Smell Disorders as a Prognostic Tool for COVID-19

Original Article

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ABSTRACT

Objectives: The purpose of this prospective study was to check the value of smell disorders as a prognostic tool for COVID-19.

Background: Viruses that give rise to the common cold are well known to cause post-infectious loss of smell. The severity of post-viral anosmia is variable at its risk and duration of presentation.

Patients and Methods: The study is conducted on 100 patients suffering from CSF rhinorrhea who are admitted to Alexandria Main University Hospital for operative intervention from January 2018 to May 2021.

Results: Four hundred patients with positive PCR testing of COVID-19 but they had smell disorders were randomly included in this study. All patients were divided into two groups according to the severity of manifestations. Patients were scheduled for follow-up visit with smell test and computed topography to the chest. The mean age of studied group was 38.4 ± 11.8 years. 60.5% of studied cases were females and 39.5% of studied cases were males. The patients with mild manifestations were 81.25% and 18.75% of cases were presented with severe chest manifestations. 6.5% presented with anosmia after one month, and only 8.25% of patients presented with parosmia after one month and 341 cases showed improved smell disorders.

Conclusion: Olfactory manifestations for COVID-19 are common and should be added to suspected clinical criteria of COVID-19 particularly if nasal examination was non-significant.

Key Words: Anosmia, COVID-19, parosmia, smell test.

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INTRODUCTION

Post-viral anosmia is one of the leading causes of loss of sense of smell in adults, accounting for up to 40% cases of anosmia. Viruses that give rise to the common cold are well known to cause post-infectious loss of smell, and over 200 different viruses are known to cause upper respiratory tract infections. Previously described corona viruses are thought to account for 10- 15% cases. World Health Organization (WHO) reported novel coronavirus infection that may be presented with fever, shortness of breath, and invasive pneumonic infiltrates on chest radiography. Some cases were reported to have smell dysfunction as early manifestation for COVID-19[1].

Although publicized symptoms for COVID-19 include fever, fatigue, cough and shortness of breath, several studies have also reported chemosensory dysfunction, such as anosmia and ageusia, as common findings in COVID-19 – positive patients. Although upper respiratory infections are known to cause hyposmia in general, in COVID-19 patients, these symptoms can present in the absence of other nasal symptoms, suggesting that they are related to direct viral damage to the chemosensory system[2].

Several studies have developed prediction models for COVID-19, most of which have focused on prognostic factors for survival. A few prediction models for diagnosis have been published but have mostly identified chest computed tomography (CT) and other laboratory findings as predictors. One COVID-19 diagnostic model identified the following key symptoms: fever, fatigue, shortness of breath, headache, and sore throat. Smell and taste change have not been evaluated in any prediction models to date[3].

The purpose of this prospective study was to check the value of smell disorders as a prognostic tool for COVID-19.

PATIENTS AND METHODS:

Four hundred patients were collected from Shebin El-Kom Teaching Hospital and Banha University Hospital for patients confirmed to be diagnosis as COVID-19 and were randomly included in this study. Patients having

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positive PCR testing of COVID-19 but they had smell disorders were included in this study. Exclusion criteria were patients with negative tested PCR (Polymerase chain reaction) for COVID-19 and patients with smell disorders due to allergic nasal history. Patients with known chronic diseases as cardiac, renal or hepatic diseases were also excluded.

Patients were divided into two groups according to the chest involvement as: Group A for mild COVID-19 manifestations and Group B for severe COVID-19 manifestations for those patients presented with chest affection. Written consents were taken from all patients before being introduced in this study after approval of the ethical committee of the hospital.

Routine assessments were done to all patients as routine full history, routine clinical otorhino-laryngological and chest examination. PCR test was done routinely to all patients prior to be included in this study. Routine investigations routinely were done to assess the general condition as CBC, CRP, serum ferritin, liver function and kidney function testing. Standard assessments were done as Computed Topography (CT) for chest affection were assessed by CO-RADS score as shown in (Table 1), smell sensation was tested by quantitative method: as Screening 12 Test with Taste Strips, and qualitative method: as questions were based on Screening Questionnaire for Parosmia as shown in the (Table 2).

Table 1: CO-RADS classification (4)

CO-RAD Score	Level of suspicion (COVID-19)	CT chest findings
CO-RADS 1	Very low	Normal or non-infectious effects
CO-RADS 2	Low	Abnormalities with infections other than COVID-19
CO-RADS 3	Unsure	Unclear whether COVID-19 is present
CO-RADS 4	High	Suspicious for COVID-19
CO-RADS 5	Very high	Typical COVID-19
CO-RADS 6	Sure	

Table 2: Screening Questionnaire for smell disorders (5)

Question /Answer	Always	Often	Rarely	Never
Food tastes different than it should taste due to my case.	1	2	3	4
I always have a bad odor in my nose, regardless of any odor source is present	1	2	3	4
Odors which are pleasant to other people are unpleasant for me.	1	2	3	4
The biggest problem is not that I do not or weakly perceive odors, but that they smell different than they should.	1	2	3	4
The minimum Score is 4 and the maximum score is 16. Total score for all questions; if more than 14= normosmia, if below 10= parosmia, if below 4= anosmia				

Follow-up for disease prognosis were assessed as patients' visits were every week to assess the clinical status and after one month to assess the full routine investigations plus CT chest as standard score for chest assessment and Questionnaire Screening as standard score for smell assessment.

Statistical Methods

Descriptive statistics included the mean value and standard deviation. The ANOVAs test was used for the analysis of the correlation between data. The SPSS 22.0 program was used for statistical analysis. So, the p-value was considered significant as the following: Probability *(P-value): P-value 0.05* was considered insignificant.

RESULTS:

A total of 400 patients with positive PCR testing of COVID-19 and smell disorders were included in our research. Patients were collected from Shebin El-Kom Teaching Hospital and Banha University Hospital. Our patients will be divided into two groups according to the chest involvement as Group A for mild COVID-19 manifestations and Group B for severe COVID-19 manifestations for those patients presented with chest affection. Our results show that mean age of studied group was 38.4 ± 11.8 years. 60.5% of studied cases were females and 39.5% of studied cases were males. 72.75% of studied group live in rural areas and 27.25% of studied group live urban areas. Our results shows that the patients with mild manifestations were 81.25% and 18.75% of cases were presented with severe chest manifestations.

Table 3: Distribution of studied cases according to clinical presentations

Clinical findings		Total cases = 400	
		No.	%
Ventilated patients		Total cases = 24	
	Fever	21	5.25%
	Tachypnea	24	6%
	Cyanosis	8	2%
Non-ventilated patients		Total cases = 376	
	• Fever	332	83%
	• Cough	374	93.5%
	• Runny nose	75	18.75%
	• Headache	72	18%
	• Sore throat	256	64%
	• Itchy nose	289	72.25%
	• Sneezing	42	10.5%

This table shows that ventilated patients were 6% but only 2% had cyanosis, fever (5.25%) and tachypnea (6%). Non-ventilated patients presented with fever (83%), cough (93.5%), runny nose (18.75%), headache (18%), sore throat (64%) and itchy nose (72.25%). The twenty-four ventilated patients stayed on ICU under ventilation less than one week in 16 patients and 8 only patients were ventilated more than one week.

Table 4: Duration of manifestations during follow-up period

Duration of Clinical manifestations	Total cases = 400	
	No.	%
• Group A		
- ≤ 7 days	271	83.4%
- > 7 days	54	16.6%
• Group B		
- ≤ 7 days	16	21.33%
- > 7 days	59	78.67%

This table shows that the majority of Group A (83.4%) had short period of manifestations (less than one week) and 54 only patients had longer period of manifestations more than one week. While in group B, the majority of studied cases manifested for more than a week (78.67%).

Table 5: Parosmia scoring system to studied patients

Parosmia scoring system	Total cases = 400	
	No.	%
• 4 <	284	71%
• 4-10	112	28%
• 10-12	4	1%
• 12 >	-	-

This table shows that the 284 cases presented with anosmia, 116 patients presented with parosmia, and 4 cases only showed fine smell sensation changes.

Table 6: Follow-up of smell disorders after two weeks

Parosmia scoring system (after 2 weeks)	No. of cases = 400	
	No.	%
• 4 <	26	6.5%
• 4-10	33	8.25%
• 10-12	140	35%
• 12 >	201	50.25%

This table shows that 6.5% presented with anosmia after one month, and only 8.25% of patients presented with parosmia after one month and 341 cases showed improved smell disorders.

DISCUSSION

A novel coronavirus (COVID-19) epidemic, produced by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), began in December 2019 from China. COVID-19 manifests with a wide clinical range extending from no symptoms to multi-organ dysfunctions and septic shock. Despite its rapid distribution worldwide, the clinical features of COVID-19 remain to a variable extent non-specific[6].

The nasal, nasopharyngeal, and/or the oro-pharyngeal tissues are part of the main harbor locations of the infection, main site of sample taking for testing, and a main source of infection transmission. However, most COVID-19 published studies are focused on the lower respiratory tract manifestation and sequels because of their life-threatening potentiality[7].

In a study conducted at two main Hospitals in Iraq, patients with a chief complaint of parosmia due to COVID-19 disease were followed up for 7 months (August 2020–February 2021). Detailed demographic and clinical characteristics and treatment options with their outcome were recorded and analyzed. Median age at the first visit was 43 years while in our study mean age of patients was 38.4[8].

The highest occupation affected in a study conducted by Rashid *et al*. was a housewife (n = 150, 56%). This may be attributed to the highest proportion of our patients were females[8].

Our patients were divided into two groups according to the chest involvement as Group A (325 cases) for mild COVID-19 manifestations and Group B (75 hospitalized cases) for severe COVID-19 manifestations for those patients presented with chest affection. While Augustin *et al*. 2021 showed only 3% of cases were hospitalized and only 0.7% of cases introduced to ICU. This could be explained by late presentation of discovered patients according to COVID-19 protocol in our country[9].

The results of the current study agree with previous reports that fever (recounted in 57.4% of the included patients) and cough (reported in 69.8%) are the principal symptoms of COVID-19 whereas gastrointestinal and ENT symptoms were less common, suggesting the difference in viral tropism as compared with influenza, SARS-CoV, and MERS-CoV[10].

In another study, the percentage of COVID-19 patients complaining of smell disorder was about 57% with the fact that questionnaire as a tool in smell identification with poor sensitivity value 65.6%.

The most common ENT manifestation of COVID-19 in descending order were smell dysfunction (55.6%), taste disorder (49.2%), headache (42.8%), nasal congestion and blockage (26.3%), and sore throat (25.7%). On the other hand, the most prevalent associated general symptoms in relation to smell and taste disorder in descending order were cough (69.8%), fever (57.4%), arthralgia/myalgia (44.5%), asthenia/fatigue (36.7%), loss of appetite (27.3%), and dyspnea (22.2%)[11].

All patients in Rashid *et al*. (2021) have complained of anosmia (89.9%) or hyposmia (10.1%). Troposmia was reported in the majority of participants. The majority of the patients were suffering from severe parosmia (65.7%). Around 3 quarters of the cases were presented in ≤ 4 months. In other side, our results showed that the majority of our studied cases presented with either anosmia (284 cases) or parosmia (116 cases) and only 4 cases presented with fine smell sensation changes[8].

Degree of smell affection shows variability, anosmia accounts to about 58%, while hyposmia about 41.6%. About 28.3% of affected patients complained of early smell affection as the only or first presentation with only 0.9% possibility of progression to severe or critical COVID-19. Late smell affection occurred 3–5 days after common acute respiratory tract infection in about 71.7%[11].

As an overall view regarding the severity of COVID-19 and smell disorder, in less than 5% of the smell-affected patients, the COVID-19 was severe or critical. This may reflect no association between disease severity and smell affection, but smell disorder could be masked by both respiratory and critical manifestations in those severe and critical COVID-19 patients. Post-viral anosmia is a widespread cause of adult smell dysfunction (40% of anosmia cases). Viruses that induce the common cold or upper respiratory tract infections are well known to lead to post-infectious smell loss. The previously defined corona viruses are assumed to account for 10 – 15% cases. This novel viral infection seems to affect smell sensation over other viruses. Odds ratio describing likelihood of COVID-19 associating with smell disorder is over that of influenza virus by 4.5 folds. Moreover, acute smell dysfunction is reported in COVID-19 infection over normal persons by 13.2 times (odds ratio of smell disorder in normal and COVID-19-positive persons in two studies) with exclusion of obstructive olfactory disorder[11, 12].

Between May 2020 and October 2020, a prospective, longitudinal study evaluating subjective and measured olfactory function was conducted on ambulatory COVID-19 subjects. Adults presenting to the UC San Diego Health System with confirmed polymerase chain reaction (PCR)-positive severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) viral nucleic acid from nasopharyngeal/nasal cavity swabs were eligible for inclusion., subjects were recruited within 3 days of COVID-19 test confirmation. During initial recruitment (within 3 days of COVID-19 diagnosis), 33 subjects reported COVID-19–induced smell loss (33/52, 63%) in response to a binary yes/no question, whereas 19 reported no smell loss (19/52, 37%). The mean baseline (pre–COVID-19) Visual Analogue Score (VAS) for olfactory function was 9.60 ± 1.11[13].

Between April and December 2020, a total of 958 COVID-19- convalescent individuals presented to the post-COVID outpatient clinic by a study prepared by Augustin *et al*. (2021), of which 442 were followed up until the second follow-up visit at 4.3 months (median 131 days (IQR 112 – 149) and 353 until the third follow-up visit at 6.8 months (median 207 days (IQR 187–234). According to WHO COVID-19 clinical progression scale, 97.1% of patients (930/958) initially presented with mild disease (score 1 – 3). Only 2.2% (21/958) and 0.7% (7/958) of all patients experienced moderate (score 4 – 5) or severe disease (score 6 – 9), respectively[9].

As well as, in our study that showed the patients with mild manifestations were 81.25% and 18.75% of cases were presented with severe chest manifestations. The 24 ventilated patients stayed on ICU under ventilation less than one week in 16 patients and 8 only patients were ventilated more than one week.

Smell and taste dysfunctions were sparsely declared in the COVID-19 literature, and there is still a lack of peer-reviewed literature to support a causal association between COVID-19 and anosmia. Olfactory neuritis is the most accepted theory of smell disorder but some studies emphasize on the presence of inflammatory change in olfactory cleft to be more than the changes affecting the olfactory neural pathway which is clearly detected by radiological studies like CT or Magnetic Resonance Imaging[14].

Among the 33 subjects with a binary self-reported smell loss during recruitment, 32 (97.0%) continued to report subjective loss at the time of first Binary smell identification test (BSIT), whereas only 16 (48.5%) had measurable olfactory dysfunction on BSIT testing. Although 75.8% achieved normalization on BSIT testing, only 30.3% (10/33) of those with subjective COVID-19 – related smell loss reported full recovery (VAS = 10/10) at the completion of all study time points, suggesting either a delayed subjective recovery or the presence of olfactory deficits undetectable on BSIT testing. However, when a VAS cutoff ≥ 8 was

used, a 75.8% subjective olfactory improvement rate was noted[13].

From 22 March to 3 June 2020, 2581 COVID-19 patients were identified from 18 European hospitals in certain study. Epidemiological and clinical data were extracted at baseline and within the 2-month post-infection. The prevalence of OD (Olfactory Dysfunction) was significantly higher in mild form (85.9%) compared with moderate-to-critical forms (4.5-6.9%; $P = 0.001$). Of the 1916 patients with OD, 1363 completed the evaluations (71.1%). A total of 328 patients (24.1%) did not subjectively recover olfaction 60 days after the onset of the dysfunction. The mean duration of self-reported OD was 21.6 +/- 17.9 days. Objective olfactory evaluations identified hyposmia/anosmia in 54.7% and 36.6% of mild and moderate-to-critical forms, respectively ($P = 0.001$). At 60 days and 6 months, 15.3% and 4.7% of anosmic/hyposmic patients did not objectively recover olfaction, respectively. The higher baseline severity of objective olfactory evaluations was strongly predictive of persistent OD ($P < 0.001$)[15].

Prajapati *et al*. showed also that the longitudinal BSIT and VAS assessment were conducted weekly until subjects demonstrated recovery of olfaction (either subjective or objective) at two time points. Subjects who continued to exhibit olfactory dysfunction underwent repeated testing for a maximum of four time points. Four time points of data were collected at a median of 7, 12, 21, and 33 days after COVID-19 diagnosis from a total of 52, 52, 27, and 14 subjects, respectively. demonstrates longitudinal concurrent BSIT and VAS scores for subject cohorts which each completed two (n = 52; red), three (n = 27; green), and four (n = 14; blue) time points[13].

This study was limited by sampling at a single institution, as well as a notable dropout of initially recruited subjects due to a lack of completion of longitudinal UPSIT assessments to assess return of olfactory function (subsequent assessments until normalization of UPSIT or subjective recovery was required as per inclusion criteria) or disease progression. In surveying home-quarantined subjects after COVID-19 diagnosis, there was a risk of post hoc interpretations of smell loss, and potential recall bias in the context of extensive media coverage of COVID-19 anosmia.

CONCLUSION

Olfactory manifestations for COVID-19 are common and should be added to suspected clinical criteria of COVID-19 particularly if nasal examination was non-significant. However, a standard universal questionnaire by well-defined COVID-19 manifestations is needed to make the COVID-19 data accurately defined, homogenous, and complete.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Roland LT, Gurrola JG, Lous PA, Cheung SW, Chang JL. Smell and taste symptom-based predictive model for COVID-19 diagnosis. Int Forum Allergy Rhinol. 2020; 10:1-7.

2. Russell B, Moss C, Rigg A, Hopkins C, Papa S, Van Hemelrijck M. Anosmia and ageusia are emerging as symptoms in patients with COVID-19: what does the current evidence say? Ecancer medical science. 2020; 14:ed98.

3. Wynants L, Van Calster B, Bonten M. Prediction models for diagnosis and prognosis of COVID-19 infection: systematic review and critical appraisal. BMJ. 2020; 369:m1328.

4. Prokop M, van Everdingen W, van Rees Vellinga T, CO-RADS: A Categorical CT Assessment Scheme for Patients Suspected of Having COVID-19-Definition and Evaluation. Radiology. 2020 Aug;296(2):E97-E104.

5. Landis BN, Frasnelli J, Croy I, Hummel T. Evaluating the clinical usefulness of structured questions in parosmia assessment. Laryngoscope. 2010;120(8):1708.

6. Lee Y, Min P, Lee S, Kim SW.Prevalence and duration of acute loss of smell or taste in COVID-19 patients. J Korean Med Sci. 2020; 35(18):e174.

7. Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: a review based on up-to-date knowledge. Am J Otolaryngol. 2020; 41(5):102581.

8. Rashid RA, Alaqeedy AA, Al-Ani RM. Parosmia Due to COVID-19 Disease: A 268 Case Series. Indian J Otolaryngol Head Neck Surg. 2021 May 23:1-8.

9. Augustin M, Schommers P, Stecher M, Dewald F, Gieselmann L, Gruell H, *et al*. Post-COVID syndrome in non-hospitalised patients with COVID-19: a longitudinal prospective cohort study. Lancet Reg Health Eur. 2021; 6:(100)122.

10. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-Corral J, *et al*. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multi-center polymerase chain reaction-based case-control study. Eur J Neurol. 2020; 27(9):1738–1741.

11. El-Anwar MW, Elzayat S, Fouad YA. ENT manifestation in COVID-19 patients. Auris Nasus Larynx. 2020; 47(4):559–564.

12. Dubé M, Le Coupanec A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. J Virol, 2018; 92(17):e00404–e00418.

13. Prajapati DP, Shahrvini B, Said M, Srinivas S, DeConde AS, Yan CH. Assessment of patient recognition of coronavirus disease 2019 (COVID-19)-associated olfactory loss and recovery: a longitudinal study. Int Forum Allergy Rhinol. 2021 Nov;11(11):1529-1537.

14. Eliezer M, Hautefort C, Hamel AL, Verillaud B, Herman P, Houdart E, Eloit C. Sudden and complete olfactory loss of function as a possible symptom of COVID-19. JAMA Otolaryngol Head Neck Surg. 2020; 146(7):674–675.

15. Lechien J, Chiesa-Estomba M, Beckers E, Mustin V, Ducarme M, Journe F, *et al*. Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients. J Internal Medecine, 2021; 290(2): 451461.