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PERSISTENT POST-COVID OLFACTORY DYSFUNCTION: MECHANISTIC INSIGHTS AND EMERGING THERAPEUTIC APPROACHES

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ABSTRACT Persistent olfactory dysfunction (OD) is a common, often debilitating, sequela of coronavirus disease 2019 (COVID-19), significantly impacting quality of life. This narrative review synthesizes current understanding of the epidemiology, underlying pathophysiological mechanisms, and evolving therapeutic landscape for post-COVID OD. Epidemiological data highlight the varying prevalence and persistence of symptoms, underscoring the scale of this clinical challenge. Mechanistically, damage to the olfactory neuroepithelium, particularly the sustentacular cells, coupled with neuroinflammation and potential central nervous system involvement, are key factors driving symptom chronicity. The review discusses established management strategies, such as olfactory training, alongside promising novel approaches including various pharmacologic agents.

KEYWORDS : Olfactory dysfunction, COVID-19, Neuroinflammation, Olfactory training, Sustentacular cells.

INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rapidly evolved into a global pandemic, causing unprecedented mortality and morbidity. While primarily recognized as a respiratory illness, COVID-19 is now understood as a multisystem disease (1). Among the most distinctive and prevalent non-respiratory symptoms is olfactory dysfunction (OD), encompassing anosmia (complete loss), hyposmia (reduced sense), and parosmia (distortion of smell) (2). Initially considered a transient marker of acute infection, a substantial proportion of patients experience persistent post-COVID OD, lasting months or even years after viral clearance (3). This chronic symptom significantly impairs quality of life, affecting nutrition, safety, and emotional well-being (4). Understanding the intricate pathophysiological mechanisms is crucial for developing effective, targeted therapies for this growing population of patients (5).

Methods

This narrative review was compiled through a focused and iterative literature search across four primary biomedical and academic databases: PubMed, Scopus, Embase, and Google Scholar. The search strategy employed a combination of terms related to the condition and its context, specifically targeting "olfactory dysfunction," "anosmia," "parosmia," "COVID-19," "SARS-CoV-2," "pathophysiology," and "treatment." The inclusion criteria prioritized peer-reviewed articles published in English or Spanish that addressed the persistent nature of post-COVID OD, its underlying mechanisms, and current or emerging therapeutic interventions. Following an initial screening of titles and abstracts to ensure topical relevance, a final set of 15 highly relevant articles was selected for in-depth, full-text qualitative synthesis (6) (**Figure 1**).

Epidemiology and Clinical Spectrum of Post-COVID Olfactory Dysfunction

The prevalence of OD in the acute phase of COVID-19 has been reported to be as high as 80% in some cohorts, though estimates vary widely due to differences in methodology, patient populations, and variant-specific effects (7). Importantly, a significant fraction of these individuals do not experience a spontaneous and complete recovery. Studies tracking the natural history of the condition suggest that OD persists in approximately 5-15% of patients at 6 months post-infection (8). The persistence is often characterized by the emergence or worsening of qualitative ODs, such as parosmia and phantosmia (phantom smells), which can be particularly distressing (9). Parosmia, often described as a distorted and usually unpleasant smell perception (e.g., garbage, burning, or chemicals), tends to appear during the recovery phase, indicating aberrant neuroregenerative or neuroplastic changes (10).

Pathophysiological Mechanisms

The mechanisms underlying the persistent nature of post-COVID OD are complex and involve multiple components of the olfactory system, spanning from the peripheral neuroepithelium to central processing centers (5).

Neuroinflammatory Pathways

SARS-CoV-2 primarily initiates infection by binding to the angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed on sustentacular cells—the supporting cells of the olfactory neuroepithelium—and basal cells, but is largely absent on the olfactory sensory neurons (OSNs) themselves (11). The infection of sustentacular cells triggers a robust local inflammatory response characterized by the infiltration of immune cells (e.g., macrophages, T cells) and the release of pro-inflammatory cytokines (e.g., IL-6, TNF) (12). This cytokine storm in the olfactory cleft is thought to cause a "bystander effect," leading to transient or sustained disruption of the delicate neuroepithelial microenvironment and damaging the adjacent, uninfected OSNs (5). Persistent or unresolved inflammation may impede proper neuronal regeneration, contributing to chronic symptoms.

Sustentacular Cell Injury

The sustentacular cells are critical for maintaining the structural and metabolic integrity of the olfactory neuroepithelium (11). Their infection and subsequent damage by SARS-CoV-2 lead to a loss of their supportive function, disrupting the ionic balance, removing physical support, and potentially hindering the clearance of pathogens or debris (13-15). This direct cellular injury, even without primary infection of the OSNs, can compromise the olfactory cilia and the neuronal signal transduction cascade, which is essential for smell detection (5). Failure of the sustentacular cell layer to fully recover or prolonged damage to the basal cell layer (the progenitor cells) can result in a thinned, scarred, and dysfunctional neuroepithelium, underpinning chronic OD.

Diagnostic Evaluation And Objective Assessment Tools

The diagnosis of post-COVID OD begins with a thorough patient history, focusing on the onset, severity, type of dysfunction (anosmia, hyposmia, parosmia, phantosmia), and the impact on daily life. Subjective assessment using validated questionnaires, such as the Sniffin' Sticks Screening Test or the University of Pennsylvania Smell Identification Test (UPSIT), is essential (8).

Objective Assessment Tools

While self-reporting is useful, objective psychophysical testing is crucial for quantifying the degree of impairment and tracking therapeutic progress (4).

- Olfactory Identification Tests: Standardized tests like the UPSIT, which uses microencapsulated odors for scratch-and-sniff identification, provide a quantifiable measure of the ability to recognize smells (8).
- Olfactory Detection Threshold Tests: These measure the lowest concentration of an odorant a person can detect, providing a measure of sensory sensitivity (4).
- Olfactory Discrimination Tests: These assess the ability to distinguish between different odors (7).

Natural History And Prognostic Factors

The natural history of post-COVID OD is characterized by a high rate of initial spontaneous recovery, followed by a plateau phase where recovery becomes less frequent and slower (8). Most recovery occurs within the first three to six months (10).

Prognostic factors are being investigated to predict long-term outcomes:

- **Initial Severity:** Some studies suggest that the severity of the initial OD may correlate with a less favorable long-term prognosis, although evidence is conflicting (7).
- **Gender:** Females have been reported to have a slightly lower rate of full recovery compared to males, particularly in the development of persistent parosmia (9).
- **Presence of Parosmia:** The development of parosmia is often considered a sign of ongoing, albeit aberrant, neuroregeneration (10). While it indicates some activity in the system, it is often associated with protracted recovery and can be a significant source of distress, suggesting a complex underlying pathology (9).
- **Viral Load and Systemic Symptoms:** Contrary to expectations, the initial severity of the respiratory illness, as measured by hospital admission or systemic inflammatory markers, often does not strongly correlate with the persistence of OD, further supporting the localized, neuroepithelial basis of the pathology (3).

Current Therapeutic Approaches

Therapeutic strategies for persistent post-COVID OD aim to promote neuroregeneration, reduce inflammation, and improve the central processing of olfactory signals.

Olfactory training (OT) remains the most widely recommended and evidence-based first-line treatment (10). This non-pharmacological intervention involves the repetitive, conscious sniffing of a set of high-concentration odorants (typically rose, eucalyptus, lemon, and clove, often expanding to a 12-odor set) over several months (4). The mechanism is thought to involve neural plasticity, strengthening the remaining functional olfactory pathways and potentially encouraging the maturation and correct integration of newly generated OSNs (10). Optimal results are generally achieved with twice-daily training for a minimum of 6 months (7).

Pharmacologic Treatments

The use of pharmacologic agents is largely based on the assumed role of inflammation and is often extrapolated from treatments for post-viral OD caused by other viruses.

Corticosteroids: Topical intranasal corticosteroids (e.g., mometasone, fluticasone) are commonly prescribed to reduce local inflammation and edema in the olfactory cleft (12). However, clinical trials have shown only limited benefit for persistent OD (4). Oral steroids are generally not recommended due to systemic side effects (7).

Fatty Acids and Antioxidants: Supplements such as ω-3 fatty acids (e.g., docosahexaenoic acid, DHA) have been investigated for their potential neuroprotective and anti-inflammatory properties, aiming to support the recovery of neuronal membranes and reduce oxidative stress (13). Evidence for their efficacy is still emerging and requires larger, controlled trials (13).

Emerging Biologic And Regenerative Therapies

Focus is shifting towards therapies that directly target regeneration and modulate the inflammatory response (14).

Platelet-Rich Plasma (PRP): PRP contains a high concentration of growth factors (e.g., vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF)) that promote tissue repair and neuroregeneration (14). Initial studies involving intranasal or trans-nasal injections of autologous PRP into the olfactory cleft have shown promising results in accelerating recovery in some patients with persistent OD (14).

Stem Cell Therapy: While highly experimental, the administration of mesenchymal stem cells (MSCs) is a future direction, leveraging their potent immunomodulatory and paracrine effects to protect remaining OSNs and encourage the correct differentiation of basal stem cells (1).

Neuromodulation And Experimental Interventions

Neuromodulation techniques are being explored for patients who are refractory to conventional treatments, particularly those with severe parosmia or phantosmia.

Transcranial Magnetic Stimulation (TMS): TMS can modulate the excitability of cortical regions (e.g., the piriform cortex) involved in olfactory processing. Preliminary reports suggest potential benefits in reducing the severity of parosmia by recalibrating central neural networks (15).

Other Interventions: Further experimental treatments include the use of vitamin A (retinoic acid) due to its role in neurogenesis and Alpha-lipoic acid for its antioxidant properties, though their clinical utility remains uncertain (7).

Future Directions In Research And Clinical Management

Future research must focus on translating mechanistic insights into clinical breakthroughs.

Targeted Anti-Inflammatory Agents: Developing novel, locally administered **anti-inflammatory agents** that specifically target the inflammation in the olfactory cleft without systemic side effects could prevent or reverse sustentacular cell injury and promote OSN survival (12).

Neurotrophic Factor Delivery: Investigating methods for sustained, localized delivery of neurotrophic factors (e.g., BDNF, GDNF) to the olfactory epithelium could directly enhance the quality and speed of neuroregeneration (13).

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