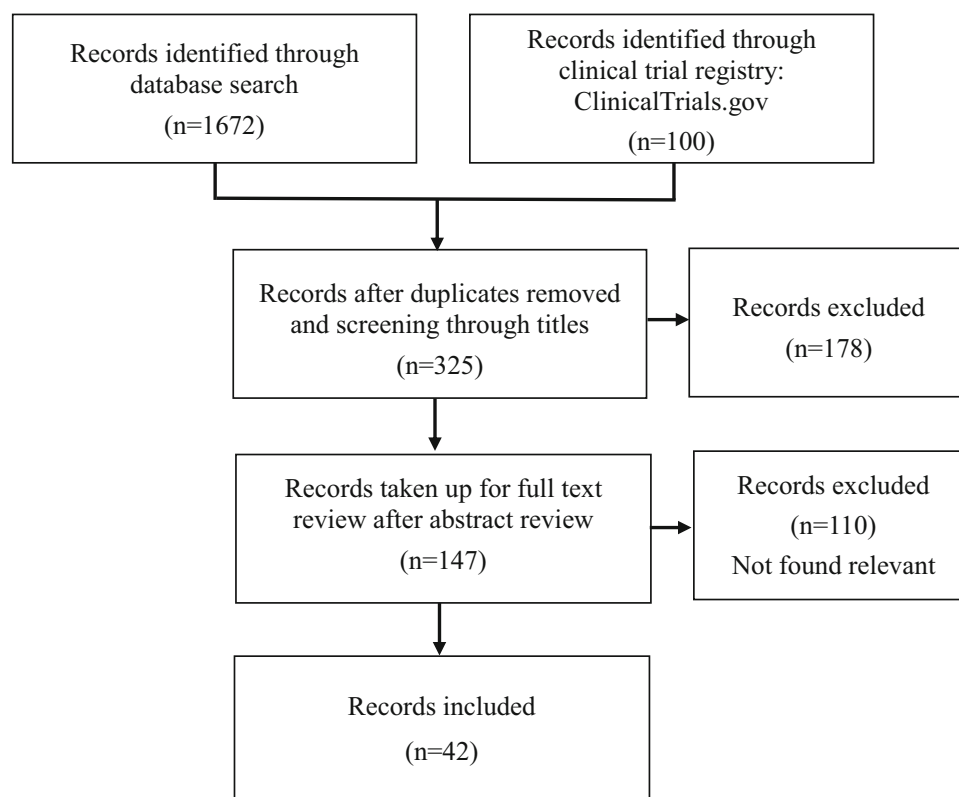
Discussion

The prevalence of ODs among patients with active COVID-19, is reported as high as 61% with an even higher number being detected using objective tests [4]. It is more prevalent in young adults, women and Caucasians and less prevalent in children and elderly [5, 6]. All the more, a staggering 12% of patients continued to be affected with PVOD after 1.5 to 6 months of remission of COVID-19 [1]. Despite ample research and multiple hypotheses for causation, we have yet to reach a consensus in defining PVOD for starting intervention, and evaluating and treating it.

When to Label PVOD in COVID-19 Patients?

In their study, Kosugi EM et al. [2] conducted an online survey for sudden onset OD in active COVID-19, and estimated the median time for recovery to be 15 days (IQR 10–21 days) with a full recovery in 52.6% individuals at the end of 15 days. The recovery was observed to be more frequent in cases of hyposmia in comparison to anosmia. However, 46% and 19% individuals reported partial and no

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart



recovery respectively after a median 31 days follow-up. While, Stavem et al. [1] conducted a postal survey for PVOD, and reported 12% prevalence in COVID-19 survivors, with a median follow-up of 117 days, in a population-based cohort study. Although subjectively, majority of sufferers of sudden onset OD due to COVID-19 infection report improvement in olfaction, objective tests reveal that only half of patients with persistent hyposmia actually realized their persistent disability in olfactory identification and discrimination [7].

In a 60 day prospective objective olfactory assessment of COVID-19 infected patients with sudden onset ODs [8], authors deduced that risk of PVOD became significant after 20 days from onset of OD (odds ratio 58.5, 95% confidence interval 3.278–1043.5, $p = 0.005$). The patients with moderate OD at 20 days improved by the end of 60 days observation period, but the 20% patients in the cohort who had severe OD at end of 20 days, continued to persist with the problem even after 60 days of follow-up period. So, based on the available evidence, patients suffering with persisting OD after 20 days of symptom onset, should be labelled PVOD and considered for therapy. However, a definite consensus is yet to be reached.

How Does SARS-CoV-2 Cause Olfactory Dysfunction?

Traditionally, ODs due to viral infection are mainly attributed to mucus deposition over the sensory mucosa and decreased air entry, secondary to nasal congestion and rhinorrhoea. But, SARS-CoV-2 is hypothesized to cause OD by all three known ways: conductive dysfunction, by preventing odorant from reaching neuroepithelium; sensorineural dysfunction, by damage/loss of olfactory neuroepithelium or olfactory sensory neurons (OSNs); and central dysfunction, by damage or loss of olfactory processing pathways in the CNS.

Lechien et al. [9] found OC obstruction on computed tomography (CT) scans in 3 of 16 anosmic patients. Eliezer et al. [10] evaluated the olfactory clefts (OCs) and olfactory function in a cohort of OD inflicted COVID-19 patients, and found that early in the disease, patients developed OD as well as OC obstruction, as evident on magnetic resonance imaging (MRI). On follow-up at one month both OD and OC obstruction had improved in most patients except a few, who remained affected with PVOD after 1 month, despite reversal in OC obstruction. However, Kandemirli et al. found olfactory cleft opacification in CT scans of 73.9% of recovered COVID-19 patients with OD persisting after one month [11]. So, OC obstruction in active COVID-19 may be, in part, responsible for the OD as it prevents inhaled odorants from reaching the olfactory epithelium. Yet, this alone cannot fully explain the

persistent and delayed smell disturbances especially in the post recovery and long-haul patients. It is especially interesting to note that, 66.9% of COVID-19 patients with anosmia do not complain of nasal congestion (cf. other flu illnesses) [5].

The second and the major mechanism of ODs hypothesized in COVID-19 infection is, injury to non-neuronal cells in olfactory epithelium, causing secondary damage to OSNs. These cells include sustentacular cells, microvillar cells, Bowman's gland cells, horizontal basal cells, and olfactory bulb pericytes in olfactory epithelium. Brann et al. found that these cells express angiotensin-converting enzyme-2 (ACE-2) in significantly higher quantities than the surrounding olfactory epithelium. ACE-2 is the principal mechanism used by the virus for entry into host cell after priming of spike (S) protein using host proteases [12, 13]. Transmembrane serine protease 2 (TRPMSS2) is one such protease which is also expressed along with ACE-2 in similar cells. Higher ACE-2 expression in adults as compared to the children also correlates with the higher prevalence of the disease in adults [14]. Body reacts to this insult with release of proinflammatory cytokines in the vicinity, especially tumour necrosis factor- α (TNF- α), first leading to physiological desensitization of OSNs and later neuronal loss, causing sensorineural olfactory loss [15, 16]. When the insult ceases, OSNs re-sensitize, and in case of neuronal loss, basal cells are able to regenerate new olfactory neurons and the individual eventually regains sense of olfaction.

Since Brann et al. also found that OSNs do not express ACE-2, the aforementioned hypothesis fails to explain the presence of SARS-CoV-2 in brains of murine models which were inoculated with the virus, intranasally [17]. In vitro studies revealed, neuropilin-1 (NRP1) as another host factor which binds to the primed S protein of SARS-CoV-2 and is responsible for entry into host cell [18, 19]. NRP1 is found abundantly in OSNs and axons of mitral cells but not in the olfactory epithelium [20]. In an in silico study by Davies et al., NRP1 was found abundantly expressed in parts of the brain concerned with olfaction, as olfactory tubercles and para-olfactory gyri [21]. It can thus be hypothesized that with the possible role of NRP1, SARS-CoV-2 invades the brain by retrograde axonal transport from nasal cavity, quite similar to human herpes virus [22]. However, more evidence is required for elucidating the exact mechanism. Additional molecules, as BSG and PIKfyve, are also being identified as contributors to mediation of infection [23].

Kandemirli et al. [11] conducted Magnetic Resonance Imaging on COVID-19 recovered patients with OD persisting after one month of onset, and found that, 54.2% of cases had changes in normal inverted J shape of the bulb. 91.3% of cases had abnormality in olfactory bulb signal

intensity like diffusely increased signal intensity, scattered hyperintense foci or microhaemorrhages. Evident clumping of olfactory filia was seen in 34.8% of cases and thinning with scarcity of filia in 17.4%. Primary olfactory cortical signal abnormality was seen in 21.7% of cases. Axiomatically, the resultant axonal injury, neuronal loss and microhaemorrhages in olfactory bulb, can be considered important contributors and an explanation to PVOD in long-COVID.

What Are the Available Tools for Evaluation of Olfactory Dysfunction?

For long, the Sniffin' Sticks test and Sinonasal Outcome Test (SNOT) -22 tests were used widely for diagnosing as well as following up of patients with OD. But these tests score low on the scale of feasibility for implementation in the out-patient setting. The COVID-19 pandemic and the need for distancing has led to the invention of new scales and tools for the same purpose which have proved to be both handy as well as helpful in limiting contact with the patients.

Subjective test being used popularly now is visual analogue scale (VAS) of European position paper on rhinosinusitis and nasal polyps (EPOS) which is both feasible and cheap. Among objective tests, a modification of Davidson's alcohol sniff test was tested as a screening tool for COVID-19 [24]. It has shown a sensitivity of 75% in a Phase II trial with odds ratio of 6.56 with 10% ethanol. It offers a non-cumbersome and easy option for screening of COVID-19. Another standardised test available for olfactory identification is University of Pennsylvania Smell Identification Test (UPSIT). It has been proven of value in the pandemic especially because it also limits contact with patient. Although it has been used for evaluating olfaction in Iranians [25] and shown higher detection of OD than subjective tests, it has a certain downside to its use. It is resource intensive as the materials need to be disposed after single use. In addition, a validated set of odorants needs to be prepared for every region pertaining to the differences in culture and food habits of people.

Despite increased availability of tests and questionnaires as screening tools for COVID-19, there is a lack of validated and handy tools for use as point-of-care olfactory tests for diagnosing and following-up OD. There is an ongoing trial at the time of writing this article led by Maes R P in Yale New Haven Hospital for validation of a rapid quantitative test for loss of smell (ClinicalTrials.gov Identifier: NCT04431908).

Otte et al. [26] evaluated the OD objectively in 91 patients after a mean of 57.94 days and concluded that there was a poor correlation between measured olfactory performance and patients' self-assessment as nearly

51.35% (19 patients) who had hyposmia objectively, did not realize it. Based on the available evidence, we recommend baseline objective and subjective tests at onset of symptoms in active COVID-19 and only subjective tests in case of PVOD in long-COVID, to target the subjective relief in symptoms.

What Are the Options for Treatment of PVOD?

Throughout the past year of pandemic, the modality of treatment for persistent OD has been debated. Physicians have used olfactory training, saline nasal irrigations and corticosteroids, both intranasal and systemic, for initiation of treatment for OD [2, 27]. Treatment options for persistent OD after viral infections, in general, has been systematically reviewed by Hura N et al. based on the evidence of the studies of which they have recommended olfactory training to be the best treatment modality [28]. Specifically for PVOD after COVID-19, there is a repertoire of pharmacological options, but are yet to be proven. Table 1 enlists the ongoing trials for potential pharmacological options for treatment of PVOD in long-COVID at the time of writing the article. For prevention of PVOD, in vitro studies have shown that a protease inhibitor, camostat mesylate, inhibits the cell entry of SARS-CoV-2 and thus is a potential therapeutic agent during active COVID-19 [29]. It has also been hypothesized that nasal lavage with ACE-2 antagonist or angiotensin receptor blocker will also help in reducing viral load in COVID-19, which we believe, can in turn can decrease the incidence and severity of PVOD itself [30].

Olfactory Training (OT) is a promising and cost-effective solution to sensorineural olfactory loss [31]. It is based on the principle similar to that of physical therapy after a neurologic insult or balance therapy for vestibular disease. After a neural insult, repeated stimulation and retraining can help reorganize functional network with a resultant significant gain of function or compensation [32]. Traditional OT involves exposure to four intense odours twice daily [33]. Modified OT involves exposure to 3 sets of 4 different odours, changed every 12 weeks [34]. This exercise is generally done for at least 6 to 8 months. Both traditional and modified OT are shown to have a significant improvement in olfaction, although the superiority of either one has not been clearly established. A higher efficacy of high concentration odorants has also been demonstrated over low concentration odorants in OT for post infectious OD [35]. A harmless intervention as OT can be considered early in the disease. However, it is practically irrelevant to implement *en masse* an intervention with high demand of manpower, considering majority of olfactory dysfunctions in COVID-19 are reversible. A better OT programme can

Table 1 List of clinical trials on post viral olfactory dysfunction after coronavirus disease-19 registered with ClinicalTrials.gov

Principal investigator (ClinicalTrials.gov Identifier)	Drug/intervention	Phase	Study type	Primary outcome(s)	Secondary outcome(s)	Rationale
Iloreta AM (NCT04495816)	Omega-3 Fatty Acid Supplement versus Placebo	2	Randomised, parallel arm Control Trial	BSIT at Week 0 Week 6	1. mQOD-NS at 1 week 2 weeks 4 weeks 6 weeks 2. SNOT-22 at 1 week 2 weeks 4 weeks 6 weeks	Preclinical studies have shown improvement in OD in mice receiving the drug RCT in humans receiving the drug after endoscopic endonasal skull base surgery have shown greater return of normal olfaction
Abdelalim AA (NCT04484493)	Mometasone furoate nasal spray dose of 2 puff in each nostril (100 µg once daily each nostril) alongwith Olfactory Trining versus only Olfactory Training	3	Randomised, parallel arm, clinical trial	Improvement of olfaction after 3 weeks in subjective scoring of 0–10	NP	Olfactory improvement improved with the drug in other PVOD [28]
NP (Trial not yet recruiting at the time of writing this article) (NCT04422275)	Four study arms: Budesonide nasal lavage with OT with high concentration essential oils; Placebo with OT with high concentration essential oils; Budesonide nasal lavage with OT with low concentration essential oils; placebo with OT with low concentration essential oils	2	Blinded Randomised, parallel arm clinical trial	UPSIT at Week 0, 12 and 24	1. QOD-NS between baseline and assessment time frame 2. Global Rating of Smell at 12 weeks 3. Global Rating of Change of Smell at 12 weeks and 24 weeks	Olfactory improvement improved with the drug and OT in other PVOD
Al-Ani RM (NCT04569825)	Steroid (Ophtamesone) local application intranasally as drops versus normal saline drops	1	Randomised parallel-arm clinical trial	Recovery rate of anosmia and recovery time	NP	Olfactory improvement improved with the drug in other PVOD
Issak ER (NCT04528329)	Early Dexamethasone: early use of dexamethasone as early as laboratory evidence of high inflammatory markers versus Late Dexamethasone: Use of dexamethasone on deterioration of the cases with increased severity	4	Open-label randomised, parallel arm, clinical trial	Time to recovery (1–6 weeks)	NP	NP

Table 1 continued

Principal investigator (ClinicalTrials.gov Identifier)	Drug/intervention	Phase	Study type	Primary outcome(s)	Secondary outcome(s)	Rationale
Daval M et al. (NCT04361474)	Budesonide saline nasal irrigation with olfactory rehabilitation twice a day vs saline nasal irrigation with olfactory rehabilitation twice a day	3	Randomised Parallel Arm Clinical Trial	Percentage of patients with an improvement of more than 2 points on the ODORATEST score (5) after 30 days of treatment	NP	The treatment of viral hyposmias is based on local and/or general corticosteroid treatment combined with saline nasal irrigation at the onset of signs. To avoid development of severe forms of COVID-19, local treatment with corticosteroids could be instituted from 30 days after the onset of symptoms of COVID-19 without risk of dissemination
Mohamed S (NCT04657809)	Formulated bioadhesive fast dissolving film containing 100IU insulin versus placebo fast dissolving film with no drug	2	Randomised Parallel Arm Clinical Trial	Smell sensation improvement by decrease in the threshold sensation with butanol test at end of 4 weeks	NP	NP

BSIT brief smell identification test, *mQOD-NS* modified brief questionnaire of olfactory dysfunction, *NP* not provided, *OT* olfactory training, *SNOT-22* sinonasal outcome test

be planned once a consensus is reached for definition of PVOD.

What Are the Potential Areas of Future Research?

An improved understanding is required for the exact mechanism of neuronal injury leading to long-term and permanent disability. An anticipated increase in patients with OD also warrants for better and feasible tests for its evaluation which have a higher diagnostic accuracy, ease of performance and suitability for repeated use during follow-up in the out-patient setting. There is an urgent need to define the timeline for PVOD whence treatment should be initiated. There is a dearth of information for recommending a pharmacological option as of now. So, olfactory training remains the cornerstone in management of such patients. Despite the ongoing trials comparing various treatment options for post-COVID OD, there is a continued need to study the role of inflammatory mediators and use of their inhibitors in reducing and reverting this disability. There is a need of randomized trials for proving efficacy of OT over other modalities especially in case of post viral olfactory dysfunction.

Conclusion

Post-viral Olfactory Dysfunction is an important clinical entity, and with the resumption of health services, the attendance of post-COVID patients demanding its solution is highly likely to increase in the coming months. Olfactory dysfunction warrants attention and intervention, if it persists after 20 days of symptom onset. SARS-CoV-2 is hypothesized to cause olfactory dysfunction by all three possible means: conductive, sensorineural and central. Even though, objective assessment of olfactory dysfunction is more reliable, especially for detection of persistent hyposmia, subjective tests should be preferred in cases with persistent dysfunction as the target is alleviation of symptoms. Olfactory training is the mainstay of treatment and rehabilitation at present.

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Declarations

Conflict of interest None of the authors have any competing interests.

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