





# Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case–control study

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**Background and purpose:** Specific respiratory tract infections, including COVID-19, may cause smell and/or taste disorders (STDs) with increased frequency. The aim was to determine whether new-onset STDs are more frequent amongst COVID-19 patients than influenza patients.

**Method:** This was a case–control study including hospitalized patients of two tertiary care centres. Consecutive patients positive for COVID-19 polymerase chain reaction (cases) and patients positive for influenza polymerase chain reaction (historical control sample) were assessed during specific periods, employing a self-reported STD questionnaire.

**Results:** Seventy-nine cases and 40 controls were included. No significant differences were found in basal features between the two groups. New-onset STDs were significantly more frequent amongst cases (31, 39.2%) than in the control group (5, 12.5 %) [adjusted odds ratio 21.4 (2.77–165.4,  $P = 0.003$ )]. COVID-19 patients with new-onset STDs were significantly younger than COVID-19 patients without STDs ( $52.6 \pm 17.2$  vs.  $67.4 \pm 15.1$ ,  $P < 0.001$ ). Amongst COVID-19 patients who presented STDs, 22 (70.9%) recalled an acute onset and it was an initial manifestation in 11 (35.5%). Twenty-five (80.6%) presented smell disorders (mostly anosmia, 14, 45.2%) and 28 (90.3%) taste disorders (mostly ageusia, 14, 45.2%). Only four (12.9 %) reported concomitant nasal obstruction. The mean duration of STD was  $7.5 \pm 3.2$  days and 12 patients (40%) manifested complete recovery after  $7.4 \pm 2.3$  days of onset.

**Conclusion:** New-onset STDs were significantly more frequent amongst COVID-19 patients than influenza patients; they usually had an acute onset and were commonly an initial manifestation. The use of STD assessment in anamnesis as a hint for COVID-19 and to support individuals' self-isolation in the current epidemic context is suggested.

## Introduction

The partial or total loss of smell (anosmia/hyposmia) and taste (hypogeusia/ageusia), with or without a distorted perception of smells and flavours (dysosmia/dysgeusia), has a wide differential diagnosis [1,2].

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Upper respiratory tract infections (URIs) are a common cause of smell and/or taste disorders (STDs) [3], and some microorganisms might cause STDs with increased frequency [4].

Previous studies have analysed STDs in coronavirus disease 2019 (COVID-19) with a highly variable prevalence, between 5% and 48% [5-8], but underreporting was likely due to the benignity of the symptom. In fact, several scientific societies have stated that STDs could be a frequent manifestation of COVID-19 and have published recommendations in this regard [9,10].

The aim was to assess whether acute-onset STDs are more frequent in COVID-19 than in influenza patients, and to analyse associated clinical features. STDs are easily recognizable symptoms, which could indicate a COVID-19 in citizens and healthcare professionals, allowing earlier and more efficacious isolation procedures and treatment whenever necessary.

## Methods

A multicentre case-control study with historical controls was designed. A brief questionnaire exploring STDs was created (see Appendix S1). From 23 to 25 March 2020 and during hospitalization routine clinical assessments, five physicians handed out the questionnaire to COVID-19 patients admitted in two tertiary care centres of Madrid, Spain (cases).

Due to the epidemic context and the lack of reliable COVID-19 polymerase chain reaction (PCR) negative patients with URIs of different aetiology, a historical group of 2019/2020 season influenza patients was chosen as control. Influenza PCR is routinely made upon clinical suspicion (unlike URIs due to other viruses) in the tertiary care setting, allowing a certainty diagnosis and equivalent inpatient status in controls. A single physician retrospectively delivered the same questionnaire by telephone call to influenza patients who were admitted to one of our centres during the first 15 days of January 2020.

Inclusion criteria were age >18 and a positive PCR for COVID-19 or influenza in the above-mentioned periods. Exclusion criteria were dementia, low level of consciousness, previous history of STDs or a drug-induced, neurological, rhinological or systemic disease-related STD, and (for controls) lack of response to the telephone call.

The use of specific chemosensory testing, although ideal, was not contemplated by the authors in this study. Regarding a benefit-risk balance, its use was considered to imply an unnecessary additional time of exposure to COVID-19 for physicians, as well as an unessential bother to patients given their condition. The local board of the ethics committee of our centre (Comité de Ética e Investigación de Medicamentos

IRICYS – Fundación para la Investigación Biomédica del Hospital Universitario Ramón y Cajal) approved the research protocol of this study and deemed a written informed consent not required. Verbal informed consent was obtained from all cases and controls.

Statistical analysis was performed with SPSS 23.0 software (IBM SPSS Statistics 23.0.0.0, New York, NY, USA). Basal features of both samples were described and compared (descriptive statistics, chi-squared test and *t* test were used whenever appropriate according to the type of variable). For comparison of STDs between cases and control samples, both crude and multivariate logistic regression models were employed. Clinical features of COVID-19 patients with and without STDs were also described and compared (descriptive statistics, chi-squared and *t* test were used whenever appropriate according to the type of variable). Due to the scarce and highly variable previous reports of STDs in COVID-19 and other respiratory tract infections, formal sample sizes and power calculations were not determined.

## Results

Eighty-six patients with COVID-19 were assessed. Two patients with dementia and five with an initial negative PCR for COVID-19 were excluded, and 79 patients were included in the case group. Forty-six patients with influenza (41 with A-H1, 1 with A-H3, four with B subtypes) were assessed for the control group. Four patients who did not answer the phone call, one with previous anosmia due to rhinological pathology and one with history of intranasal drug abuse were excluded, and 40 patients were included in the control group.

No significant differences were found in basal characteristics between the two groups. The number of men in the COVID-19 group was 48 (60.8%) and in the influenza group 19 (47.5%). Mean age in the COVID-19 group was 61.6 years (SD 17.4) and 61.1 (SD 17.1) in the influenza group. Number of smokers or former smokers was 19 in the COVID-19 group (24.1%) and 12 (30%) in the influenza group.

The presence of new-onset STD was significantly higher in the case group [31, 39.2%, 95% confidence interval (CI) 28.9–50.6] than in the control group (5, 12.5%, 95% CI 5.1–27.6), crude odds ratio 4.5 (95% CI 1.6–12.3, *P* = 0.0045). A multivariate logistic regression model adjusting for smoking habit and nasal obstruction showed an adjusted odds ratio of 21.4 (95% CI 2.77–165.4, *P* = 0.003). Significant differences were also found regarding smell and taste disorders separately (Table 1).

Within the cases group, between those who presented new-onset STD (*n* = 31) and those who did not

**Table 1** Comparison of smell and/or taste disorders (STDs) between COVID-19 and influenza patients

Pattern of STD	COVID-19 ( <i>n</i> = 79), <i>N</i> (%), 95% CI)	Influenza ( <i>n</i> = 40), <i>N</i> (%), 95% CI)	Crude odds ratio (95% CI)	<i>P</i> value	Adjusted odds ratio (95% CI) <sup>a</sup>	<i>P</i> value
Smell and/or taste disorder	31 (39.2%, 28.9–50.6)	5 (12.5%, 5.1–27.6)	4.52 (1.6–12.8)	0.004	21.4 (2.77–165.4)	0.003
Smell disorder	25 (31.65%, 22.2–42.9)	4 (10%, 3.6–24.6)	4.17 (1.3–12.98)	0.014	18.47 (2.31–147.7)	0.006
Taste disorder	28 (35.44%, 25.5–46.8)	4 (10%, 3.6–24.6)	4.86 (1.56–15.1)	0.006	4.76 (1.5–14.8)	0.007

CI, confidence interval. <sup>a</sup>A multivariate logistic regression model adjusting for smoking habit and nasal obstruction was performed.

(*n* = 48), there were no significant differences regarding gender (males 19, 61.9%, vs. 29, 60.4%, respectively), smoking habit (7, 22.58%, vs. 12, 25%, respectively) or severe COVID-19 criteria (need of mechanical ventilation and/or tocilizumab) (2, 6.5%, vs. 5, 10.4%, respectively).

Patients with COVID-19 and new-onset STD were significantly younger than patients with COVID-19 without STD ( $52.6 \pm 17$  vs.  $67.4 \pm 15.1$  years, *t* test, *P* = 0.001). Taking an arbitrary cut-off point of 60 years, 19 (57.6%) of the patients below 60 (*n* = 33) presented new-onset STD, in contrast to 12 (26.01%) of those over 60 (*n* = 46) (chi-squared, *P* = 0.006).

Amongst COVID-19 patients with new-onset STD (*n* = 31), 25 (80.6%) presented smell disorders (mostly anosmia, *n* = 14, 45.2%) and 28 (90.3%) taste disorders (mostly ageusia, *n* = 14, 45.2%). Twenty-two (70.9%) had an acute onset of STD. In 11 (35.5%), STDs were the initial manifestation of COVID-19. Four patients (12.9%) reported concomitant nasal obstruction, and 21 patients (67.7%) were capable of distinguishing sweetness, saltiness and bitterness despite their STD. The mean duration of STD was  $7.5 \pm 3.2$  days. Twelve patients (40%) reported complete recovery after  $7.4 \pm 2.3$  days and five (16.7%) partial recovery after  $9.1 \pm 3.6$  days. One patient was lost to follow-up and recovery data were unavailable. However, amongst influenza patients, all who recalled new-onset STD described a total recovery at the moment of data collection (Table 2).

## Discussion

Upper respiratory tract infections are one of the most frequent causes of STDs [3]. A few studies have suggested that specific viruses (rhinovirus, coronavirus including SARS-CoV-2 [5–8] parainfluenza virus and Epstein Barr virus) could cause postviral olfactory dysfunction through mechanisms other than nasal obstruction, suggesting a specific tropism of these viruses for structures of the olfactory sensory epithelium [4].

Our results suggest that new-onset STDs are significantly more frequent amongst COVID-19 than in other URIs, specifically influenza. A previous study estimated the presence of STDs in the common cold

**Table 2** Description of smell and/or taste disorder (STD) features in COVID-19 and influenza patients

STD characteristic	COVID-19 ( <i>n</i> = 31)	Influenza ( <i>n</i> = 5)
Nasal obstruction, <i>N</i> (%)	4 (12.9%)	4 (80%)
Smell disorder pattern		
Anosmia, <i>N</i> (%)	14 (45.2%)	0 (0%)
Hyposmia, <i>N</i> (%)	9 (29.0%)	4 (80%)
Dysosmia, <i>N</i> (%)	2 (6.5%)	0 (0%)
Taste disorder pattern		
Ageusia, <i>N</i> (%)	14 (45.2%)	4 (80%)
Hypogeusia, <i>N</i> (%)	7 (22.6%)	1 (20%)
Dysgeusia, <i>N</i> (%)	8 (25.8%)	2 (40%)
Capable of distinguishing sweetness/saltiness/bitterness, <i>N</i> (%)	21 (67.7%)	5 (100%)
Pattern of onset of STD		
Acute, <i>N</i> (%)	21 (67.7%)	2 (40%)
Subacute, <i>N</i> (%)	10 (32.3%)	3 (60%)
Duration of taste/smell disorder, mean (SD), days	7.1 (3.1)	9.8 (4.8)

at 60% [11]. The use of intense chemosensory stimuli in this study may have revealed subtle STDs that patients are not able to perceive (and therefore report in a questionnaire). In addition, most COVID-19 patients affected with STD reported no nasal obstruction and were capable of distinguishing sweetness, saltiness and bitterness (specific gustatory afferents), suggesting a specific tropism of SARS-CoV-2 for structures of the olfactory sensory epithelium.

Our results show an increased frequency of STDs in the youngest. Although age-related olfactory loss is common, patients judged not able to detect changes from the basal situation due to previous STDs were excluded.

Regarding new-onset STDs, acute and early onset were common. The majority of patients (56.7%) also reported a total or partial recovery at the moment of data collection, suggesting reversibility due to repair of the damaged structures of the olfactory sensory epithelium.

This study has limitations, most derived from the exceptional current pandemic context: case-control design and historical controls (with possibility of recall bias in the control sample), restriction to hospitalized patients, lack of comparison with other viruses besides influenza, determination of STD using a self-

reported questionnaire without specific chemosensory testing, and absence of formal sample size and power calculations. Nevertheless, the results of our study warrant the consideration of new-onset STDs as specific manifestations of COVID-19. Furthermore, stronger evidence to support this statement is provided, beyond online surveys or polls, uncontrolled for PCR and lacking a complete clinical assessment.

In the current epidemiological setting, this easily detectable symptom may be useful for citizens to suspect a developing COVID-19. This would allow further strengthening of the measures of self-isolation and urge communication to their healthcare providers, especially in social groups at higher risk for the disease (i.e. healthcare professionals). As for physicians, this symptom may help focus a COVID-19 suspicion in subjects with respiratory symptoms.

Finally, in our study, new-onset STDs were significantly more frequent amongst COVID-19 than amongst influenza patients. It is suggested that new-onset STD is considered as a specific manifestation of COVID-19 and that it is used to focus clinical suspicions and speed-up self-isolation procedures. This may help contain the quick spreading of the disease. Of note, COVID-19-related STDs were more frequent amongst young patients and had an acute presentation in most cases.

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### Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

### Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Questionnaire.

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