Editorial I

COVID-19 and Anosmia: Remaining Gaps to Knowledge

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Since the emergence of the first cases of Sars-Cov-2 infection in November 2019, more than 224 million people have tested positive for COVID-19, and of these, more than 4.6 million have lost their lives worldwide.[1] Despite the rapid development of several types of vaccines that allowed a decrease in the rise of the number of new cases and deaths, the end of this story does not seem so close since fully vaccinated patients can also be infected. The virus has undergone constant mutations that sometimes produce milder symptoms and less resistance, sometimes manifest themselves more aggressively and with greater transmissibility.

The olfactory disturbances in COVID-19 patients have drawn worldwide attention to an extremely important and often neglected sense. Smell plays a fundamental role in our lives, both for safety reasons as detecting odors of burning, gas leak or spoiled food, as well as in the quality of life by providing us with pleasure while eating, in interpersonal relationships, and also preventing us from hygiene issues.

Despite the fact that there is no consensus regarding the exact pathophysiological mechanism, prevalence, and recovery of olfactory disorders in COVID-19, there is still a lot to understand about the persistent changes and how to intervene for adequate recovery of these patients.

The olfactory neuroepithelium expresses receptors for the angiotensin-converting enzyme 2 (ACE2), the transmembrane protease serine 2 (TMPRSS2), and Neuropilin-1 (NRP1) on its surface. These structures are related to the mechanism of cell binding and invasion by SARS-COV-2, with the consequent inflammatory process and local destruction. As in other viral infections of the upper respiratory tract, the local severity of the infection can lead to more extensive lesions involving basal cells and reducing the regenerative capacity of the neuroepithelium. These lesions can lead to a partial replacement by metaplastic squamous epithelium.

In Brazil, the first large survey on chemosensory dysfunctions pointed 82.4% general prevalence of smell impairment on COVID-19 infected patients.[2] A second study in the same country, pointed that there is no apparent difference in the prevalence of olfactory disorders between health professionals working on the front lines of combating the pandemic and the general population.[3] However, in the context of disease with significant clinical variability, publications regarding prevalence diverged, pointing from 5.1% to 98% in different parts of the world.[2,4]. There is just one study showing a short prevalence of olfactory loss during the acute phase of COVID-19. All the other papers agree that this prevalence is high-ranging from 51% to up to 98%.[5] Multiple factors are listed as responsible for this variability, but two mechanisms are more commonly accepted and may manifest themselves individually or together:

- quantitative differences in host expression of surface proteins related to the ability of the virus to bind to human cells (ACE-2, NRP1, TMPRSS2);
- mutations of the virus spike protein responsible for binding to target host cells.

Fortunately, the recovery of quantitative olfactory disorders seems to occur spontaneously in a very high proportion of patients within two months, reducing the chance of its occurrence over time. On the other hand, qualitative disorders, such as parosmia and phantosmia, seem to start late and persist for a more extended time.[6] A Boscolo-Rizzo et al. cohort study showed a 43% prevalence of parosmia, with an average onset after 2.5 months and persistence of the complaint, without any improvement, of 40.6% after 6 months from the COVID-19 initiation.[7]

The olfactory afferent pathway has complex relationships with different areas of the central nervous system. Therefore, a hypothesis regarding the association between a permanent loss of olfaction and taste known as chemosensory loss and neuropsychiatric disorders has been raised latterly. These correlated pathways might explain at least in part the possible association between olfactory dysfunctions and depressive symptoms raised by several previous studies. One small sample size study investigated the association between olfactory and taste dysfunction and psychiatric

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symptoms during COVID-19 pandemic. Authors found a positive correlation between severities of smell and taste loss, depression, and anxiety in a sample of COVID-19 survivors.[8,9] However, there is no information regarding cognitive impairment and chemosensory disorders. Studies on the association of chemosensory loss and cognitive functions evaluated by dimensional and structured questionnaires are welcome.

Several medications have been suggested to treat olfactory disorders, such as α-lipoic acid, omega-3, and sodium citrate. However, they still lack robust evidence to support their recommendation. A therapy that presents a tremendous biological plausibility is topical corticosteroids in high-volume washes or even orally. The suggested use must occur soon after polymerase chain reaction (PCR) negative in the rhinopharynx, aiming to reduce the inflammatory process and avoid the olfactory neuroepithelium's destruction. In a recent publication by an Italian group, a supplement composed of Palmitoylethanolamide (PEA) and Luteolin has shown anti-inflammatory effects. Like steroids, it has also been considered promising in olfactory recovery.[10] Olfactory training therapy can be beneficial both in the acute phase as in patients with chronic olfactory impairment, betting on the plasticity of the neural circuit as a route to at least partial recovery of the olfactory function.

One of the methodological limitations in investigating treatments for olfaction recovery is the spontaneous character of recovery from the disease. Therefore, to prove that a difference between the intervention and control groups did not occur by chance, it is necessary to either have a large magnitude of effect or a large number of patients. However, up to date, very few randomized clinical trials have been published, all with a limited number of patients after infection by COVID-19.

Conflict of Interest

The authors have no conflict of interest to declare.

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