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Review Article

The Reduced Frequency of Olfactory Dysfunction in Patients with Omicron SARS-CoV-2 Variant Infection

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Abstract

Anosmia is a prevalent symptom of COVID-19 and has become almost synonymous with COVID-19 infection. It is known to emerge as either the sole symptom of the infection or at least prior to other symptoms. Surprisingly, it has been shown that the phenomenon is much less common in the COVID-19 Omicron variant infection compared with other previous variants of the disease. Our review explores several theories explaining the reduced frequency of olfactory dysfunction among the Omicron variant infected patients. Regarding viral host cell invasion, the process may occur by two distinct routes involving either the plasma cell membrane fusion or by viral uptake via endocytosis. The Omicron variant prefers using the endosomal pathway, which is less dependent on transmembrane serine protease 2 (TMPRSS2) activation. Therefore, the Omicron penetration of the olfactory epithelium, which expresses high levels of TMPRSS2, is less efficient and leads to the reduced frequency of anosmia. Moreover, the less-dependent TMPRSS2 pathway of the Omicron variant diminishes its ability to produce syncytia arrangement, a phenomenon associated with more severe symptoms. In addition, the new mutations make the Omicron variant more hydrophobic and alkaline, which may reduce its ability to appropriately penetrate the mucosal layer. Furthermore, there is evidence to show that the Omicron variant produces a milder inflammatory response and less of a cytokine storm. In conclusion, anosmia is much less common symptom within the Omicron variant, however, the expeditious spread of the Omicron can still lead to a significant number of patients with olfactory dysfunction.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China, in December 2019 [1]. Since then, the virus has spread, with the World Health Organization (WHO) declaring the COVID-19 a worldwide pandemic on March 11th, 2020. Extensive international efforts have been done in an attempt to produce a viable vaccine for the disease [2]. Nevertheless, despite the current vaccinations, the pandemic continues to cause devastation with more than 6.3 million casualties so far.

One of the most significant explanations for the failure to control the pandemic despite the emergence of the vaccines are the viral adaptive mutations in its genome. The different variants of the virus may evade the immune system even among vaccinated and previously infected patients [3]. Due to genomic mutations, the newer strains could potentially have entirely different characteristics in comparison with the previous stains, including transmissibility, virulence and symptomatology.

The current Coronavirus variant of concern is the Omicron (B.1.1.529) strain, first reported in South Africa in November 2021 [4]. Mohsin et al. [5], presented several studies in their literature review, which demonstrated a faster spreading of the Omicron variants than other variants, particularly among both vaccinated and boosted individuals [6]. On the other hand, all the studies consistently reported a significantly decreased risk of severe disease. Thus, the Omicron variant may have a lower risk of hospital admissions, ICU hospitalizations, mechanical ventilation as well as shorter duration of hospitalization and lower mortality rates (5,7).

Smelling alterations

Covid-19 has been characterized by a wide spectrum of symptoms, particularly fever, and cough, shortness of breath and myalgia. Olfactory dysfunction (OD), including anosmia and hyposmia, is another prominent symptom that has been described in different COVID-19 variants (8).

In a meta-analysis with 23,533 patients diagnosed with COVID-19, the reported prevalence of anosmia was 38% (9). In an Iranians study, with a cohort of 10,069 patients, the rate of anosmia was even higher with 76.24% of patients reporting a sudden onset of OD and 60.90% reporting persistent anosmia from the beginning of the pandemic (10). Interestingly, it has also been reported that many patients present with anosmia as their sole symptom or at least as the symptom presenting prior to others (11). Accordingly, there are attempts to identify

or confirm infected patients based on self-reported changes in olfaction (8,12).

Surprisingly, the reported prevalence of OD in the Omicron variant is lower. Based on 12 reports of 190,778 patients, Butowt et al. (13) calculated a pooled weighted estimate of olfactory dysfunction of 13%, which is a significantly lower rate than in the aforementioned reports. In another study, the authors conducted a comparison between 338 patients infected during the Omicron prevalent period to 441 infected patients in the comparator period, in which other strains were more prevalent. They found out that the prevalence of self-reported OD during the Omicron period was significantly lower from the prevalence reported in the comparator previously periods (32.5% vs 66.9% respectively) (14).

In a novel Brazilian retrospective study, the authors examined 6,053 patients with confirmed mild COVID-19 cases and compared the prevalence of anosmia between different periods with different variants including original lineages (B.1.1.28 and B.1.1.33), Gamma, Delta and Omicron periods. A lineage was considered predominant when it was detected in more than 90% of the COVID-19 infected patients during a specific period. In their cohort, 2,650 participants reported OD, with lowering odds of anosmia for patients infected during Omicron period compared to the original lineage period (5.8% vs. 52.6% respectively, adjusted OR 0.07, PV<0.001). Even after additional adjustment for vaccination status, the OD during the Omicron period was significantly lower in comparison with the Gamma period.

Our study aimed to clarify the reasoning for Omicron variant sparing of OD compared to previous variants.

Pathophysiology of olfactory dysfunction

Despite numerous studies, the exact mechanism of COVID-19-induced anosmia remains unclear. Generally, olfactory problems may be classified as either a conductive or sensorineural impairments. In conductive impairments, some pathologies such as nasal polyps and rhinosinusitis, may block inspired odorants from reaching the olfactory epithelium in the nasal cavity. On the other hand, in sensorineural impairments, the dysfunction is attributed to an injury of the olfactory receptor neurons or other sensory structures (15). It is reasonable to assume that conductive loss of COVID-19 infected patients does not play a significant role in patients anosmia since the prevalence of obstruction is quite low in COVID-19 infection (14,16).

The olfactory mucosa is composed of the olfactory epithelium and the lamina propria. Different types of cells are found in the olfactory epithelium, including olfactory sensory neurons, sustentacular cells, and basal stem cells. Olfactory sensory neurons are the neuronal receptor cells responsible for the smelling function. Sustentacular cells are associated with structural support and participate in phagocytosis of dead neurons (17), odorant transformation and metabolizing enzymes (18). Basal cells of the olfactory epithelium act as stem cells and can generate new sensory neurons and sustentacular cells throughout life (19).

In a literature review, Meng et al (20,21) summarized various well-known theories for COVID-19-induced anosmia. The angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane serine protease 2 (TMPRSS2) have been described as key factors responsible for the invasion and fusion of the virion to the host cell (22). Hence, cells with high quantities of these receptors are more susceptible to viral infection.

Brann et al. (23) found that ACE2 receptors are not expressed in olfactory sensory neurons and instead, the receptors were observed in sustentacular and in basal cells of the epithelium. It is possible that damage to sustentacular cells may lead to impaired olfactory function even without viral transferring to the sensory neurons. The damage is due to either their role in detoxification of airborne pollutants, their capability of supplying metabolites, or their involvement in the signal transduction of smell (24). Indeed, in studies using hamster models, there is evidence to suggest viral accumulation specifically in sustentacular cells only (25). However, there is no evidence regarding infection of basal stem cells. If the basal cell are indeed damaged, it may explain why a small portion of COVID-19 patients suffer from persistent long-term anosmia (24,26) as the basal cells are responsible for regeneration of new neurons and sustentacular cells.

Nevertheless, Zazhytska et al. (16) claimed that in comparison with hamster models, the viral load in human olfactory epithelium is lower due to infrequent sustentacular cells infection. Therefore, they suggested another explanation for COVID-19-induced anosmia involving the ability to impair the olfactory function without infection of the epithelium and even the sustentacular cells. Thus, the virus causes a dramatic reorganization of the neuronal nuclear architecture which results in modifying of genomic compartments harboring olfactory receptor genes including their signaling pathway.

Moreover, it is well known that the spike protein D614G mutation among COVID-19 variants may intensify the infection of sustentacular cells by enhancing membrane fusion. Accordingly, COVID-19 variants with D614G mutation may have a higher prevalence of anosmia (27).

Another important possible mechanism involves the presence of a local or systemic inflammatory process. Several different cytokines such as TNF-α and IL-6 could impair the olfactory function, either by interfering with the cell-signaling process, or by direct destruction of the olfactory epithelium. Indeed, elevated levels of TNF-α were found in the olfactory epithelium of infected patients (28), and a correlation was discovered between IL-6 blood levels to dysosmia (change in the smelling ability) status (29).

A less popular explanation relates to the adaptive response of locally decreased nasopharyngeal zinc. Zinc deficiencies result in a lower ACE-2 expression, and thereby decrease the invasion of the virions to the host cell. The phenomenon was exhibited in other pathogens causing respiratory illness (30).

The Omicron variant sparing of the olfactory function

To understand the ranges of anosmia prevalence in Omicron infections compared to other variants, we should properly evaluate the above mechanisms described for COVID-19-induced anosmia. It may be explained by various mechanisms such as host cell entry, inflammatory process and vaccination status.

Different mechanisms of viral host cell invasion

It is critical to mention that in comparison with other variants, the Omicron variant carries the D614G mutation as well as identical affinity to the ACE2 receptor (13). Nevertheless, in hamster models, the Omicron infection caused only mild pathological changes of the olfactory epithelium in comparison with previous identified variants such as SARS-CoV-2 614G, Gamma and Delta (31). Moreover, Bentley et al. (32) found that viral loads in nasal tissue and nasopharyngeal swabs were significantly lower in Omicron-infected mice than Pango B lineage or Delta variants.

Viral membrane fusion, the process by which enveloped viruses enter host cells, may occur by 2 distinct routes - either at the plasma cell membrane or in endosomes upon virus uptake by endocytosis (33). In general, COVID-19 variants enter host cells by surface membrane fusion involving the TMPRSS2, mentioned above. However, the Omicron variant prefers using the endosomal pathway, which is less dependent on TMPRSS2 activation. Hence, the Omicron invasion of sustentacular cells, which express high rate of TMPRSS2, is less efficient, and therefore probably leads to the reduced frequency of anosmia (13).

In a literature review, Rodriguez-Selliva et al. (26) clarified that the Omicron variant has a broader spectrum of target cells and a more rapid replication compared to other variants, due to its ability to invade host cells by both mechanisms. Nonetheless, the less-dependent TMPRSS2 activation course diminishes the affinity for syncytia arrangement. A syncytium is a multinucleate cell resulting from multiple cell fusions of uninuclear cells (34) and can form due to infection with certain types of viruses, such as HSV-1, HIV, RSV and SARS-CoV-2. The phenomenon has been associated with symptoms severity in animal model and accordingly, variants without syncytia arrangement would result in milder disease.

Another theory regarding the viral invasion of its host cell is the penetration of the mucus layer, which protects the olfactory epithelium from toxins and pathogens. It seems that hydrophilic and acidic proteins are more soluble and may easily go through the mucus layer. However, the mutations of the Omicron variant generate more hydrophobic and alkaline proteins, with lower solubility characteristics and consequently cause decreased epithelium infection (13).

Inflammatory processes of different COVID-19 variants

It is possible that the Omicron variant produces only a milder inflammatory response and less of cytokine storm (26). Bauer et al. (35), examined the difference of neuroinvasion and neuroinflammation among SARS-COV-2 variants using the hamster model. They demonstrated that the hamsters infected with Omicron variant showed less inflammatory lesions within the olfactory mucosa compared to Delta and D614G variants. Yet, there is not a satisfactory explanation as to why the Omicron variant induces a decreased inflammatory response.

Availability of Vaccines in different variant periods

Boscolo-Rizzo et al. (14), examined the clinical presentation in patients infected during the Omicron period compared to previous periods. Based on the study results, they concluded that the prevalence of the smell and taste dysfunction was lower significantly in the Omicron period. One of the possible explanations for the difference is the vaccination status of the patients in the Omicron period, which may reduce symptoms severity. For various reasons, this suggestion was rejected.

In their cohort study, no difference in anosmia prevalence was found depending on the vaccination status. Second, the vaccine protection is induced mainly by the generation of IgG antibodies and cytotoxic T cells, which less effective than IgA at producing mucosal immune response. Third, the Omicron period emerged in the post vaccination era and as mentioned previously, the vaccine was less effective against this variant. So, it is unreasonable to assume that the vaccine would protect only from the olfactory function and not from other symptoms. Finally, in the Delta variant period, olfactory changes were one of the most frequent symptoms, even among vaccinated patients. In summary, it seems that the vaccination status does not play a significant role in preventing the olfactory impairments among Omicron infected patients.

CONCLUSION

Anosmia is a characteristic and prevalent symptom of COVID-19 which emerges as a sole symptom or prior to others. Surprisingly, it is much less common within the Omicron variant and in this review, several theories are suggested for the phenomenon. Additional studies are required in order to confirm the aforementioned theoretical explanations.

The absence of the unique symptom may make the distinction of COVID-19 from other viral diseases more difficult and thus potentially delay the diagnosis and the isolation of the infected patients.

The reduced prevalence of OD in the Omicron period should not lead to decrease in the intensive efforts and research regarding COVID-19-induced anosmia. Even in the Omicron period, the reported prevalence of olfactory problems was approximately 10-30%, with numerous affected patients. Moreover, the increased spread of the Omicron variant can still lead to a significant number of patients with olfactory problems (14).

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