Rhinology Online

ORIGINAL CONTRIBUTION

OPEN ACCESS

A longitudinal study of olfactory dysfunction and parosmia in mild COVID-19 cases*

Aurelia S. Monk[1], Daniel R. Bacon[1], Princess Onuorah[1], Alexander Murr[1], Christopher A. Wiesen[2], Jonathan Oakes[3], Brian D. Thorp[1], Charles S. Ebert Jr.[1], David Wohl[4], Brent A. Senior[1,#], Adam J. Kimple[1,5,#]

[1] Department of Otolaryngology, Head & Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[2] Odum Institute, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[3] Institute for Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[4] Department of Medicine, Division of infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

[5] Marsico Lung Institute, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Rhinology Online, Vol 5: 168 - 172, 2022

http://doi.org/10.4193/RHINOL/22.022

***Received for publication:**

July 25, 2022

Accepted: October 24, 2022

Published: November 12, 2022

co-senior author

Abstract

Background: COVID-19-related olfactory dysfunction (OD) can persist long after patients recover from acute infection, yet few studies have investigated the long-term progression of this complication. Moreover, existing studies are focused on hyposmia/anosmia but parosmia is becoming an increasingly recognized long-term symptom.

Methods: We completed a longitudinal study about OD in individuals with mild cases of COVID-19. Participants completed a questionnaire and Brief Smell Identification Test (BSIT) one week, one month and one year after diagnosis. At one-year, participants completed an additional survey about parosmia.

Results: We obtained questionnaires and psychophysical olfactory testing information from participants at one week (n=45), one month (n=38), and one year (n=33) post-COVID-19 diagnosis. At one-year, 15.2% of participants had persistent OD and 66.7% of participants reported experiencing parosmia at some point following COVID-19 diagnosis. The mean onset of parosmia was 1.3 weeks (SD: 1.9 weeks) after diagnosis, although two patients reported delayed onset (>4 weeks after diagnosis). Eight patients (24.2%) reported ongoing parosmia one year after diagnosis. Of the patients whose parosmia resolved, the mean duration of symptoms was 7.2 weeks (SD: 7.3 weeks).

Conclusion: Decreased sense of smell associated with COVID-19 infection has received significant recognition in both the media and in the medical literature. Symptoms of OD and parosmia were common in our patients with COVID-19. Hyposmia, anosmia, and parosmia, all decrease quality of life, necessitating continued research to understand the pathogenesis, course of symptoms, and possible treatment for these complications.

Key words: parosmia, COVID-19, olfaction disorders, SARS-CoV-2

Introduction

Olfactory dysfunction (OD) is a common symptom following respiratory tract infection that has gained widespread recognition since being identified as a prominent symptom of COVID-19 [1,2]. Multiple studies report high rates of OD (40-70% of patients) during acute COVID-19 infection [3–5]. For most of these patients, OD resolves within one month from the onset of disease [5–7]. The most well-described types of COVID-19-associated OD include anosmia and hyposmia; however, reports of parosmia are increasing. This condition is a qualitative form of olfactory dysfunction in which odors are distorted, often resulting in typically good-smelling odorants perceived as smelling bad. This distortion only occurs in the presence of an odorant. For example, freshly baked bread may be perceived as smelling like rotten eggs.

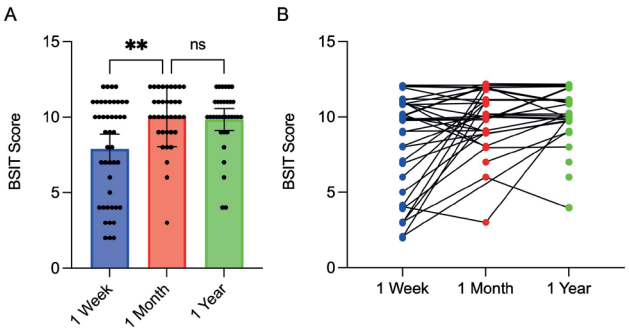

Figure 1. BSIT score improved significantly in COVID-19 patients between one week and one month post-diagnosis but stabilized thereafter. A) BSIT scores in COVID-19 patients at baseline (one week post-diagnosis; blue) compared to one month later (red), or one year later (green). Scores improved by 2.1 (95% CI 0.75-3.8, p=0.0012), from 7.9 at baseline (95% CI 6.9-8.9) to 10 at one month post-diagnosis (95% CI 9.3-10.7). BSIT scores did not improve significantly from one month to one year. B) Changes in BSIT scores (y-axis) in individual participants from baseline (blue) to one month (red) to one year (green). A score <9 indicates olfactory dysfunction.

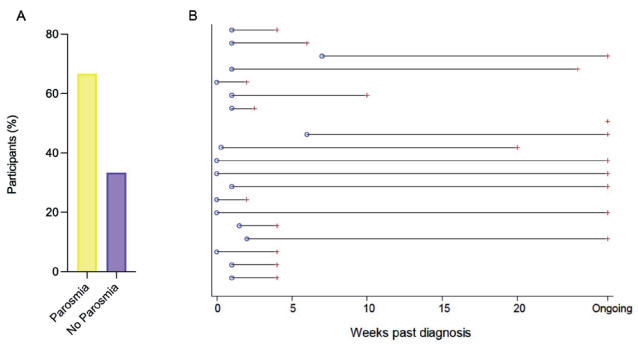

Figure 2. One-year post-diagnosis the majority of participants reported experiencing symptoms of parosmia. A) Percentage of participants who reported experiencing parosmia or had no symptoms of parosmia during the one-year period following a COVID-19 diagnosis. B) Time of onset (blue circles) and resolution (red crosses) of parosmia in individuals who experienced symptoms within one year of a COVID-19 diagnosis. Mean onset was 1.3 weeks (95% CI 0.40-2.2) and mean resolution was 7.2 weeks (95% CI 2.6-11.8). The timelines of two participants are not depicted here due to failure to answer questions regarding onset and resolution of symptoms.

Parosmia is thought to occur post-infection, including post-COVID-19 infection, due to the mistargeting of olfactory receptor axons when reconnecting to the olfactory bulb following damage [8,9]. Of note, parosmia that occurs post-infection tends to occur more frequently in younger populations, possibly due to the increased capability of axons to regenerate [10,11]. A recent study of COVID-19 patients reported that time from parosmia onset to resolution is variable in length, ranging from 2 weeks to > 6 months [11]. However, there is lack of additional information about the typical time-course of parosmia, specifically in COVID-19 patients.

Parosmia can significantly decrease quality of life [10,11]. As the pandemic continues and the risk of parosmia remains high, it is important to continue delineating the natural history of parosmia so that patients can be informed of expected outcomes and new avenues to alleviate discomfort can be advanced. Although reports of parosmia after COVID-19 infection are common, few studies have attempted to document its rate, onset, and duration. Moreover, current psychophysical tests of olfactory dysfunction are designed to measure quantitative data, and therefore do not reliably detect parosmia [12]. However, a clinically-valuable four-question survey was recently identified that could distinguish parosmia from other ODs such as hyposmia, anosmia, and phantosmia [13]. Therefore, to elucidate the natural history of parosmia in COVID-19 infection, we performed a longitudinal, prospective cohort study using a Brief Smell Identification Test (BSIT) and parosmia questionnaire in patients with ambulatory COVID-19.

Materials and methods

Study design and patient population

We previously described the result of BSIT testing in a cohort of patients with mild COVID-19 one week and one month after diagnosis [7]. Here, we extend these data to incorporate the results of BSIT testing performed at one year following a COVID-19 diagnosis and provide new data on parosmia symptoms. Patients did not receive physician supervised medical therapy for their OD.

Olfactory testing and questionnaire

The BSIT and subjective questionnaires were administered at one week, one month, and one year after COVID-19 diagnosis, as previously described [7]. We administered an additional parosmia survey at the one-year assessment. This included four questions about the quality of parosmia symptoms that were derived from the questionnaire by Landis, et al. The questions were as follows: Q1: Because of my olfactory problem, food tastes/tasted different than it should taste. Q2: I always have/had a bad odor in my nose, regardless if any odor source is present. Q3: Odors which are pleasant to other people are/were unpleasant to me. Q4: The biggest problem is not that I do/did or weakly perceive/perceived odors, but that they smell/smelled different than they should [13]. Two open-ended questions were added to this survey to determine when symptoms began and were resolved.

Statistical analysis

Descriptive statistics were used to report demographics, comorbid conditions, BSIT score, and prevalence of OD and parosmia.

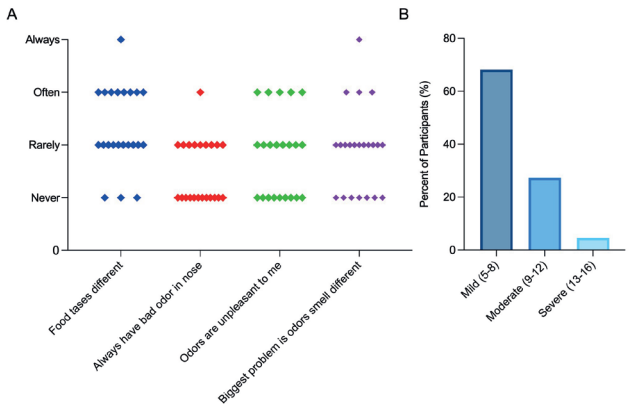

Figure 3. Parosmia survey results by question and overall severity. Presence of parosmia was determined using a four-question symptom survey. Questions are answered on a four-point Likert scale, (1=never, 2=rarely, 3=often, 4=always). 01: Because of my olfactory problem, food tastes/tasted different than it should taste. 02: I always have/had a bad odor in my nose, regardless whether any odor source is present. 03: Odors which are pleasant to other people are/were unpleasant to me. 04: The biggest problem is not that I do/did or weakly perceive/perceived odors, but that they smell/smelled different than they should. A) Each diamond represents one participant. B) Percent of participants with mild, moderate, and severe parosmia symptoms based on their cumulative survey score. Higher scores indicated increased severity.

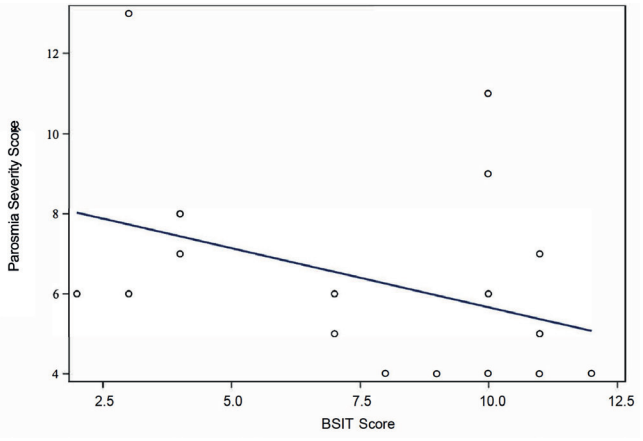

Figure 4. Correlation between initial BSIT score and severity of parosmia. Severity of parosmia is reflected by the total score on the parosmia symptom survey, with different points being assigned to different frequencies (1=never, 2=rarely, 3=often, 4=always) in response to each question. Higher total scores reflect increased severity. Lower BSIT scores indicated worse olfactory dysfunction at the time of the test. There was no significant correlation between parosmia severity and initial BSIT score (one week post COVID-19 diagnosis).

Analysis was conducted using GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA) and SAS Version 9.4 (Cary, NC, USA). A correlation model was used to determine the relationship between the BSIT score one week after COVID-19 diagnosis and development of parosmias.

Results

Patients completed BSITs and questionnaires at one week (45 participants), one month (36 participants), and one year (33 participants) after a COVID-19 diagnosis. At one week post-diagnosis, 46.7% of participants (24 of 45) had OD as defined by BSIT score, whereas only 16.7% (6 of 36) and 15.2% (5 of 33) had OD at one month and one year post-diagnosis, respectively. Mean BSIT scores were 7.9 at one week, 10.0 at one month, and 9.8 at on year post-COVID-19 diagnosis (Figure 1).

One year after their COVID-19 diagnosis, 66.7% (22 of 33) of participants reported experiencing parosmia at one point during their disease course (Figure 2A). The ages of patients reporting parosmia ranged from 19-80. The average age was 39.5 years and the median age was 34. There was no significant correlation between the age of the participant and the severity of parosmia. Of patients who reported experiencing parosmia at one point during their disease course, 18.2%. (4 of 22) had OD at the time of the parosmia survey (one-year post-diagnosis) as indicated by BSIT score. The severity of parosmia was reflected by a higher score on the parosmia survey; 68.2% of participants with parosmia had scores of 5-8 correlating with mild symptoms, 27.3% had scores of 9-12 correlating with moderate symptoms, and 4.5% had scores of 13-16 correlating with severe symptoms (Figure 3).

There was no significant correlation between initial BSIT score at one-week post-diagnosis and the development or severity of parosmia (Figure 4). The mean onset of parosmia in this group was 1.3 weeks (SD: 1.9 weeks) after COVID-19 diagnosis. Of the 22 participants that reported parosmia, two had delayed onset (>4 weeks after diagnosis). Among participants whose parosmia was resolved, the mean duration of symptoms was 7.2 weeks (SD: 7.3 weeks). Two participants did not specify the time of onset or resolution for their parosmia symptoms (Figure 2B).

Discussion

We assessed the natural history of OD and parosmia in ambulatory COVID-19 patients over one year post diagnosis. We previously showed that one month following a COVID-19 diagnosis, 83.3% of patients with OD had improved olfactory function [7]; in contrast, there was no significant improvement in patients with OD between assessment at one year post diagnosis relative to the one-month time point. Although we observed minimal improvement at one year post diagnosis in this cohort, recovery of olfaction may take up to 2-3 years, as reported in other studies of post-infectious OD (non-COVID related) [14,15].

The majority of participants who reported parosmia after their

Table 1. Demographics and relevant olfactory/gustatory history were collected at study enrollment via phone survey.

	COVID-19 (+) Phone Encounter	COVID-19 (+) 1 Week [a]	COVID-19 (+) 1 Month	COVID-19 (+) 1 Year
Sample size	81	43	33	33
Mean age, years				
(SD; range)	38.21 (19;18-81)	39.87 (18; 18-81)	39.68 (18; 18-70)	42.09 (19; 19-80)
Sex	52F/29M	31F/12M	24F/9M	22F/11M
Race/Ethnicity, n (%)				
Black	7 (8.6)	2 (4.9)	2 (6.1)	1 (3.0)
Caucasian	43 (53.1)	30 (69.8)	22 (66.7)	22 (66.7)
Hispanic	8 (9.9)	2 (4.9)	2 (7.1)	1 (3.0)
Unknown	23 (28.4)	9 (20.9)	7 (21.2)	9 (27.3)
Smoking history	10 (12.7)	4 (9.7)	5 (12.2)	6 (18.2)
Self-reported OD during phone encounter [b] (%)	39 (57.5)	22 (57.1)	13 (50)	19 (57.6)
History of smell loss [c] (%)	7 (9.5)	5 (12.5)	3 (11.1)	3 (9.1)
History of taste loss [c] (%)	6 (8.0)	4 (9.3)	3 (9.1)	3 (9.1)

[a] 1-week sample size refers to the number of patients who completed a BSIT at 1-week. [b] Participants were asked at enrollment during phone encounter if they experienced smell loss at any point since the onset of symptoms. [c] Prior history of smell or taste loss was determined by telephone prior to enrollment. Smell loss had to be resolved prior to onset of acute symptoms, and any patient with baseline smell loss was excluded. Values may not add to 100% due to sporadic missingness.

initial COVID-19 diagnosis also indicated that these symptoms began during the acute infection period (one week post-diagnosis or earlier), whereas only two participants reported delayed onset (>4 weeks). Transient parosmia occurred in 12 participants, most of whom recovered within two to six weeks. However, longer durations (up to 24 weeks) were reported in four participants. Our data demonstrates that parosmias can take a considerable amount of time to resolve, consistent with other reports [11]. When necessary, olfactory retraining is a viable treatment for this condition, with clinically relevant improvement observed in both COVID-19 and other postinfectious parosmia cases [16,17]. In addition, we did not identify a relationship between the degree of initial OD based on BSIT score and development of parosmia. These data could reassure patients with initially severe OD during the acute phase of COVID-19 who may be worried about long-term olfactory complications such as parosmia.

This study is limited by its retrospective assessment of parosmia. A prospective assessment of parosmia after diagnosis may have more clearly delineated when symptoms arose and resolved, making it easier to elucidate the natural history of this condition. Selection bias is also a potential limitation of this study as patients with olfactory changes may be more likely to participate. Additionally, it would have been ideal to administer the parosmia survey at all time points, but parosmia as a complication of COVID-19 did not gain notoriety until later in the pandemic, after the initial study began.

Conclusions

Collectively, our study extends prior work regarding the natural history of OD and parosmia in patients with COVID-19, which is knowledge that can be used in the clinic by those that counsel patients experiencing such symptoms. As more people recover from COVID-19 and consequently develop chronic complications from this disease, the emphasis in research needs to shift from solely focusing on well-recognized early symptoms of acute infection, such as hyposmia and anosmia, to include consideration of long-term complications such as parosmia. A better understanding of long-term complications of COVID-19, as well as the identification of any potential correlation between initial symptoms and those that develop later, may help counsel patients and identify new avenues for treatment.

Acknowledgments

No acknowledgements. The project described was supported by NIH grants KL2TR002490 to AJK.

Funding

The project described was supported by NIH grants KL2TR002490 to AJK. The content is solely the responsibility of the authors and does not necessarily represent the official views

of the NIH.

Authorship contribution

ASM, DRB, PO, AM: data collection, data curation, data analysis, writing original draft. CAW: data analysis. JO: data collection, data curation, data analysis, writing original draft. BDT, CSE Jr, DW, BAS, AJK: conceptualization, analysis, writing, review and editing.

Ethics approval and consent to participate

We received approval to conduct this research on the patient database from University of North Carolina at Chapel Hill Office of Human Research Ethics, IRB 20-1992.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to data being comprised of patient protected health information but are available from the corresponding author on reasonable request.

Conflict of interest

No authors have any financial conflicts of interest.

References

1. CDC. Coronavirus Disease 2019 (COVID-19) – Symptoms [Internet]. Centers for Disease Control and Prevention. 2021 [cited 2021 Sep 28]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
2. WHO Coronavirus (COVID-19) Dashboard [Internet]. [cited 2021 Sep 28]. Available from: https://covid19.who.int
3. Saniasiaya J, Islam MA, Abdullah B. Prevalence of Olfactory Dysfunction in Coronavirus Disease 2019 (COVID-19): A Meta-analysis of 27,492 Patients. Laryngoscope. 2021;131(4):865–78.
4. Lee DJ, Lockwood J, Das P, Wang R, Grinspun E, Lee JM. Self-reported anosmia and dysgeusia as key symptoms of coronavirus disease 2019. CJEM. 2020 Sep;22(5):595–602.
5. Niklassen AS, Draf J, Huart C, Hintschich C, Bocksberger S, Trecca EMC, et al. COVID-19: Recovery from Chemosensory Dysfunction. A Multicentre study on Smell and Taste. Laryngoscope. 2021;131(5):1095–100.
6. Gorzkowski V, Bevilacqua S, Charmillon A, Jankowski R, Gallet P, Rumeau C, et al. Evolution of Olfactory Disorders in COVID-19 Patients. Laryngoscope. 2020;130(11):2667–73.
7. Bacon DR, Onuorah P, Murr A, Wiesen CA, Oakes J, Thorp BD, et al. COVID-19 related olfactory dysfunction prevalence and natural history in ambulatory patients. Rhinol Online. 2021;4(4):131–9.
8. Di Stadio A, D'Ascanio L, La Mantia I, Ralli M, Brenner MJ. Parosmia after COVID-19: olfactory training, neuroinflammation and distortions of smell. Eur Rev Med Pharmacol Sci. 2022 Jan;26(1):1–3.
9. Holbrook EH, Leopold DA, Schwob JE. Abnormalities of Axon Growth in Human Olfactory Mucosa. Laryngoscope. 2005;115(12):2144–54.
10. Pellegrino R, Mainland JD, Kelly CE, Parker JK, Hummel T. Prevalence and correlates of parosmia and phantosmia among smell disorders. Chem Senses. 2021 Jan 1;46:bjab046.
11. Lerner DK, Garvey KL, Arrighi-Allisan AE, Filimonov A, Filip P, Shah J, et al. Clinical Features of Parosmia Associated With COVID-19 Infection. Laryngoscope. 2022;132(3):633–9.
12. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). Laryngoscope. 1996 Mar;106(3 Pt 1):353–6.
13. Landis BN, Frasnelli J, Croy I, Hummel T. Evaluating the clinical usefulness of structured questions in parosmia assessment. Laryngoscope. 2010;120(8):1707–13.
14. Cavazzana A, Larsson M, Münch M, Hähner A, Hummel T. Postinfectious olfactory loss: A retrospective study on 791 patients. Laryngoscope. 2018;128(1):10–5.
15. Ogawa T, Nakamura K, Yamamoto S, Tojima I, Shimizu T. Recovery Over Time and Prognostic Factors in Treated Patients with Post-Infectious Olfactory Dysfunction: A Retrospective Study. Ann Otol Rhinol Laryngol. 2020 Oct 1;129(10):977–82.
16. Liu DT, Sabha M, Damm M, Philpott C, Oleszkiewicz A, Hähner A, et al. Parosmia is Associated with Relevant Olfactory Recovery After Olfactory Training. Laryngoscope. 2021;131(3):618–23.
17. Raad N, Ghorbani J, Safavi Naeini A, Tajik N, Karimi-Galougahi M. Parosmia in patients with COVID-19 and olfactory dysfunction. Int Forum Allergy Rhinol. 2021;11(10):1497–500.

Adam J. Kimple
170 Manning Drive, CB#7070
Physicians Office Bldg Rm G112
UNC Dept of Otolaryngology
Chapel Hill
NC 27599-7070
USA

Tel: +1-919-843-3503
E-mail: kimplead@med.unc.edu