



Smell and Taste Disturbance in COVID-19 Patients: A Prospective Multicenteric Review

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Abstract To study the incidence of the smell and taste disturbance in the COVID-19 patients and a follow up at 4 months to observe for the duration of resolution of these symptoms. This is a multicentric prospective study carried out in 3 different countries, from April, 2020 to January, 2021. The COVID-19 positive patients, aged between 15 and 60 years, were inquired about the presence of any smell or taste related symptoms. The same patients were followed up with the telephonic interview after 2 months and then after 4 months, respectively. The duration of resolution of the smell and taste disturbance symptoms was noted. Total of 188 COVID-19 positive patients, average age 33.1 ± 1.7 years, 54.2% males and 45.8% female were included in the study. The smell disturbance was present in 60.6% (hyposmia 36.1%, anosmia 20.2%, and parosmia

4.2%) and taste disturbance in 28.7% of patients (hypogeusia 20.2%, ageusia 6.9%, and parageusia 1.6%). There was improvement of anosmia by 97.4, hyposmia by 95.6%, parosmia by 100%, ageusia by 100%, hypogeusia 94.8%, and parageusia by 66.7%, at 4 months follow up. The present study concludes that the smell and taste disturbances are one of the main early presenting features of the COVID-19 infection. The temporary effect of the COVID-19 infection on the olfactory and gustatory pathway was also highlighted with more than 95% patients improving at 4 months of follow up.

Keywords COVID-19 infection · Smell disturbance · Taste disturbance · Prospective

This manuscript has been read and approved by all the authors and the requirements for authorship have been met. Each author approves that the manuscript represents original work.

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Introduction

The Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. It was declared pandemic by WHO on March 11, 2020 [3]. The COVID-19 targets those cells of the body, which expresses angiotensin-converting enzyme 2 (ACE-2) receptors such as; stratified epithelial cells, type II alveolar cells, absorptive enterocytes from ileum and colon, glial cells and neurons, myocardial cells, bladder urothelial cells, proximal tubule cells of the kidney, oral epithelial cells, and nasal epithelial cells [4–8]. As a result, the COVID-19 infection has very diverse presentation such as, fever, sore throat, cough, breathing difficulty, olfactory and gustatory disturbances, headache, diarrhea, myalgia, rhinorrhea, nasal obstruction, fatigue, post nasal drip, and expectoration [9–15].

The smell and taste disorders have long been studied in association with various viral upper respiratory tract

infections such as; influenza and parainfluenza virus, respiratory syncytial virus, rhinovirus, and other endemic coronavirus [16, 17]. The highest concentration of the ACE-2 has been described in the epithelium of the nasal and oral mucosa [6, 7]. It has been proposed in the recent literature that the COVID-19 virus invades the central nervous system epithelium via the olfactory neuroepithelium, and subsequently spreads to the olfactory bulb utilizing the neuron-to-neuron propagation [18, 19]. This has resulted in the olfactory and gustatory disturbances in the patients with COVID-19 infection.

The chemo sensitive dysfunctions such as; the anosmia, hyposmia, parosmia, ageusia, hypogeusia, and par ageusia, constitute one of the most frequent symptoms in the early stages of the COVID-19 infection [20]. Various studies have elaborated the smell and taste dysfunction during the COVID-19 infection [17, 21–26]. The present study is a first multicentric research performed in 3 different countries to evaluate the incidence of smell and taste disturbance with the duration of their resolution, in the patients with COVID-19 infection, with 4 months follow up. Vaira et al. [20] have performed the similar study in 3 different institutes of Italy with a 60 day follow up.

Method and materials

This was the prospective study conducted from April 2020 to January 2021. It was simultaneously carried out in 10 different institutes namely; Indira Gandhi memorial hospital (IGMH) (Male', Maldives), Patan academy of health sciences (PAHS) (Patan, Nepal), Deenanath Mangeshkar hospital and research center (DMH) (Pune, India), Hospital for advanced medicine and surgery (HAMS) (Kathmandu, Nepal), Devdaha Medical college (DMC) (Butwal, Nepal), National Medical college (NMC) (Birgunj, Nepal), Osmania Medical college (OMC) (Hyderabad, India), Continental hospital and research center (CHRC) (Hyderabad, India) and Rajshree Medical Research Institute (RMRI) (Bareilly, India). The ethical approval for the study was granted from the institutional ethical committee of the respective hospitals.

The patients found positive for COVID-19 infection with the reverse transcriptase polymerase chain reaction (RT PCR) were included in the study. Patients of all genders and age between 14 and 60 years, and without any previous history of the smell and taste disorder, were included in the study. The patients with any previously known nasal pathology or any previously known allergies were excluded from the study. Patients with previous history of trauma, surgery or radiotherapy in the nasal cavity or oral cavity, along with the patients with any known neurological or psychiatric disease, were also excluded

from the study. The patients were described in the brief about the research article in their respective local languages. The participation into the study was only considered after taking the consent from the patients. The participants were assured regarding the confidentiality of the information provided.

The detailed history was obtained for all the COVID-19 positive patients included in the study. The demographic profile, age, gender, and the presence or absence of smell and taste disturbance were elaborated in detail. The disturbance of smell or taste was elaborated under four headings: normal smell or taste, parosmia or parageusia, hyposmia or hypogeusia and anosmia or ageusia. The normal smell or taste was defined as the no disturbance in the smell or taste, parosmia or parageusia was defined as the alteration of smell or taste sensation for the previously known substances, hyposmia or hypogeusia was defined as the decreased sensation of smell or taste, and anosmia or ageusia was defined as total absence of smell or taste, respectively. The patients with smell and taste disturbance symptoms were followed up after 2 months and then after 4 months with the telephonic interview. During the follow up, the patients were inquired about resolution of the smell and taste symptoms. The resolution was defined as the complete absence of the symptoms previously present. The decrease in symptom intensity was not considered as the resolution of the symptoms. The COVID-19 patients who were not having any smell or taste disturbances initially were also inquired, through telephonic interview, at 2 months follow up for the recent onset of smell and taste disturbance, if any. The patient who could not be reached during the follow up, were excluded from the study.

Results

A total of 188 COVID-19 positive patients were included in the study; IGMH (21), PAHS (23), HAMS (17), NMC (23), DMC (12), OMC (24), DMH (27), CHRC (18) and RMRI (23). The average age of the patients was 33.1 ± 1.7 years (21–43 years). There were 102/188 (54.2%) males and 86/188 (45.8%) female patients. The presenting features of the patients at the initial presentation is as shown in the Fig. 1. The duration of the smell and taste disturbance symptoms onset before the COVID-19 RT PCR positive test is as shown in Fig. 2.

The cough and sore throat were the most common clinical manifestations. The number of patients with smell and taste disturbance initially, and then after 2 months and 4 months are as shown in the Fig. 3.

There was improvement of anosmia by 81.6% after 2 months and by 97.4 after 4 months. Similarly, hyposmia improved by 63.6% and 95.6%, parosmia by 100% and

Fig. 1 Presenting features of COVID-19 positive patients

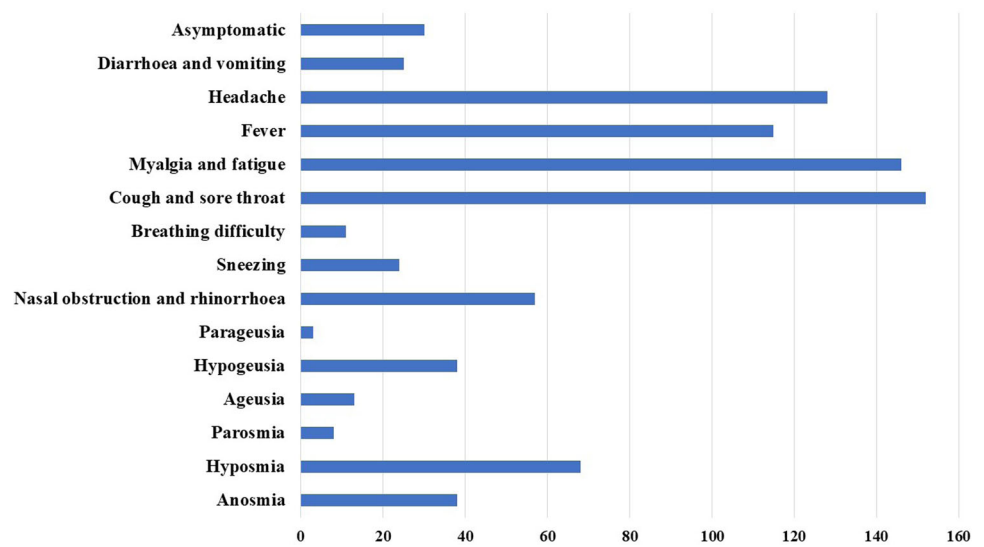


Fig. 2 Duration of smell and taste disturbance symptoms onset before the positive COVID-19 RT PCR test, along with the SD

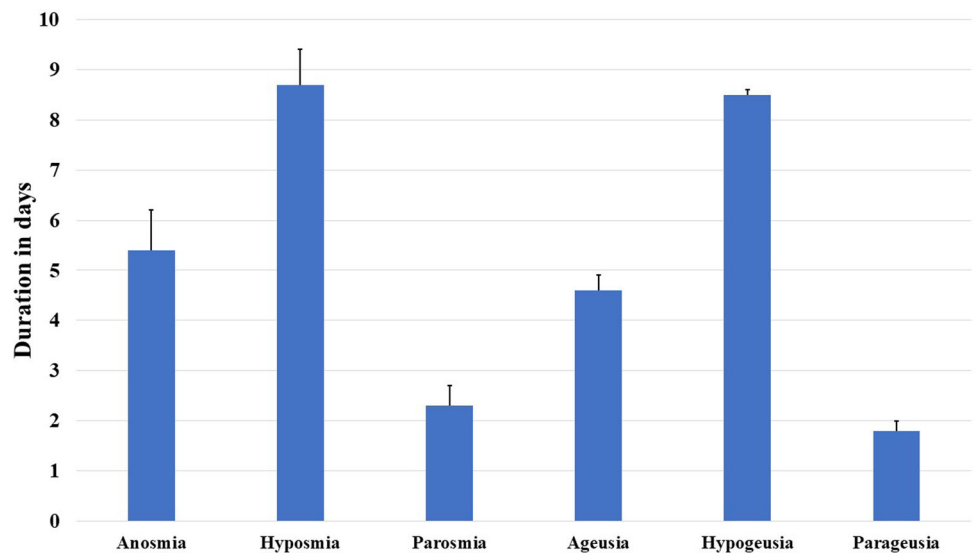
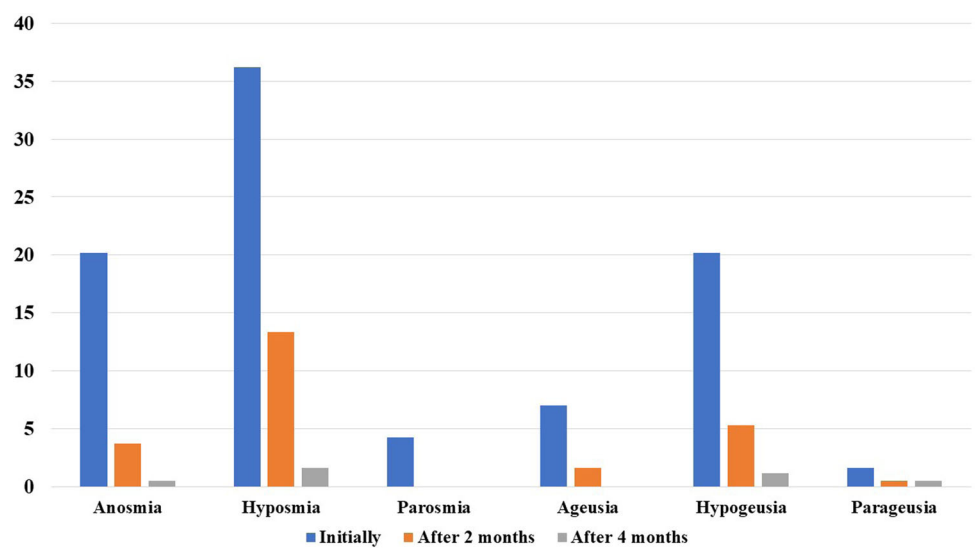


Fig. 3 COVID-19 positive patients with smell and taste disturbance initially, after 2 months and after 4 months follow up



100%, ageusia by 77% and 100%, hypogeusia by 73.7% and 94.8%, and parageusia by 66.7 and 66.7%, after 2 months and 4 months follow up, respectively. The 30 asymptomatic patients were also called after 2 months to check for emergence of any new symptoms. There were no new onset smell and taste disturbance symptoms in the asymptomatic patients. The asymptomatic patients were not called for the 4 months follow up.

Discussion

This study evaluates the COVID-19 positive patients for the presence of smell and taste disturbance and also follows them at 4 months to look for the resolution of these symptoms. The patients were inquired about the presence and absence of the smell and taste disturbance subjectively during the history taking procedure. This study did not incorporate any objective or psychophysical methods for evaluation of smell and test as described by some other studies in the literature [20, 27–29]. The mandate for adopting strict safety protocols for COVID-19 was the reason behind not being able to evaluate the smell and taste disturbance by any other methods. Similarly, the lower inclusion criteria for age was set at 15 years in order to avoid the bias from the subjective evaluation of the smell and taste with the younger childhood age group. The upper age limit was set at 60 years with an intention to avoid the age-related smell and taste disturbance, as described by studies in the literature [30–32]. Various other studies have also selected a similar age demographic for lower age [20, 33].

The study showed smell disturbance present in 60.6% of patients, (hyposmia 36.1%, anosmia 20.2%, and parosmia 4.2%) and taste disturbance in 28.7% of patients, (hypogeusia 20.2%, ageusia 6.9%, and parageusia 1.6%). There were no patients with isolated taste disturbance symptoms, however, 52.6% of the patients with smell disturbance had no taste disturbance. These findings can be inferred to the mechanism of loss of the taste caused by the loss of smell due to the retro nasal olfaction as mentioned by studies in the literature [34, 35]. In contrast to these findings, there are studies suggesting the etiology behind the loss of taste, due to the bonding between COVID-19 and receptor of sialic acid, resulting in degradation of taste particles [36, 37]. There was no study found in the literature that has described the loss of smell and taste sensation in COVID-19 infection separately with the underlying pathophysiology behind it.

This study further classifies the loss of smell and taste sensation into hyposmia, anosmia, and parosmia and hypogeusia, ageusia and parageusia, respectively. These all symptoms were defined previously and then clearly

described to the patients, so that the patients would be able to exactly figure out the problem in smell or taste. As this was a subjective evaluation, the preciseness during the history taking was felt to be essential. The loss of smell and taste was generally very vague explanation from the patients, and it did not include the parosmia or parageusia. Since there were significant number of COVID-19 patients with complain of parosmia or parageusia, these were also evaluated separately.

The study performed by Cazzola et al. [33] have demonstrated isolated smell dysfunction in 65.7%, isolated taste dysfunction in 25.4% (in contrast to the present study, where there were no patients with isolated taste dysfunction) and combined smell and taste dysfunction in 8.5%. They have not described pathophysiology behind the higher frequency of isolated smell and taste dysfunction. The present study was performed amongst the COVID-19 positive patients only, in contrast Izquierdo-Domínguez et al. [26] selected the control group also in their study in addition to the COVID-19 patients. The control group consisted of the patients with symptoms of flu but having 2 consecutively negative RT PCR test for COVID-19 infection. They demonstrated loss of taste in 53.7% with exclusive loss of taste in 5% and loss of smell in 52.2% with exclusive loss of smell in 6.5% of the COVID-19 patients, the incidence of smell and taste disturbance as demonstrated by them was double in the COVID-19 patients in comparison to the control group. Similarly, Lechian [21] demonstrated olfactory disturbance in 85.6% (anosmia 7.6%, hyposmia 20.4%, phantosmia 12.6% and parosmia 32.4%) and taste disturbance in 88.8%. Valentina Parma et al. [17] showed smell disturbance in 90.18% and taste disturbance in 91.44% with chemesthesia in 84.96%, the parosmia was present in 7.77% and phantosmia in 7.8%. Unlike the present study, Valentina Parma et al. [17] further sub divided loss of taste according to different types of taste sensation (sweet, salt, sour and bitter), with 11% having loss of single taste sensation and 48% having loss of 2 or more taste sensation. Subash Bhatta et al. [15] in their study of 600 patients with COVID-19 demonstrated smell disturbance in 63.6% and taste disturbance in 63.5% of the patients.

The present study demonstrated improvement in anosmia by 97.4%, hyposmia by 95.6%, parosmia by 100%, ageusia by 100%, hypogeusia by 94.8% and parageusia by 66.7% at 4 months follow up respectively. Vaira et al. [38] reported the presence of mild hyposmia and hypogeusia in 15.2% and 3.6% cases, respectively at the end of 60 days follow up. Izquierdo-Domínguez A et al. [26] reported recovery of smell and taste disturbance in 45.5% of COVID-19 patients, with 90.6% patients recovering in less than 2 weeks and 9.4% patients requiring more than 2 weeks for recovery. Yonghyun Lee et al. [39]

demonstrated the median time for recovery of anosmia and ageusia to be 7 days, similarly mean time of improvement of the anosmia was shown to be 7.2 days, by Rachel Kaye et al. [40]. Hence, it can be inferred that the smell and taste disturbance tend to recover with time in the patients with COVID-19 infection. However, there still is lack of firm evidence suggesting the exact natural course of improvement or persistence of these symptoms. The improvement in the olfactory and gustatory symptoms over the period of time in the patients following COVID-19 infection suggests some transient inflammatory response of the virus over the nasal and oral epithelial cells and the sensory receptors [38, 41]. The occurrence of the permanent damage to the olfactory and gustatory pathway however seems unlikely due to the COVID-19 infection [2, 5, 7, 16, 29]. The variation in the time duration and frequency of the olfactory and gustatory symptoms resolution for COVID-19 positive patients could not be explained.

There were no patients who complained of late onset smell and taste disturbance as demonstrated by the present study. Similarly, Vaira et al. [20], demonstrated no deterioration in smell and taste scores within the initial 10 days after symptoms onset. However, they did not inquire the asymptomatic COVID-19 positive patients for emergence of new olfactory and gustatory symptoms. The disturbance in taste and smell has been shown by various study as the early manifestations of the COVID-19 infection, and the evidence of these symptoms occurring late in the course of infection is very scarce [42, 43].

The present study, being a unique study of its kind, had few limitations such as a smaller number of sample size and the telephonic interview for follow up of the patients. The lack of the firm evidence on the smell and taste disturbance during the COVID-19 infection demands more future research regarding the smell and taste disturbance in COVID-19 infection. The present study recommends a research with larger sample size and with increased duration of in-person follow up for the better understanding of the subject matter.

Conclusion

It can be concluded from the present study that the olfactory and gustatory disturbance are one of the main early presentations of the COVID-19 infection. The temporary affect of the COVID-19 infection on the olfactory and gustatory pathway was also highlighted with more than 95% patients improving at the 4 months of follow up. The presence of olfactory and gustatory symptoms in this time of pandemic must be evaluated precisely, with the suspicion of COVID-19 infection. The smaller sample size and telephonic follow up interview were felt to be the

limitation of the study, hence a larger sample sized research with in person follow up has been suggested.

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Declarations

Conflict of interest There was no conflict of interest.

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