



## LEADING TOPIC

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# SARS-CoV-2 neurotropism and other possible causes of olfactory disorders in COVID-19

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) is an acute infectious respiratory disease (AIRD) caused by infection with the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first cases were diagnosed and reported in Wuhan, central China, in November 2019. The disease initially occurred locally. However, the number of infected individuals increased dynamically and spread worldwide. The most common symptoms of the SARS-CoV-2 infection include malaise, fever, dry cough and dyspnoea. Over time, reports of new COVID-19 symptoms included taste and smell disorders. A potential cause of these disorders is related to neurotropism, i.e. the affinity of SARS-CoV-2 to the nervous system. Angiotensin-converting enzyme 2 receptor is essential in the pathogenesis of SARS-CoV-2 infection. The receptor is found in many tissues and organs, including the olfactory epithelium, neurons and neuroglial cells. Another potential cause is neuroinvasiveness, i.e. the ability of the virus to invade the central nervous system, and thereby damage its structures. As a result, olfactory disorders may occur. Other concepts, such as the inflammatory response of the body and the concept of stroke or damage to olfactory supporting cells, are also considered.

**Key words:** SARS-CoV-2, COVID-19, smell, taste, coronavirus, neurotropic

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## Introduction

In November 2019, coronavirus disease 2019 (COVID-19) caused by infection with the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first diagnosed and reported in Wuhan, China. The epidemic initially occurred locally, with the first cases detected in individuals at a sea-food market [1]. Over time, the number of patients increased rapidly and spread worldwide, reaching even Antarctica [2, 3]. Coronaviruses are RNA viruses that were originally associated with mild upper respiratory infections. However, in 2002, the first cases of severe acute respiratory syndrome (SARS) were reported in China. This syndrome causes severe respiratory failure due to an uncontrolled immune response leading to significant lung damage. The mortality rate for SARS is estimated to be 11% [4]. The first cases of Middle East Respiratory Syndrome (MERS), also caused by coronavirus

infection, were reported in Saudi Arabia in 2012. The course of the disease can be asymptomatic or symptomatic. The symptoms may include a mild cold with flu-like symptoms or pneumonia. Furthermore, severe acute respiratory distress syndrome (SARS), multiple organ failure and death can also occur. Frequent gastrointestinal complaints and kidney failure are also common.

MERS has a high mortality rate of up to 35%. However, it is characterised by relatively low infectiousness [5]. In turn, the COVID-19-related mortality rate ranges from 2.3–7.2% due to the different courses of the disease resulting from age, race and comorbidities [6]. SARS-CoV-2, SARS-CoV-1 and MERS-CoV are coronaviruses of animal origin (zoonoses) [7].

COVID-19 is the first pandemic to have been caused by coronaviruses and the fifth documented pandemic overall, starting from the Spanish flu outbreak in 1918 [8]. From the outbreak of the COVID-19 pandemic until 29 October 2022,

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more than 626 million cases of infection and more than 6.5 million deaths had been confirmed worldwide [9]. Of note, the pandemic has had a devastating impact on the global economy and social life caused by many restrictions whose aim was to limit the spread of the virus [10], which occurs via airborne particles and droplets through direct contact with a sick person or contact with contaminated objects and other surfaces. Therefore, maintaining social distance and personal protective measures are of vital importance [6, 11]. The introduction of the COVID-19 vaccines was a significant breakthrough in the fight against the pandemic in November 2020. The vaccines reduce the risk of disease, hospitalisation and death, and carry a low risk of adverse reactions [12, 13].

Fever, dry cough, malaise and shortness of breath (dyspnoea) are the most common symptoms of SARS-CoV-2 infection [11]. However, smell and taste disorders became the symptoms increasingly reported by patients. Indeed sometimes such symptoms were the only symptoms reported. In our study, we focused on olfactory and taste disorders in COVID-19, paying particular attention to possible causes of their occurrence, including potential neurotropism, i.e. the affinity of SARS-Cov-2 to the nervous system.

### Smell and taste disorders and other symptoms of COVID-19

During the first months of the COVID-19 pandemic, researchers paid special attention to the most common systemic symptoms, such as fever, dry cough, malaise, or shortness of breath. In their meta-analysis summarising 54 papers, Alimohamadi et al. found fever (81.2%), cough (58.5%), fatigue (38.5%), and dyspnoea (26.1%) to be the most prevalent symptoms. Of note, of these 54 reports, as many as 50 came from China [14]. In another meta-analysis, Grant et al. summarised the symptoms in 24,410 patients from nine countries based on 148 papers (127 of them from China). The most prevalent symptoms were fever (78%), cough (57%) and fatigue (31%). Smell disorders were very rare, being found in 317 (1.3%) patients [15]. Over time, the virus spread to other countries and continents. As a result, new reports began to appear, describing patients from many countries and races. New symptoms were often reported. Their severity and type were related to patients' age, the time elapsed since infection, and the occurrence of comorbidities. In their meta-analysis, Aziz et al. summarised reports from European, Asian and North and South American countries that included the symptoms of 11,074 patients with COVID-19. Of the 51 papers, only three came from China. Smell disorders were found in many patients (52%) [16]. The above differences may have been due to the fact that at the beginning of the pandemic, more attention was paid to the most prevalent severe systemic symptoms that could be health- and life-threatening. Smell and taste disorders in COVID-19 may not have been included since they may well have been considered less important. Early identification and diagnosis of systemic

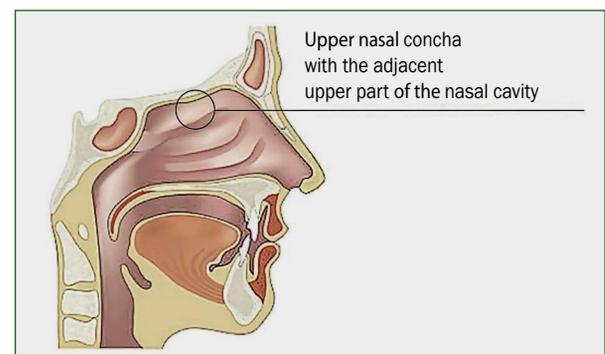
symptoms were significant for adequate treatment and isolation of patients. These differences may have been caused by mutations of the virus that could have led to different symptoms. They may also have been due to genetic and racial variability of patients, and hence a different immune response to infection and a diversity of symptoms. Over time, smell and taste disorders in COVID-19 were recognised as the early indicator of the disease.

Callejon-Leblic et al. analysed symptoms in 777 patients, and observed that smell and taste disorders correlated with a subsequent diagnosis of COVID-19 with an accuracy of 80%, sensitivity of 82%, and specificity of 78% [17]. Smell and taste disorders were also analysed as predictors of disease severity and subsequent hospitalisation. In their meta-analysis, Purja et al. noted a lower prevalence of smell and taste disorders in patients with severe disease and in those who required hospitalisation [18]. Next to smell and taste disorders, the occurrence of a wide range of other neurological disorders in COVID-19 was also significant. These symptoms could have resulted from damage to the central nervous system, such as encephalitis, headache, or encephalopathy, as well as to the peripheral nervous system, such as Guillain-Barré syndrome, or skeletal muscle symptoms (myalgia and myasthenia gravis). Delirium and psychosis were also reported [19, 20].

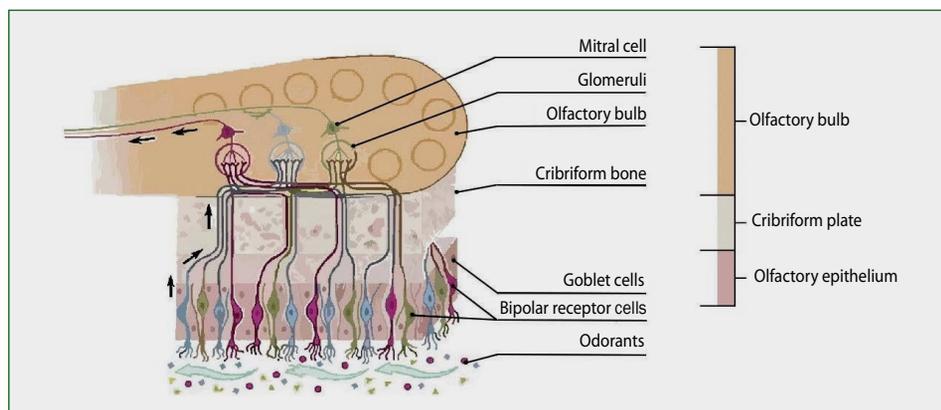
### Anatomy and characteristics of olfactory epithelium

The olfactory epithelium is located in the upper nasal cavities, in the area known as the olfactory field or olfactory region. It occupies an area of about 4–6 cm<sup>2</sup>. It is formed by the upper nasal concha with the adjacent upper part of the nasal cavity. Sometimes the olfactory field reaches the middle concha [21]. The approximate location of the olfactory epithelium is given in Figure 1.

The olfactory epithelium is composed of basal cells, olfactory sensory neurons (bipolar neurons) and sustentacular (or supporting) cells. It is covered with mucus produced by Bowman's glands on the lamina propria of the mucous membrane and by the secretion of goblet cells and supporting cells of the olfactory epithelium. The mucus contains odorant-binding proteins essential for binding odorants to bipolar



**Figure 1.** Approximate location of olfactory epithelium (olfactory field)



**Figure 2.** Structure of olfactory epithelium

cell receptors [22]. The structure of the olfactory epithelium is shown in Figure 2.

The olfactory epithelium, including bipolar cells, is characterised by high regenerative abilities after damage and constant cell replacement. However, these abilities decrease as a result of ageing, neurodegenerative diseases (e.g. Alzheimer's Disease, Parkinson's Disease), chronic and acute inflammation (e.g. chronic sinusitis, chronic rhinitis), and as a result of surgical treatment of the anterior cranial fossa [22, 23].

### Does SARS-CoV-2 virus have neurotropic properties?

The neurotropism of the SARS-Cov-2 virus can be understood as its affinity and ability to penetrate, and replicate within, cells of the nervous system. Angiotensin-converting enzyme 2 (ACE2) is vital in this process. This is the main membrane receptor for SARS-Cov-2 to which the virus attaches via the spike protein. In addition, transmembrane serine protease 2 (TMPRSS2), which catalyses this process, is also crucial [24]. SARS-CoV-2 has a high affinity to the ACE2 receptor. It binds to this receptor 10–20 times more strongly than SARS-CoV. ACE2 is a commonly found receptor in the human body. It is located in the vascular endothelium, skeletal muscle, and nervous system cells. As a result, it can infect many organs and tissues [25]. In the brain, ACE2 is highly expressed in the choroid plexus, olfactory bulb and paraventricular nuclei of the thalamus [26, 27]. It is present in neuronal and non-neuronal cells of the central nervous system, such as endothelial cells and neuroglial cells (astrocytes and oligodendrocytes).

However, the highest expression of this receptor is found in excitable nerve cells of the medial temporal gyrus and posterior cingulate cortex. Note that very low expression of ACE2 is found in the hippocampus, which is the cortical olfactory centre [27]. When analysing neurotropism as a potential feature of the SARS-CoV-2 virus, three possible ways in which the virus could enter the CNS should be considered:

- I. *Blood-borne route via the systemic circulation.* Crossing the blood-brain barrier (BBB) is crucial for the entry of SARS-CoV-2. One of the theories about the penetration of SARS-CoV-2 through the BBB is its ability to infect the endothelium of BBB vessels due to the presence of the ACE2 receptor in its cells [28]. Another potential cause is the ability of the virus to induce a cytokine storm, i.e. an excessive inflammatory and immune response which is typical of COVID-19. This results in increased permeability of the BBB by the increased inflammatory response of the vascular endothelium [29]. Another theory is related to the possibility of the virus entering the CNS through the mechanism known as the *Trojan horse*. It is possible that infected leukocytes, which express ACE2, can carry SARS-CoV-2 across the BBB to infect the CNS. This is facilitated by the increased production of leukocytes during infection and hypoxia often associated with COVID-19 [30]. The rich blood supply of the nasal mucosa and olfactory epithelium, as well as their vascular connection to the brain, may also be important in the blood-borne mechanism of viral access to the CNS [31].
- II. *Peripheral nerve route.* Another possible route of infection is penetration of SARS-CoV-2 through the axons of the peripheral nerves. The following may be of vital importance: the trigeminal (V) and olfactory (I) nerves due to innervation of the nasal cavities, the vagus nerve (X) innervating the lower respiratory tract, and the glossopharyngeal (IX) and facial (VII) nerves innervating the upper respiratory tract. Of the above nerve pathways, no evidence of viral invasion via the glossopharyngeal or facial nerves has been reported yet [32].
- III. *Lymphatic route.* The exact structure of the lymphatic system of the brain is not fully understood. It must be underlined that there is no classical lymphatic system in the CNS. However, it may be related to the pathogenesis of neuroinvasiveness of SARS-CoV-2. Bostancikligliu proposed the thesis that the

olfactory and cervical lymphatic vessels could be part of the lymphatic drainage of the brain, which could provide a direct entry route for SARS-CoV-2 to the CNS [33].

### Possible mechanisms of smell disorders in COVID-19

#### Local/systemic inflammation

An important aspect of a viral infection such as COVID-19 is related to increased inflammatory parameters in the serum of patients. This phenomenon can affect the occurrence of hyposmia. As early as 2013, Henkin et al. noted a clear relationship between the severity of systemic or local inflammation and the loss of smell. Levels of IL-6 were measured in samples of plasma, urine, saliva, and nasal mucus. The levels of IL-6 in nasal mucus were higher than those in any other biological fluid [34]. The above thesis may be confirmed by the occurrence of hyposmia in chronic systemic inflammatory rheumatic diseases, such as rheumatoid arthritis [35] or granulomatosis with polyangiitis [36]. In turn, Cazzolla et al. analysed serum IL-6 levels in patients with COVID-19 and found a correlation between increased serum IL-6 levels and the severity of olfactory impairment. In addition, it was noted that as hyposmia resolved, IL-6 levels decreased. Of note, there have also been frequent cases of a short duration of hyposmia in COVID-19, which may suggest the effect of local inflammation on olfactory receptor cells, rather than their permanent damage resulting from the SARS-CoV-2 infection [37].

#### Indirect damage to bipolar receptor cells and olfactory bulb neurons

As mentioned above, ACE2 receptor is a key enzyme in the aetiopathogenesis of the SARS-CoV-2 infection. It is found in the cells of many organs and tissues. However, ACE2 is not expressed in bipolar receptor cells or olfactory bulb neurons. The expression of ACE2 in non-neuronal cells of the olfactory epithelium, such as supporting cells and vascular pericytes, is also important. They are significant for the normal functioning of the olfactory epithelium through the delivery of nutrients and oxygen, and the removal of metabolic products [37, 38]. Therefore, olfactory impairment may be the result of indirect damage to neuronal and receptor cells due to a lack of nutrition resulting from the destruction of supporting cells by SARS-CoV-2. A potential cause of olfactory impairment in COVID-19 is also the effect of SARS-CoV-2 on olfactory epithelial cells at the molecular level. The viral infection causes a decrease in the activity of olfactory receptors and their signalling pathways. This is caused by reorganisation of the nuclear architecture of neuronal cells, which results in dispersion of the genes encoding olfactory receptors [40].

#### Concept of stroke/brain tissue damage

As stated previously, SARS-CoV-2 is neuroinvasive and can cause changes in the CNS. The causes of stroke in COVID-19 are usually complex and result from three factors

known as Virchow's triad. They can occur due to venous stasis resulting from patient immobilisation during treatment, vascular endothelial injury resulting from the inflammatory response, and coagulopathy as a result of a generalised inflammatory response [41].

Nannoni et al. performed a meta-analysis that included 108,571 patients with COVID-19. Acute cerebrovascular disease was found in 1.4%. The most common manifestation was ischaemic stroke (87.4%), while intracerebral haemorrhage was much less prevalent (11.6%). The risk of stroke was significantly increased by cardiovascular disease, diabetes, and smoking [42]. However, when analysing the stroke/vascular aetiology of olfactory impairment in COVID-19, it is important to consider the relatively rapid recovery of the sense of smell in patients. Printza et al. reported that the great majority of patients (88%) had recovered their sense of smell by 61 days [43]. In another paper, McWilliams et al. summarised the severity of olfactory impairment during a 2-year follow-up. 38.2% of patients reported complete recovery, 54.3% partial, and 7.5% no recovery [44]. Based on the above, it can be concluded that the recovery of smell function in most patients was reported in a relatively short period of time. However, in some patients recovery was longer, or no recovery was reported. Neurological recovery in stroke patients is usually the highest during the first weeks of rehabilitation, reaching a plateau after three months. Six months after the occurrence of stroke, the effects of rehabilitation are usually lower [45]. Analysing the duration of symptoms, it is difficult to conclude whether olfactory impairment is related to the stroke/vascular concept of the CNS, since the recovery of smell function is characterised by relatively high variability in patients. Of note, stroke must involve the structures of the olfactory pathway to lead to olfactory impairment. Given the above-mentioned prevalence of stroke in COVID-19 (1.4% of cases), the concept of stroke would seem to be only a marginal cause of olfactory disorders in COVID-19.

### Is COVID-19-related hearing loss also an example of SARS-CoV-2 neurotropism?

As the pandemic continued, there were reports of new disease symptoms, including hearing loss. Jaffari et al. and Dusan et al. reported the prevalence of hearing loss at 3.1% and 40.5% respectively, which is a large discrepancy. Therefore, it is impossible to assess the approximate prevalence of hearing loss in COVID-19 patients [46, 47]. Uranaka et al. evaluated the expression of ACE2, TMPRSS2 and Furin in mouse ear tissue. ACE2 was present in the nucleus of the epithelium of the middle ear and Eustachian tube, as well as in some nuclei of the hair cells in the organ of Corti, in the stria vascularis, and the spiral ganglion cells. The expression of TMPRSS2 and Furin was also reported in the cochlea [48]. The presence of the above substances in the human ear is possible, but further studies are warranted to confirm it.

## Olfactory disorders in COVID-19 as a potential cause of neurodegeneration

Olfactory impairment is a common symptom in neurodegenerative diseases such as Parkinson's and Alzheimer's Diseases. Olfactory impairment is one of the initial symptoms of these conditions, and occurs long before cognitive impairment or motor dysfunction. Indeed it is considered one of the clinical markers of the early stages of the disease [49, 50]. Damage to brain tissue in the area of the limbic system and the olfactory bulb in the early stages of the disease can lead to long-term hearing impairment, which is characteristic of both Parkinson's and Alzheimer's and can occur in the course of COVID-19 [51, 52]. Given the previously mentioned similarities between neurodegenerative diseases and COVID-19, long-term olfactory loss with cognitive and emotional disturbances in the course of SARS-CoV-2 may be a symptom of dementia in the course of neurodegenerative processes [53]. To limit the extent of neurodegenerative processes in COVID-19, olfactory training is significant [54].

### Conclusions

The COVID-19 pandemic that began in November 2019 has caused millions of deaths and paralysed the global economy and social life. The most common symptoms of SARS-CoV-2 infection were systemic symptoms such as fever, shortness of breath, malaise and cough. Over time, reports of new non-specific symptoms during COVID-19 were published. They included olfactory and taste disorders, which became characteristic features of the disease. Neurotropism, defined as the affinity to the nervous system and the ability of the virus to infect cells, was identified as a potential cause of these disorders. There have been several theories attempting to explain this phenomenon.

The crucial role is attributed to ACE2, which is the membrane receptor for the SARS-CoV-2 virus in many organs and tissues, including nervous tissue and the olfactory epithelium. It is also likely that the SARS-CoV-2 virus is characterised by neuroinvasiveness, i.e. the ability to invade the CNS, which can lead to olfactory disorders due to damage caused by the virus to CNS structures. Several potential pathomechanisms for these disorders are listed, i.e. inflammatory response, the concept of stroke, and damage to the supporting olfactory cells. This issue has not yet been fully understood, and requires further research.

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