Dysosmia in Recovered COVID-19 Patients

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Disorder of smell sensations has been detected as a common feature in corona virus disease 2019 (COVID-19), it may be the initial symptom in more than a quarter of COVID-19 patients and may affect more than 3 quarters of those patients.[1] Although the condition is usually temporary in most cases as it lasts 1 to 3 weeks, persistent smell disorder has been reported in some patients, and it was considered as a part of long-COVID-19.[2,3] Furthermore, dysosmia which is the qualitative alteration of smell sensation in the form of parosmia or phantosmia is increasingly recognized as annoying late sequelae of COVID-19.[4,5] Parosmia means that the patients feel bad odor for most odorants and foods, while phantosmia is the perception of smell which is usually unpleasant with no odor present, and this may decrease appetite resulting in malnutrition and even depression.[6]

The mechanism of smell affection in COVID-19 is not exactly known yet. This problem may occur through one or more of three modes: conductive mode, in which the nasal congestion prevents odorants to reach the olfactory neuroepithelium; sensory mode, through damage of the olfactory neuroepithelium; and central mode, through affection of the olfactory pathways in the brain.[7] Olfactory cleft obstruction by congested mucosa during the active stage of COVID-19 as seen on imaging may support the conductive mode.[8] However, most COVID-19 anosmic patients do not complain of nasal congetion.[9] The sensory mode is interpreted by direct entry of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) to the supporting cells of the olfactory neuroepithelium which express angiotensin converting enzyme 2 (ACE2). This ACE2 receptors are the host cells of SARS-CoV-2, they bind to the viral S proteins leading to endocytosis and release of inflammatory cytokines such as tumor necrosis factor resulting in injury of the olfactory neuroepithelium.[6,10] The basal stem cells are capable to regenerate the olfactory neuronal cells in a self-renewing manner, so patients can regain their sense of olfaction.[7,11] These 2 aforementioned mechanisms may explain the recovery of olfaction within days to few weeks after primary loss.

The olfactory sensory neurons of the olfactory neuroepithelium extend through the cribriform plate of the skull base to the glomerular layer of the olfactory bulb forming a spatial odor map. Many studies reported olfactory bulb abnormalities in COVID-19 anosmic patients. Neurodegenerative changes in the olfactory bulb have been suggested as a possible cause of persistent loss of smell in long COVID-19 patients. As the olfactory bulb holds spatial orientations of axons arriving from the olfactory neuroepithelium to the bulbar glomeruli, and this spatial mapping could be responsible for odor discrimination, dysosmia may be due to miswiring of these regenerating axons into the glomeruli as a result of loss of spatial topographic mapping of odorant receptors.[5,11]

Smell is transferred from the olfactory bulb to the central olfactory pathways in the brain. Odor discrimination is thought to be affected by affection of these pathways. Also, the emotional part of smell is thought to be perceived by limbic projections of the amygdala and hypothalamus beneath the medial temporal lobe of the brain.[12] Direct invasion of the cerebral tissue by the SARS-CoV-2 is still a questionable matter, while indirect invasion has been suggested through cerebral microangiopathy with microcirculatory thrombi.[6,13] Cerebral hemorrhage involving the temporal lobe due to untreated hypertension has been described before as a cause of episodic attacks of bad smell.[14] However, the problem in COVID-19 patients is usually persistent and not episodic, also, some authors found no radiographic evidence of central olfactory pathway involvement in long COVID-19 patients.[3]

The appearance of dysosmia may be a positive clinical outcome as it may denote gradual recovery of olfaction. Due to the paucity of data, scientists usually search for solutions.[15] Many therapeutic methods have been proposed for the treatment of postviral smell disorders. These methods include pharmacological treatment such as oral and/or topical corticosteroids, caroverine, alpha lipoic acid, vitamin A, minocycline, zinc sulfate and ginkgo biloba, and nonpharmacological treatment such as olfactory training and nasal saline irrigation.[6,16] However, up till now, there is no standard treatment protocol for post-COVID-19 olfactory dysfunction, and there is a need for evidence-based studies to recommend the most appropriate treatment.

Olfactory training therapy is suggested to be the first-line treatment for olfactory dysfunction, as it is an inexpensive method with no serious side effects. It intends to strengthen the olfactory recovery according to the neuronal plasticity of the olfactory system, and also it may increase cognitive processing of the incomplete sensory information. It is performed by patients themselves, 2 times a day over at least 3 months, exposed to 4 intensive odors (phenyl ethyl alcohol: rose, eucalyptol: eucalyptus, citronellal: lemon, and eugenol: cloves).[6] However, some authors found no significant increase in olfactory function in patients treated with olfactory training alone, and they recommend a combination with corticosteroids.[16] While, others reported that it is still too early to evaluate this treatment option in COVID-19 patients with olfactory disorder, and they advised extending the duration of training up to a year and also changing the used odors to enhance the regenerative capacity of olfactory neurons.[6]

Corticosteroids treatment either topical or oral are the most used method in patients with olfactory dysfunction. However, the efficacy of systemic corticosteroids on postinfectious olfactory disorder is debatable. The duration of illness, safety concerns, age, and general condition of the patients could affect the decision of treatment with systemic corticosteroids.[6] Le Bon et al[16] reported that steroid treatment may be effective in the

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early stages of the postinfectious olfactory disorder. Also, Saussez et al[17] suggested that the use of oral or nasal steroids for treatment of post-COVID 19 smell loss may lower the rate of occurrence of dysosmia in recovered patients later on. On the other hand, the European Academy of Allergy and Clinical Immunology (EAACI) stated that prescription of nasal corticosteroids for treatment of post-COVID-19 anosmia is still questionable, and the scientific basis for this recommendation is lacking. Furthermore, the British Association of Otorhinolaryngology-Head and Neck Surgery (ENTUK) recommended not to prescribe corticosteroids (both nasal and systemic) in patients with a sudden loss of smell.[6]

In conclusion, some recovered COVID-19 patients may develop dysosmia. The exact cause is unknown. However, early onset of smell loss may be due to viral invasion to the olfactory neuroepithelium via ACE2 receptors, and olfactory recovery may be caused by the ability of the basal cells to regenerate the olfactory neurons. Delayed onset of dysosmia may be due to miswiring of the regenerating axons into the glomeruli of the olfactory bulb with loss of spatial topographic mapping of odorant receptors. Till now, there is no consensus for the appropriate therapeutic method; however, olfactory training is considered the first-line treatment for olfactory dysfunction.

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