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Qualitative Olfactory Dysfunction and COVID-19: An Evidence-Based Review with Recommendations for the Clinician

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Abstract

Background: Nearly 40% of patients who experience smell loss during SARS-CoV-2 infection may develop qualitative olfactory dysfunction, most commonly parosmia. Our evidence-based review summarizes the evolving literature and offers recommendations for the clinician on the management of patients experiencing parosmia associated with COVID-19.

Methods: We performed a systematic search using independent queries in PubMed, Embase, Ovid, and Cochrane databases, then categorized articles according to themes that emerged regarding epidemiology, effect on quality of life, disease progression, prognosis, pathophysiology, diagnosis, and treatment of parosmia.

Results: We identified 123 unique references meeting eligibility and performed title and abstract review with 2 independent reviewers, with 74 articles undergoing full-text review. An inductive approach to thematic development provided 7 central themes regarding qualitative olfactory dysfunction following COVID-19.

Conclusions: While other respiratory viruses are known to cause qualitative olfactory disturbances, the incidence of parosmia following COVID-19 is notable, and correlates negatively with age. The presence of parosmia predicts persistent quantitative olfactory dysfunction. Onset can occur months after infection, and symptoms may persist for well over 7 months. Affected patients report increased anxiety and decreased quality of life. Structured olfactory training with essential oils is the preferred treatment, where parosmia predicts recovery of aspects of quantitative smell loss when undergoing training. There is limited evidence that nasal corticosteroids may accelerate recovery of olfactory function. Patients should be prepared for the possibility that symptoms may persist for years, and providers should guide them to resources for coping with their psychosocial burden.

Keywords

parosmia, phantosmia, COVID-19, SARS-CoV-2, long COVID, post viral olfactory dysfunction, qualitative olfactory dysfunction, anosmia, hyposmia, olfactory training

Introduction

Olfactory dysfunction (OD), which includes reduction and alteration of smell perception, came into the spotlight of scientific investigation and popular culture by its intriguing association with SARS-CoV-2 infection. Early in the COVID-19 pandemic, acute loss of smell and taste were recognized as key diagnostic symptoms reported by approximately 60% of infected individuals.[1–3] The predominant clinical course of OD in COVID-19 is acute onset of anosmia or hyposmia, an absence or reduction in olfactory ability, respectively. This deficit is followed by recovery over subsequent days to weeks for most individuals. Upwards of 20% of patients, however, report persistently diminished smell at 6 months[4]

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and 1 year,[5] with 40% of individuals experiencing qualitative smell distortion known as parosmia.[6] Investigating the patterns and mechanisms of protracted OD—particularly qualitative components like parosmia and phantosmia—is an essential part of understanding the long-term sequelae of COVID-19, but one that is often overlooked in the setting of numerous long-term neurologic symptoms.[7]

Parosmia is a distortion of a previously known scent, whereas phantosmia is a smell precept in the absence of a physical odorant. Assessing these in a standardized fashion is challenging due to nuanced and personal manifestations. There is a dearth of English vocabulary to describe smell, often requiring borrowed language from other sensory modalities (eg, "smelling in black and white"). Patients can be unreliable in evaluating their OD as compared to objective psychometric testing.[8,9] These challenges are amplified with qualitative smell distortions, such as parosmia and phantosmia, making it difficult for providers to characterize severity.

The objective of this review is to synthesize the current literature on parosmia and phantosmia as related to COVID-19. We provide recommendations on how to evaluate and surveil patients with parosmia, assess the prognostic value of parosmia, summarize potential therapies, and finally, identify opportunities for additional research to address existing knowledge gaps.

What is Parosmia and How Does it Impact Quality of Life?

Parosmia is a qualitative form of OD characterized by a distorted perception of odorants, and the misalignment of expectation and experience of a known odor. Odorants previously perceived as neutral or positive can elicit disgust and are described as "burned," "chemical," "putrid," or "rotten."[8,10] When foul, the distorted interpretation is classified as *cacosmia*. Conversely, a pleasant distortion is termed *euosmia*, which is rare.[11] These terms should not be confused with *phantosmia*, which is also a qualitative distortion, but is the experience of a smell precept despite the absence of physical odorants. Parosmia and phantosmia are parallel to quantitative smell loss, which exists on a spectrum from anosmia (total loss of olfaction) to hyposmia (diminished olfactory ability). Following COVID-19 infection, parosmia typically appears 2 to 3 months after the onset of anosmia.[12]

Parosmia is most commonly associated with postviral OD (PVOD), and less frequently with other common causes of quantitative OD, such as sinonasal disease, head trauma, neurodegenerative disease, and epileptic disorders. Parosmia is typically comorbid with anosmia/hyposmia, however, idiopathic cases of parosmia are frequently reported within the setting of normal quantitative smell capacity.[13,14]

The burden of quantitative smell loss stems from a lack of awareness of the surrounding environment. This leads to an increased risk of morbidity from fires, gas leaks, or spoiled food, as well as increased anxiety surrounding body odor.[15] In contrast, the burden of parosmia and phantosmia is a hyperawareness of intrusive smells. Patients may have powerful negative responses to quotidian stimuli such as coffee, perfume, or even a romantic partner. Burges Watson et al[16] painted a picture of individuals shocked by the sudden onset of smell distortion, who then feel alone because of the ineffability of the experience and the inability of others to comprehend the experiential intensity or sense of loss. They may subsequently have a slew of lifestyle, physical, and psychological changes. Foods are common triggers of parosmia, leading to profoundly altered relationships with eating, socializing, and sense of self. These sentiments may contribute to weight loss or gain, increased consumption of unhealthy foods, decreased socialization, anhedonia, and increased depression.[16–20] In a case series of 268 patients with parosmia from COVID-19, 91.8% reported altered quality of life.[21]

The impact of parosmia on quality of life has psychiatric implications, where a survey of 496 respondents with OD found increased rates of anxiety ($P = .007$), and a study showed higher rates of depression in patients with distorted smell and taste compared to those with purely quantitative loss.[17,22] Persistent and debilitating qualitative OD can even lead to suicidal ideation.[10]

Parosmia Prevalence in COVID-19

Chemosensory deficits are found in approximately 60% of COVID-19 patients by self-report,[2,3,23] where assessment using objective psychophysical testing suggests even higher rates of olfactory disruption.[24] Approximately 7.0% to 27.7% of COVID-positive patients experience parosmia within the first 15 days of diagnosis or symptom onset.[2,23,25,26] In a study of patients 4 to 6 weeks after symptom onset, 29.7% had parosmia.

But studies of acutely ill individuals likely underestimate the eventual toll of parosmia because the onset is often months after recovery from active infection.[27] At 6-month follow-up, parosmia was present in 43.1% of subjects who reported smell loss at the beginning of the COVID-19 pandemic.[6] In a survey that followed-up COVID-19 infection by a median of 200 days, 47% of 1468 participants reported parosmia (vs. 10% immediately following infection).[28] In an online observational study of 3111 respondents with COVID-19-related OD, 55.8% reported parosmia, which was significantly correlated with the presence of persistent OD, as well as age.[29]

Due to its latent delayed onset and the recency of the COVID-19 pandemic, there will be increasingly greater prevalence and thus extensive opportunity for further investigation.

When is the Onset of Parosmia?

In COVID-19 patients, parosmia onset is frequently delayed: Hopkins et al[6] found a median onset of parosmia 2.5 months

after smell loss and Lerner et al[30] found that over 40% of patients developed parosmia a month or more after the onset of other symptoms. Patients are often reporting a perceived recovery in their sense of smell following an initial loss, only to develop the secondary intrusion of parosmia.

How Long Does Parosmia Persist?

In a case series of 268 patients with parosmia from COVID-19, the average duration was 3.4 months, and recent literature shows many cases may last well over 7 months.[21,31] Lerner et al[30] showed that time from initial olfactory symptoms to any improvement was minimum 2 to 4 weeks, and more likely 4 to 6 months or longer.

What is the Prognostic Value of Parosmia in Predicting Quantitative Smell Recovery?

There is conflicting evidence on whether parosmia predicts spontaneous recovery from quantitative smell loss. In COVID-19 specifically, parosmia may predict protracted smell loss, although it is unclear if its presence is a prognostic factor of recovery of smell.[32] Notably, parosmia was a stronger predictor for persistent OD than sex, smoking, or severity of quantitative loss. Ohla et al[28] found that the presence of parosmia was correlated with being a "smell long-hauler" (having persistent quantitative OD). These patients also had more nonolfaction long-COVID symptoms, such as headaches.

In PVOD patients specifically, Cavazzana et al[33] found no significant relationship between parosmia and clinically relevant improvement of OD. However, when examining the impact of olfactory training (OT) in 153 cases of PVOD, parosmia predicted modest recovery for 2 aspects of quantitative olfaction, discrimination, and identification; although it was nonsignificant for improvement of threshold detection and overall score.[34] Given the nuanced and conflicting evidence, this relationship warrants further study.

Why Does Parosmia Occur?

There are 2 main hypotheses for the pathophysiological mechanism of parosmia: (1) distortion of peripheral processing within olfactory neurons in the nasal epithelium and/or their projections to the olfactory bulb (OB) and (2) distortion of central processing in the OB or brain. These mechanisms are not mutually exclusive, and it is important to note that any observed changes in brain volume or processing patterns may be secondary to diminished/distorted input from peripheral receptors/projections. Central changes alone are not sufficient as evidence for the central hypothesis (eg OB volume diminishes with the duration of OD).[35]

The pathogenesis of OD in COVID-19 is abnormal compared to other upper respiratory infections (URIs) in that infected individuals experience a low prevalence of concurrent rhinitis and congestion; thus, it is possible that the pathogenesis of parosmia in COVID-19 is distinct from how other viral illnesses cause parosmia.[36,37] Mechanisms may be heterogenous, and thus research into both central and peripheral hypotheses may provide insight into potential therapeutic targets.

Peripheral Hypothesis

The peripheral hypothesis posits that olfactory neuroepithelium is unable to "correctly" convey information to central olfactory centers after the damage that may be induced by direct viral infection of nonneuronal sustentacular cells from SARS-CoV-2,[10,25,36] or an inflammatory environment that may induce changes in neuronal expression of olfactory receptors.[37] This theory is supported by data showing that most cases of parosmia are concurrent with quantitative OD, a deficit generally reflecting diminished peripheral input.

Parker et al[38] used gas chromatograph olfactometry to identify 15 odorant molecules within instant coffee that triggered parosmia. These shared common molecular structures and extremely low olfactory thresholds, offering credence to a receptor-level peripheral hypothesis.

In 20 PVOD parosmia cases, nasal thallium-201 was used for scintigraphic visualization of the olfactory pathways, showing that uptake into the olfactory cleft was significantly decreased when patients were *hyposmic* with parosmia, as opposed to *normosmic* with parosmia. However, thallium-201 migration from the cleft to the OB was no different between the 2 groups, suggesting parosmia is a product of damaged or immature projections to the OB, and not from diminished odorant uptake into the cleft.[39]

Distorted communication may arise from dysregulated gene expression, thus altering the production of proteins, including olfactory receptors, necessary for signal transduction.[37] Human olfactory receptors are typically classified into 2 groups, class 1 and class 2, as distinguished by their ability to bind hydrophilic versus hydrophobic ligands.[40] With recent work suggesting that class 1 receptors are less downregulated than class 2 receptors in acute COVID-19, it is possible that perception of hydrophilic ligands like carboxylic acids (eg, sweaty) would remain in mild cases of COVID-19, while perception of hydrophobic ligands (eg, musk) may be lost. Preferential receptor loss might explain why recovery and parosmia tend to present with a perception of bad odors with the reemergence of class 1 receptor function.[41,42]

Central Hypothesis

In contrast, the central hypothesis suggests that smells are aberrantly processed in the OB and/or interpretative olfactory eloquent brain structures. In 1 patient with 3 months of parosmia following COVID-19-induced anosmia, imaging showed normal OB and olfactory tract volumes, but revealed

hypometabolism in tertiary olfactory cortex areas without any volume reduction, which gives credence to the central hypothesis of parosmia pathogenesis.[43] Prior studies have also shown that patients with parosmia and quantitative OD have smaller OBs than patients with quantitative OD only.[35, 44] Closely related is a study from Shiga et al,[39] which found that patients with parosmia and quantitative OD have smaller OBs than patients with parosmia only (who also had reduced volume of the OB as compared to healthy individuals). This is a nuanced difference: patients with both parosmia and quantitative OD have a smaller OB than patients with either parosmia only or hyposmia only. This corroborates studies demonstrating that increased severity and duration of OD can further decrease OB volume.[44]

An functional magnetic resonance imaging (fMRI) study of 23 hyposmic patients with and without parosmia showed entirely different patterns of central activation, including greater activation in the putamen and thalamus for the parosmia group, suggesting that the qualitative distortion of odorous information occurs very early on at the level of olfactory epithelium or OB.[45] This finding supports neither peripheral nor central hypotheses since the changes could have occurred in the OB (central) or before it (peripheral).

How do We Detect Parosmia?

It is inherently difficult for clinicians to assess qualitative OD because humans are poorly equipped to verbalize olfactory experiences. Many studies use a single question to ascertain if a patient has parosmia, but this method codes parosmia as binary, and does not elicit much nuance in a disease process that can vary tremendously in terms of triggers, severity, and timing. Furthermore, patients are poor at self-assessing olfactory ability and may overreport qualitative chemosensory disorders in questionnaires.[46,47] For a more comprehensive history, Landis et al[48] proposed 4 questions to establish a parosmia score; a high score virtually excludes a parosmia diagnosis, and a low score may alert a physician to question further.

A recently developed psychophysical metric to assess parosmia is the Sniffin" Sticks Parosmia Test, which pairs pleasant and unpleasant odors (ie, pineapple vs. fish) to assess hedonic estimates as a proxy for distorted perception.[49] Although these instruments are neither universal nor fully validated, they are potentially useful supplemental tools in the clinical assessment of parosmia.

How do We Currently Treat Parosmia?

Parosmia is generally coincident with quantitative OD, so our clinical approach for treating OD should build upon the current standard of care for anosmia: OT.[50] OT is as follows: quick and gentle "bunny sniffs" of essential oils for 20 s at a time, while mindfully concentrating on the smell. This sequence is performed twice a day, with at least 4 different scents, for at least 4 months. The UK-based organization, AbScent, has detailed instructions on its website on how to assemble and use a proper smell training kit.[51] OT is maximally efficacious when started as soon as possible to the onset of smell loss, when performed for 9 months, and when 12 essential oils are rotated to increase novelty—the introduction of additional essential oil scents has been termed Modified Olfactory Training.[52] Altundag et al[53] showed that this regimen also works for COVID-19-induced parosmia, significantly improving parosmia and quantitative olfaction as compared to controls ($P = .001$ and $P < .001$, respectively).

There is a possible role for oral or nasal corticosteroids, with Saussez et al[54] showing a statistically significant reduction in parosmia prevalence following treatment including oral corticosteroids + OT versus OT alone after 2 months of treatment ($n = 152$). Although topical steroids have been useful in certain settings of quantitative OD,[55] the utility of all forms of steroids in resolving qualitative smell disturbances appears more limited and is an area of ongoing research.[21,56]

A 2-week treatment of PVOD with intranasal sodium citrate was associated with a nonstatistically significant reduction in parosmia.[56] Nasal saline may provide temporary relief while in the head-down-and-forward or the Kaiteki positions.[13,58,59] Many other medications have been trialed, including gabapentin, venlafaxine, cocaine, and alpha-lipoic acid, with 1 successful treatment of parosmia using olanzapine in Olfactory Reference Syndrome.[13,60–62] None is empirically shown to have benefit. Recently, intranasal application of nitrilotriacetic acid trisodium salt improved quantitative olfactory (TDI) outcomes, however, the impact on parosmia remains unknown as the study population was acute (average 16 days since onset of symptoms) post-COVID anosmic patients.[63]

For many cases of parosmia, "watchful waiting" may be a valid adjuvant treatment plan following a comprehensive evaluation that includes nasal endoscopy if a patient is unwilling to participate in interventions. If neurological, psychiatric, or metabolic causes are suspected, the patient should be referred accordingly. Patients should be assured of no underlying neoplastic disease or infection, and that their symptoms are quite common.

Phantosmia in COVID-19

Phantosmia is an olfactory precept where an individual perceives an odor stimulation in the absence of a source odorant. Phantosmia remains an enigma perpetuated by its infrequent and varied presentation. Although commonly associated with a diminished sense of smell,[64] phantosmia may exist without a quantitative olfactory deficit. Like parosmia, current theories on the underlying pathophysiology for this aberration pertain to abnormal intrinsic activation,

suppression, or incidental peripheral stimulation of peripheral olfactory neurons within the nasal cavity. These then trigger a central nervous system response.[10]

Our understanding of phantosmia as a manifestation of COVID-related OD remains limited. Analysis from a patient report on social media indicates that the most common type of phantosmia is "smoke/ashtray/cigarette/burnt" followed by "chemical" and "ammonia/vinegar."[65] Prevalence of phantosmia seems to depend on the phase of recovery, where few patients report phantosmia coincident with acute phase COVID-19 respiratory symptoms within 2 weeks (9.5% in a multinational questionnaire [$N = 2637$]).[26]

Prevalence clearly increases over time following infection. About 25% of 1468 individuals reported phantosmia at a median time of 200 days post-COVID-19 infection.[28] Self-report of 774 COVID-19 patients in Europe showed a phantosmia prevalence of 13.6%.[48] In a multicenter prospective study of hospitalized COVID-19 patients, phantosmia prevalence was 2.5% at 4 weeks postinfection, and 9% at 8 weeks postinfection ($N = 442$). However, the presence of OD was *inversely* correlated with disease severity, and so this 9% prevalence may be an underestimate of the general population since the study included only hospitalized patients.[66]

Rates of reporting increase among individuals with persistent olfactory symptoms. In an observational online study of those recovering from COVID-19-related OD, 34.6% of 3111 respondents had phantosmia, where persistent OD correlated with increasing age, being female, and the presence of parosmia or phantosmia. About 26.6% of those respondents reported both parosmia and phantosmia.[29]

How do We Counsel Patients with Parosmia and Phantosmia?

Patients should be prepared for the possibility that their parosmia and/or phantosmia persists for months or years, where prevalence is greater in patients with PVOD compared to other smell-loss etiologies. There are potential implications of increased anxiety, and decreased quality of life. While not specifically reassuring, the conveyance of this information helps contextualize their experience and provides expectations that their psychosocial responses to parosmia/phantosmia are not abnormal. For patients with non-COVID-19 PVOD, it seems unlikely that parosmia predicts spontaneous recovery of smell loss. However, if PVOD patients are undergoing OT with essential oils, having parosmia predicts modest improvement of certain aspects of smell. For the many patients with OD following infection with SARS-CoV-2, early studies, albeit limited, suggest parosmia may be associated with protracted hyposmia.

Providers may direct patients to advocacy groups such as the Smell and Taste Association of North America and AbScent.[67] These groups provide social support for people with chemosensory disorders, and also help patients to collectively advocate for additional research, especially translational and treatment studies.[68] The formation of a community based on mutual experience and the sense of empowerment from advocacy is helpful for some patients. Patient-oriented podcasts are another resource (eg, The Smell Podcast).[69]

Conclusion

Qualitative OD is a potentially debilitating condition that occurs in upwards of 40% of COVID-19 patients with persistent olfactory deficits.[6] Our current best treatment is OT. Parosmia may predict protracted quantitative OD in COVID-19 patients, and yet among PVOD patients undergoing OT therapy, parosmia is associated with clinically relevant improvement in discrimination and identification capacity, but not threshold detection of odors. The high prevalence of OD following COVID-19 warrants further investigation into the pathogenesis and unique clinical manifestations of both qualitative and quantitative deficits, and into the development of targeted treatments for parosmia.

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