



Neurotropism of SARS-CoV-2 in idiopathic hearing disorders

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Abstract

Introduction and objective. The article focuses mainly on SARS-CoV-2 neurotropism and its consequences for hearing and otolaryngological disorders. The leading hypotheses regarding the mechanisms of the virus internalisation as well as its influence on the nervous system *in extenso* are presented, as well as the latest available knowledge, after a selective choice of articles relating to the subject.

Brief description of the state of knowledge. Dizziness, tinnitus and sudden hearing loss are the main symptoms in the organ of hearing and balance, but it is often not possible to objectively investigate their etiology and make a proper diagnosis. Among the most common causes of hearing disorders, such as vestibular neuritis, sudden sensorineural hearing loss and tinnitus, there are infections, injuries, and diseases that predispose to the occurrence of symptoms of hearing disorders. Despite the numerous possible causes, a high percentage of clinical symptoms still remain without diagnosis.

Conclusions. The global health crisis has provoked a change in the perspective of thinking about infections and the consequences of viral infections; it has also given rise to a new perception and conceptualisation of the impact of infections on other human systems. The challenge faced by scientists due to this virus is multi-dimensional, and it requires explication and reinterpretation of the knowledge to-date. It even forces us to retrospect the existing explanations of the known disorders, as well as to conduct prospective correlative studies that will help in understanding the mechanisms of SARS-CoV-2 pathogenesis, and consequently, to be able to establish a management pattern in order to prevent the spread of the virus causing the pandemic.

Key words

neuroinfection, Neurotropism SARS-CoV-2, cytokine storm syndrome, taste or smell dysfunction

INTRODUCTION

The coronavirus (CoV) is a group of unsegmented positive-sense RNA viruses belonging to the family of Coronaviridae, order Nidovirales, i.e. respiratory viruses demonstrating high neurotropism, already known in the 1940s, reaching a size of 60 nm to 140 nm in diameter, with spikes on its surface that give a crown-like appearance under an electron microscope. They are represented by four genera: Alpha (α CoV), Beta (β CoV), Delta (δ CoV) and Gamma (γ CoV) [1]. Most coronaviruses cause diseases in animals, and until recently, only four of them were known to cause self-limiting upper and lower respiratory tract infections in humans. Two of them are α CoV (HCoV-229E and NL63), the other two belong to the β CoV genus (HCoV-OC43 and HKU1). At the beginning of the 21st century, another three representatives of β CoV genus that were highly pathogenic for humans were detected, and caused the severe acute respiratory syndrome (SARS-CoV) outbreak and the Middle East respiratory syndrome (MERS-CoV) outbreak. Currently, they are responsible for the COVID-19 pandemic (SARS-CoV-2). All three are closely related to coronaviruses infecting the lower species of animals, and it is believed that these three viruses originated from these animals [6]. Common symptoms of CoV infection include fever, dry cough, chest tightness, myalgia and arthralgia, headache, diarrhoea, dyspnoea, and fatigue, which is similar to symptoms caused by rhinoviruses,

the influenza virus, parainfluenza virus, respiratory syncytial viruses, adenoviruses and enteroviruses. In severe cases, this virus leads to pneumonia and Acute Respiratory Distress Syndrome (ARDS) and, in extreme cases, to death. The affinity of respiratory viruses to both the central and peripheral nervous systems is characterised by high morbidity and mortality rates, which is a huge problem for global public health, especially in vulnerable populations [2].

CURRENT STATE OF KNOWLEDGE

Neurological disorders have been reported in 30% of patients who required hospitalisation due to COVID-19 infection, in 45% of patients with severe respiratory disease, and in 85% of patients with ARDS. The neurological symptoms observed in patients with viral infection are caused by the cytokine release syndrome, i.e. 'cytokine storm syndrome' that includes inflammatory and anti-inflammatory cytokines as an immune response to the presence of a virus in the Central Nervous System (CNS). This over-reaction to infection can lead to meningitis and cerebrospinal meningitis, encephalitis, and death in severe cases of infection. The virus can infect the nervous system in two ways. First, as a result of direct infection of nerve endings in tissues and the use of trans-synaptic transport to access the CNS [3]. Second, by infecting the cells of the blood and the immune systems that eventually spread the infection across the Blood Brain Barrier (BBB) into the brain. In this mechanism, the virus infects BBB endothelial cells or choroidal plexus epithelial cells, breaking the blood-cerebrospinal fluid barrier, or using leukocytes as

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a vector for spreading to the brain. When the virus breaks out of this physical barrier and attacks the CNS, the first line of defence is the activation of the microglia, or mononuclear phagocytic cells of the brain [4]. The presence of activated glial cells is indicative of neuropathology, and is considered a marker of brain damage and a marker of neuroinflammation. The speed of the microglial inflammatory response and the immune response in the brain make them aggressive effector cells that damage neurons. For this reason, the same cells that play a neuroprotective role quickly become cells that can trigger long-term neurodegeneration [5].

As already mentioned, the β CoV coronaviruses (SARS-CoV and CoV-2, MERS-CoV, CoV 229E, CoV-OC43) demonstrate neuroinvasive properties, but the routes of entry have not been fully ascertained, and the hypothesis on this subject is based solely on pathways developed for other coronaviruses. It is known, however, that both CoV and CoV-2 demonstrate a high affinity for the Angiotensin-converting enzyme 2 (ACE2) receptor, i.e. membrane-bound angiotensin-converting enzyme-metalloproteinase 2. ACE2 is especially abundant in epithelial cells lining the nasal mucosa, upper respiratory tract, oral cavity, bronchoalveolar type II cells in the lung parenchyma, and intestinal enterocytes. ACE2 protein has been observed in human cerebral vessels, and also in neuronal and glial cells of the central nervous system, although their representation is low, reaching only 2%. In addition to the main docking receptor, the virus uses TMPRSS2 (Transmembrane protease serine 2), i.e. a transmembrane proteolytic enzyme that processes the entry protein in the cell in order to facilitate entry of the virus into the cell. In addition to ACE2, SARS-CoV-2 can use basigin (BSG) and neuropilin-1 (NRP1) as a docking receptor, and a number of proteases, including TMPRSS11A/B, cathepsin B and L, and furin (FURIN) to facilitate entry into the cell [6]. At the top of the spiky shape of SARS-CoV-2, there is the spike (S) protein with the structure of a class I fusion protein, which consists of two subunits, S1 and S2. One S1 subunit recognises the host receptor (most often ACE2) and initiates fusion, while the S2 subunit proteins mediate the internalisation of the virus by binding to the transmembrane enzyme [7, 8]. There is also a suspicion that the virus may attach to haemoglobin and, in the form of a complex with haemoglobin, it is transported by erythrocytes to all tissues containing ACE2 in its structure [9]. However, this has not been effectively confirmed, and data on this subject originate mainly from studies on other representatives of coronaviruses.

Another important hypothesis, and at the same time an important predictor of SARS-CoV-2 neuroinfection, is the immune response – a late humoral response. CoV can remain in a latent form in the host cells, slowly inducing an autoreactive microglia response by promoting the exocytotoxicity of glutamate metabolism products. In the case of SARS-CoV studies, memantine has been used as an agent of neuroprotective importance. Memantine is an NMDA glutamate receptor antagonist which reduces the toxicity of the cell's own products [10]. The late response of the nervous system is of particular importance not only in the observation of patients with neurodegenerative diseases, such as multiple sclerosis (MS), Parkinson's disease or Alzheimer's disease, but also in patients with sudden symptoms in the nervous system that occur at some time distance from virus infection.

Increasingly in recent months, there have been reports on the influence of the virus on the body and the wide-ranging consequences of the infection, including otolaryngological symptoms, such as smell and taste disorders (which is largely a factor differentiating COVID-19 from other infections) [11]. In the research by Varia et al. on the sense of smell and taste in 72 patients with positive test results for COVID-19, the authors demonstrated that smell and/or taste disturbances occurred in 73.6% of patients [12]. Among COVID-19 + patients at the Sacco Hospital in Milan, Italy, taste or smell dysfunction was reported by 33.9% of patients [13]. In a retrospective study conducted in Poland on 1,942 non-hospitalised patients using the questionnaire method, it was shown that 54.2% of subjects indicated one of the two dysfunctions, and 42.5% reported both abnormalities [14]. Initial studies suggested a lower percentage of patients with anosmia and ageusia, but patients with mild to moderate symptoms treated at home were not analysed. Meanwhile, it has been shown that in asymptomatic and mildly symptomatic individuals, disturbances of the sense of taste and smell may be the only and isolated symptoms of infection. Disorders may occur as the first symptom of an infection as well as during and at the end of the infection, but in most cases they are observed at the beginning. Although the exact mechanism of impairing smell and taste perception by SARS-CoV-2 has not been clearly established; two hypotheses seem plausible: damage to the olfactory epithelium caused by the cellular expression of angiotensin-converting enzyme 2 (ACE2) receptors, which act as the binding point for the virus, or a direct attack on the olfactory neurons. A relatively rapid and spontaneous recovery in most patients supports epithelial pathogenesis, taking into account the ability of the epithelium to quickly restore its function after damage [13].

Among other reports, there were also presumptions that the SARS-CoV-2 virus may also cause acute otitis media [15], sudden sensorineural hearing loss [16], other disorders of the cochleovestibular nerves (CN VIII), including tinnitus and dizziness [17]. At present, it is still not possible to confirm that SARS-CoV-2 contributes to this type of symptoms; however, considering the mechanisms of virus penetration into the nervous system through peripheral routes, it is necessary to remain alert to the non-specific symptoms reported by patients. The results of the research also show that not only the cranial nerve VIII itself, but also the cochlear hair cells may be damaged, and despite the fact that the patient is asymptomatic, a reduction in the high-frequency pure-tone thresholds and the TEOAE amplitude are detected [12].

During the current pandemic, several cases of virus impact on hearing and vestibular system have been described. Researchers from the Mayo Clinic in the USA described a 60-year-old healthy patient who developed bilateral deafness with loud white noise after pneumonia in the course of COVID-19. As a result of the performed diagnostics and treatment, it was found that the ototoxic effect of drugs administered during the basic treatment was unlikely, it was therefore concluded that the hearing loss resulted directly from complications following coronavirus infection. It has also been suggested that hearing loss may be more common in patients who develop meningitis during COVID-19 [18].

Another report describes the presence of sudden hearing loss in a patient with a positive SARS-CoV-2 RT-PCR test result at a hospital in Istanbul, Turkey. The patient manifested no symptoms typical for COVID-19 and no other health

problems. As part of a comparative study, four other male subjects were also assessed. These patients underwent RT-PCR testing for the presence of SARS-CoV-2 genetic material, and reported to the clinic due to sudden hearing loss, but with a negative test result for the presence of the virus. The patient with a positive test result was treated with hydroxychloroquine in the dose of 200 mg for five days, while the remaining patients underwent the standard treatment for sudden hearing loss – administration of prednisolone in the dose of 1 mg/1 kg/day to 16 mg every three days with a complex of vitamin B1 and folic acid, and a proton pump inhibitor. The effect of the treatment was a return to normal hearing in the patient with a positive test result for SARS-CoV-2 on day 11. The remaining patients on day 11 reported hearing improvement in three out of four cases; one did not feel any improvement [16].

Other studies indicating that the virus causes damage to the hair cells include observations of researchers in Cairo, Egypt, who reported that the mechanisms of damage of the peripheral auditory system may include direct viral damage to the Corti organ, vascular ganglia or the spiral ganglion. Damage is mediated by the patient's immune system against viral proteins (as in case of cytomegalovirus); and an immunocompromising mechanism leads to a secondary bacterial ear infection. Infection with COVID-19 can have a detrimental effect on the function of the cochlear sensory cells, and the mechanism of these effects requires further research [19].

In addition to hearing impairment, there are reports of concomitant labyrinth symptoms in the form of dizziness, but it is rarely the only symptom of infection. At a hospital in Dover, USA, a case was described of a 29-year-old female patient with severe dizziness and vegetative symptoms (nausea and vomiting), that started two days before her admission to hospital. The dizziness was not accompanied by symptoms characteristic for the SARS-CoV-2 infection, but according to the patient's report, she was staying in the outbreak of infection. Computed tomography (CT) of the chest revealed inflammatory lesions in the lungs, which suggested that performing RT-PCR test was necessary. The positive result did not correlate with the markers of inflammation in the blood (ESR, C-reactive protein, ferritin), or with the coagulation parameters (d-dimers, fibrinogen, platelet count). According to the authors, there were no other symptoms in this case except for the presence of virus-induced vestibular neuritis [20].

Table 1. Most common reported complications in the peripheral nerves in patients after Covid-19 in analyzed studies

Type of disorder	Patients	Research methodology	Reference
Sudden hearing loss	11 patients	Small research sample	[16]
Dizziness and vegetative symptoms	29-year-old patient	Case report	[20]
Bilateral deafness with loud white noise (tinnitus)	60-year-old	Case report	[18]
Smell and/or taste disturbances	72 patients	Small research sample	[12]
	1,942 patients	Retrospective study	[14]

Particular attention should be paid to the presence of idiopathic symptoms from the nervous system in the absence of infection symptoms and with a positive RT-PCR test result. It remains problematic to identify and then verify whether

such symptoms as sudden hearing loss, tinnitus, dizziness or other hearing or otolaryngological disorders occurred in a patient as the result of contracting COVID-19 in the past. In the case of other betacoronaviruses (β CoV), it has been observed in animal models that symptoms of neuroinfection may appear up to as many as 216 days after infection, and the presence of viral RNA in the RT-PCR test was detected in the brains of animals with MS [21].

The above data can presumably contribute to the occurrence of nervous system disorders of varying intensity at an undetermined time and in an unknown location of the nervous system. Severe neurological symptoms appear statistically most often in elderly patients and in patients with comorbidities, who experience a natural decline in ACE2 expression. These patients mainly suffer from acute and subacute encephalitis, meningitis and cerebrospinal meningitis, or encephalopathy, which may be related to the weakening of BBB and facilitates the penetration of the virus into the brain [22]. In younger patients without comorbidities, mild peripheral neuropathies, hyposmia or anosmia, ageusia, headaches and dizziness are most commonly observed. Guillain-Barré syndrome (GBS) may be a later and more severe symptom of SARS-CoV-2 infection, and its symptoms appear between days five and ten after the first symptoms of infection. Typical GBS is a disease with significant clinical and phenotypic variability (it can also occur in the rare variant – Miller Fisher syndrome (MFS), characterised by ophthalmoplegia, ataxia and areflexia). GBS occurs sporadically as a complication of viral infections affecting the nervous system, and it is not new in the case of SARS-CoV-2. However, attention should be paid to the virus because of its influence on the nervous system and its ability to invade many nerves simultaneously, as well as to the time when an autoimmune reaction may occur even in the case of mild symptoms caused by primary infection [23]. Therefore, it can be hypothesised that the virus may accumulate in nerve endings without an initial manifestation of any symptoms. It is estimated that 10%- 40% of patients are asymptomatic carriers of the infection, and 80–95% of patients infected with SARS-CoV-2 manifest mild symptoms of infection, which does not exclude the possibility that under favourable conditions for virus activation, symptoms related to the peripheral nervous system may also occur. In patients who develop severe respiratory complications (1–5% of the infected individuals), the function of the nervous system should also be constantly monitored and assessed [24, 25,26].

CONCLUSIONS

There are several other reports describing disorders of cerebral nerve VIII as a consequence of COVID-19, but there is still no clear evidence linking the current epidemic to hearing loss, tinnitus or dizziness [19, 27, 28]. Attempts to formulate hypotheses are extremely important not only because of the current epidemic, but also because of recently etiology, where a neuroinfectious cause is an important presumption. The current attempts to systematise the influence of the virus on the nervous system open an important research field that includes coexisting related areas which are highly likely to be responsible for other symptoms. It is important that during the presence of symptoms in the head and the neck, research on the use of pharmacotherapy in indications other than

those previously registered for use, was accelerated, which in the case of sudden hearing loss, for instance, allows to better differentiate those of viral origin.

In addition to introducing treatment procedures, consideration should be given to using neuroprotective drugs in RT-PCR positive patients without neurological symptoms. The use of memantine is known, but this drug was developed in order to block NMDA receptors (to maintain glutamate homeostasis) in the previous SARS-CoV epidemic, and at the same time, to independently reduce viral replication [17, 29]. The currently used methods of antiviral therapy (remdesivir, convalescent plasma or hydroxychloroquine) do not constitute treatment methods registered for use in SARS-CoV-2 infection, and the full effectiveness of such management has not been confirmed, but it has the potential to limit excessive viral RNA replication, so these medicines shorten the infection duration and hence, reduce the probability (allegedly at present) of virus incubation in the nerve endings, and the occurrence of late symptoms of neuroinfection and neurodegeneration [30, 31, 32].

An important consequence of identifying SARS-CoV-2 in the etiology of disorders of the cranial nerve VIII is the selection of an appropriate treatment strategy that minimises complications, as well as the use of pharmacotherapy with a lower ototoxic effect, which should arouse high vigilance and systematic assessment of the effects [33].

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