LETTER TO EDITOR

Potential pathogenesis of ageusia and anosmia in COVID-19 patients.

What we know from the literature

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Abstract
From the first reports, ageusia and anosmia appear to be frequent clinical features in coronavirus disease 19 (COVID-19) patients. We have performed a survey of the literature, analyzing the possible causes of these chemosensory alterations, which may be useful as a starting point for specific further studies.

Dear Editor,

The rapid spread of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Europe and America is enabling researchers to acquire a large amount of clinical data. Interestingly, some of these findings differ significantly from those reported in Chinese case studies. In particular, the presence of taste and smell alterations seems to be a frequent clinical feature of the coronavirus disease 19 (COVID-19), with a frequency ranging from 19.4% to 88% of patients\textsuperscript{1-4}.

The exact pathogenesis of these chemonsensitive disorders has not yet been clarified. At the same time, the comprehension of these mechanisms could be fruitful to understand the way in which the virus spreads through the organism.
We report our survey of the literature up to April 14, 2020, analyzing the possible causes of these chemosensory alterations, which may be useful as a starting point for specific future studies.

**Ageusia**

There are no studies in the literature regarding the possible relationship between coronavirus and the development of taste disorders. Angiotensin-converting enzyme 2 (ACE2) has been identified as the cellular receptor for SARS-CoV-2\(^5\). ACE2 receptors are expressed diffusely on the mucous membrane of the whole oral cavity, particularly on the tongue\(^6\). The role of ACE2 in modulating taste perception has been highlighted in many studies analyzing the chemosensitive side effects of ACE2 inhibitors and angiotensin II blockers\(^7,8\). The mechanism by which ACE2 inhibitors cause taste disturbance is unclear but does not appear to be related to any alteration in serum\(^7,8\) and saliva\(^7\) zinc levels. Presumably, these drugs inactivate the G-protein-coupled proteins and sodium-ion channels present in the taste receptors\(^5\). The taste disturbance generally regresses after the suspension of treatment\(^8\).

Moreover, the Middle East Respiratory Syndrome (MERS) coronavirus may bind to the sialic acid receptors\(^9\), an ability which has also recently been described for SARS-CoV-2\(^10\). Sialic acid is a fundamental component of the salivary mucin, and it protects the glycoproteins that convey gustatory molecules inside the taste pores from premature enzymatic degradation\(^11\). A reduction of sialic acid in the saliva is associated with an increase in the gustatory threshold\(^12\). In such a way, SARS-CoV-2 could therefore occupy the binding sites of sialic acid on the taste buds, accelerating the degradation of the gustatory particles.
Another possibility is that the ability to perceive flavors in these patients is adversely affected by the concomitant presence of olfactory disturbances, due to the intimate functional correlation between these two chemosensory systems\textsuperscript{13}. However, in the first published case series, taste dysfunctions are always more frequent than olfactory disturbances, presenting alone in 10.2-22.5\% of patients\textsuperscript{2-4}. This finding could lead to the hypothesis that the correlation between the two dysfunctions is not so close and that there are other factors behind the gustatory disorders in these patients.

**Anosmia**

ACE2 is expressed on the nasal mucosa, where it participates in respiratory inflammatory diseases by regulating the levels of inflammatory peptides, such as bradykinin\textsuperscript{14}. However, in COVID-19 patients there does not seem to be present such an important inflammatory component and the alteration of the sense of smell is generally not accompanied by rhinitis symptoms\textsuperscript{1,3}.

Therefore, one hypothesis could be that the alterations are due to damage caused by the virus to the olfactory pathways. Anosmia has already been described in common coronavirus infections\textsuperscript{15,16}. In 2006, Hwang\textsuperscript{17} described a case of anosmia that persisted for two years after SARS had been contracted. In 2001, Schwob et al.\textsuperscript{18} and Yougentob et al.\textsuperscript{19} evaluated the anatomopathological and functional consequences of olfactory bulb line variant mouse hepatitis virus intranasal inoculation in murine models. The histopathological analysis of the anosmic mice revealed a minimal destruction of the olfactory epithelium which was nonetheless abnormal due to the predominance of immature neurons, an indication of an accelerated cell turnover\textsuperscript{18,19}. The reduction in the neuronal lifespan in the epithelium is most likely to be the consequence of a decrease in the trophic support supplied by the bulb to the
sensory neurons, caused by the loss of mitral cells and the absence of dendrites of the surviving mitral and tufted cells from the glomerular layer\textsuperscript{18,19}. Accordingly, the virus may carry out its damage at the level of the olfactory bulb rather than the epithelium. However, the coronavirus used in these studies has been laboratory modified to target specifically the olfactory bulb. This is not necessarily the same for SARS-CoV-2, which we know has different organ targets.

Nevertheless, these authors, while clarifying the target of the virus, did not provide clear indications on the exact pathogenesis of neuronal death. In 2008, Netland et al.\textsuperscript{20} reported the effects of the SARS-CoV infection on the central central nervous system in mice transgenic for the human ACE2 receptor. The authors, not detecting any signs of inflammatory infiltration, hypothesized that neuronal death occurs due to a storm of cytokines, in particular IL-6, produced by neurons under the stimulation of the viral N-spike\textsuperscript{20}.

However, recent COVID-19 case series reports are showing a high rate of recovery of olfactory function within 1-2 weeks after the onset of the dysfunction\textsuperscript{3,4,21}. Furthermore, it would seem that the frequency (around 25%)\textsuperscript{22} of central nervous system symptoms is much lower than that of olfactory disorders. For these reasons, it is reasonable to hypothesize that the olfactory disorders are not related to, directly or indirectly, definitive viral damage to the neuronal cells. Conversely, the target of the virus may not be the neurons but other non-neuronal cells that express ACE2 receptors such as the olfactory epithelium sustentacular cells, microvillar cells, Bowman’s gland cells, horizontal basal cells and olfactory bulb pericytes\textsuperscript{23}. Brann et al.\textsuperscript{23}, speculated that the loss of smell reported by COVID-19 patients is due to the infection of the supporting cells and vascular pericytes of the olfactory epithelium and bulb which, consequently, alters the function of the olfactory neurons. The further
involvement of stem cells (which express lower levels of ACE2 receptors) could be the basis of the long-lasting olfactory dysfunctions\textsuperscript{23}.

Future research lines

In conclusion, from the first reports\textsuperscript{1-4}, ageusia and anosmia appear to be a frequent clinical feature during COVID-19. The pathogenic mechanism underlying the chemosensitive disorders in these patients has not yet been clarified. In our opinion, three lines of research could be useful to provide important indications regarding some still unclear pathogenic aspects. First, it will be necessary to obtain clinical data on large patient cohorts to determine the exact frequency of these symptoms and monitor their recovery over time. Secondly, it may be useful to evaluate the correlation between the viral load in the nasopharyngal swab and the extent of these chemosensitive disorders. Concluding, the histopathological analysis on samples obtained from patients who have died due to COVID-19 will be crucial to understand the nature and location of the olfactory dysfunction.

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