JAMA Otolaryngology–Head & Neck Surgery | Original Investigation

Evolution of Altered Sense of Smell or Taste in Patients With Mildly Symptomatic COVID-19

Paolo Boscolo-Rizzo, MD; Daniele Borsetto, MD; Cristoforo Fabbris, MD; Giacomo Spinato, MD; Daniele Frezza, MD; Anna Menegaldo, MD; Francesca Mularoni, MD; Piergiorgio Gaudioso, MD; Diego Cazzador, MD; Silvia Marciani, MD; Samuele Frasconi, MD; Maria Ferraro, MD; Cecilia Berro, MD; Chiara Varago, MD; Piero Nicolai, MD; Giancarlo Tirelli, MD; Maria Cristina Da Mosto, MD; Rupert Obholzer, MA, MBBS; Roberto Rigoli, MD; Jerry Polesel, ScD; Claire Hopkins, MBBS

IMPORTANCE An altered sense of smell and taste has been reported to be associated with coronavirus disease 2019 (COVID-19). To understand the evolution of these symptoms during the course of the disease is important to identify patients with persistent loss of smell or taste and estimate the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on the burden of olfactory and gustative dysfunctions.

OBJECTIVE To evaluate the evolution of the loss of sense of smell and taste in a case series of mildly symptomatic patients with SARS-CoV-2 infection.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional survey-based study included 202 mildly symptomatic adults (≥18 years) consecutively assessed at Treviso Regional Hospital, Italy, between March 19 and March 22, 2020, who tested positive for SARS-CoV-2 RNA by polymerase chain reaction on nasopharyngeal and throat swabs.

MAIN OUTCOMES AND MEASURES Prevalence of altered sense of smell and taste at follow-up and their variation from baseline.

RESULTS Of 202 patients completing the survey at baseline, 187 (92.6%) also completed the follow-up survey (103 [55.1%] women; median age, 56 years). The evaluation of the evolution of altered sense of smell or taste in the 113 patients reporting sudden onset of these symptoms at baseline showed that 55 patients (48.7%; 95% CI, 39.2-58.3) reported complete resolution of smell or taste impairment, 46 (40.7%; 95% CI, 31.6-50.4) reported an improvement in the severity, and only 12 (10.6%; 95% CI, 5.6-17.8) reported the symptom was unchanged or worse. Persistent loss of smell or taste was not associated with persistent SARS-CoV-2 infection.

CONCLUSIONS AND RELEVANCE At 4 weeks from the onset, 89% of the SARS-CoV-2–positive mildly symptomatic patients who had had a sudden onset of altered sense of smell or taste experienced a complete resolution or improvement of these symptoms. Persistent loss of smell or taste was not associated with persistent SARS-CoV-2 infection.

JAMA Otolaryngol Head Neck Surg. 2020;146(8):1-5. doi:10.1001/jamaoto.2020.1379
Published online July 2, 2020.

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Author Affiliations: Section of Otorhinolaryngology, University of Padova, Treviso, Italy (Boscolo-Rizzo, Fabbris, Spinato, Frezza, Menegaldo, Mularoni, Gaudioso, Marciani, Ferraro, Berro, Varago, Da Mosto); Guy's and St Thomas' Hospitals, London, United Kingdom (Borsetto, Obholzer, Hopkins); Section of Otorhinolaryngology, University of Padova, Padova, Italy (Cazzador, Frasconi, Nicolai); Head and Neck Department, Cattinara Hospital, University of Trieste, Trieste, Italy (Tirelli); Department of Clinical Pathology, AULSS 2 - Marca Trevigiana, Treviso, Italy (Rigoli); Unit of Cancer Epidemiology, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy (Polesel); King's College, London, United Kingdom (Hopkins).

Corresponding Author: Daniele Borsetto, MD, Guy's and St Thomas' Hospitals, London SE1 9RT, United Kingdom (daniele.borsetto@gmail.com).

Since December 2019, a pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread rapidly from Wuhan, Hubei Province, China, to all over the world.[1] As of April 20, 2020, SARS-CoV-2 has been responsible for 2 414 595 infections and 165 174 deaths worldwide, with Italy accounting for 178 972 cases and 23 660 deaths.[2] The clinical spectrum of COVID-19 ranges from an asymptomatic or mild flu-like illness to a severe pneumonia and systemic disease requiring critical care. Main symptoms are fever, dry or productive cough, and dyspnea.[3]

Human strains of coronavirus have been demonstrated to invade the central nervous system through the olfactory neuroepithelium and propagate from within the olfactory bulb.[4] Furthermore, nasal epithelial cells display the highest expression of the SARS-CoV-2 receptor, angiotensin converting enzyme 2, in the respiratory tree.[5] Smell impairment was first observed among other neurologic manifestations of COVID-19 in hospitalized patients,[6] and subsequently has been reported to be a common symptom reported in patients with mild disease.[7,8]

Recently, we reported the prevalence of altered smell or taste to be 64% among a case series of 202 mildly symptomatic home-isolated patients with confirmed SARS-CoV-2 infection.[8] The aim of this study was to evaluate the evolu-

tion of altered sense of smell or taste and other COVID-19 associated symptoms in that case series.

Methods

The study was conducted with the approval of the institutional ethical review boards of Treviso and Belluno provinces and informed consent was obtained verbally for telephone interviews.

Mildly symptomatic adults (≥18 years) consecutively assessed at Treviso Regional Hospital between March 19 and March 22, 2020, who tested positive for SARS-CoV-2 RNA by polymerase chain reaction (PCR) on nasopharyngeal and throat swabs performed according to World Health Organization recommendation,[9] were included in our previous study.[8] Patients were contacted 5 to 6 days after the swab for the baseline interview. Patients were considered mildly symptomatic if they had less severe clinical symptoms with no evidence of pneumonia, not requiring hospitalization, and therefore considered suitable for being treated at home.

All 202 patients who completed the baseline interview were contacted 4 weeks after the first swab; in case of a nonresponse, patients were recontacted twice. During both phone interviews, symptoms were assessed through a structured questionnaire, including the ARTIQ (Acute Respiratory Tract Infection Questionnaire) and the SNOT-22 (Sino-Nasal Outcome Test 22), item "sense of smell or taste", as reported in Spinato et al.[8] Specifically, patients were asked to rate impairment of smell or taste using a 6-point Likeart scale, scoring 0 for no problem, to 5 for worst possible.

Symptom prevalence was expressed as percentage of total patients, and 95% confidence intervals (CI) were calculated using the Clopper-Pearson method. Statistical analyses were performed using R statistical software (version 3.6, R Foundation).

Results

The median duration of illness prior to capturing baseline smell or taste status was 9.5 days. Of 202 patients completing the survey at baseline, 2 patients died after study enrollment due to a sudden and rapid deterioration of general conditions and an additional 13 patients, of which 2 needed hospitalization, did not answer or refused the follow-up interview, thus leaving 187 responders (92.6%). Women represented 103 patients (55.1%) and the median (range) age was 56 (20-89) years. Overall, 113 of 187 responders (60.4%) reported smell or taste impairment at baseline that had started in the 2 weeks before testing (median SNOT-22 score, 4). Among the 74 patients who were negative for altered smell or taste at baseline, 11 reported subsequent onsets of these symptoms (**Table 1**), thus raising the overall prevalence of smell or taste impairment during the course of the disease to 66.3% (95% CI, 59.1%-73.0%). After 4 weeks, alteration of sense of smell or taste was present in 69 patients (36.9%; median SNOT-22 score, 2), ranking as one of the most frequent symptoms reported at follow-up (Table 1).

Key Points

Question What is the evolution of sudden-onset altered sense of smell or taste in patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection?

Findings In this prospective survey-based study of 202 patients, at 4 weeks from the onset 55 patients (48.7%) reported complete resolution of smell or taste impairment, 46 (40.7%) reported an improvement in the severity, and only 12 (10.6%) reported the symptom was unchanged or worse. Persistent loss of smell or taste was not associated with persistent SARS-CoV-2 infection.

Meaning The loss of smell or taste is among the most common and persistent symptoms of mildly symptomatic patients with coronavirus disease 2019; however, most patients reported a complete resolution or improvement of these symptoms.

The evolution of altered sense of smell or taste was specifically evaluated in the 113 patients reporting sudden onset of these symptoms in the 2 weeks before the initial swabs who were asked to report symptom's modification in the 4 weeks after the initial onset (**Table 2**). Fifty-five patients (48.7%; 95% CI, 39.2%-58.3%) reported complete resolution of smell or taste impairment, whereas 46 (40.7%; 95% CI, 31.6%-50.4%) reported a decrease in the severity, and 12 (10.6%; 95% CI, 5.6%-17.8%) reported the symptom was unchanged or worse. The mean duration of smell or taste impairment in 55 patients who recovered their sense of smell and taste completely was 11.2 days.

Table 2 shows that, of the 20 patients with SNOT-22 score of 1 (very mild) or 2 (mild or slight) on the alteration of sense of smell or taste at baseline question, 14 (70.0%) had no alteration of sense of smell or taste after 4 weeks (ie, complete recovery). Of the 93 patients who rated the SNOT-22 score of 3 (moderate) or higher on the alteration of sense of smell or taste at baseline question, 41 (44.1%) had no alteration of sense of smell or taste after 4 weeks (ie, complete recovery). The difference in the recovery rates as a function of baseline severity was 25.9% (95% CI, 3.4%-48.4%). The relative risk of not recovering sense of smell and taste was 1.86 (95% CI, 0.93-3.7) or nearly twice as great for patients who presented with more severe alteration in sense of smell than those with mild alteration. The severity of the alteration of sense of smell did not vary between sex, age group, smoking status or nasal comorbidities at baseline (namely, allergic rhinitis and chronic rhinosinusitis). The rate of recovery of smell and taste was similar in men and women (52.5% and 46.6%, respectively; Cohen d = 0.12; 95% CI, -0.27 to 0.50) as well as in patients younger and older than 55 years (51.7% and 45.5%, respectively; Cohen d = 0.13; 95% CI, -0.24 to 0.49). No differences in recovery rate emerged in patients with and without nasal comorbidities at baseline. Among all the 113 patients, main COVID-19-associated symptoms were still present in 61 (54.0%) with fever being present in 5 (4.4%), cough in 36 (31.9%), and problems in breathing in 26 (23.0%) patients.

After 4 weeks, among the 28 patients whose blocked nose resolved, 16 (57.1%) recovered sense of smell, whereas among

Table 1. Symptom Evolution From Baseline to the 4-week Follow-up in 187 Patients Positive for SARS-CoV-2

Symptom	No. (%)			
	Symptomatic at baseline	Symptom evolution in 4 weeks		Onset during follow-up
		Recovered	Still present	
Fever	104	99 (95.2)	5 (4.8)	3
Dry cough or coughing up mucus	116	70 (60.3)	46 (39.7)	8
Blocked nose	70	54 (77.1)	16 (22.9)	12
Problems breathing	77	47 (61.0)	30 (39.0)	14
Headache	80	61 (76.3)	19 (23.7)	4
Sore throat	59	51 (86.4)	8 (13.6)	5
Muscle or joint pains	85	68 (80.0)	17 (20.0)	13
Chest pain	29	27 (93.1)	2 (6.9)	9
Sinonasal pain	31	28 (90.3)	3 (9.7)	3
Loss of appetite	101	87 (86.1)	14 (13.9)	6
Felt tired	130	101 (86.1)	29 (13.9)	0
Diarrhea	84	74 (88.1)	10 (11.9)	1
Nausea	38	37 (97.4)	1 (2.6)	1
Vomiting	12	12 (100)	0 (0.0)	1
Abdominal pain	23	21 (91.3)	2 (8.7)	5
Dizziness	25	22 (88.0)	3 (12.0)	2
Altered sense of smell or taste	113	55 (48.7)	58 (51.3)	11

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2. Evolution of Alteration of Sense of Smell or Taste in 113 Patients Positive for SARS-CoV-2

Alteration of sense of smell or taste at baseline[a]	No. (%)						
	Total	Alteration of sense of smell or taste after 4 weeks[a]					
		0: No	1: Very mild	2: Mild or slight	3: Moderate	4: Severe	5: As bad as it can be
1: Very mild	5 (4.4)	4	0	0	0	1	0
2: Mild or slight	15 (13.3)	10	1	2	1	1	0
3: Moderate	26 (23.0)	10	10	3	0	3	0
4: Severe	24 (21.2)	12	6	3	3	0	0
5: As bad as it can be	43 (38.1)	19	4	4	8	4	4
Total	113	55 (48.7)	21 (18.6)	12 (10.6)	12 (10.6)	9 (8.0)	4 (3.5)

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus.

[a] According to Sino-Nasal Outcome Test 22 (SNOT-22), item "sense of smell or taste."

the 12 whose blocked nose was still present, 6 (50%) recovered sense of smell (difference in recovery rates was 7.1%; 95% CI, -26.6% to 40.9%).

During the fourth week after the first swab, the swab test for SARS-CoV-2 was repeated in 163 patients, with 52 (31.9%; 95% CI, 24.8%-39.6%) of them being found to be still positive and 111 (68.1%; 95% CI, 60.4%-75.2%) having no detectable SARS-CoV-2 RNA on PCR results. Fever was a strong predictor of positive results at the time of repeated testing: 4 of 5 (80.0%) patients reporting fever at follow-up were still positive compared with only 48 (30.4%) of 158 patients without fever, with a relative risk for positivity at follow-up of 2.63 (95% CI, 1.60-4.33) in patients with fever at follow-up compared those without. Conversely, persistency of SARS-CoV-2 infection at control swab test was similar in patients with persistent altered sense of smell or taste (53.6%) compared with those with recovered sense of smell or taste (46.4%; relative risk = 1.06; 95% CI, 0.57-1.99).

Discussion

At 4 weeks from our initial survey of mildly symptomatic patients with SARS-CoV-2 who reported smell or taste loss, 101 (89%) experienced a complete resolution or improvement of these symptoms with only 12 (11%) reporting that the sense of smell or taste was unchanged or worse. Although we found an altered sense of smell or taste being more frequent among women at baseline,[8] small and clinically meaningless associations were observed between the persistence of these symptoms and sex or age. Conversely, a higher severity of smell and taste impairment at baseline, reasonably due to a more severe injury of the olfactory neuroepithelium, was associated with a lower likelihood of recovery at 4 weeks.

Postviral anosmia is one of the most commonly identified causes of olfactory dysfunction in adults, accounting for up to 40% of cases.[10] Sense of smell and taste are strongly as-

sociated, and recent reports on the prevalence of olfactory and gustative dysfunction in patients with SARS-CoV-2 infection have observed that altered sense of smell and taste are almost always reported as overlapping symptoms.[7,11] This likely reflects the common usage of "taste sensation" by the lay public to reflect flavor, a function of retronasal olfaction, as opposed to true sense to taste in being able to differentiate between sweet, salty, bitter, sour, or umami tastes. In the absence of objective testing of olfactory and gustatory function, any patient-rated response is therefore likely to be difficult to interpret accordingly, we evaluated these symptoms using the SNOT-22 questionnaire that clusters together in 1 item the scoring of sense of smell and taste.[12]

The pathogenesis of olfactory dysfunction in COVID-19 may be secondary to mucosal obstruction of the olfactory cleft, leading to a conductive loss, or may reflect a direct effect on olfactory mucosa and the olfactory sensory neurons with consequently a sensorineural loss. This latter mechanism seems to be supported by our observation that most patients did not report nasal obstruction, and in those who did, the recovery of altered sense of smell or taste was independent from improvement in blocked nose.

Although altered sense of smell or taste showed an improvement in most cases during the course of the disease, these symptoms were still the most frequently reported by patients with COVID-19 4 weeks after testing. However, the persistence of altered sense of smell or taste was not associated with the persistence of the SARS-CoV-2 infection at control swab with lasting fever being the only symptom associated with the persistence of the infection. Thus, unrelated to viral clearance, time is likely needed for the olfactory epithelium to repair and regenerate, and persistence of anosmia does not reflect ongoing viral shedding and a contagious state. We were surprised to find that more than 30% of patients still had detectable COVID-19 on repeated testing; in a series of patients with mild to moderate disease reported on in Singapore, viral PCR was detected up to but not beyond day 27 of illness.[13] The persistence of detectable viral RNA does not necessarily mean a patient is still infectious, although a patient is not usually considered cured until 2 negative test results are achieved on consecutive days.

Further follow-up will be required to determine if the 10.6% of patients who had not experienced any improvement and the 40.7% with incomplete recovery will experience future improvement. However, given the high incidence of COVID-19 infection globally, this is likely to result in a considerable number of patients with long-term dysfunction and its associated morbidity.

Limitations

These results must be taken cautiously owing to several study limitations. Data were self-reported, based on cross-sectional surveys, and thus may contain suboptimal sensitivity; the sample was relatively small, with patients with more severe disease excluded.

Conclusions

The loss of smell or taste is among the most common and persistent symptoms of COVID-19 in patients with mildly symptomatic disease. However, at 4 weeks from the onset, most patients reported a complete resolution or improvement of these symptoms. Ongoing disturbance in smell and taste was not predictive of persistent SARS-CoV-2 infection.

ARTICLE INFORMATION

Accepted for Publication: April 29, 2020.

Published Online: July 2, 2020. doi:10.1001/jamaoto.2020.1379

Author Contributions: Dr Boscolo-Rizzo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Boscolo-Rizzo, Borsetto, Fabbris, Spinato, Tirelli, Obholzer, Hopkins.
Acquisition, analysis, or interpretation of data: Boscolo-Rizzo, Frezza, Menegaldo, Mularoni, Gaudioso, Cazzador, Marciani, Frasconi, Ferraro, Berro, Varago, Nicolai, Da Mosto, Rigoli, Polesel.
Drafting of the manuscript: Boscolo-Rizzo, Fabbris, Frezza, Mularoni, Gaudioso, Cazzador, Marciani, Frasconi, Ferraro, Berro, Varago, Da Mosto, Rigoli.
Critical revision of the manuscript for important intellectual content: Boscolo-Rizzo, Borsetto, Spinato, Menegaldo, Nicolai, Tirelli, Obholzer, Polesel, Hopkins.
Statistical analysis: Boscolo-Rizzo, Polesel.
Administrative, technical, or material support: Borsetto, Fabbris, Menegaldo.
Supervision: Boscolo-Rizzo, Borsetto, Spinato, Nicolai, Tirelli, Obholzer, Hopkins.

Conflict of Interest Disclosures: None reported.

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