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LETTER TO THE EDITOR

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Causes of hypogeusia/hyposmia in SARS-CoV2 infected patients

To the Editor,

It is well appreciated that severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) does not exclusively affect the lungs.[1,2] Virus-RNA can be detected in most of the body compartments, including the cerebrospinal fluid (CSF).[3] Neurological manifestations have been recently investigated in a retrospective study of 214 SARS-CoV2-infected patients.[1] Neurological manifestations particularly occurred in severe infections.[1,4] There are indications that SARS-CoV2 carries a neuro-invasive potential.[5] The most common complaints in case of peripheral nervous system (PNS) involvement were hypogeusia (5.6%) and hyposmia (5.1%).[1] In a study of 59 coronavirus disease (COVID-19) positive patients with influenza-like symptoms, smell and taste loss was reported by 71% of them.[6] Transient abnormal taste/smelling may even occur before pulmonary manifestations. However, the cause of abnormal taste/smelling in patients with COVID-19 remains elusive.

Several speculations can be raised to explain the phenomenon. First, there is involvement of the central nervous system, meaning that some patients develop focal meningitis/encephalitis affecting the rhino- or gustatory-cortex representations or appropriate subcortical ascending/descending tracts. An argument in favor of this hypothesis is that virus RNA can be detected in the CSF of infected patients.[1] A further argument in favor of this speculation is the case of a Chinese male from Wuhan who experienced coma, seizures, and neck stiffness.[7] SARS-CoV2 RNA was found in the CSF, why SARS-CoV2-associated meningitis was diagnosed.[7] Arguments against the speculation one are that taste/smelling abnormalities are usually transient (maximal duration: 21 days) but meningitis/encephalitis lasts for days/weeks and that this hypothesis cannot sufficiently explain why only taste/smelling is impaired. A further argument against hypothesis one is that SARS-CoV2-associated meningitis is rare but smelling/taste abnormalities are frequent. Thus, a cerebral origin of sensory disturbances is rather unlikely.

Second, the PNS is targeted by SARS-Cov2, in particular cranial nerves I, VII, IX, and X. From other viral infections (eg, VZV) it is well-known that they can involve peripheral nerves, including the cranial nerves (eg, Ramsey-Hunt syndrome).[8] Affection of the peripheral nerves has been even documented in SARS-CoV2 infected patients.[1] Involvement of only four cranial nerves may be due to nonsystematic investigations of cranial nerves but more likely is that patients experiencing visual impairment (cranial nerve II), double vision (cranial nerves III, IV, VI), hypoacusis (cranial nerve VIII), dysphagia, or dysarthria (cranial nerves IX, X) would definitely communicate such complaints.

Third hypothesis, a stomatitis and/or a rhinitis triggers a local inflammatory response and the resulting edema hampers the normal functioning of the taste buds and/or olfactory epithelium. Hypothesis three is supported by a recent study of 605 patients with COVID from the Wuhan area showing that 3.5% (21 patients) reported a running nose, 1.3% a stuffy nose (8 patients), and 4.0% (24 patients) complained about a sore and dry throat.[9] However, loss of smell and/or taste may precede the occurrence of local signs of inflammation, such as a rhinorrhea or a sore throat.

Fourth, there is a focal immune reaction. It is conceivable that the virus triggers the production of antibodies against certain components of epithelial cell membranes or receptors, which are predominantly expressed in the tongue/olfactory epithelium. In a recent negative co-expression analysis using big data of 60 000 Affymetrix expression arrays and 5000 The Cancer Genome Atlas data sets to determine the functions of type-2 taste receptors (TAS2Rs) it was found that TAS2Rs may play an important role in host defense mechanisms.[10]

Fifth, smelling and taste impairment are side effects of certain drugs.[11] Many infected patients take drugs, including antibiotics, virostatics, or antipyretics. From some of them it is well-known that they impair smelling/tasting.[11] However, the phenomenon occurs also in drug-free patients, which is why speculation five remains unsupported.

Sixth, since the phenomenon is unanimously reported it could be due to direct contact of the virus or its components with gustatory receptors or olfactory cells. In patients with COVID-19, ACE2-expressing cells of the taste buds and/or olfactory epithelium might be targeted by SARS-Cov2 via a cytopathic effect. Alternatively, an altered neurotransmission in the absence of neurosensory cell death might similarly hamper taste and/or smell. Supporting this view, a recent clinical study showed that in patients with COVID-19, partial anosmia or ageusia could fluctuate over time.[12] Interestingly, ACE2 was found to coregulate with DOPA-decarboxylase (DDC) indicating that the dopamine and serotonin synthesis pathways might be hampered in patients with COVID-19.[13] ACE2 and DDC are expressed by murine taste buds[14] and the DDC-dependent synthesis of serotonin was found to be mandatory for normal taste functions.[15] Besides the hypothesis of a cytopathic effect on neurosensory cells, the high incidence of smell and/or taste loss in COVID-19 patients might thus reflect the impact of SARS-Cov2 on the synthesis of neurotransmitters (notably serotonin and dopamine) by ACE2-expressing cells.

In summary, the most likely cause for transient hypogeusia and hyposmia in SARS-CoV2-infected patients is a direct contact and interaction of the virus with gustatory receptors or olfactory receptor cells.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTION

JF: design, literature search, discussion, first draft; CS: literature search, critical comments.

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