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REVIEW ARTICLE

Olfactory Dysfunction: A Diagnostic Symptom of COVID-19

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ABSTRACT

Besides the common respiratory symptoms or viral pneumonia, COVID-19 is also presented with different neurological symptoms. Olfactory dysfunction (OD) or impairment of the sense of smell is one of the common neurological symptoms being reported in infection caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The severity varies from anosmia to microsmia or hyposmia. OD could have a potential early screening and diagnostic value besides other neurological and common respiratory symptoms. In our descriptive concise review, we aimed to elicit the manifestation of olfactory dysfunction as an early predictor of SARS-CoV-2 infection. We are also aiming to establish, OD as a quick and reliable assessment tool of COVID-19 risk, among the healthcare workers and contact tracers, which can justify self-quarantine of the person as well as recommendation for testing on a priority basis. We have also focused on, any effect to produce this symptom by the drug used for treatment in COVID-19, and if the old age of the patient showing any extra influence to develop OD in COVID-19.

INTRODUCTION

Drugs Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a novel member of the coronavirus family, responsible for devastating pandemic Corona Virus Disease 2019 (COVID-19) worldwide. The first case was officially claimed to be found in Wuhan, China on 18 December 2019, which rapidly spread all over the world. The world has seen 1.082 million deaths and 37.802 million positive

cases until 12 October 2020. Many countries have started experiencing a second wave of the pandemic.

In the beginning, according to the World Health Organization (WHO), tiredness, fever, cough and breathing difficulty, were the presenting symptoms in COVID-19 patients (Moein et al., 2020). Almost every organ of the human body could be involved with the damaging effects of COVID-19 besides the most common respiratory symptoms (White-Dzuro et al., 2021). The percentage of the patients who recover spontaneously is 85% to 95% while 5% to 14% may become seriously ill (Grasselli et al., 2020; Eastin & Eastin, 2020; Richardson et al., 2020).

Sudden loss of smell and taste were reported as cardinal signs in many publications (Paderno et al., 2020; Giacomelli et al., 2020; Yan et al., 2020; Lechien et al., 2020; Moein et al., 2020; Hornuss et al., 2020; Parma et al., 2020). These potential specific symptoms of COVID-19 patients were reported even in otherwise asymptomatic patients (Menni et al., 2020; Walsh-Messinger et al., 2020; Hopkins et al., 2020).

Pathophysiology of Olfactory Dysfunction

The pathophysiology of olfactory dysfunction (OD) is still hypothetical even though it is an established fact that olfactory neuroepithelium can be damaged by any viral infection (Doty, 2008). This disruption may cause inflammatory changes which affect the function of olfactory receptor neuron. Later it may cause damage to the olfactory receptor neuron, and/ or impair subsequent neurogenesis. This is how the cause of temporary OD of different severity level and/ or duration, can be explained (Netland et al., 2008).

It is also known that several viruses can enter the brain through olfactory neuroepithelium by cellular and pericellular transport mechanisms (Doty, 2008). The older work regarding the intracranial entry of SARS-CoV in transgenic animal models suggested that the olfactory bulb could be the entry point (Netland et al., 2008). So, it can be speculated that the intracranial penetration of SARS-CoV-2 is possible with downstream effects on the olfactory region as well as non-olfactory regions of the brain, by which the olfactory function may be adversely affected.

Most of the study reported that SARS-CoV-2 can reach the central nervous system from the bloodstream or olfactory pathway by binding the angiotensin-converting enzyme 2 (ACE2) receptor and the spike protein transmembrane protease serine 2 (TMPRSS2) (Brouwer et al., 2020). The SARS-CoV-2 enters the nasal epithelial cell by directly binding with ACE2 protein in the cell wall (Qi et al., 2020). Olfactory receptor cells neither have expressions of the ACE2 nor TMPRSS2. Possibly the involvement of another gene, most likely the epithelial sustentacular cell and stem cells are responsible for SARS-CoV-2 (Brann et al., 2020). So, the olfactory receptors may be indirectly damaged by the uptake of SARS-CoV2 into nasal epithelial cells. At this point, a rapid immune response in the host may be initiated by the olfactory receptor neurons and the olfactory dysfunction may be manifested (Butowt & Bilinska, 2020).

Regarding regeneration of olfactory neuroepithelium, it is suggested that there is a considerable propensity, if the stem cell layer is not significantly damaged, spontaneous improvement of OD is observed over time (Chang & Glezer, 2018; Choi & Goldstein, 2018; Joiner et al., 2015; London et al., 2008).

OD as Diagnostic Symptom of COVID-19

About 37.802 million people all over the world got infected until 12 October 2020, with the novel SARS-CoV-2 virus since the first case was officially announced in Wuhan, China on 18 December 2019. The total number of deaths reported to date is 1.082 million.

Scientists all over the world are trying their best to explore the disease and regularly reporting in the clinical presentation, pathophysiology, and treatment outcomes (Eastin & Eastin, 2020; Goyal et al., 2020). Another group of scientists are trying to come out with a safe vaccine against this devastating disease. Few of the vaccines are in the 3rd stage of the trial.

In the initial days, the most focused characteristics of COVID-19 were reported as pulmonary symptoms. Within a short time, it was observed that the disease had started showing non-pulmonary presentations. A significant quantity of virus was detected in the kidney, liver, heart, and brain by autopsy examination (Puelles et al., 2020). It was scientifically proven that there is a massive activation of the coagulation system in response to severe inflammation (Jose & Manuel, 2020). This results in cerebral infraction besides deep venous thrombosis, pulmonary embolisms, and renal failure (Lodigiani et al., 2020). Numerous publication reports and reviews, about neurological complications of COVID-19, with a significant number of stroke cases (Brouwer et al., 2020). We are aiming to summarise some findings. Two studies suggest that SARS-CoV-2 can reach the central nervous system from the bloodstream or olfactory pathway by binding ACE2 receptor and the spike protein protease TMPRSS2, but the clinical relevance of such brain invasion is unclear. An experimental model of SARS-CoV-1 infection did not report brain inflammation (Ng Kee Kwong et al., 2020; Baig et al., 2020; Netland et al., 2008). Direct infection of the central nervous system by SARS-CoV-2 is considered unlikely since cerebrospinal fluid (CSF) analysis is often normal (Brouwer et al., 2020). No case was tested positive for SARS-CoV-2 by PCR on cerebrospinal fluid and all patients had a positive nasopharyngeal PCR test and chest imaging characteristic of COVID-19 (Brouwer et al., 2020).

A typical finding of COVID-19 is the loss of smell (or anosmia), which has been described in 40% of cases in a Spanish case-control study and 34% in an Italian study (Beltrán-Corbellini et al., 2020; Giacomelli et al., (2020). Generally, loss of smell is most noticeable to the patient when it is marked, such as anosmia (Doty et al., 1988). Another study claimed that out of 60 COVID-19 positive patients, 59 showed some level of olfactory dysfunction. Among them 58% were anosmic or severe microsmic, 33% moderate and 13% showed mild microsmia and only 1 patient (2%) with normal olfactory function. Almost everyone was free from severe nasal congestion or inflammation (Moein et al., 2020). The demographic and clinical data of their study resembles the reported complication of 43 studies involving 3,600 COVID-19 positive patients (Fu et al., 2020). Some article suggested that the severity of the disease can be indicated by OD in COVID-19 (Lüers et al., 2020). Patients with negative COVID-19 test having idiopathic OD needed to be prioritized to repeat the test. OD in COVID-19 along with or without other neurological symptoms has a strong predictive value where the resource for testing is not available or is limited. Around 50% of the participants in other studies showed that the recovery period of OD is within 40 days (Yan et al., 2020; Rawal et al. 2016). Few studies suggested that the number of patients with OD and other chemosensory disorder will greatly increase in COVID-19 and the quality of life will be significantly affected (Smeets et al., 2009; Croy et al., 2014) and endangered especially patients with other neurological comorbidities like Alzheimer's disease (AD) and Parkinson's disease (PD) (Balin & Hudson, 2018; Olsen et al., 2019).

In another study, the researchers were observing for drug-induced OD, while COVID-19 positive participants were under treatment with different drugs, but no significant relationship was found (Moein et al., 2020). Drugs like hydroxychloroquine, lopinavir/ritonavir, or intravenous immunoglobulin (IVIg) used for

COVID-19 treatment was reported to have mild taste alterations as side effects but affecting the smell function are relatively rare (Schiffman, 2018). Usually, the degenerative olfactory dysfunction started to appear after the age of 65 years. Smell test among the COVID-19 patient under 65 years of age showed strong sensitivity and specificity which is the same as a normal person (Doty et al., 1984).

Even though the real-time reverse transcription-polymerase chain reaction (rRT-PCR) test is the gold standard to diagnose COVID-19, the false-negative result of 15% of cases is always kept under consideration (Li et al., 2020; Jing-Wen et al., 2020; Liang et al., 2020). In a large population where resources are limited for the COVID-19 test, a quantitative smell test can be considered as an alternative inexpensive diagnostic screening test (Moein et al., 2020).

CONCLUSION

Neurological symptoms are common in COVID-19 patient, but no evidence was found regarding direct inflammation of the brain by SARS CoV-2. Smell dysfunction is found to be one of the common neurological symptoms which could be the one determining symptoms of COVID-19 and a test of olfaction can be helpful where diagnostic resources are expensive and not easily available. Sometimes it can be only presenting symptoms. Quality of life is markedly affected especially in regards to the taste of food. There is no evidence of the age of the patient, and the drug used for the treatment in the COVID-19 patient, causing olfactory disfunction. Further research is required on the onset, duration, and severity of OD in relation to the severity of COVID-19.

CONFLICT OF INTEREST

The authors declare that they have no competing interests in publishing this article.

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