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BRIEF COMMUNICATION

Gustatory Dysfunction: A Highly Specific and Smell-Independent Symptom of COVID-19

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Abstract Chemosensitive dysfunctions are now considered as frequent and early symptoms of coronavirus disease 2019 (COVID-19). In the last few weeks, researchers' greatest efforts have been focusing mainly on the analysis of olfactory disorders, neglecting taste dysfunctions. According to our psychophysical evaluations, it can be inferred that the pathogenesis of taste disorders in COVID-19 patients is largely smell-independent. Moreover, isolated gustatory disorders are highly specific of SARS-CoV-2 infection. For these reasons, it is essential that gustatory dysfunctions, like olfactory disorders, are included in the COVID-19 guidelines.

Keywords COVID-19 · SARS-CoV-2 · Coronavirus · Chemosensitive dysfunction · Olfactory dysfunction · Ageusia · Taste · Gustatory dysfunction · Anosmia

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Introduction

Chemosensitive dysfunctions are now considered as frequent and early symptoms of coronavirus disease 2019 (COVID-19) in Europe and America, affecting 60–80% of patients [1–4]. In the last few weeks, researchers' greatest efforts have been focusing mainly on the analysis of olfactory disorders, neglecting taste dysfunctions, for two main reasons. According to a first hypothesis, the olfactory pathway could represent a way of access to the central nervous system for the coronavirus [5]. Therefore, olfactory dysfunctions could represent a sign of neuroinvasion, while ageusia and hypogeusia would not have any possible interesting pathogenetic implication. Secondly, the gustatory disturbances have generally been classified as a consequence of the retronasal olfactory loss and for this reason they have been often overlooked [6].

After the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in Italy, we immediately began evaluating patients with psychophysical tests [7–10]. In this way, we were able to obtain a large amount of objective data that allowed us to evaluate the relationships between olfactory and gustatory disorders in COVID-19 patients.

Methodology

A standardized and validated test, which investigates the ability to perceive four primary tastes (sweet, salty, sour and bitter) was used to evaluate the gustatory function in patients with confirmed diagnosis of SARS-CoV-2 infection [7–10]. Four solutions, one for each primary taste, were prepared as follows [11]:

- Salted solution: 30 g of table salt were added to 1 L of deionized water.
- Sweet solution: 30 g of refined sugar were dissolved in 1 L of deionized water.
- Sour solution: 90 mL of commercial 100% lemon juice added to 1 L of deionized water.
- Bitter solution: unsweetened decaffeinated coffee.

Deionized water was used as control. During the trial, 1 ml of each solution was dropped onto the center of the patient tongue. Taste score ranged from 0 to 4 allowing to classify the patients into four categories: Normal (score 4), mild hypogeusia (score 3), moderate hypogeusia (score 2), severe hypogeusia (score 1) and ageusia (score 0). At the same time, all the patients underwent olfactory assessment with the Connecticut Chemosensory Clinical Research Center orthonasal olfaction test and a self-administered psychophysical olfactory test recently validated by our group [7–10].

Results

With this methodology, we obtained objective assessments of the olfactory and gustatory functions of 556 patients, many of which have been prospectively assessed several times. In the 801 evaluations performed, isolated taste disturbances were found in 9.4% of cases. Considering also subjects with combined dysfunctions, a total of 51.1% of patients reported gustatory disorders. Moreover, in 17.9% of patients with combined dysfunctions, taste disorders were more severe than the olfactory ones. This frequency is probably underestimated as 74.4% of these evaluations were performed over 10 days after the symptom onset. As a matter of fact, in most patients the gustatory dysfunction tends to regress completely within 10 days, while the recovery of the olfactory disorder takes longer [7, 9, 12]. Taking into consideration only the 205 assessments that took place within 10 days after clinical onset, patients with gustatory disorders rose to 69.2% with a frequency of isolated disorders of 11.6%. In this early stage subgroup, 26.3% of patients who presented combined chemosensitive disorders had a gustatory dysfunctions more severe than the olfactory one (Table 1).

Discussion

The studies currently present in the literature, have not been able to detect these results as they are based exclusively on anamnestic data or on psychophysical evaluation of patients in the late stage of the disease, when the gustatory disorder had already regressed. Only the objective evaluation of the patients during the early stage of the infection permits to appropriately compare the frequency and severity of the two chemosensitive disorders.

According to these results, it can be inferred that the pathogenesis of taste disorders in COVID-19 patients is largely smell-independent. Anosmia is typically associated with viral infections while ageusia could represent a further manifestation, related to the loss of the retronasal olfactory function. The ability of SARS-CoV-2 to induce gustatory disturbances in the absence of olfactory dysfunctions is instead a unique peculiarity for a virus.

The mechanism by which SARS-CoV-2 is capable of causing gustatory disturbances could be twofold. First, the virus uses the angiotensin converting enzyme 2 (ACE2), receptors widely expressed on the taste buds, to infect cells. Ageusia is a well known side effect of ACE2-inhibitors and it is caused by a complex mechanism which involves sodium channel and G-protein-coupled protein present in taste receptors. SARS-CoV-2, binding these receptors, might inactivate them, hindering the conversion of chemical gustatory signals into action potential, consequently precluding the sensory perception of taste [13, 14].

Moreover, SARS-CoV-2 might bind to sialic acid receptors [15]. Sialic acid is a fundamental component of the salivary mucin and protects the glycoproteins that convey gustatory molecules inside the taste pores from premature enzymatic degradation. A reduction of sialic acid in the saliva is associated with an increase in the gustatory threshold. Therefore, SARS-CoV-2 could occupy the binding sites of sialic acid on the taste buds, accelerating the degradation of the gustatory particles [13].

From a diagnostic point of view, isolated gustatory disorders are very important as they are highly specific of SARS-CoV-2 infection. In fact, olfactory dysfunction is also present in 12% of cases of common flu [16] and, although useful as a screening marker, it can give a significant number of false positives. At the beginning of the epidemic in Italy, an abnormal number of patients turned to our clinic for the detection of sudden onset ageusia, not associated with any other symptoms. Punctually, SARS-CoV-2 infection was then diagnosed in these patients following the further onset of fever and cough.

Conclusion

Otorhinolaryngologists, maxillofacial surgeons, neurologists and dentists should be warned that in patients seeking assistance for the isolated sudden onset of ageusia, suspicion of ongoing coronavirus infection should be considered in differential diagnosis. For these reasons, in our opinion it is essential that gustatory dysfunctions, like olfactory disorders, are included in the COVID-19 guidelines as they

Table 1 Chemosensitive function psychophysical analysis results

	Overall (No. 801)	< 10 days (No. 205)
Isolated taste dysfunction	76 (9.4%)	23 (11.6%)
Combined dysfunction	334 (41.7%)	114 (57.6%)
Taste > smell	36 (10.8%)	30 (26.3%)
Taste = smell	107 (32%)	51 (44.7%)
Taste < smell	191 (57.2%)	33 (28.9%)
Isolated olfactory dysfunction	217 (27.1%)	35 (17.7%)
No dysfunction	174 (21.7%)	35 (17.7%)

are frequent, highly specific and smell-independent symptoms of SARS-CoV-2 infection.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval The evaluation protocol was approved by an independent ethical committee (No. 378-2020-OSS-AUSLBO).

Informed Consent All patients gave their consent to participate in the study.

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