RHINOLOGY



Evolution of olfactory and gustatory dysfunctions in COVID-19 patients in India

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Abstract

Purpose The ongoing coronavirus disease 19 (COVID-19) pandemic is spreading at an alarming rate across the globe. Sudden onset loss of smell and/or taste has been increasingly reported as a symptom of COVID-19. However, prevalence of these symptoms, and its severity varies widely between studies, with little data on its duration and recovery rate. Since this significantly impacts the quality of life of patients, there is a need for a study to provide insight into the loss of smell or taste in terms of its correlation with other upper respiratory tract symptoms, natural history and resolution rates.

Methods This cross-sectional study included 718 mild to moderately symptomatic adult patients (\geq 18 years), admitted consecutively to Kalinga Institute of Medical Sciences (KIMS), Odisha, India between June 25 and July 24, 2020, who tested positive for SARS-CoV-2 by polymerase chain reaction on nasopharyngeal and throat swabs.

Prevalence, severity, duration and factors associated with altered smell or taste sensation, and their follow-up were recorded. **Results** Of the 718 patients included in the study at baseline [563 (78%) men; median age 34 years], 101 (14%) patients experienced either altered smell or taste, with 52 (7%) experiencing both altered smell and taste. Seventy-seven (10.7%) patients had altered smell and 76 patients had altered taste (10.5%). Of these, 71 (92%) and 73 (96%) regained their sense of smell and taste, respectively, by 14 days after their swab tested positive. Presence of fever (OR = 5.4, 95% CI = 2.7–10.6, p < 0.001), cough (OR = 2.3, 95% CI = 1.2–4.2, p = 0.009) and nasal obstruction (OR = 3.1, 95% CI = 1.4–6.7, p = 0.006) were independently associated with increased likelihood of experiencing both altered taste and smell in multivariable models. **Conclusion** The prevalence of altered smell and taste in Indians was much lower compared to Europeans and similar to East Asians. Majority regained these senses by 2 weeks. Identification of these symptoms can help in early detection of the disease in suspected individuals.

Keywords COVID-19 · Anosmia · Ageusia · East Asians · Indians · Recovery

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Introduction

The severe acute respiratory syndrome coronavirus (SARS-CoV-2), which emerged in Wuhan, China by the end of December 2019, has been spreading all across the globe since January 2020, and forcing the world into an unprecedented crisis [1]. The virus has a high potential of human to human transmission leading to expedited spread of the global pandemic [1]. Anosmia (complete or partial loss of smell) and ageusia (complete or partial loss of taste) have been increasingly reported in patients with suspected or confirmed infection [2].

Initial reports from Italy and South Korea demonstrated anosmia in almost 34% of the patients [3, 4] whereas a later major report from a cross European multicentric analysis

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revealed anosmia in as high as 85.6% of the cases with mild to moderate SARS-CoV-2 disease [5]. The large multicenter CORANOSMIA study conducted in France showed the positive predictive value and the specificity of loss of smell and/ or taste were 78.5% and 90.3%, respectively, in diagnosed COVID-19 [6].

There is a dearth of evidence on the findings of anosmia and ageusia from Asia, and more so from India, which was the main reason for the inception of this study. This study evaluated the prevalence, timing of onset of altered smell and taste in relation to other general and upper respiratory symptoms, severity of these symptoms, the duration of the symptoms and their time to recovery, and the factors associated with these two symptoms, in patients with confirmed mild to moderate SARS-CoV-2 infections.

Methods

The study was conducted after obtaining the approval of the institutional ethics committee of Kalinga Institute of Medical Sciences (KIMS) in Odisha state of India. Informed consent was obtained from all patients included in the study and the study was performed as per the tenets of the declaration of Helsinki.

Adult patients (\geq 18 years) with mild to moderate symptoms admitted to the KIMS, a dedicated COVID hospital in Eastern India, between June 25 and July 24 2020 were included in the study. Consecutive patients who tested positive for SARS-CoV-2 RNA by polymerase chain reaction on nasopharyngeal and throat swabs, performed in accordance with World Health Organization (WHO) recommendations [7], and who were able to fulfill the study questionnaire were included. Patients admitted to the hospital were considered to be mild to moderate COVID-19 if they had less severe clinical symptoms, without evidence of any pneumonia, not requiring oxygen, and therefore could comfortably answer study questionnaire. Included patients were interviewed on day 3 after the PCR test positive report was obtained, and this was considered as the baseline.

The patients were asked a fixed set of binary (yes/no) questions about their symptoms in the last 2 weeks leading up to their test or admission at the hospital. The questions were: any change in smell/taste, presence of fever or chills, having any unexplained body aches, having any new onset headache, appearance of any new sore throat, having shortness of breath, developing any new cough or worsening of cough, presence of any nasal congestion, presence of runny nose and appearance of nausea or diarrhea. They were also asked regarding onset of the altered smell or taste in relation to the other ENT symptoms, as to whether it occurred prior to, or at the same time or after the onset of other ENT symptoms. The patients who had altered smell or taste were

asked to rate the severity of their symptoms according to the 6-point Likert scale, scoring 0 for no problems, 1 for very mild, 2 for mild or slight, 3 for moderate, 4 for severe or 5 for as bad as it can be.

All the patients who had altered smell or taste symptoms at the baseline were followed after 2 weeks of their positive PCR test report. At follow-up, they were asked regarding the disappearance of symptoms or its persistence, and if persistent were asked to rate it according to the same severity scale.

Statistical analysis

All continuous variables were expressed as mean with standard deviation or median with interquartile range (IQR) and categorical variables were expressed as proportions (n, %). Normality of distribution for continuous variables was assessed using the Shapiro-Wilk test. Differences in continuous variables between two groups was analyzed using the student t test or the Wilcoxon ranksum test for non-parametric variables and using the analysis of variance (ANOVA) or the Kruskall Wallis test when comparing across more than two groups. Differences between categorical variables across groups were accessed using the chi square test or the Fischer's exact test. Univariate and multivariable logistic regression analysis was carried out to assess associations between covariates, including general and ENT symptoms, and olfactory (i.e., altered smell) and gustatory (i.e., altered taste) symptoms using separate models for each of these. The Akaike information criteria and stepwise regression were used to assess the goodness of fit of the multivariable models. Outcomes were expressed as odds ratios (OR) with 95% confidence intervals (CI).

All data were entered into Microsoft Excel and analyzed using STATA 12.1 I/c (Stata Corp, Fort Worth, Texas, USA). All *p* values < 0.05 were considered statistically significant.

Results

We included 718 consecutive patients with mild or moderate symptoms of COVID admitted to our institution during the study period. The mean age of patients was 36.7 ± 12.5 years (median = 34, IQR = 27–45 years, range 15–80 years) and 563 (78%) were men. Of these, 77 patients (10.7%) reported altered sense of smell and 76 reported altered sense of taste (10.5%). Overall, general symptoms of fever were seen in 228 (32%) patients, persistent headache in 91 (13%) and generalized myalgia in 93 (13%) patients. ENT symptoms of cough were seen in 176 (25%) patients, while 51 (3%) complained of throat pain, 56 (3%) of nasal obstruction, 5 (<1%) of ear pain and 67 (9%) patients complained of rhinorrhea.

	Smell intact $(n = 641)$	Altered smell $(n=77)$	p value	Taste intact $(n=642)$	Altered taste $(n=76)$	p value
Age (mean \pm SD)	37.2 ± 12.6	31.6±9.6	< 0.001	36.9 ± 12.6	34.7±11.8	0.16
Gender (% male)	498 (79%)	65 (84%)	0.18	502 (78.2%)	61 (80.3%)	0.68
Addictions						
Alcohol	5 (0.8%)	1 (1.3%)	0.19	5 (0.8%)	1 (1.3%)	0.51
Smoking	15 (2.3%)	5 (6.5%)		16 (2.5%)	4 (5.3%)	
Tobacco	33 (5.2%)	3 (3.9%)		33 (5.1%)	3 (3.9%)	
Allergy	4 (0.6%)	1 (1.3%)	0.50	5 (0.8%)	0 (0%)	0.44
General symptoms						
Fever	177 (27.6%)	51 (66.2%)	< 0.001	168 (26.2%)	60 (78.9%)	< 0.001
Headache	72 (11.2%)	19 (24.7%)	0.001	69 (10.8%)	22 (28.9%)	< 0.001
Myalgia	72 (11.2%)	21 (27.3%)	< 0.001	72 (11.2%)	21 (27.6%)	< 0.001
Cough	143 (22.3%)	33 (42.86%)	< 0.001	138 (21.5%)	38 (50.0%)	< 0.001
ENT symptoms						
Throat Pain	47 (7.3%)	4 (5.2%)	0.49	43 (6.7%)	8 (10.5%)	0.22
Ear pain	4 (0.6%)	1 (1.3%)	0.50	4 (0.6%)	1 (1.3%)	0.49
Nasal obstruction	37 (5.8%)	19 (24.7%)	< 0.001	43 (6.7%)	13 (17.1%)	0.001
Rhinorrhoea	55 (82.09%)	12 (17.91%)	0.046	58 (9.0%)	9 (11.8%)	0.43
PND	1 (0.2%)	0 (0%)	0.73	1 (0.2%)	0 (0%)	0.73

Table 1 Comparison of patients with and without altered smell and taste in our study

Of the 77 patients with altered smell, majority (n = 47,61%) developed this after onset of ENT symptoms, while 7 (9%) had altered smell before ENT symptoms, 15 (19%) had onset at the same time and 8 (10%) reported not remembering exactly about time of onset. Table 1 shows a comparison between baseline demographics and symptomatology between those with and without altered smell. We found that those with altered smell were significantly younger, had a higher proportion of fever, myalgia, headache, cough and other ENT symptoms such as nasal obstruction and rhinorrhea, however, the proportion of ear and throat pain did not differ between groups. On comparing those with different times of onset of altered smell with respect to ENT symptoms (i.e., before, at the same time and after), we did not find any significant differences in general and ENT specific symptomatology. In terms of severity of altered smell (Table 2), majority of patients reported mild or moderate loss of smell at baseline. Majority of the patients reported improvement and regained smell, with 92% (n=71) reporting no smell loss at 2 weeks (Table 2). Of the patients with altered smell, 8% (n=6) had persistence of the symptom, although diminished in severity at 34th,20th, 20th, 18th, 17th and 16th day of their follow-up, as on the date of completion of the study. Univariate and multivariable logistic regression, after adjusting for all covariates, showed that presence of fever and nasal obstruction increased the likelihood of experiencing altered smell by four fold (p < 0.001for both) (Table 3).

Of the 76 patients with altered taste, majority (n = 46, 61%) developed this after onset of ENT symptoms, while 2 (3%) had altered taste before ENT symptoms, 16 (19%) had onset at the same time and 12 (10%) reported not remembering exactly about time of onset. Table 1 shows a comparison between baseline demographics and symptomatology between those with and without altered taste. We found that

Table 2Comparison of theseverity of altered smell atbaseline and at 2-week timepoint

Severity of altered smell at baseline	Severity of altered smell at 2-week follow-up						
	Smell normal	Very mild	Mild or slight	Moderate	Total		
Very mild	2 (3%)	0	0	0	2 (3%)		
Mild or slight	18 (25%)	0	0	0	18 (23%)		
Moderate	41 (58%)	0	0	0	41 (53%)		
Severe	10 (14%)	1 (100%)	3 (75%)	0	14 (18%)		
As bad as it can be	0	0	1 (25%)	1 (100%)	2 (3%)		
Total	71 (100%)	1 (100%)	4 (100%)	1 (100%)	77 (100%)		

 Table 3
 Univariate and

 multivariable logistic regression
 analysis to determine factors

 associated with altered smell
 and altered taste at presentation

Logistic regression analysis						
Covariate	Altered smell		Altered taste			
	Univariate	Multivariable	Univariate	Multivariable		
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)		
Age	0.98 (0.9–1.04)	-				
Addictions	1.09 (0.8–1.9)	-	1.1 (0.7–1.4)			
Allergy	2.09 (0.2–18.9)	-	1			
Fever	5.1 (3.1-8.5)	4.1 (2.3–7.1)	10.6 (5.93-18.9)	7.8 (4.3–14.2)		
Headache	2.6 (1.5-4.6)	_	3.4 (1.9–5.8)	2.2 (1.2-4.2)		
Myalgia	2.9 (1.7-5.2)	1.5 (0.8–2.7)	3.0 (1.7–5.3)			
Cough	2.6 (1.6-4.3)	1.6 (0.9–2.8)	3.7 (2.2–5.9)	2.2 (1.3-3.8)		
Throat Pain	0.7 (0.2-2.0)	-	1.6 (0.7–3.6)			
Ear pain	2.1 (0.2–18.9)	_	2.1 (0.2–19.3)			
Nasal obstruction	5.3 (2.9–9.9)	4.3 (2.2-8.6)	2.9 (1.5-5.6)	1.9 (0.9–4.2)		
Rhinorrhoea	1.9 (1.0-3.9)	_	1.4 (0.6–2.9)			

 Table 4 Comparison of the severity of altered taste at baseline and at 2-week time point

Severity of altered taste at baseline	Severity of altered taste at 2-week follow-up				
	Taste normal	Very mild	Mild or slight	Total	
Very mild	2 (3%)	0	0	2 (3%)	
Mild or slight	40 (55%)	0	0	40 (53%)	
Moderate	30 (41%)	0	0	30 (39%)	
Severe	1 (1%)	2 (100%)	0	3 (4%)	
As bad as it can be	0	0	1 (100%)	1 (1%)	
Total	73 (100%)	2 (100%)	1 (100%)	76 (100%)	

those with altered taste had a significantly higher proportion of fever, myalgia, headache, cough and nasal obstruction, however, the proportion of ear and throat pain and rhinorrhea did not differ between groups. On comparing those with different times of onset of altered taste with respect to ENT symptoms (i.e., before, at the same time and after), we did not find any significant differences in general and ENT specific symptomatology. In terms of severity of altered taste (Table 4), majority of patients reported mild or moderate loss of taste at baseline. Most of the patients reported improvement and regained taste sensation, with 96% (n = 73) reporting no loss of taste at 2 weeks (Table 4). Of the patients altered taste, 4% (n=3) had persistence of the symptom, although diminished in severity at 20th, 18thand 16th day of their follow-up, as on the date of completion of the study. Univariate and multivariable logistic regression, after adjusting for all covariates, showed that presence of fever had the strongest association with altered taste, with febrile patients having an almost eight times higher likelihood of experiencing altered taste. Headache and myalgia also independently increased the likelihood of altered taste (Table 3).

Among the 718 patients included in our study, 46 were elderly (60 years and above) and the rest 672 were below 60 years of age. All of the 77 patients who had altered smell were below 60 years of age, and 71 of them had regained their sense of smell by the end of the study follow-up period, whereas rest 6 of them had some persistence of loss of smell. Out of the 76 patients who had altered taste, 3 were elderly and 73 were below 60 years of age. All the 3 elderly patients had regained their taste sensation by the end of follow-up, whereas 3 of the 73 younger patients had some persistence of loss of taste sensation by the end of the follow-up period.

A total of 101 (14%) patients experienced either altered smell or taste. Fever was again found to be the strongest factor associated with this (OR = 5.8, 95% CI = 3.6–9.6, p < 0.001). Lastly, 52 (7%) patients experienced both altered smell and taste. Presence of fever (OR = 5.4, 95% CI = 2.7–10.6, p < 0.001), cough (OR = 2.3, 95% CI = 1.2–4.2, p = 0.009) and nasal obstruction (OR = 3.1, 95% CI = 1.4–6.7, p = 0.006) were independently associated with increased likelihood of experiencing both altered taste and smell in multivariable models, even after adjusting for other covariates.

Discussion

We found a low incidence of altered smell and taste which were reported by approximately 14% out of a relatively large cohort of Indian patients with mild to moderate COVID-19 disease. A significantly higher proportion of this cohort had fever (seen in 2/3rd to 3/4th) and other general symptoms of COVID-19 such as myalgia and headache. While specific ENT symptoms such as nasal obstruction were more common in those with altered smell and taste, rhinorrhoea was more common in altered smell group but not in the altered taste group. Majority of patients complained of smell and taste alterations after the onset of other ENT symptoms. While these alterations were mild to moderate in severity for most, all experienced improvement over hospital stay and more than 90% had no alterations in smell and taste at 2 weeks. Presence of fever was the main factor associated with four-eightfold-increased likelihood of developing altered smell and taste.

There is only 1 published study from India on anosmia in COVID-19 by Mishra et al. who found anosmia in 11 out of 74 (14.8%) of the patients [8]. Studies from East Asia have shown anosmia to be prevalent ranging from 5.6% patients in China [9], 8.9% in Japan [10], to 30% in Korea [4]. The prevalence in East Asians is much less as compared to the Caucasians, where the prevalence of anosmia was as high as 85.6% (n=417) in a multicentric study by Leichen et al. in Europe [5], 87% in Belgium [11] and 73% in USA (*n*=237) [12]. A similar trend was seen in terms of ageusia, which ranged from 5.6% in China [9] to 8.1% in Japan [10] as compared to 88.8% in the multicentric study in Europe by Leichen et al. (n = 417) [5], and 56% in Belgium (n = 2013)[11]. Additionally, presence of any chemosensory disorder in East Asians was lower in the range of 5.6% in China [9], 17% in Japan [10] to 15.3% in Korea [13] while it was much higher in Caucasians in the range of 63% in UK [14], 73% in USA [12], 87% in Belgium [11] and 88.8% in Europe [5]. Our findings corroborate with the findings of the studies on East Asians.

The meta-analysis by Bartheld et al. showed that ethnicity was a highly significant factor contributing to the difference in findings of anosmia, ageusia or any chemosensory disorder amongst the East Asians and the Caucasians [15]. The estimated random prevalence of loss of sense of smell was 43.2% (95% CI 31.9-55.3%) in Caucasians as compared to 15.1% (95% CI 8.3-25.7%) in East Asians; and that of loss of taste was 38.3% (95% CI 27.0-51.0%) in Caucasians as compared to 6.4% (95% CI 5.7-51.0%) in East Asians. Overall estimates of presence of any chemosensory loss were about three times more in the Caucasians as compared to the East Asians. This evident difference between the East Asians and the Caucasians has been ascribed to the ethnic differences in the Angiotensin-Converting Enzyme 2 (ACE2) virus entry protein [5]. ACE2 variants are genetically determined and they vary in their frequency between the Caucasians and the East Asians [16, 17]. A dedicated study of the olfactory epithelium cell types revealed that ACE2 is expressed directly on the sustentacular cells and basal cells of the olfactory epithelium [18]. According to Bilinska et al., Caucasians are more likely to have increased number of the ACE2 variants expressed on the sustentacular

cells of their olfactory epithelium, thus resulting in the binding of the SARS-CoV-2 virus with higher affinity, resulting in occurrence of olfactory symptoms at a higher frequency as compared to the East Asians, who have lesser number of these ACE2 variants and thus lesser anosmia [19].

Also there is higher lingual expression of the ACE2 receptors than the cheek and gingiva, this differential expression probably partly accounting for the gustatory loss found in SARS-CoV-2 infection [20]. As the nasal epithelium has a higher viral load than the rest of the respiratory epithelium [21], and higher number of ACE2 receptors [19], this ethnic difference can have far-fetching implications in the infectivity and spread of the virus and thus, could possibly explain the more rapid spread of the pandemic in the Caucasians.

In our study, we found that the patients having altered smell were significantly younger, with a higher proportion having fever, cough and other ENT symptoms such as nasal obstruction and rhinorrhea. The study by Speth et al. also showed similar findings of a negative association with older age (OR = 0.96; 95% CI 0.98–0.99; p = 0.007). It also showed that, olfactory dysfunction was prevalent in 61% of COVID-19 patients and 95% of them who had olfactory dysfunction also had other symptoms such as fever (75%), cough (68%) [22]. Other ENT symptoms such as nasal obstruction and rhinorrhea were reported with lower incidence in prior studies, but the study by Speth et al. showed that nasal obstruction (49%) and rhinorrhea (35%) were significantly associated with the patients having altered smell or taste, which corroborates with the finding in our study.

Analysis of the severity of the smell and taste alteration revealed that majority of the patients in our study who had olfactory dysfunction reported mild or moderate loss of smell at baseline, and 92% regained olfaction and 96% regained taste sensation, on follow-up at the 2 weeks of the PCR positivity. Our study showed comparable results with the study conducted by Boscolo-Rizzo et al. in Italy where 89% experienced complete resolution or improvement of these symptoms, and only the remaining 11% (n=12) reported that the smell or taste sensation remained unchanged or worsened [23]. The study by Hopkins et al. showed that 80.1% of the patients reported an improvement in olfaction in 1 week [24], and the study by Chary et al. showed that 64% of the patients had complete recovery in olfaction after 15 days [25]. The study by Parente-Arias et al. which had a longer follow-up period, showed a total recovery of smell in 85.3% of the patients in the first 2 months [26]. Most of the studies reveal that recovery of the alterations in the smell and taste occurs in majority of the patients.

Follow-up of the patients is further required for those who had not completely recovered and reported persistence of symptoms. Moreover, given the rapidity at which the disease is spreading and taking the whole world in its clutches, there is more likelihood that a sizeable number of people would have olfactory and gustatory dysfunctions.

Limitations

This study has several limitations. First, objective approaches were not used for assessing the loss of smell and taste. Second, our sample size included only mild and moderate COVID-19 patients, excluding the severe cases, which may not be representative of the whole infected population. Third, the sample size was small and further follow-up of the patients with persisting altered smell and taste needs to be done.

Conclusions

Loss of smell and/or taste sensation has emerged to be among the common manifestations in COVID-19 patients with mild to moderate symptoms. However, the prevalence is relatively lower in the Indian and other East Asian populations. Recovery occurs within 2 weeks of onset in almost all patients. Those with fever, cough and nasal obstruction should be informed about their high likelihood of experiencing altered smell and/or taste during the disease course. Alteration of smell or taste sensation can serve as screening symptoms, and early identification of these symptoms can help in timely detection of suspected cases, and can provide an opportunity to contain the rapid spread of the pandemic.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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