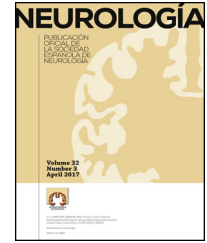




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## ORIGINAL ARTICLE

# Smell and taste disorders in Spanish patients with mild COVID-19



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### KEYWORDS

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### Abstract

**Introduction:** Coronavirus disease 2019 (COVID-19) has spread rapidly throughout the world. Smell and/or taste disorders have emerged as a very frequent symptom as the disease has spread in Europe. Spain is one of the European countries with the highest number of infections. **Objective:** This study aimed to investigate the clinical progression of smell and taste disorders in Spanish patients with mild COVID-19.

**Methods:** An online survey was used to conduct a cross-sectional study of patients who presented sudden smell and/or taste disorders during the 2 months of total lockdown due to COVID-19 in Spain.

**Results:** In our sample, 91.18% of respondents with impaired smell and/or taste and who were able to undergo PCR testing were positive for SARS-CoV-2 infection. Anosmia and ageusia presented in isolation in 6.5% of participants. The remaining 93.5% presented other mild symptoms: headache (51.6%), cough (51.6%), myalgia (45.2%), asthenia (38.7%), nasal congestion or rhinorrhoea (35.5%), fever (41.9%), low-grade fever (29.0%), odynophagia (25.8%), or diarrhoea (6.5%). The mean duration of anosmia was 8.33 days, with patients subsequently manifesting hyposmia; complete resolution occurred after a mean of 17.79 days. In 22.6% of respondents, olfactory deficits persisted. All participants recovered their sense of taste.

**Conclusions:** Olfactory and gustatory disorders are prevalent symptoms in mild COVID-19. Most patients do not present associated nasal congestion or rhinorrhoea and a small group of patients present these alterations in isolation.

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**PALABRAS CLAVE**

Anosmia;  
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Hiposmia;  
COVID-19;  
Pandemia

## Afectación del sentido del olfato y el gusto en la enfermedad leve por coronavirus (COVID-19) en pacientes españoles

**Resumen**

**Introducción:** La enfermedad por coronavirus-2019 (COVID-19), se ha expandido con gran rapidez en todo el mundo. Las alteraciones del olfato y/o gusto han emergido como un síntoma muy frecuente a medida que la enfermedad se propagó en Europa. Uno de los países con mayor número de contagios en este continente ha sido España.

**Objetivo:** Investigar la evolución clínica de los trastornos del olfato y el gusto en la enfermedad leve por COVID-19 en pacientes españoles.

**Métodos:** Se realizó un estudio transversal a través de encuesta on-line, en pacientes que presentaron afección súbita del olfato y/o el gusto, durante los dos meses de confinamiento total por COVID-19 en España.

**Resultados:** El 91,18% de los sujetos con afectación del olfato y/o el gusto, que tuvieron acceso a la realización de PCR, fueron positivos para COVID-19. El 6,5% presentó anosmia y ageusia de forma aislada. El 93,5% manifestó otros síntomas leves asociados: cefalea (51,6%), tos (51,6%), mialgias (45,2%), astenia (38,7%), congestión nasal o rinorrea (35,5%), fiebre (41,9%), febrícula (29,0%), odinofagia (25,8%) y diarrea (6,5%). La duración media de la anosmia fue de 8,33 días, posteriormente los pacientes manifestaron hiposmia, con resolución completa en 17,79 días de media. En el 22,6% de los pacientes el déficit olfatorio persistió. Todos los sujetos recuperaron el sentido del gusto.

**Conclusiones:** Los trastornos olfativos y gustativos son síntomas prevalentes en la infección leve por COVID-19. Gran parte de los pacientes no presentan congestión nasal o rinorrea asociada y un grupo reducido de pacientes los presentan de forma aislada.

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**Introduction**

Coronavirus disease 2019 (COVID-19) is a viral disease that has rapidly spread across the world. The causal agent, a novel RNA virus from the coronavirus family, is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) due to its phylogenetic similarity to the SARS-CoV virus.<sup>1</sup> Although SARS-CoV-2 shares 70%-80% of its genome with SARS-CoV, it presents genetic and structural differences.<sup>2,3</sup> In fact, it is more similar to a coronavirus strain detected in horseshoe bats (*Rhinolophus*), BtCoV/4991, with the RNA-dependent RNA polymerase gene showing a 98.7% similarity.<sup>4-6</sup>

The initially reported symptoms of COVID-19 were fever, cough, asthenia, dyspnoea, odinophagia, headache, joint and muscle pain, and diarrhoea.<sup>7-9</sup> However, as the disease spread to Europe, olfactory disorders (anosmia/hyposmia) emerged as a new symptom of SARS-CoV-2 infection.<sup>10,11</sup> Although these disorders initially went undetected due to their mild nature, they have progressively been recognised due to their distinctiveness and high prevalence.

Other coronaviruses and families of respiratory viruses (rhinoviruses, parainfluenza viruses, Epstein-Barr virus) can also cause olfactory alterations due to inflammation of the nasal mucosa; however, these alterations are different from those observed in patients with COVID-19.<sup>12-14</sup> The olfactory alterations associated with SARS-CoV-2 infection present sudden onset, are generally not accompanied by rhinorrhoea or nasal obstruction with mucus, and are of variable intensity, although patients frequently report complete loss of the sense of smell. Anosmia may appear as the only manifestation of COVID-19,<sup>15</sup> although it is frequently accompanied by taste disorders (ageusia) or other symptoms of SARS-CoV-2 infection.<sup>12,16</sup>

Recent evidence suggests that the route of entry of SARS-CoV-2 into the human host is mediated by a cellular receptor of

angiotensin-converting enzyme 2 (ACE2), which is expressed in epithelial cells of the respiratory tract, lung parenchyma, and vascular endothelium; and in kidney and small intestine cells. However, it has been suggested that the virus is able to infect the central nervous system (CNS),<sup>17</sup> where ACE2 expression is very low.<sup>18-21</sup> Several hypotheses have been proposed regarding the pathogenesis of anosmia secondary to SARS-CoV-2 infection. Some authors suggest that smell disorders may be mediated by direct infection of the olfactory mucosa, which would result in destruction of olfactory sensory neurons; recovery would therefore be slower, with olfactory alterations lasting longer and even a risk of permanent deficits.<sup>15</sup> Another hypothesis suggests direct involvement of the frontal lobe.<sup>22,23</sup>

The purpose of this study was to analyse the characteristics and clinical progression of smell and taste disorders in Spanish patients with mild COVID-19.

**Material and methods****Design**

We conducted a cross-sectional, observational study of individuals presenting sudden-onset olfactory/gustatory alterations during the 2 months of lockdown due to the COVID-19 pandemic in Spain.

**Population**

We recruited members of the general population who were subject to confinement at home as a result of the state of alarm; participants were acquaintances of the researchers and their relatives and friends. Inclusion criteria were as follows: age older than 18 years,

sudden onset of olfactory or gustatory loss or alterations presenting between 15 March and 30 April 2020, and ability to complete a survey either online or via telephone.

Exclusion criteria were as follows: age younger than 18 years, presence of smell or taste disorders before the pandemic, admission to hospital during the study period, and treatment with inhaled corticosteroids. Therefore, our study mainly included paucisymptomatic individuals with suspected COVID-19. Clinical presentation of COVID-19 was not considered an inclusion criterion, since our study focused on olfactory and gustatory alterations.

## Variables

Participants meeting the inclusion criteria were asked to complete a questionnaire, which gathered the following data: sex; age; medical history; characteristics of olfactory/gustatory alterations (complete loss of the sense of smell/taste [anosmia/ageusia], decreased sense of smell [hyposmia], altered sense of taste [dysgeusia]); date of onset and resolution of the alterations; symptom progression; associated symptoms; close contact with a patient with COVID-19 (confirmed by PCR testing); and PCR results for COVID-19, if the test was performed.

Participants were followed up via e-mail every 7-8 days until olfactory and gustatory symptoms resolved, or until 30 April.

## Ethical considerations

The project was approved by the drug research ethics committee of the Zamora health district (project no. PI 496). Participants gave informed consent via telephone or electronically. Our study complies with the principles of the Declaration of Helsinki and with good practice guidelines.

## Statistical analysis

Statistical analysis was performed using the SPSS statistical software (version 25; IBM). Qualitative variables are expressed as percentages and quantitative variables as means, standard deviation (SD), and range. Qualitative variables were compared with the chi square test and quantitative variables with non-parametric tests (Mann-Whitney U test); data were tested for normal distribution using the Kolmogorov-Smirnov test.

## Results

A total of 101 individuals completed our questionnaire (online: 83; telephone: 18); 15 were excluded. Therefore, the final sample included 86 participants.

Close contact with a patient with PCR-confirmed COVID-19 was reported by 60.5% of the participants. Thirty-four participants (39.5%) underwent PCR testing for SARS-CoV-2 infection, with 91.18% testing positive for the virus. The remaining 52 individuals were not able to access the test, although 48.1% of this group reported having been in close contact with a patient with PCR-confirmed COVID-19 (friends or colleagues in 30.8%, relatives in 15.4%, and hospitalised patients in one case).

### Individuals with positive PCR results

Of the 31 participants with positive PCR results for SARS-CoV-2, 19 were women (61.3%) and 12 were men (38.7%). These individuals' ages ranged from 25 to 72 years, with a mean age (SD) of 44.61 (13.08) years.

Anosmia and ageusia were reported by 83.9% of participants, whereas 3.2% presented anosmia with normal gustatory function. The remaining 12.9% presented hyposmia associated with dysgeusia.

Two participants (6.5%) presented complete loss of the sense of smell/taste in isolation, whereas the remaining 93.5% presented other associated symptoms, including nasal congestion or rhinorrhoea (35.5%) and odinophagia (25.8%).

The most frequent non-specific symptoms were headache (51.6%), cough (51.6%), muscle pain (45.2%), asthenia (38.7%), and fever (41.9%) or mild fever (29.0%). Diarrhoea was also reported by 6.5% of participants.

Mean (SD) duration of anosmia was 8.33 (7.12) days (range, 2-28); 77.4% of the participants reported gradual improvement in olfactory function, with complete recovery after a mean of 17.79 (8.88) days (range, 6-41). However, 7 individuals (22.6%) had only partially recovered olfactory function after a mean follow-up period of 38.47 (3.62) days. These individuals reported a certain degree of hyposmia, with inability to perceive the smell of bleach, vinegar, faeces, or sweat.

We identified a slight positive correlation between age and time until complete recovery ( $Rho = 0.302$ ); however, this association was not statistically significant ( $P > .05$ ).

Participants reported a progressive recovery of the sense of taste, coinciding with recovery of olfactory function (mean duration of 8.33 days). Fifteen individuals (48.4%) indicated which taste or tastes they recovered first: salty tastes in 66.7%, sweet in 33.3%, sour in 33.3%, and bitter in 33.3%. All participants fully recovered gustatory function.

### Comparison between participants with positive PCR results and those who were not tested

The duration of anosmia was determined in 18 PCR-positive patients and 42 individuals not undergoing PCR testing. Anosmia lasted slightly longer in PCR-positive patients than in those not undergoing PCR testing (8.33 [7.12] vs 6.02 [3.85] days), although this difference was not statistically significant.

Furthermore, complete recovery of olfactory function was significantly slower in PCR-positive patients than in those not undergoing PCR testing (17.79 [8.88] vs 13.16 [8.05] days;  $P = .011$ ).

Clinical progression (defined as progression of the associated symptoms) was similar in both groups. No statistically significant differences were observed in the frequency of any of the associated symptoms analysed (nasal congestion, odinophagia, cough, headache, asthenia, muscle pain, fever, or mild fever).

## Discussion

In our study, only 8.4% of individuals with olfactory/gustatory alterations undergoing PCR testing were negative for SARS-CoV-2; this supports the hypothesis that these symptoms are highly prevalent in patients with mild COVID-19. Sudden-onset anosmia associated with ageusia was the most frequently reported alteration (83.9%). Anosmia without taste disorders and hyposmia with dysgeusia were less frequently reported. Interestingly, participants with anosmia recovered progressively, progressing from complete loss of the sense of smell lasting approximately one week (mean of 8.33 days) to hyposmia, which resolved in around 2 weeks in most cases (mean of 17.79 days).

However, a considerable percentage (22.7%) did not fully recover the sense of smell, with some degree of hyposmia persisting. Although our study could not objectively evaluate our patients' olfactory and gustatory function, we should point out that it was the patients themselves who, on their own initiative, reported inability to perceive such smells as bleach, vinegar, sweat, or faeces, which points to persistence of a true loss of the sense of smell. However, future studies should aim to objectively evaluate these alterations. Furthermore, our results show that anosmia is not age-dependent.

Similarly, ageusia resolved gradually: while most patients could not indicate the exact duration of this symptom, they did report recovering the ability to perceive some tastes in parallel with recovery of olfactory function. However, it is unclear whether anosmia and ageusia are associated. The glossopharyngeal, facial, and vagus nerves provide the sense of taste, identifying the basic tastes (sweet, salty, sour, bitter, umami); however, most gustatory experiences (recognising the product being consumed) are associated with more complex flavours and require the involvement of the olfactory nerve.<sup>24</sup>

Our study participants were initially able to identify basic tastes, with salt being the most frequently reported, followed by sweet, sour, and bitter tastes. Furthermore, recovery of olfactory function was faster than and independent of recovery of gustatory function in most cases; most individuals with smell disorders experienced complete recovery. This suggests distinct pathophysiological mechanisms for olfactory and gustatory alterations, involving different nerve pathways. This is consistent with the experience of Luers et al.,<sup>24</sup> who described a case of isolated ageusia (without olfactory involvement) in a patient with COVID-19. However, further research is needed.

Some studies suggest that a large percentage of the patients with smell disorders secondary to SARS-CoV-2 infection do not present nasal congestion or rhinorrhoea.<sup>15</sup> Our results support this finding, as more than half of participants did not present these symptoms. Furthermore, a small percentage of patients (6.5%) presented sudden, isolated anosmia. These findings may indicate primary neurological involvement mediated by independent or overlapping pathophysiological mechanisms. The virus may cause direct damage to olfactory receptor neurons located in the olfactory epithelium; this hypothesis is plausible since these cells express the 2 proteins necessary for entry of the virus into the cytoplasm: ACE2 and transmembrane protease serine 2 (TMPRSS2).<sup>25–27</sup> In fact, a recent histopathological study of tissue collected post mortem confirmed presence of SARS-CoV-2 in the olfactory nerve.<sup>28</sup>

Furthermore, the virus may directly invade the frontal lobe through olfactory nerve axons,<sup>23,27,29</sup> causing olfactory alterations through sensorineural mechanisms. Likewise, the previously cited post mortem study revealed extensive tissue damage affecting neurons, glial cells, axons, and myelin sheaths, in association with numerous SARS-CoV-2 virions; severity increased progressively from the olfactory nerve to the gyrus rectus in the frontal lobe and the brainstem.<sup>28</sup>

The long-term impact of SARS-CoV-2 on the CNS is still unknown. Recent studies suggest that the virus may easily penetrate the CNS<sup>30</sup>; however, neurological complications are rare during active SARS-CoV-2 infection.<sup>31</sup> This may be explained by the low expression of ACE2 and TMPRSS2 receptors in the CNS,<sup>32</sup> which may enable cells to generate such defence mechanisms as vacuolisation to isolate the virus in the cytoplasm.<sup>29</sup> As a result, the virus could remain within cells, which would support the hypothesis that the CNS can act as a reservoir for SARS-CoV-2.<sup>29,33</sup>

Furthermore, patients with smell and taste disorders reported other mild symptoms that commonly appear in other viral processes, with headache being the most frequently reported symptom. They also reported cough, asthenia, muscle pain, fever, mild fever, odinophagia, and to a lesser extent diarrhoea; this is consistent with the findings reported in the most recent studies.<sup>12,34,35</sup>

Due to the state of alarm during March and April in Spain, a large percentage of patients with mild symptoms were unable to access PCR testing for SARS-CoV-2. This was also observed in our sample: 60.5% of individuals with smell and taste disorders did not undergo PCR testing. Further research is needed to confirm the presence of antibodies in these patients. As the epidemiological situation is currently more favourable, the occupational health department of the Zamora health district, through our research group, intends to determine the levels of IgG and IgM antibodies in this population to confirm our results.

According to the predictive model proposed by Menni et al.,<sup>34</sup> 13.06% of patients with suspected COVID-19 who do not undergo laboratory tests may have SARS-CoV-2 infection.<sup>34</sup> To date, no study has compared individuals with smell and taste disorders with and without PCR results.

We found no statistically significant differences in the duration of anosmia between participants with and without PCR results. Similarly, both groups presented similar symptoms (nasal congestion, odinophagia, headache, cough, asthenia, muscle pain, fever, and mild fever), and no significant differences were observed in the frequency of these symptoms.

In the light of the above, sudden-onset anosmia and ageusia, either alone or in combination with the previously mentioned symptoms, should be cause for suspicion of COVID-19. This may help not only in detecting the disease in the acute stage and preventing transmission of the infection, but also in identifying COVID-19 seropositive individuals who are no longer in the acute stage, in whom infection may not have been confirmed by laboratory tests during the peak of the pandemic due to the reduced availability of healthcare resources.

Our study has several limitations. Firstly, the participants did not undergo specific tests for olfactory/gustatory function, which would have provided objective data on the presence of smell and taste disorders. Secondly, a longer follow-up period is needed to confirm residual olfactory deficits. Lastly, our sample included colleagues (healthcare professionals) and their relatives and friends, and therefore may not be representative of the population with SARS-CoV-2 infection. However, this was the most accessible population during the state of alarm.

## Conclusions

Many questions remain unanswered due to the novelty and complexity of SARS-CoV-2 and the different clinical patterns of COVID-19. Our findings support the high prevalence of smell and taste disorders among Spanish patients with mild COVID-19. According to our results, patients with SARS-CoV-2 infection may present olfactory and/or gustatory alterations either alone or in association with other mild symptoms of viral infection (with headache being the most frequent). Likewise, over half of individuals reported smell and taste disorders with no associated symptoms of common cold (nasal congestion or rhinorrhoea); this may indicate primary involvement of the olfactory nerve and retrograde invasion of the frontal lobe, causing sensorineural anosmia/hyposmia.

Furthermore, a large proportion of our sample showed rapid, complete recovery, but olfactory alterations persisted in a small percentage of participants. Future studies are needed to analyse residual olfactory deficits.

Patients presenting sudden-onset smell and taste disorders, either alone or in association with mild symptoms of viral infection, during the pandemic are very likely to have contracted COVID-19. Healthcare authorities should therefore recognise smell and taste disorders as potential symptoms of COVID-19. This would not only help to prevent transmission of the disease during the acute stage but also enable the implementation of effective strategies for recognising immunity in individuals who have had paucisymptomatic COVID-19, which may be extremely useful for the lockdown de-escalation plan and the return to normal life.

## Conflicts of interest

The authors have no conflicts of interest to declare.



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