Anosmia in SARS-CoV-2 Patients: a Retrospective Study

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Research Article

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Abstract

Background

Post viral anosmia has been reported in human coronavirus infections. In this current pandemic, olfactory dysfunction (OD) has emerged as a common key presenting symptom of COVID-19 infection. In this study, we describe OD assessment in the inpatient setting of patients both suspected of and with confirmed COVID-19 infection via University of Pennsylvania Smell Identification Test (UPSIT) objective assessment and a simple self-reported 3-item questionnaire.

Methods

Thirty patients admitted to the isolation wards of the National University Hospital, Singapore for either suspected or confirmed COVID-19 infection from April to May 2020 were recruited to this study. 10 patients who tested negative for SARS-CoV-2 were recruited as control subjects. The 20 patients with COVID-19 infection were divided into two groups (10 had olfactory testing performed during the first week of illness, 10 in the second week of illness). A simple 3-question survey was administered to each participant - to rank the severity, state the onset and duration of their hyposmia. Olfactory testing was performed using an English version of the UPSIT.

Results

Loss of smell was reported in 2 participants from the control group, 6 participants from the in the first week of illness and 5 participants from the second week of illness. Two COVID-19 patients have anosmia on the UPSIT. COVID-19 patients were more likely to have severe hyposmia or anosmia by objective assessment, a difference that was statistically significant ($P = 0.0485$). The differences in degree of OD among COVID-19 patients in their first and second week of illness were not statistically significant ($P= 0.6563$).

Conclusion

Self-reported anosmia was higher among COVID-19 patients compared to controls who were admitted to isolation wards for respiratory symptoms but were tested negative for SARS-CoV-2 infection. On objective assessment by the UPSIT, COVID-19 patients were found to have higher rates of severe hyposmia or anosmia, a difference that was statistically significant ($P = 0.0485$). A limitation of this study is the odorants used in UPSIT which may be less familiar to the primarily Asian participants in this study, owing to cultural differences.

Background

Post viral anosmia lasting weeks to months has been previously reported in the setting of rhinovirus and human coronavirus infections (1, 2) but in this current pandemic, olfactory dysfunction (OD) has emerged as a common key presenting symptom of COVID-19 infection. Early meta-analysis by Tong et al. (3) of

studies published up to 19 April 2020 reported a prevalence of 52.7% of OD among 1627 COVID-19 patients. The associated symptom of loss of taste was also reported in 43.9% of 1390 COVID-19 patients. More recent meta-analysis by Pang et al. (4) examining studies prior to 1 August 2020 demonstrated a pooled frequency of 56% among 17,401 COVID-19 positive patients from 60 studies. The reports of COVID-19 associated OD, led to the United States Centers for Disease Control and Prevention (5) and the World Health Organization (6) including smell and taste dysfunction as early presenting symptoms of COVID-19 infection, and a reason for patients to self-isolate.

Proposed mechanisms of OD in COVID-19 infection include conductive anosmia, damage to olfactory epithelium and direct SARS-CoV-2 virus infection of the olfactory cortex within the central nervous system. Respiratory virus infections including human coronaviruses apart from SARS-CoV-2 can cause nasal oedema or congestion which can impair conductive airflow and thus odorant delivery to olfactory epithelium (2). Temporal correlation has also been found between transient anosmia and upper respiratory tract symptoms such as nasal obstruction in COVID-19 infection (7). More specifically, the olfactory epithelium has been proposed to be the site of nasal infection causing anosmia due to the localisation of SARS-CoV-2 host receptors ACE2 and the protease TMPRSS2 on the sustentacular cells of human and rodent olfactory epithelium (8, 9). Although these receptors are absent on olfactory sensory neurons, evidence towards a central cause for anosmia derives from studies showing hyperintensities within the olfactory bulbs of COVID-19 patients on magnetic resonance imaging (10, 11).

The majority of the present literature on prevalence of OD in COVID-19 infection relies on patient self-reporting. This has resulted in heterogeneity between studies, ranging from study author designed questionnaires relying on patient recall (12) to more formal validated questionnaires such as the Sino-Nasal Outcome Test (SNOT-22) (13). However, Pang et al. found that patient reported symptoms of olfactory dysfunction, although specific (93%), have been found not to be sensitive (48%) for COVID-19 infection (4). In their meta-analysis, pooled frequency of OD in COVID-19 patients was found to be higher in patients assessed by objective olfactory testing (0.76) as compared to subjective surveys (0.53), although admittedly this difference did not amount to statistical significance ($p = 0.089$).

Subjective reporting of OD in COVID-19 infection may not indicate objective presence of hyposmia or anosmia. Vaira et al. (14) evaluated 345 COVID-19 patients and found that while 225 (65%) of patients self-reported OD during illness, a total of 241 (70%) were found to be objectively hyposmic or anosmic by evaluation with the Connecticut Chemosensory Clinical Research Centre orthonasal olfaction test (CCCRC). Furthermore, of 89 patients who self-reported no smell or taste dysfunction, an additional 30.3% were found to be objectively hyposmic. Conversely, Lechien et al. found that among 78 COVID-19 patients with sudden onset anosmia recruited in Belgium during the early pandemic in April 2020, 87.5% of patients were SARS-CoV-2 viral load positive if they had anosmia < 12 days, and only 24% of all evaluated subjects with self-reported anosmia were objectively found by the “Sniffin’ Sticks” test to actually be normosmic by objective criteria (15).

Validated means of objective evaluation of OD during the COVID-19 pandemic have involved the use of tests such as the CCCRC and “Sniffin’ Sticks” as mentioned above in addition to the University of Pennsylvania Smell Identification Test (UPSIT) (16). These three tests evaluate discrimination between various provided odorants and provide an assessment of the participant’s degree of hyposmia. Olfactory threshold is also assessed using the CCCRC by having subjects attempt to detect increasing dilutions of denatured ethyl-alcohol (17, 18).

In this study, we describe OD assessment in the inpatient setting of patients both suspected of and with confirmed COVID-19 infection via UPSIT objective assessment and a simple self-reported 3-item questionnaire.

Method

Study subjects

30 patients admitted to the isolation wards of the National University Hospital, Singapore for either suspected or confirmed COVID-19 infection from April to May 2020 were recruited to this study. 20 of these participants had COVID-19 infection diagnosed by reverse transcriptase polymerase chain reaction (RT-PCR) testing of nasopharyngeal swabs for the SARS-CoV-2 virus. 10 patients who tested negative for SARS-CoV-2 were also recruited for olfactory testing as control subjects.

The 20 patients with COVID-19 infection were divided into two groups. The first group of 10 patients had olfactory testing performed during the first week of illness, defined as within the first seven days of patient reported onset of symptoms. The second group of 10 patients were assessed during their second week of illness (Day 7–14 of symptom onset).

The electronic health record for each participant was reviewed for five presenting symptoms suggestive of respiratory illness (rhinorrhoea or nasal obstruction, sore throat, cough, fever and breathlessness), use of supplemental oxygen during admission and chest radiography at the time of admission for presence of pulmonary opacities suggestive of pneumonia.

Olfactory testing

A simple 3-question survey was also administered to each participant (Annex 1). Subjects were first asked to rank the severity of their hyposmia on a scale of 0 to 10. 0 indicated no loss of smell and 10 indicated complete anosmia. Participants were then asked to indicate if the onset of hyposmia was at the same time, before or after other symptoms of current illness of if they unsure of onset. Finally, participants with hyposmia then reported the duration of sustained loss of smell before recovery. For this question, participants could answer one of three options: Firstly, if they still had loss of smell despite recovery from other symptoms, secondly if they had still had loss of smell in conjunction with other symptoms or thirdly if they have recovered from other symptoms but loss of smell persisted. If participants chose this third option, they would also indicate the duration of loss of smell.

Olfactory testing was performed using an English version of the UPSIT (19). The UPSIT can be self-administered and consists of 40 odorants contained within “scratch and sniff” microcapsules. Participants scratch individual odorant microcapsule strips on each page, eliciting its unique odour and selecting one of four multiple choice options. Scores out of 40 for each subject are then rated on a scale of degree of OD ranging from normosmia, mild microsmia, moderate microsmia, severe microsmia, anosmia and probable malingering. Scores are also adjusted for sex and age based on normative percentile values. Performance of the UPSIT was explained to each participant by the authors of this study. The test kit was left to each participant to be self-administered and collected the following day.

Statistical analysis

Patient categorical and quantitative variables were reported with descriptive statistics in numerals, the mean or median and percentages of the total. For statistical analysis, degree of hyposmia was qualified and divided into two groups: “Normosmia to moderate hyposmia” and “Severe hyposmia”. Patients rated with normosmia, mild and moderate microsmia by the UPSIT were placed in the former group and patients rated with severe microsmia and anosmia were placed in the latter group. Fisher’s exact test was then used to analyse the difference in degree of OD between population subgroups with the level of statistical significance set at $P \leq 0.05$. COVID-19 patients were compared with controls and among the COVID-19 patients, subjects in their first and second weeks of illness were also compared.

Ethics and Consent to Participate

The study was submitted to and approved by National Healthcare Group (NHG) Domain Specific Review Board (DSRB) with DSRB Reference Number: 2020/00603.

We wish to confirm that all methods were carried out were in accordance with relevant guidelines and regulations.

Informed consent was not obtained from study participants as the raw data has been de-identified, the study posed no more than minimal risk to study participants, the study had no active intervention, the information collected was not sensitive in nature and the data were derived from clinically indicated procedures that had already been performed. Waiver of informed consent was obtained as patient would have received routine care by treating doctors. Thus, their rights and access to healthcare were unaffected.

Results

Patient characteristics

Demographic and clinical characteristics of the 30 participants are listed in Table 1. Reported presenting symptoms were similar between COVID-19 patients and controls with the most common symptoms being cough (n = 15, 75% and n = 7, 70% respectively), fever (n = 12, 60% and n = 6, 60%) and sore throat (n = 11, 55% and n = 5, 50% respectively). Two (10%) of the COVID-19 patients had required supplemental oxygen

during admission, one of whom had olfactory testing performed while on two litres of oxygen by nasal prongs. No control patient required supplemental oxygen. A larger proportion of COVID-19 patients (n = 8, 40%) had pulmonary opacities on chest radiography as compared to the controls (n = 1, 10%). Chest radiograph changes were more likely to be seen in patients within the second week of illness (n = 5, 50%) as compared to during the first week (n = 3, 30%).

Table 1
Demographic and clinical characteristics of participants

Parameters	**COVID-19 patients**		**Controls**
	First week of illness (n = 10)	**Second week of illness (n = 10)**	**(n = 10)**
Age (years), Median	35.0	36.5	37
Male, n	7	6	3
Symptoms, n			
Rhinorrhea or nasal obstruction	2	3	4
Sore throat	6	5	5
Cough	7	8	7
Fever	6	6	6
Breathlessness	1	1	2
Objective measures, n			
Use of supplemental oxygen	1	1	0
Chest radiograph pulmonary opacity	3	5	1

Olfactory dysfunction assessment

Table 2 summarises the subjective and objective assessment of OD of the participants. COVID-19 patients fared worse (Mean=3.7) in subjective rating of degree of OD on a scale of 0 (normosmia) to 10 (anosmia) as compared to controls (Mean=0.8). Onset of reported hyposmia was similar in both groups (COVID-19 patients Mean=2.6, Controls Mean=3.0). Loss of smell was reported in 2 participants from the control group, 6 participants from the in the first week of illness and 5 participants from the second week of illness.

Table 2
Subjective and objective assessment of olfactory dysfunction

Parameters	COVID-19 patients		Controls
	First week of illness (n = 10)	Second week of illness (n = 10)	(n = 10)
Subjective assessment			
Degree of hyposmia on scale 0–10, Mean	3.8	3.6	0.8
Onset of hyposmia (days), Mean	2.7	2.5	3
UPSIT Olfactory test			
Day of illness of olfactory test, Mean	5.5	13.5	6.5
UPSIT Score, Mean	22.2	27.7	28.8
Normosmia, n (%)	0 (0)	1 (10)	0 (0)
Mild microsmia, n (%)	2 (20)	2 (20)	3 (30)
Moderate microsmia, n (%)	2 (20)	3 (30)	6 (60)
Severe microsmia, n (%)	4 (40)	4 (40)	1 (10)
Anosmia, n (%)	2 (20)	0 (0)	0 (0)
Probable malingering, n (%)	0 (0)	0 (0)	0 (0)

Statistical analysis

Table 3 shows the comparison of degree of OD between population subgroups using Fisher's exact test. Although both COVID-19 patients and controls showed some degree of mild to moderate microsmia, COVID-19 patients were more likely to have severe hyposmia or anosmia by objective assessment, a difference that was statistically significant ($P = 0.0485$). The differences in degree of OD among COVID-19 patients in their first and second week of illness were not statistically significant ($P = 0.6563$).

Table 3
Statistical analysis results

Population subgroup	Normosmia to moderate hyposmia	Severe hyposmia to anosmia	Fisher's exact test
COVID-19 patients (n = 20)	10	10	$P = 0.0485$
Controls (n = 10)	9	1	
COVID-19 patients First week of illness (n = 10)	4	6	$P = 0.6563$
COVID-19 patients Second week of illness (n = 10)	6	4	

Discussion

This study adds to the growing body of literature assessing OD objectively in the COVID-19 patient population.

The findings of this study show that self-reported anosmia was higher among COVID-19 patients compared to controls who were admitted to isolation wards for respiratory symptoms but were tested negative for SARS-CoV-2 infection. Additionally, on objective assessment by the UPSIT, COVID-19 patients were found to have higher rates of severe hyposmia or anosmia, a difference that was statistically significant ($P = 0.0485$). Both COVID-19 patients and controls exhibited mild and moderate microsmia, likely due to the population from which controls were recruited: hospital inpatients with respiratory symptoms, possibly suggesting presence of alternative upper respiratory tract illnesses other than COVID-19.

In this cohort, there was no statistically significant difference in the degree of OD in patients within the first and second week of COVID-19 infection although our sample size was small. Various authors however have found improvement in degree of OD with duration of COVID-19 illness by objective assessment (20–22). In these studies, improvement in olfactory function was found at later time points during illness, minimally from the 3rd week of illness onwards. Therefore, although OD is fortunately expected to improve for COVID-19 patients, it is perhaps delayed as compared to other respiratory symptoms.

Although the mechanism of COVID-19 associated anosmia is yet to be established, conductive anosmia probably plays a less important role. Only a minority of participants reported symptoms of rhinorrhea or nasal obstruction (n = 5, 25% of COVID-19 patients and n = 4, 40% of controls) as compared to the larger proportion of patients with objectively assessed OD, as has been shown with previous studies (7, 13, 17).

A limitation of this study includes use of the UPSIT itself, an olfactory test designed initially for U.S. patient populations. As such, certain odorants included in this study (e.g. Wintergreen, Pine, Cedar, Lilac) may be less familiar to the primarily Asian participants in this study, owing to cultural differences. Moien et al. (16) was the first group to publish use of the UPSIT for OD assessment in COVID-19 patients. The authors used a modified Persian version of the UPSIT but found an abnormally high proportion of patients (98%) with some degree of OD. In critique of this study, Mariño-Sánchez et al. (23) pointed out that the UPSIT has not been well validated in Iranian populations and a modified version such as the Iran Smell Identification Test designed by Taherkhani et al. (24) using only 24 of the 40 original items of the UPSIT would be more appropriate instead. As such, perhaps use of a modified and validated version of the UPSIT may have been more appropriate for our local patient population instead.

Conclusions

Self-reported anosmia was higher among COVID-19 patients compared to controls who were admitted to isolation wards for respiratory symptoms but were tested negative for SARS-CoV-2 infection. On objective assessment by the UPSIT, COVID-19 patients were found to have higher rates of severe hyposmia or anosmia, a difference that was statistically significant (P = 0.0485). A limitation of this study is the odorants used in UPSIT which may be less familiar to the primarily Asian participants in this study, owing to cultural differences.

Smell identification test kits are easy to administer to patients and results can be obtained quickly. This allows for more objective assessment of any loss of smell and can aid with risk stratifying patients with upper respiratory tract symptoms, while confirmatory reverse transcriptase polymerase chain reaction (RT-PCR) testing of nasopharyngeal swabs for the SARS-CoV-2 virus are awaited. This may be especially useful in places where the turnaround time for COVID-19 testing is prolonged. This study demonstrates the applicability of a simple diagnostic tool which can assist with predicting the likelihood of COVID-19 diagnosis. In the setting of resource limitation, this can prove to be helpful in triaging patients with respiratory tract infections suspected for COVID-19. We hope that this study can evoke the use of smell kit tests in the clinical setting.

Abbreviations

CCCRC - Connecticut Chemosensory Clinical Research Centre

COVID-19 - Coronavirus disease

DSRB - Domain Specific Review Board

NHG - National Healthcare Group

OD - olfactory dysfunction

RT-PCR - reverse transcriptase polymerase chain reaction

SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2

SNOT - Sino-Nasal Outcome Test

TMPRSS2 - Transmembrane protease, serine 2

UPSIT - University of Pennsylvania Smell Identification Test

Declarations

Ethics approval and consent to participate

Approved by National Healthcare Group (NHG) Domain Specific Review Board (DSRB)

DSRB Reference Number: 2020/00603

We wish to confirm that all methods were carried out were in accordance with relevant guidelines and regulations

Consent for publication

Informed consent was not obtained as the raw data has been de-identified.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

CHY and MK collected the data and wrote up the manuscript.

PAT, DA and JS provided guidance on the study design.

DYW and WSL contributed the University of Pennsylvania Smell Identification Test (UPSIT).

All authors have read and approved the manuscript.

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