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COVID-19 ANOSMIA AND GUSTATORY SYMPTOMS AS A PROGNOSTIC FACTOR

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ABSTRACT

INTRODUCTION

Corona virus pandemic has affected millions of people all across the globe. Along with fever sore throat respiratory difficulty anosmia and ageusia are important symptoms being seen. It has been proposed that the neuroinvasive potential of the novel SARS-CoV-2 could be due to olfactory bulb invasion, conversely studies suggest it could be a good prognostic factor.

MATERIAL & METHODS

This study evaluates the prevalence of olfactory and gustatory dysfunction in patients with SARS CoV-2 infection and the severity and duration of altered taste and smell along with time taken for recovery. A total number of 300 patients that had tested positive for COVID 19 in Lady Hardinge Medical College and associated hospitals were assessed for presence and severity of olfactory and gustatory dysfunction.

Conclusion: the olfactory system is a interface of neuron and immune system where interaction between nervous and immune systems occur. The inflammation in Covid-19 may induce olfactive sensitive neurons degeneration and apoptosis as a protective mechanism. The reactions should be harmonic, because new olfactory sensory neurons (OSN) may help in the repair of nasal damaged tissue.

Keywords: Covid-19 Anosmia, Covid-19 Gustatory Symptoms, Covid-19 Prognostic Factor

INTRODUCTION

Coronavirus (CoV) causes a wide range of human respiratory tract infections varying from mild cold to severe respiratory distress syndrome. “Coronavirus” (CoV) is derived from the Latin word 'corona' meaning 'crown'.[1]

The start of COVID-19 epidemic can be traced back from the City of Wuhan, China towards the end of December 2019. This was when WHO declared COVID-19 outbreak as a pandemic. On February 12, 2020, (World Health Organization) WHO named the disease caused by the novel coronavirus as COVID-19.[2]

COVID-19 is the cause of a debilitating pandemic that has, till 24thMay , 2023 claimed over 766,895,075 confirmed cases. According to WHO, over 6,935,889 deaths have been reported globally.3 Covid-19 is caused by the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2). It is a single-stranded RNA virus which belongs to the family

Coronaviridae. Infection is mainly transmitted by patient's droplets and aerosols. The clinical presentation of COVID-19 ranges from the complete absence of symptoms to a severe acute respiratory distress syndrome, potentially leading to death. COVID-19 causes massive burden on the economic, social, and psychological status as well as a huge negative impact on the health-care system. In symptomatic patients, the most common presentation includes fever, myalgia and fatigue, associated with upper and lower respiratory tract involvement, resulting in nasal congestion, sore throat, anosmia, ageusia, dry cough and dyspnoea.[3] In addition to these respiratory symptoms, gastrointestinal, cardiovascular and neurological manifestations have also been described. The coronavirus outbreaks (SARS-CoV-2) is also the causative agent of olfactory impairment.[4] Olfactory dysfunction during or after upper respiratory tract infection (URTI) has been attributed to be caused by many families of virus. The chemosensory deficits are typically transient and can last somewhere from several days to about 2 weeks. Most symptoms resolve or significantly improve within 7–10 days.[5]

Many theories have been suggested as the possible cause of olfactory dysfunction in covid-19. It has been suggested that the SARS-CoV-2 causes obstructive inflammation of olfactory clefts. Another theory suggests that covid-19 targets and damages olfactory epithelium support and stem cells leading to olfactory disturbances in COVID-19 patients. Some coronaviruses have been shown to propagate via inhalation, from the nasal epithelium past the cribriform plate to infect the olfactory bulb and downstream areas like the piriform cortex and the brain stem.[6]

Thus, the aim of this study was to investigate the spontaneous evolution of olfactory and gustatory disorders in COVID-19 patients.Treatment strategies for Olfactory dysfunction secondary to Sino nasal diseases aim to resolve the specific underlying condition. Various medications and supplementations, like vitamin B12 supplementation, zinc supplementation etc. have been given to treat smell disorders, even though their exact role has not yet been established. Olfactory training (OT) aims to enhance olfactory recovery based on the neuronal plasticity of the olfactory system.[7] OT is recommended as conscious sniffing of at least four different odours, at least twice daily for several months. It has emerged as a simple and side-effect free treatment option for various causes of smell loss.[8]

The aim of conducting this study was to understand the pattern of olfactory and gustatory changes in COVID-19 positive patients and to find a pattern in their appearance, progression and reversal. Sometimes, these symptoms could be the only presenting complaint for covid. In some patients, the initial symptom was loss of smell even before they tested positive. This is what prompted the patients to get tested. Also, since the disease appeared very contagious, we designed it as a Questionnairebased study in which meaningful information and data can be obtained even by an interview on a telephone.

METHODOLOGY

A prospective among all positive patients was conducted in our institution from 1 june 2021 to June 2022. The study included admitted

patients in Lady Hardinge medical college as well as patients who were in home isolation after tested positive. A total 300 patients wereincluded.

All the patients between age 18-60 years who were tested positive for covid-19 either by RTPCR or CBNAAT were enrolled in the study, and patients having Previous history of smell disorder, Previous nasal surgery, Known psychiatric illness, Patients admitted in ICU and Patients having Sino-nasal tumours were excluded.

PROCEDURE

Informed written consent was obtained from each patient. Each patient were intervied with a standardised questionnaire regarding olfactory and gustatory dysfunction faced by them.

Patients who were in home isolation were called telephonically. Those patients who were admitted in the hospital in the covid isolation ward were interviewed after taking the all safety measures and wearing personal protective equipment.[9]

Patients were given a score between 0-10 on a visual analogue scale (VAS), wherein 0 means complete anosmia and a score of 10 means normal smell.[10]

Same score was used to address the change in taste perception as well. VAS score was noted on the day of onset of symptoms and again on the 7th day to compare the progression/ regression of symptoms.

Follow up was done telephonically after the patients were discharged from hospital till their symptoms improved. Interview was conducted according to the questionnaire (annexure 1).

For assessing the loss of smell, common household materials were used such as coconut oil,[11]coffee powder, cloves and Vicks. Regular Follow-up was done telephonically (including video calls wherever possible) on weekly basis. Patients were enquired about the recovery of smell and taste for maximum period of 4 months to check any residual or permanent loss of sensation.

RESULTS

Our of 300 patients,184(61.3%) of the patients were female and 116 (38.7%)were male.

In our study, prevalence of olfactory dysfunction was found to be more than gustatory dysfunction.

177 (59.0%) patients reported anosmia while 143 (47.7%) patients reported ageusia and 105 (35.0%) patients had both the symptoms of Anosmia as well as Ageusia.

The mean age of our study population was 31.65 ± 9.53 years The Majority of population in our study were below 30 years of age (173/300) attributing to 57.7%. This was followed by age group of 31-40 years (22.0%), then 41-50 years (14.3%) and only 6.0% patients were above the age of 51 years. It was found that 72(24%) patients had isolated smell loss and 38(12.7%) had isolated taste loss. The time taken for resolution of anosmia was 11.33 ± 3.48 days and that of ageusia was 10.70 ± 5.45 days. It was observed that 97.17% of patients of anosmia and 98.6% of the patients of ageusia were recovered completely within 15 days.

In our study, the results supported the fact that, olfactory and gustatory dysfunction both are prevalent in mild to moderate Covid-19 infection. In mild or moderate infection, the only symptom was fever, malaise and OGD for a short period. In these patients, VAS score was nearly around 5. While in the severe cases, patients had more complaints such as longer duration of fever, malaise and OGD, along with sore throat and sometimes shortness of breath. These patients had VAS score towards the lower side. It was seen that time taken for recovery was also more in such patients.

Majority of the patients recovered within 15 days of illness. All the patients recovered within 60 days with no permanent or residual loss of either sensation. It was found that during recovery, smell sensation started to resolve faster than taste. During the recovery phase of anosmia, smell of cloves and coconut oil recovered faster than smell of coffee. For the gustatory disorders the sweet taste recovered first, followed by salt and sour. The flavour sensation was last to recover.

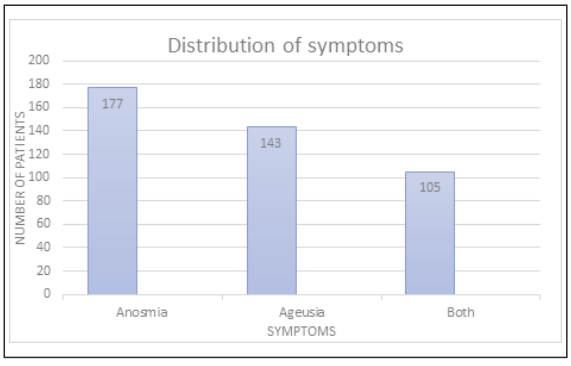
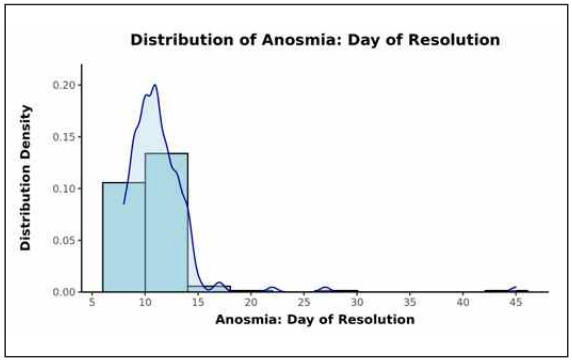


FIGURE 1-SHOWING THE DISTRIBUTUION OF SY

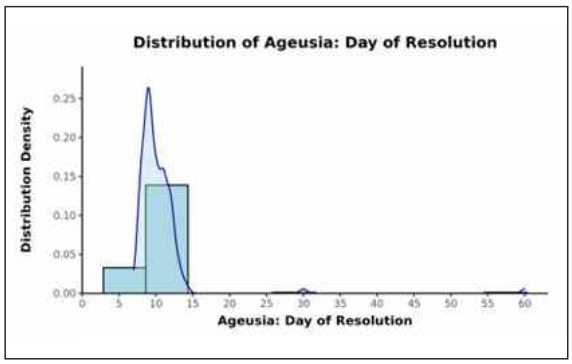
The mean (SD) of Anosmia: Day of Resolution was 11.33 (3.48). The median (IQR) of Anosmia: Day of Resolution was 11.00 (10-12). The Anosmia: Day of Resolution ranged from 8-45

FIGURE 2- RESOLUTION OF ANOSMIA



The mean (SD) of Ageusia: Day of Resolution was 10.42 (4.76). The median (IQR) of Ageusia: Day of Resolution was 10.00 (9-11). The Ageusia: Day of Resolution ranged from 7– 60

FIGURE-3: RESOLUTION OF AGEUSIA



DISCUSSION

Covid-19 outbreak is a pandemic that has affected people all over the world. Its wide clinical spectrum ranges from no symptoms to multi organ dysfunction. The classical covid-19 symptoms comprise of fever, cough, sore throat, malaise, arthralgia along with chemosensory dysfunctions which include smell and taste dysfunction (12). It has been found that the virus binds to ACE receptors in nasal epithelium causing damage to neural receptors which are responsible for anosmia and dysgeusia.

Anosmia possible mechanism

Chronic olfactory dysfunction is most commonly caused by Acute viral upper respiratory tract infections and are responsible for olfactory disorders. The causative pathogens are usually viruses leading to common cold or influenza that manifest themselves without rhino-sinusitis. Approximately 20% of common cold cases can be accounted for by a type of coronavirus (non-SARS) and up 30% by a type of rhinovirus. Other viruses are adenovirus, respiratory syncytial virus (RSV) or human parainfluenza virus (13)

The virus can affect the sense of smell by mainly two mechanisms of action. First is via the physical effect: Through local inflammation. The lining of nasal passages becomes swollen, mucosa gets lined by a film of nasal discharge. This causes a hinderance to the odorant molecules to reach the corresponding receptors and bind to them, resulting in reduced ability to smell. The airway obstruction causes reduction in the airflow and the odorant molecules enter the cavity in insufficient quantities. This mechanism is seen in other coronavirus infections or in the common cold, but not in SARSCoV2.

In a study by Åkerlund et al (14) post-viral olfactory disorder developed after healthy human subjects with no previous olfactory deficiencies were inoculated with coronavirus (229E) which is known to induce the common cold. Olfactory testing 4 days after inoculation showed a reduction in olfactory function in the patients who developed cold. The outcome correlated with increased nasal obstruction as measured by airflow and assessment of nasal discharge. In this study, olfactory dysfunction was measured during acute phase of infection. This may have resulted due to swelling of the nasal mucosa/airflow obstruction, virus induced damage to the olfactory epithelium or both.

Another possible mechanism involves the virus directly damaging the olfactory epithelium and peripheral nerves and cells. The exact location of this damage in post-upper respiratory tract infections is not clearly known till now. It has been disputed if the olfactory receptor neurons (not expressing ACE2) themselves or other cells like supporting cells are damaged in the pathological process (16). The viruses can also cause olfactory dysfunction by penetrating into the CNS. This can cause damage to regions that are components of the olfactory system, such as the olfactory bulb, the piriform cortex, amygdala, the olfactory tubercle and more. In a rodent study (17), Influenza A virus was administered into mice intra-nasally. This resulted in some changes in the olfactory receptor neurons (ORNs). The coronavirus was detected in the brain and the CSF by travelling trans-neuronally (18). It has been seen that when anosmia does not occur with the symptoms of rhinitis, it often persists long after. In such cases, the possibility of neurological damage cannot be ruled out. In our study, during the interviews, many patients shared their prior experience with taste and smell changes during viral infections (common cold and URI). That is why, many patients were very apprehensive regarding possibility of total loss of smell. They were very anxious whether the symptoms would reverse or not.

Degree of anosmia seen in omicron variant

Since the advent of the Omicron variant, a lower

incidence of hyposmia has been reported in infected people. However, only few studies are available as for now. a study from Norway had reported only 12% alterations in smell as compared to 38% in the other variants.19 This lower incidence of the new variant may be attributed to its virus-host interaction, host body's response to infection. The role of previously acquired immunity, either by previous infection or vaccination can also be a factor.

The Omicron variant presents a series of mutations in the spike protein that affect its affinity for the ACE2 receptor. This generates a less specialized cell tropism, which results in a lower capacity for cell fusion. This new variant appears to be less pathogenic. Hence, it might generate a lower viral load and less local or systemic inflammation. This may be due to previous immunity by vaccines or past infections. It was concluded that less direct damage and inflammation due to virus was due to its characteristics or previous immunity. This could explain less damage to the olfactory epithelium and/or central nervous system (76)

Covid-19-associated diarrhoea

GIT dysfunction and diarrhoea along with respiratory symptoms are common in members of the coronavirus family.20 A retrospective study evaluated the gastrointestinal symptoms of patients with SARS.21 Nearly, 20.3% of patients presented with watery diarrhoea, without blood or mucus as the disease presentation.

In the SARS-CoV-2 pandemic, most of the attention is still exclusively focused on the respiratory symptoms of the disease. However, it is important to consider that the number of COVID-19 patients experiencing diarrhoea is significant and cannot be overlooked. There is high variability among published studies in the percentage of patients with diarrhoea, ranging from 2% to 50% of cases, An overall diarrhoea rate of about 10% is seen in COVID19 patients (22). This value is lower than the percentage of diarrhoea reported with other coronaviruses (23). It is also possible that the available data may underestimate the burden of diarrhoea associated with COVID-19 (24).

Time taken for onset and recovery

In the studies reviewed, it was difficult to establish a relationship between the time of onset of smell and/or taste changes in patients with COVID-19. This was because of the extent to which they differ from one another. Some of the authors indicate that these changes may precede the development of other common symptoms of the disease, such as fever, shortness of breath, dry cough and fatigue. (25,26,27).

The results of the studies also diverged regarding the duration of symptoms of loss of smell and/or taste. It ranged from five days to four weeks, with an average of one to two weeks for recovery. In addition, a case-control study28 found that the average duration of smell and/or taste disorders was 7.5 ± 3.2 days. Around 40% of individuals recovered completely 7.4 ± 2.3 days after the onset of symptoms, without having to seek hospital care.

A review of various studies across the world was done. It was concluded that, COVID-19 associated loss of smell and taste onset was 4 to 5 days after other symptoms. These symptoms lasted for7 to 14 days. These findings however

varied in different populations (29).

Positive corelation ($p<0.05$) has been found between anosmia and fever, Shortness of breath, sore throat and malaise in our study.

The follow up of our patients was done till 4 months after being tested positive. Complete recovery was seen in the majority of patients with anosmia, ageusia and both within 15 days. 3 patients had persistent symptoms, however their anosmia got resolved in 45 days and ageusia got resolved in 60 days. There was no permanent loss of smell and taste seen in any of these patients.

One of the studies showed the prevalence of olfactory dysfunction in European population as high as 85.6%.8 Another study (30) reported that, it was found around 47%. In the same study, it was observed that diarrhoea occurred in more than 50% of patients. Upon review of literature, the occurrence of diarrhoea is otherwise reported as less than 20% (86) Thus, the frequency of diarrhoea seems to be high in patients with anosmia.

In a similar study,31 it was found that around 70% of the patients had both loss of smell and loss of taste before testing of COVID-19. It suggested that both the symptoms had a higher positive predictive value for COVID-19. It means if both loss of smell and loss of taste are present in any patient, he/she is more likely to be affected with COVID-19. In the study, these symptoms lasted for around 7–9 days and showed complete recovery in 97% of patients (87).

A study conducted Kandakure VT at al (32). concluded that viral load is a key factor to determine if covid patients were more susceptible to long term anosmia. When SARS-CoV-2 invades cells, it causes inflammation that knocks out sense of smell. Hence, the recovery time is related to how long the surrounding cells take time to heal depending on supply of stem cell within nose lining (33).

Anxiety and depression in covid-19 patients

Chemosensory dysfunction, outside of the context of COVID-19, has been previously shown to be associated with decreased quality of life as well as anxiety and depression (89). It has been described that depression may also lead to OD (34). However, with COVID-19 pandemic, potential lethality of SARS-CoV-2 infection was recognised publicly. It was reported that the severities of classic and worrisome symptoms of COVID-19—such as fever, cough or SOB were not associated with emotional disturbance while chemosensory dysfunction was (35).

One element of COVID-19, that had lasting consequences was the emotional disturbance of affected patients (36). Diseases that are inherently dangerous or have severe consequences are great source of depression and anxiety in affected patients. In a study, the disturbances in emotional health due to COVID-19 were found. This study investigated the burden of depressed mood and anxiety in COVID-19 patients in relation to their symptoms. They affirmed that depressed mood and anxiety were positively associated with symptoms of decreased sense of smell and taste. Surprisingly, depressed mood and anxiety were not associated with symptoms such as fever, cough, or shortness of breath.

Additionally, they found that older age and pre-COVID levels of depressed mood and anxiety were positively associated with greater depressed mood and anxiety during COVID-19.

Previous animal studies37 of the closely related SARSCoV-1 demonstrated neurotropism of the virus with infection of the olfactory tract. That resulted in the spread of infection into the central nervous system (CNS). More recently, CNS manifestations of COVID-19 have been described as agitation, confusion and seizures (38). The direct effect of COVID-19 on the CNS has been confirmed with the detection of SARS-CoV-2 in cerebrospinal fluid. A Trans-cribriform mechanism for CNS invasion via the olfactory neurons has been proposed (40). CNS manifestations of COVID-19 like depressed mood and anxiety are associated with decreased senses of smell and taste. Hence, it raised the possibility of emotional disturbances as a possible CNS manifestation of COVID-19. That is why steps should be taken to increase awareness regarding these symptoms and their reversibility. Also, appropriate help and guidance should be provided to these patients to avoid unwanted stress or even mishaps.

In this study, we developed the questions to address the onset progression and recovery pattern of smell and taste loss. The most important finding to emerge from the analysis of our data is that anosmia and ageusia related to corona virus infection was reversible.

Covid-19 anosmia and gustatory symptoms as a prognostic factor

OGD is an important symptom in COVID-19. It is a frequent symptom and also an important infection and infective marker. Although it could be possible that anosmia is more frequent in mild disease. In a study, this dysfunction was found more frequent in younger patients as compare to those without this disorder. Although, it was not related to any other factor, it seemed clear that the presence of anosmia would imply a more benign prognosis of the disease.

CONCLUSION

Indeed, the olfactory system is a interface of neuron and immune system where interaction between nervous and immune systems occure. It is well known fact that virus or environmental toxicants can induce inflammatory responses, including infiltration of immune cells and production of cytokines. This inflammation may induce olfactive sensitive neurons degeneration and apoptosis as a protective mechanism. The health of the CNS is likely to be influenced by the immune status of the olfactory system. The reactions should be harmonic, because new olfactory sensory neurons (OSN) may help in the repair of nasal damaged tissue. On the other hand, immune cells in the olfactory mucosa regulate the depletion of old OSN and generation of new OSN (41) This situation may explain that patients with an immune dysfunction might have less OGD, because could have lower immune reaction and therefore have lesser epithelial and olfactory cells degeneration.

LIMITATIONS

1. Limited number of patients as during third wave, these symptoms were less common.
2. Exclusion of patients with severe disease who got intubated and admitted in ICU.
3. Higher proportion of female participants.
4. Lack of objective testing to quantify the

loss of taste and smell.

5. Recall bias.

DECLARATION

Ethics approval and consent to participate: The study was approved by Organizational Ethics committee.

Conflict of Interests- The authors declares that there are no conflicts of interest.

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