Anosmia as a Screening Tool for COVID-19 Infection: A Prospective Cohort Study

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Keywords

Anosmia · Coronavirus disease-19 · Emergency · ENT · Olfactory dysfunction · Otolaryngology · Severe acute respiratory syndrome coronavirus 2

Abstract

Objectives: Several studies promoted anosmia as a possible isolated symptom for coronavirus disease 2019 (COVID-19). No studies used feasible methods of smell testing that the public would use to address the accuracy of these claims.

Methods: This is a single-center study conducted between April 2020 and June 2020. The sense of smell was tested in vitally stable suspected COVID-19 patients with no/mild upper respiratory tract infection symptoms prior to nasopharyngeal swabbing for reverse-transcriptase polymerase chain reaction. Patients were instructed to close their eyes. Each nostril was tested separately while the other was blocked with the patient's index finger. Patients inhaled from 2 concealed vials (coffee and strawberry essence) consecutively, kept within 30 cm of the nostril for 60 s. Patients who could not identify both odors with both nostrils were recorded as "anosmia." **Results:** Out of 346 eligible subjects, 43 had anosmia of which 26 (60%) tested COVID-19 positive. χ^2 test showed a p value <0.001 . The test showed a sensitivity of 30% (95% confidence interval [CI] 21%, 41%) and spec-

ificity 94% (95% CI 90%, 96%). Logistic regression revealed an odds ratio of 5.9 (95% CI 3.0, 12) p value <0.001 . **Conclusion:** Given the low sensitivity (30%) of this method in detecting COVID-19 infection, we conclude that this method is not a useful screening tool for COVID-19 infection. The moderate negative predictive value (80%) is nongeneralizable.

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Introduction

Anosmia has been broadcasted as an early isolated symptom of coronavirus disease 2019 (COVID-19) as a measure of encouraging individuals with a sudden loss of smell but few or no symptoms of viral infection to self-isolate [1, 2]. However, the studies that assess anosmia as a screening tool are predominantly cross-sectional or retrospective in design using telephone surveys or nonvalidated questionnaires to investigate olfactory dysfunction (OD) [3]. We aimed to prospectively measure the diagnostic value of anosmia at presentation and subsequent COVID-19 diagnosis by reverse-transcriptase polymerase chain reaction (RT-PCR) in asymptomatic or mildly symptomatic patients with upper respiratory tract infection (URTI).

Methodology

We performed a single-center prospective cohort study of patients meeting United Arab Emirates' (UAE) March 2020 case definition for suspected mild COVID-19 infection [4]. The study protocol was approved by the Institutional Review Board of the Hospital. All participants signed a written informed consent.

Study Setting

The study was conducted between April 2020 and June 2020 at the Emergency department (ED) of a tertiary care facility in Dubai, UAE. All stable patients triaged as T3–T5 by the Canadian Triage and Acuity Scale (CTAS) presenting to the ED with no or mild symptoms of URTI were sent to the influenza-like illness (ILI) clinic.

Population and Sample Size

Adults (18 + years) presenting with not >2 symptoms of URTI or asymptomatic patients presenting for screening following contact with a confirmed COVID-19 case were enrolled. At the time of the study, there were insufficient data to base estimates upon. However, we estimated that a total of 260 patients would have 80% power to show a 20% difference in COVID-19 infection between patients with and without anosmia, at a 2-sided alpha level of 0.05. We excluded age-group <18 years, patients with cognitive dysfunction, pregnancy, unstable vitals, nasal blockage, rhinorrhea, asthma, allergic rhinitis, and patients who do not meet the UAEs case definition for mild COVID-19: defined as patients with uncomplicated URTI and are stable with an oxygen saturation >93% and a respiratory rate <25. Uncomplicated URTI included nonspecific symptoms such as fever, fatigue, cough, anorexia, myalgia, sore throat, nasal congestion, headache, and gastrointestinal symptoms, such as vomiting or diarrhea [4].

Study Protocol

The method of smell testing in this study is a basic bedside clinical examination tool described in 1990 by H. Kenneth Walker for olfactory nerve assessment [5]. Two concealed vials of nonirritating common household substances were used: ground coffee (Nescafé Red Mug Instant Coffee, Nestlé) and scented artificial strawberry flavor (Strawberry Culinary Essence 28 mL, Foster Clark's, Foster Clark Products Ltd.). As soon as patients were triaged and sent to the ILI clinic, the investigators assessed their eligibility for the study. Next, the patient's presenting symptoms, age, smoking status, previous, or recent traumatic brain injury, comorbidities, such as diabetes mellitus, hypothyroidism, previous history of nasal instrumentation, or nasal polyps were recorded. Investigators then proceeded with smell testing as follows: Patients were asked to close their eyes and each nostril was tested separately while the other nostril was blocked with the patient's index finger. Investigators brought the concealed vial within 30 cm of the nostril and care was taken to avoid touching the patient and to avoid any body movement that gave a clue as to when the test object was being presented. Patients were instructed to sniff repetitively and to tell the investigator when an odor was detected, identifying the odor if recognized. The process was then repeated with the second vial containing the strawberry essence. For all patients, the duration of sniffing was standardized to within 60 s. Patients who were able to identify either of the odors were recorded as "normal sense of smell." Patients unable to identify both odors with both nostrils were recorded as "anosmia." Once smell testing was

complete, the emergency physician performed the nasopharyngeal swab collection. Emergency physicians were blinded as to the result of anosmia testing done by the investigator.

Outcome

The primary outcome of the study was a positive COVID-19 result as confirmed by nasopharyngeal swab RT-PCR (Cepheid Xpert Xpress SARS-CoV-2, GeneXpert® Systems, Sunnyvale, CA, USA). The assay detects the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid target (N2 gene) and the E-gene (envelope) which is shared by other sarbecovirus subgenus of coronaviruses. On an average, the RT-PCR nasopharyngeal swab results took 24–48 h to be reported. A test was result as "presumptive positive" when the E-gene alone was identified. A test was reported "positive" when the N2 gene is detected. As per hospital protocol at the time of the study, symptomatic patients with 1 negative swab result required a repeat swab test after 24 h and were deemed COVID-19 negative when 2 consecutive negative swabs were reported. If high suspicion for COVID-19 infection remained, further swabs were requested at the discretion of the emergency physicians. Asymptomatic patients and health-care workers presenting for screening following contact with confirmed cases required only 1 negative swab. Patients with an "inconclusive/presumptive positive" swab result required repeat testing after 24–48 h.

Statistical Analysis

A χ^2 test of independence was used to detect the relationship between anosmia and COVID-19 diagnosis by RT-PCR. We performed a simple proportion of sensitivity and specificity for the clinical method of smell testing to identify COVID-19-positive cases. These values were computed using MedCalc software (MedCalc Software Ltd.). Other analyses included logistic regression to report odds ratio (OR) with 95% confidence intervals (CIs) with and without adjustment for occupation, gender, and smoking.

Results

Out of a total of 564 patients seen in ILI clinic between April 2020 and June 2020, 346 were eligible for the study. Overall, 5 patients were excluded from the data analysis (Fig. 1). Two patients were excluded for opening their eyes during smell testing, 1 patient for testing "presumptive positive/inconclusive" without a follow-up swab and 2 patients for recording a wrong patient identification number, and hence their swab result could not be followed.

304 patients (87.9%) were labeled as normal sense of smell and 42 (12.1%) as anosmia. Sixty-one (20%) patients with normal sense of smell tested COVID-19 positive and 26 (62%) patients with anosmia tested COVID-19 positive. χ^2 test of independence showed χ^2 (1, N = 346) = 31.7, p value <0.001. Seven patients labeled as normal sense of smell were able to detect an odor but

Fig. 1. Patient flow.

falsely identified them, 2 patients took longer than 60 s to identify the odors, and 1 patient could not identify the odors with the right nostril but correctly identified them with the left nostril. From these 10 patients, only 4 tested COVID-19 positive. Table 1 shows differences in baseline characteristics between the groups. 37% of the sample presented with mild URTI symptoms. These patients also received a respiratory panel nasal swab to screen for coinfection. Three patients with anosmia had coinfection, of those only 1 was COVID-19 positive.

The method for smell testing used in our study showed a sensitivity of 30% (95% CI 21%, 41%) and specificity of 94% (95% CI 91%, 96%). In our sample, the negative predictive value was 80% (95% CI 78%, 82%) and positive predictive value was 62% (95% CI 48%, 74%) (Table 2). Logistic regression revealed an OR of 5.9 (95% CI 3.0, 11.6), p value <0.001 and OR of 3.3 (95% CI 1.6, 7.0) with adjustment for occupation, gender, and smoking (Table 3).

Discussion

Our results resonate with previous studies that addressed the association between anosmia and COVID-19 infection. Moein et al. [6] used the University of Pennsylvania Smell Identification Test on admitted COVID-19 patients diagnosed by nasopharyngeal RT-PCR assays and showed that out of their 59 COVID-19 cases 15 (25%) had anosmia. Vaira et al. [7] used the Connecticut Chemosensory Clinical Research Center (CCCRC) method

to test olfaction retrospectively. Out of their 72 cases, only 2 had anosmia (2.8%).

In our sample, 42 out of 346 (12%) patients reported not being able to detect both odors through both nostrils. Of these, 26 tested COVID-19 positive. Our method cannot differentiate between patients presenting with anosmia and other forms of OD. Our impression is that if an objective tool were used, more patients with OD would have been identified. However, the University of Pennsylvania Smell Identification Test includes 4 booklets of 10 odors each which must be completed in a specific order while the CCCRC test has a time-consuming and complex scoring system to allow their use in an emergency setting [7]) [8]. Alternatively, coffee and strawberry essence is easily attainable. Subjects who could not verbalize “strawberry” described the smell as “fruity.” Given the cost and lack of availability of objective tools for smell testing, especially during pandemics where surge capacity in the ED would limit their use, we decided to use a more practical and feasible approach to smell testing. In a retrospective Indian study, the prevalence of self-reported anosmia was 14.8% among 74 COVID-19-positive patients with mild-moderate symptoms, with all patients regaining their sense of smell within 21 days of infection [9]. In a multicenter European prospective study in the ENT clinic setting investigating the effect of OD on laboratory-confirmed mild-moderate COVID-19 patient’s quality of life, 284 out of 357 patients (79.6%) reported anosmia using questionnaire [10]. Last, in a retrospective study from France, 54 of 114 COVID-19 patients reported anosmia with the majority reporting recovery within

Table 1. Patient characteristics

Variables	Patients, <i>n</i>			<i>p</i> value*
	anosmia (<i>n</i> = 42)	normal sense of smell (<i>n</i> = 304)	total (<i>n</i> = 346)	
Gender, male, <i>n</i> (%)	34 (80.9)	172 (56.5)	206 (59.5)	0.002
Age (mean, SD)	41.8, 11.6	37.6, 8.5		
Age ≥55, <i>n</i> (%)	9 (20.9)	13 (4.3)	22 (6.4)	<0.001
Diabetes, <i>n</i> (%)	4 (9.3)	27 (8.9)	31 (9.0)	1.000
Current smoker, <i>n</i> (%)	5 (11.6)	37 (12.2)	42 (12.1)	1.000
Hypothyroidism, <i>n</i> (%)	0 (0)	18 (5.9)	18 (5.2)	0.144
Previous head injury, <i>n</i> (%)	1 (2.3)	0 (0)	1 (0.3)	0.124
Health-care worker, <i>n</i> (%)	9 (20.9)	213 (70.3)	222 (64.2)	0.001
Nasal instrumentation, <i>n</i> (%)	1 (2.3)	10 (3.3)	11 (3.2)	1.000
Coinfection, <i>n</i> (%)	3 (7)	4 (1.3)	7 (2.0)	**
Asymptomatic, <i>n</i> (%)	13 (30.2)	205 (67.7)	218 (63.0)	<0.001
Symptoms at presentation, <i>n</i>				
Fever	82			
Cough	59			
Sore throat	34			
Fatigue	12			
Shortness of breath	23			
Headache	9			
Myalgia	9			
Chest pain	5			
Skin rash	1			
Diarrhea	1			
Vomiting	1			

SD, standard deviation. * Fisher's exact *p* value. ** Only symptomatic patients received a respiratory panel screen for coinfection.

Table 2. Diagnostic value of anosmia

	Result	95% CI
Sensitivity, %	29.9	20.54–40.65
Specificity, %	93.8	90.12–96.41
Positive likelihood ratio	4.82	2.72–8.55
Negative likelihood ratio	0.75	0.65–0.86
Disease prevalence, %	25.2	20.72–30.15
PPV, %	61.9	47.80–74.25
NPV, %	79.9	77.51–82.04
Accuracy, %	77.7	72.91–81.97

PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

Table 3. Relationship between variables and outcome

Variables	OR	95% CI	<i>p</i> value*
Smell status (anosmia)	3.317	1.567–7.025	0.0035
Health-care worker	0.223	0.118–0.417	<0.0001
Gender (female)	0.508	0.250–1.035	0.0641
Smoking	0.801	0.337–1.905	0.6287

OR, odds ratio; CI, confidence interval. * Adjusted OR and *p* value calculated by logistic regression.

28 days [11]. Whether this difference in prevalence is due to ethnic or racial difference in the expression of angiotensin converting enzyme 2 (ACE-2) receptors versus the different strains of the virus remains a potential area for further research. There are no published studies on the

prevalence of anosmia with the new strains such as 501Y. V2 from South Africa and B117 from England.

Our sample was carefully selected to include either asymptomatic or mildly symptomatic suspected cases. Up to 27% of patients with confirmed COVID-19 infection reported anosmia as the initial symptom [12]. One of the attributed mechanisms of smell loss is related to

the ACE-2 receptor stimulation in the nasal tissue by the SARS-CoV-2 as opposed to rhinorrhea or nasal blockage seen with other respiratory viruses [13]. In fact, a very small percentage of patients with COVID-19 presents with rhinorrhea or nasal blockage [14]. We excluded patients who presented with self-reported anosmia, rhinorrhea, or nasal blockage. Although it was part of the hospital protocol to do a respiratory panel screen alongside the COVID-19 nasopharyngeal swab in symptomatic patients, the majority (63%) of our samples were asymptomatic patients who had contact with confirmed COVID-19 cases and hence did not receive a nasal swab screen for coinfection.

At the time of the study design, there remained insufficient evidence on factors that contribute to COVID-19 infection. Thus, we attempted to control for factors that influence a reduction in the sense of smell. A 2017 meta-analysis concluded that the sense of smell deteriorates starting at age 55 years and above in healthy humans [15]. Moreover, previous traumatic brain injury involving damage to the ethmoid bone, cribriform plate, skull base fractures, or cortical contusions can adversely affect the olfactory pathway and cause anosmia [16, 17]. Furthermore, smokers have reduced olfactory bulb volume which may contribute to decreased olfactory function [18]. Current evidence indicates that smokers have increased transmembrane serine protease 2 expression which in turn facilitates ACE-2 receptors and SARS-CoV-2 interaction [19]. However, our results show no statistically significant association between smoking and COVID-19.

The prevalence of COVID-19-negative patients in our sample is 74.6%. This is likely due to the largely asymptomatic patients in the sample and the possibility that the RT-PCR swab did not detect enough viral load [20, 21]. However, it has been suggested that the viral load does not correlate with disease severity [22]. Other reasons for a negative COVID-19 swab result are the possibility of a wrong swabbing technique [21].

The limitations of our study include possible observer bias as the investigators were not blinded to the hypotheses when testing the sense of smell. There is also selection bias as the data were collected in a nonrandom manner. In addition, due to surge capacity during the data collection period, our targeted patient population were diverted to primary health-care centers. Thus, the majority of asymptomatic patients in our sample are health-care workers who had contact with confirmed COVID-19 cases and came for screening after a breach in personal protective equipment.

Conclusion

Given the low sensitivity (30%) of this method in detecting COVID-19 infection, we conclude that it is not a useful screening tool for COVID-19 infection. The moderate NPV (80%) is nongeneralizable.

Statement of Ethics

The study protocol was approved by the Dubai Scientific Research Ethics Committee (Ref: DSREC/RRP/2020/06) on April 16, 2020, and the Emirates Institutional Review Board for COVID-19 Research (Ref: DOH/CVDC/2020/1349) on July 13, 2020. All participants signed a written informed consent to participate in this research.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Author Contributions

E.A. is the principal investigator and planned the study design, performed statistical analysis, and took the lead in writing the manuscript. S. Z. and A.A. performed data collection. F.A. conceived the idea and supervised the findings of this work. All the authors provided critical feedback and helped shape the research and manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from E.A. upon reasonable request.

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