Objective and subjective olfactory dysfunction among COVID-19 inpatients and controls: a prospective, case-control study

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Abstract

Introduction: Olfactory dysfunction associated with COVID-19 infection is frequently described, but few studies utilize validated, objective tests or a control group. We compared rates of olfactory dysfunction between adults hospitalized with COVID-19 and controls admitted with similar upper respiratory symptoms who were COVID-19-negative. Methods: Hospitalized (general ward) adults with upper respiratory symptoms who tested PCR positive or negative for SARS-CoV-2 completed the objective Brief Smell Identification Test (BSIT; [≥9 correct=normal]) and subjective assessments while hospitalized and again at 3 month follow up. Comparison of groups was performed by t test or chi-square test of independence. Results: There were no differences in mean age or gender between groups (n=26 COVID, n=28 control). Both groups demonstrated objective olfactory dysfunction (mean BSIT 7.9 ± 2.8 COVID vs. 8.3 ± 3.2 control, p=0.62). Rates of both objective and subjective dysfunction did not significantly differ between groups. Follow up data at 3 months was limited (n=6 COVID, n=5), but showed 50% olfactory dysfunction in COVID patients compared to 20% in controls. Conclusions: SARS-CoV-2 and other viral illnesses serious enough to cause hospitalization cause olfactory dysfunction. Better understanding of the trajectory of chemosensory recovery will help elucidate the pathophysiology of viral-associated olfactory dysfunction and inform the care of patients suffering from its sequelae.

Key Points

1. SARS-CoV-2 and other viral illnesses that cause hospitalization produce olfactory dysfunction.
2. Patients with COVID-19 may experience higher levels of persistent olfactory dysfunction.
3. Phantosmia is prevalent amongst patients with COVID-19.

Introduction

COVID-19-related olfactory dysfunction is common, with prevalence estimates up to 80%.¹² Reported rates of olfactory dysfunction in COVID-19 vary depending on how olfaction is measured (i.e., objective vs. subjective testing),³ time course and severity of illness,¹ viral variant,⁴ and study population demographics, including known factors that influence olfaction (i.e., age and gender).⁵ Beyond hyposmia and anosmia, distorted (parosmia) and stimuli-absent (phantosmia) smell disorders are also described in COVID-19.⁶⁷ Some patients experience long-lasting olfactory dysfunction.¹²

Despite a myriad of publications on this topic, few studies have rigorously measured olfaction using both validated objective tests and comparison with a control group. We measured objective olfactory dysfunction
among adults with upper respiratory symptoms severe enough to cause hospitalization and compared rates of olfactory dysfunction between patients who were SARS-CoV-2 positive and negative.

Materials and methods

This prospective case-control study enrolled adults hospitalized on the general wards (non-intensive care unit) at the University of Chicago Medicine with upper respiratory symptoms who tested positive or negative for SARS-CoV-2 by PCR between October 1, 2020 and April 30, 2022. Information on subjective olfactory function, demographics, and comorbidities was collected. Patients who self-reported subjective olfactory dysfunction were subsequently asked whether or not “some smells bother [them] although they do not bother other people” and if they “sometimes smell an unpleasant, bad, or burning order when nothing is there” in order to identify parosmia and phantosmia, respectively. The Short Portable Mental Status Questionnaire (SPMSQ) was utilized to test patients’ cognition. Objective olfactory function was measured with the 12-item Brief Smell Identification Test (BSIT; $\geq 9$ correct=normal). As different SARS-CoV-2 variants have been demonstrated to cause varying levels of olfactory dysfunction, it’s important to note that the majority of initial enrollment and baseline olfactory testing occurred during the early phases of the pandemic. The same subjective and objective olfactory assessments were re-collected at 3-month follow-up.

Chi-square tests of independence, two-sample $t$ tests, and multivariate regression models were used to compare group characteristics. All analyses were performed in STATA 17. Statistical significance was set at $p<0.05$.

Results

Among 54 study participants, 26 were COVID-19 positive (COVID group) and 28 were COVID-19 negative (control group). The COVID and control groups did not differ significantly in baseline age, gender, race/ethnicity, cognition, or comorbidities (Table 1). Both groups demonstrated objective olfactory dysfunction upon initial testing during hospitalization (mean BSIT score 7.9 ± 2.8 COVID vs. 8.3 ± 3.2 control, $p=0.62$). The groups also demonstrated similar rates of objective olfactory dysfunction (62% COVID vs. 47% control, $p=0.27$) and subjective olfactory dysfunction (27% COVID vs. 25% control, $p=0.87$; Figure 1). Among COVID patients who self-reported olfactory dysfunction, 71% reported phantosmia, compared to 57% of controls ($p=0.58$). Interestingly, 14% of COVID patients with subjective olfactory dysfunction reported parosmias compared to 50% of controls ($p=0.143$). On multivariate analysis, older patients were more likely to demonstrate worse objective olfaction after adjusting for COVID status, gender, and cognition ($p<0.01$).

Participation at follow-up was limited to 11 participants (6 COVID and 5 control). Mean BSIT scores at follow-up were 8.0 ± 3.9 (COVID) and 9.2 ± 2.6 (control). 50% of COVID patients met criteria for objective olfactory dysfunction at follow-up compared to 20% of control patients. While 0% of control patients reported subjective olfactory dysfunction at follow-up, 33% of COVID patients still reported experiencing subjective olfactory dysfunction.

Discussion

These results suggest that hospitalized patients with upper respiratory symptoms experience olfactory dysfunction, regardless of COVID-19 status. The high rate of olfactory dysfunction among COVID-19 negative patients reinforces the importance of including an appropriate control group in the study design when measuring olfaction in the context of viral etiologies. While not statistically significant, COVID-19 positive patients demonstrated a trend towards worse objective olfactory dysfunction relative to COVID-19 negative patients, with lower average BSIT scores and higher rates of objective olfactory dysfunction at both baseline and follow-up. This trend supports recent evidence of higher rates of persistent olfactory dysfunction in COVID-19 patients compared to other forms of post-viral olfactory dysfunction. Further, our results illuminate the prevalence of phantosmia among patients infected with SARS-CoV-2 and other viral respiratory infections, aligning with ongoing reports in the literature. The results corroborate the well-described discrepancy between objective and subjective olfactory function and identify higher rates of objective olfactory dysfunction.
in COVID-19 patients compared to subjective measurements.\textsuperscript{2,5,10} They also corroborate known age-related worsening of olfactory function.\textsuperscript{3}

Despite significant interest in COVID-19 associated olfactory dysfunction, many studies, including ours, struggle to enroll significant numbers of patients and to successfully complete longitudinal analyses. As the study began early in the pandemic, our enrollment was hindered by the acuity of illness of hospitalized patients and infection control concerns, which required remote enrollment. Furthermore, our follow-up was limited by logistical hurdles surrounding the distribution of BSITs and subsequent collection of objective olfactory data. Despite these challenges, designing high quality studies on viral-associated olfactory dysfunction is critical to generate useful information for this important condition given its global impact.

In summary, COVID-19 and other viral illnesses serious enough to require hospitalization cause olfactory dysfunction. Better understanding of the trajectory of chemosensory recovery will help elucidate the pathophysiology of viral-associated olfactory dysfunction and inform the care of patients suffering from its sequelae.

References


Table 1 | Baseline characteristics of COVID and control groups

<table>
<thead>
<tr>
<th></th>
<th>COVID Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>53.7 (23-91)</td>
<td>59.7 (18-96)</td>
</tr>
<tr>
<td>Male Gender, No. (%)</td>
<td>11/26 (42)</td>
<td>12/28 (43)</td>
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<tr>
<td>Race, No. (%)</td>
<td></td>
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<tr>
<td>Black/African American</td>
<td>18/26 (69)</td>
<td>25/28 (89)</td>
</tr>
<tr>
<td>White</td>
<td>4/26 (15)</td>
<td>2/28 (7)</td>
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</table>
Other
Ethnicity, No. (%)  
Hispanic  
SPMSQ score, mean (SD)  
Comorbidities, No. (%)  
Asthma  
Depression  
Xerostomia  
Allergic Rhinitis  
Previous LOC  
Sinusitis  
SPMSQ = Short Portable Mental Status Questionnaire; LOC = loss of consciousness from head injury; SPMSQ = Short Portable Mental Status Questionnaire

Figure 1. Comparison of olfactory testing results during hospitalization between COVID and control groups.

*Among patients reporting subjective olfactory dysfunction