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COMMENTARY

Olfactory and gustatory impairments in COVID-19 patients: Role in early diagnosis and interferences by concomitant drugs

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The COVID-19 pandemic spread worldwide with over 38 million confirmed cases and more than 1 million deaths as of October 15, 2020. The clinical manifestations of SARS-CoV-2 infection range from asymptomatic to life-threatening pneumonia, with the main symptoms being respiratory and gastrointestinal in nature. However, several patients report neurological symptoms including smell and taste impairments, such as anosmia, cacosmia, ageusia and dysgeusia.[1] Although the spread of the disease has been favoured by its contagious features, the role of many asymptomatic or paucisymptomatic patients, who can be very efficient vectors for the virus, should not be underestimated. The identification of these patients is essential to implement the isolation and tracking strategies that have proven to be our best weapon against the virus.[2] For this reason, early detection and characterization of each symptom will be a critical element in our final success against the virus. In the present commentary, we provide a brief description of the characteristics of gustatory and olfactory alterations in COVID-19 patients and discuss the diagnostic implications of drug-related gustatory and olfactory alterations on the detection of these chemosensory symptoms.

Olfactory and gustatory dysfunctions affect at least about 41% and 38%, respectively, of patients diagnosed with COVID-19, with no significant gender differences. However, the prevalence is likely influenced by self-diagnosis and under-reporting.[3] Both taste and smell alterations have been described as persistent, with a duration ranging between one to several weeks. Olfactory and/or gustatory impairments in COVID-19 patients can be the first isolated symptoms, or present either before or after additional multiple signs. The diagnostic utility attributed to smell and taste dysfunctions (mainly anosmia) [low sensitivity (23–43%) and high specificity (93–99%)] for the diagnosis of SARS-CoV-2 infection and the initial onset of these symptoms may be key points for an early diagnosis. Olfactory and gustatory impairments are associated with a mild course of SARS-CoV-2 infection and occur more frequently in young adults,[3] making these symptoms an important diagnostic element in a population that may be less inclined to be tested, thus contributing to the virus spread.[3]

The pathophysiology of these chemosensory symptoms could involve different biological targets and pathways. Olfactory and gustatory disorders are often associated with upper respiratory tract infections, but available evidence shows that smell and taste dysfunctions also occur without concomitant nasal obstruction or congestion in patients with COVID-19. Olfactory dysfunctions in COVID-19 patients are attributed to different disorders (including post-viral anosmia syndrome, cleft syndrome or impairment of brain olfactory sense centre) with a direct involvement of SARS-CoV-2.[4] The virus is thought to have neurotropic and neuroinvasive properties, which are common features reported previously for SARS-CoV.[4] However, although post-viral olfactory loss is well documented, its pathophysiology remains not fully disclosed, even though it likely involves both central or peripheral olfactory processing pathways.[4] SARS-CoV-2 is supposed to cause olfactory dysfunction of neural and non-neuronal cells through both a direct or indirect mechanism leading to a transient or persistent olfactory impairment.[5] Entry of SARS-CoV-2 into human cells results from their fusion caused by binding of the viral spike protein to the angiotensin-converting enzyme-2 (ACE2), followed by its priming by the TMPRSS2 serine protease and by spike cleavage mediated by cellular proteases, such as furin: cells expressing these proteins are virus targets.[6,7] In the

respiratory area of mammalian nasal cavity, ACE2 and TMPRSS2 are both expressed on ciliated and goblet cells, making them targets for SARS-Cov-2 and confirming the nose as a viable route for virus infection. Of note, evidence showed that nonneuronal cells of olfactory epithelium and olfactory bulb, including sustentacular cells and pericytes, express both ACE2 and other associated entry proteins[6] (Figure 1). These cells are essential for preservation of integrity and functionality of olfactory sensory neurons, and their damage can lead to smell dysfunction up to causing anosmia.[6]

Gustatory sensation can be disturbed in the setting of primary olfactory disorders. However, ageusia or dysgeusia have been reported also as isolated clinical manifestations. ACE2 has been found to be expressed in the mucosa of the oral cavity, in salivary glands (Figure 1), and it is highly represented in the epithelial cells of tongue, including taste buds, thus providing another entry route to SARS-CoV-2.[8] This mechanism also supports the observation that oral symptoms occur in the early phases of COVID-19 infection. In addition, salivary antimicrobial agents help protect the mucosa, chemosensory receptor cells and taste bud functions. Thus, an impairment of the salivary flow or an imbalance in the chemical composition of saliva can affect the maintenance of taste buds, and consequently taste. Considering that SARS-CoV-2 can target tongue, salivary glands and cells of the oral mucosa through its binding of ACE2, the virus could directly damage several structures involved in the gustatory function. However, a neurogenic source of the taste impairment cannot be ruled out.

Several commonly used drugs have been reported to affect chemosensory perceptions and their effects could have diagnostic implications in COVID-19 patients. Among the possible causes of chemosensory impairments, drugs are responsible for up to 13% of cases.[9] Drug-induced taste and smell dysfunctions can be explained by direct (e.g. alteration of both neurotransmitter function and neural interactions in sensory coding brain areas) or indirect (e.g. modifying chemical environment of sensing receptor and causing physical hindrance to chemical molecules accessing the receptors) mechanisms.[10] Local anaesthetics, several antimicrobials and antineoplastic drugs have been reported to affect smell and taste; detailed data on the putative impact of most of these drugs on olfaction is limited,[11] with exception for fluoroquinolones, which were recently investigated by the European Medicines Agency for potential permanent smell and taste disorders.[11] Gustatory dysfunctions are known to be caused also by the antifungal terbinafine, statins and some antihypertensive drugs.[9,10] Among antimicrobials, the macrolide azithromycin is being used for treating patients with COVID-19. This drug is known to induce chemosensory adverse dru reactions (ADRs) such as ageusia, dysgeusia, anosmia and parosmia, and is characterized by bitter taste.[11] The systemic intake of these drugs allows them to reach nasal and salivary secretions, thus suggesting a direct stimulation of taste and smell receptors.[9] Despite the unclear underlying mechanism, we cannot exclude that azithromycin, as well as other macrolides, could aggravate gustatory and olfactory dysfunctions in COVID-19 patients. Moreover, people aware of chemosensory ADRs to drugs could misclassify the perceived dysfunctions by attributing them to medicines instead of SARS-CoV-2.

Considering the plausible involvement of ACE2 in taste and smell disorders in COVID-19 patients, the possible effect of drugs affecting the expression and activity of this enzyme on chemosensory perception and the consequences for COVID-19 diagnosis deserve further discussion. Taste disorders, like metallic or sweet taste, and ageusia are reported also for ACE inhibitors (ACEI) and angiotensin II receptor blockers (ARB), which are widely used for hypertension, one of the prevalent COVID-19 comorbidities together with diabetes.[10,12] Initially, gustatory dysfunctions were mainly attributed to the sulfhydryl group of some ACEI, such as captopril. However, non-sulfhydryl molecules (e.g. enalapril) can produce the same taste alterations, thus suggesting that other mechanisms are implicated in the disturbance of

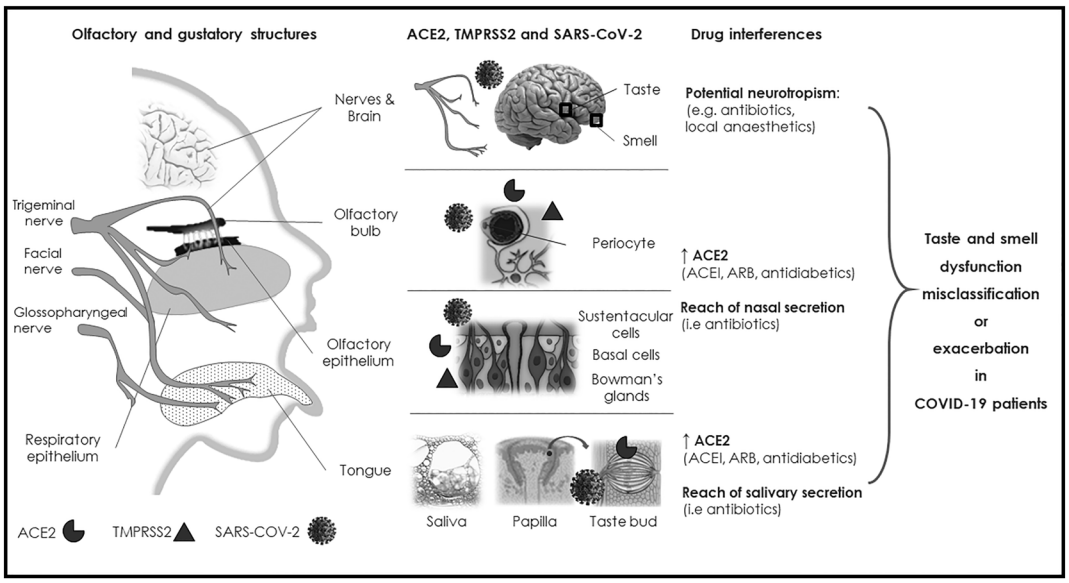

FIGURE 1 Major drug interferences for smell and taste dysfunctions in the setting of SARS-CoV-2 infection, according to potential ACE2-dependent mechanism, drug neurotropism and drug distribution in nasal and oral areas

the gustatory sense pathway. ACEI and ARB are thought to induce upregulation of the ACE2,[13] which is expressed in both olfactory and nasal cavities, tongue and oral mucosa. The potential increase in the expression of ACE2 at this level could explain a possible mechanism for severe taste and smell disorders associated with ACEI and ARB. If the ACE2-dependent mechanism were to be confirmed as the explanation for chemosensory disorders in COVID-19 patients, it is conceivable that these drugs could modulate the clinical manifestations of taste and smell impairments associated with SARS-CoV-2 infection. This could be true also for the thiazolidinedione antidiabetics, which have been reported to increase ACE2 expression.[13] Notably, antihypertensive and antidiabetic drugs could either exacerbate or mitigate the manifestation of olfactory and gustatory impairments likely caused by SARS-CoV-2 infections, with possible consequences for the diagnosis. Smell and taste impairments may develop with various degrees of intensity among COVID-19 patients and were found to be early symptoms of SARS-CoV-2 infection. Therefore, medications that interfere with these symptoms, especially mild symptoms, could cause these COVID-19-specific clinical signs to be missed, likely delaying the diagnosis. Indeed, olfactory and gustatory disorders could present as prodromal or as the only manifestation of COVID-19.

In summary, we believe that any element useful for early identification of COVID-19 infection should be used to limit the infection as much as possible. In the case of the pandemic overlapping with the seasonal flu epidemic, alteration of taste and smell are specific symptoms of COVID-19 that can be exploited to identify COVID-19 patients and prevent the spread of the infection. However, many drugs could simulate these sensory alterations and must always be considered in the differential diagnosis, to avoid them being an obstacle to the identification of COVID-19 patients. Since many of the drugs most frequently associated with taste and smell changes, such as ACE inhibitors and antibiotics, are very likely to be taken by patients with COVID-19 and other respiratory infections, the hypothesis of this interference may not be that remote and it should be considered with utmost care.

COMPETING INTERESTS

The authors have no conflicts of interest to declare.

CONTRIBUTORS

D.F. and M.T. conceived the idea for the paper. S.F., M.T., D.F., I.C., G.V. and E.C. were involved in the analysis and interpretation of the available evidence. S.F. wrote the paper in collaboration with M.T. and D.F. M.T., D.F., C.B. and F.M. provided a critical review of the paper, and S.F., M.T., D.F., I.C., G.V., E.C., C.B. and F.M. reviewed the final version. All authors agree to be accountable for all parts of the work.

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