



A Review of the Importance of Atypical Otorhinolaryngological Symptoms in the Screening of COVID-19 Patients

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Abstract While the world is fighting against the newly emerged highly contagious coronavirus strain, new evolving ideas regarding symptoms and investigations are reverberating among health care professionals to combat the public health emergency. The study aims to review various presenting symptoms of COVID-19 especially the unusual one and analyzing the importance of olfactory and taste disturbances. 20 studies published recently in the last 1 year were analyzed and discussed for insights into the unusual presentation of symptoms in COVID-19 patients. All the findings and statements in this review regarding the pandemic are based on published information as listed in

the references. Most research articles initially focused on fever and respiratory symptoms. Later gastrointestinal symptoms were also taken into consideration. Only 5 studies from the literature have mentioned any smell and taste disturbances after SARS-CoV-2 infection to date. So changing trends can be seen in publications and recognizing these symptoms has important to timely combat this disease. The majority of corona virus-infected patients suffer from mild to moderate severity of the disease. Much hyped up symptoms of the respiratory tract may not be shown by a greater number of patients. So the need of the hour especially in developing and densely populated nations is to recognize unusual symptoms of COVID-19 especially its influence over smell and taste sensation to prevent any delay or misdiagnosis.

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Introduction

The epicentre of coronavirus is well known to be the seafood market of Wuhan, China when a sudden rise of atypical and fatal cases of pneumonia occurred in the province in Dec 2019. On Jan 7, a novel coronavirus was identified by the Chinese Center for Disease Control and Prevention (CDC) from the throat swab sample of a patient and was subsequently named 2019nCoV by WHO [1]. When the genomics of the 2019-novel was sequenced, it shared 79.5% of the genetic sequence of the SARS-CoV that caused the 2002–2003 pandemic [2] and the International Committee on Taxonomy of Viruses renamed the 2019-nCoV as SARS-CoV-2 [3]. The COVID-19 has been found to have higher levels of transmissibility and

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pandemic risk as the effective reproductive number (R_0) of COVID-19 (2.9) is estimated to be higher [4]. It was likely transmitted to humans through pangolins that are illegally sold in Chinese markets [5, 6].

The common clinical manifestations which give suspicion and further forms criteria for testing of coronavirus infection include fever (98%), cough (76%), shortness of breath (55%), muscle ache(44%) and rare symptoms includes confusion, headache, sore throat, rhinorrhea, chest pain, diarrhea, nausea, and vomiting [1]. WHO has issued case definitions for the suspect, probable and confirmed cases. But no importance is given to atypical otolaryngological manifestation of viral diseases such as hyposmia, anosmia, parosmia, and dysgeusia.

Pathophysiology suggests that viruses can invade the central nervous system through the olfactory neuro-epithelium and olfactory pathways [7]. Damage may occur at the level of the epithelium and receptor cells, or in central processing pathways such as the olfactory bulb [8]. Like other respiratory viruses, SARS-CoV-2 may enter the CNS through the hematogenous or retrograde neuronal route [9]. So olfactory dysfunction in the early stages of the disease, in asymptomatic carriers or one with mild to moderate disease, cannot be ignored. Although there is no evidence of direct involvement of taste buds but the retronasal air-flow occurs during swallowing. This retronasal route is vital to the production of flavor from swallowed foods-adding smell to both taste and touch [10].

The study aims to review various presenting symptoms of COVID-19 especially the atypical one and analyzing the importance of olfactory and taste disturbances.

Methods

The review study was done and the following steps were followed:

1. Identification of research articles based on clinical features and diagnosis,
2. Selection of relevant articles,
3. Data extraction and analysis based on atypical features documentation.

Search Methods for Identification of Studies

Electronic searches or online database used was—Pubmed (Medline), google scholar, medRxiv, BioRxiv and also in “JAMA”, “BMJ”, “Oxford“ and ”THE LANCET“ journals, WHO guidelines, ENTUK guidelines, AAO-HNS guidelines on coronavirus till date. The search terms used were like nCoV19/olfaction, coronavirus/olfaction, COVID-19, olfaction/ virology, nCoV (2019 novel

coronavirus)/olfaction, coronavirus/anosmia, coronavirus/clinical features. We searched relevant literature published to date regarding coronavirus and included all the significant scientific publications written in English in the review. News articles, reports, and Non-scientific commentary were excluded from the analysis.

Identification and Selection of Relevant Studies

Studies across the globe—clinical case study, review and systematic reviews analyzing the various clinical presentations of COVID-19 in human species (adults) published in the last 1 year (as from 10/4/2020) were identified and studied. Research over olfactory and taste dysfunction was done on priority and old literature was also searched to identify the studies considering these atypical features. 62 unique academic studies were identified after discussion among reviewers. Filtering of articles based on abstract and title was done and duplicates were removed. Only articles published in English were selected for this review.

Data Retrieved from Eligible Articles Analyzed

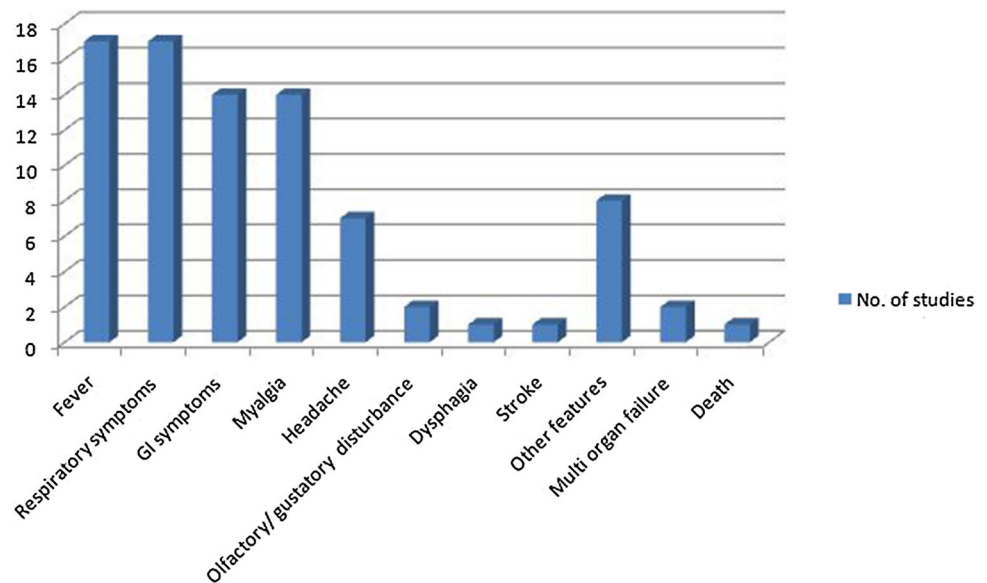
Clinical manifestations from each study were analyzed to see the changing trends or any new feature emergence. Only 5 studies from the literature have mentioned any smell and taste disturbances after SARS-CoV-2 infection till date [9, 11].

Results and Discussion

Among the 20 research articles included in the analysis, fever was found to be a dominant symptom in most of the articles [9, 11–29] (Fig. 1) as main stress was given on flu-like symptoms except for one study in which fever onset was absent and gastrointestinal symptoms were the initial presentation in coronavirus infected pneumonia patients [26]. These types of unusual presentations can spread the infection not only among the general population but also to healthcare workers sitting in outpatient or screening triage areas without proper protective equipment. But as gastrointestinal symptoms are at least included in diagnostic criteria of SARS-CoV-2 patients but symptoms like olfactory and taste dysfunction are neither assessed nor reported widely can go unnoticed and be a source of regret in near future.

Association of olfactory disturbance and viruses is an old concept. Post viral olfactory dysfunction (PVOD) is a common feature with the observed incidence of 18–45% [30]. Moreover, anosmia has been reported specifically in the course of severe acute respiratory syndrome (SARS) [31] and other coronaviruses [32] infections but it still

Fig. 1 Distribution of various presenting symptoms of COVID-19 in reviewed articles. Other features (sore throat, nasal congestion, facial pain, rhinorrhea)



holds a rare occurrence. Early indications are that the SARS-CoV-2 virus requires ACE-2 and TMPRSS2 to enter cells [33]. This functional receptor is present in multiple human organs, including type II pneumocytes of the respiratory system, enterocytes of the gastrointestinal system, nervous system and skeletal muscle [34]. Lately, RNA sequencing of olfactory neuroepithelium suggests not sensory neuron but sustentacular cells did express both *TMPRSS2* and *ACE2* and a known and critical role is played by sustentacular cells in the maintenance of the olfactory neuroepithelium integrity: if they die, the whole neuroepithelium disaggregates, leading to anosmia [35].

Furthermore, dysgeusia is a sequela of dysosmia, which will affect flavor perception adversely. This potential double effect on two chemosensory systems that share nothing at the periphery may suggest a more central alteration, involving, for example, direct infection of the brain by SARS-CoV-2 [35]. There has also been raised the probability of direct involvement of gustatory receptors by viruses in literature [36].

When clinical data is limited then we need to rewind and see what history has to teach. Akerlund et al. reported that intranasal administration of Coronavirus with the head maximally extended could increase the olfactory threshold in healthy volunteers years ago [37]. Another study in the past identified coronaviruses as the cause of PVOD clinically [38]. Now during the crisis, only the following researches were able to focus on chemosensory dysfunction.

A multicentre European study with a target population of 417 laboratory-confirmed COVID-19 found astonishingly high reporting of olfactory and taste dysfunction. The most common general symptoms consisted of cough, muscle pain, and anorexia. Face pain and nasal obstruction

were the most disease-related otolaryngological symptoms. 85.6% and 88.0% of patients reported olfactory and gustatory dysfunctions respectively. There was a significant association between both disorders ($p < 0.001$). Among them, 79.6% of patients were anosmic and 20.4% were hyposmic. Phantosmia and parosmia were concerned with 12.6% and 32.4% of patients during the disease course, respectively. Even it was found that olfactory dysfunction (OD) appeared before the other symptoms in 11.8% of cases. The olfactory and gustatory disorders were constant and unchanged over the days in 72.8% of patients [11].

A study by Mao et al. [9] found the neurological manifestations of coronavirus supported by presence ACE-2 receptors in the nervous system manifested hyposmia in 5.1% and hypogeusia in 5.6% population demonstrating injury to the peripheral nervous system. Another study that captured the data from 320 patients of Italy estimated that chemosensory dysfunction is present in 19.4%. Although research admits its shortcomings of not always investigating the olfactory and gustatory dysfunction in this emergency situation [27].

While Gane et al. have given a new direction to this dysosmias in COVID-19 infection by publishing a case report and labeling isolated sudden onset anosmia (ISOA) as the fourth important presenting syndrome and urged the international community to consider this manifestation in current management advice [28].

A hypothesis by Keyhan et al. suggests that dysosmia and dysgeusia can be attributed to olfactory nerve and trigeminal nerve damage caused by 2019-nCoV infection or excessive exposure to chemicals and disinfectants that are most commonly used by people due to viral epidemic [29].

Multiple anecdotal reports, both from SARS-CoV-2-infected patients and medical staff, suggest an association between viral infection and alterations of olfactory perception, ranging from mild perturbations to complete, although reversible anosmia [35]. Recently many doctors from China, Italy, Iran, Germany, France, and even British otolaryngological society also claim olfactory disturbances as new emerging symptoms of COVID-19. The explanation could be based on either mutation of virus strain itself [39] or earlier taste and smell sensation was not assessed and given any importance as most of the data collection was from indoor patients and not much importance is given to the unaware sensation of olfaction. People who are asymptomatic or with olfactory or taste dysfunction as the only symptom may be unknowingly spreading the virus in the community and never report to the hospital with any illness.

It is a known fact that if the power of odor is affected even then its difficult to recognize as concluded by a research paper that states the reduced applicability of selective attention combined with a theorized inhibitory mechanism and additional factors that jointly limit the place of odors in awareness [40]. So here comes the role of an objective test for olfaction like UPSIT, 12-odorant Sniffin-sticks or if smell in the standard olfactory test is unfamiliar then some indigenous method of familiar odors can be used such as 10-odourant Indian Smell Identification Test (INSIT) in India [41].

High resolution computed tomography (HRCT) chest is claimed to be a very sensitive test to evaluate pulmonary changes in coronavirus patients and CT images were reported to show the greatest severity approximately 10 days after the initial onset of symptoms [42]. If a diagnostic test can be given importance in COVID-19 patients without any symptoms of pneumonia, the mere inclusion of new-onset olfactory and taste disturbances in case definition criteria will not do any harm. New-onset dysosmia and dysgeusia in this epidemic season could serve as a warning sign and can make general public cautious of probable case and norms of self-quarantine can be followed.

Therefore, it is important to inform our ENT colleagues about paying attention as anosmia and dysgeusia can be the sole presenting feature that is manifested early in the course of the disease. Although these patients have a milder form of the disease, but they are potential carriers and can add to the burden of disease transmission. So we suggest that these symptoms should be considered highly susceptible to COVID-19 and should be included during the screening of patients.

Conclusion

In a developing country like India where many people attend pilgrimages in large number and some ignorant people hide travel history and do not disclose their contact with suspected or confirmed coronavirus patients, such atypical otolaryngological presentations of the disease should be recognized at the earliest. Silent carriers are to be captured and unknown vectors need to be reduced to break the chain of virus transmission and prevent community spread of this infection.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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