THE IMPACT OF COVID-19 CONCERNING THE CENTRAL NERVOUS SYSTEM

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Abstract

Since the beginning of the pandemic, emerging information regarding manifestations of the infection with Sars-Cov-2 virus has been laid out, mainly involving the respiratory consequences as it impacts profoundly the global death rates. In February 2020, first publications that sustain the theory the virus could also possess neuroinvasive potential, have been reported. Until present, there is consistent evidence on the consequences over the CNS (central nervous system) and PNS (peripheral nervous system). To shed light over the central nervous system implications, this paper aims to review some of the clinical entities involved.

Key-words: COVID-19, central nervous system

Introduction

Referring strictly from a genetic point of view, SARS-CoV-2 is similar to other coronaviruses from SARS family, in particular SARS-CoV and MERS-CoV. This virus uses angiotensin converting enzyme 2 (ACE2) receptors as a way to facilitate its internalization.

Once inside a brain cell, the virus accomplishes its role by disturbing the renin angiotensin system (RAS). In this respect, there is rising information that the central nervous system is more susceptibile to the virus than previously thought.

The main neurological manifestations are represented by headache, dizziness, altered mental status, confusion, agitation, delirium, ischemic and hemorrhagic stroke, cerebral venous thrombosis, meningoencephalitis, encephalitis, encephalopathy, myelitis, seizures and neurogenic respiratory failure, some of which we will enlarge upon further on [1,2].

1. Neurotropic mechanisms of COVID-19 leading to central nervous system complications

SARS-CoV-2, responsible for the disease called coronavirus disease 2019 (COVID-19), infects certain tissues by binding to the angiotensin-converting enzyme 2 (ACE2) receptors on host cells. This binding is mediated by the spike (S) glycoprotein, a structural protein on the virus's outer envelope, which allows its internalization. Consequently, SARS-CoV-2 causes oxidative stress, mitochondrial dysfunction, thrombotic response, vasodilation and neuroinflammation [1). Although the ACE2 receptor is mostly expressed in the respiratory tract, it is also found in the central nervous system, such as in neurons, astrocytes, oligodendrocytes, olfactory bulb, substantia nigra, ventricles, middle temporal gyrus and the posterior cingulate cortex (2).

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Several hypotheses describe the possible neurotropic mechanisms leading to central nervous system manifestations of COVID-19: direct viral tissue invasion (systemic hematogenous spread or axonal retrograde dissemination) and indirect inflammatory response (3)a novel coronavirus, is responsible for the outbreak of coronavirus disease 19 (COVID-19.

The first mechanism is based on viremia via systemic spread. SARS-CoV-2 infects the epithelial cells of the respiratory tract and subsequently, the endothelial cells, gaining access to the blood-stream and compromising the blood brain barrier in the choroid plexus. Through this method, the virus directly affects the neurons and glial cells in the central nervous system. The second mechanism for the virus to access the brain includes the invasion of the upper nasal cribriform plate, the olfactory bulb and axonal retrograde transport (3)a novel coronavirus, is responsible for the outbreak of coronavirus disease 19 (COVID-19.

On the other hand, indirect immune-mediated central nervous system damage could also explain the neurological symptomatology. This inflammation is mediated by monocytes and macrophages which release interleukins (IL-6, IL-8) and chemokines leading to a systemic inflammatory response syndrome, inflammation and increased permeability of the brain blood barrier (4).

2. Central nervous system manifestations associated with COVID-19

Table 1 summarizes different central nervous system symptoms and manifestations reported in patients with COVID-19, each being addressed separately in the manuscript (3)a novel coronavirus, is responsible for the outbreak of coronavirus disease 19 (COVID-19.

CNS impairment	Prevalence
Headache	14,7%
Dizziness	8,77%
Altered mental status	9,6%
Stroke	2,6%
Seizures	0,5-0,9%

Table 1. Prevalence of central nervous system manifestations in COVID-19 patients.

2.1. Headache

Headache is a common non-specific symptom in any systemic viral infection, being the most frequently reported neurological symptom in COVID-19 patients. Most often, headache is present at the time of admission in association with fever (1). The estimated pooled prevalence of this clinical manifestation in COVID-19 patients is around 14,7% (5).

The headache caused by COVID-19 can include two phases: an initial moderate diffuse pain attributed to systemic viral infection which, after 7-10 days, is accompanied by photophobia and neck stiffness resulting from citokine storm (6).

Other studies described a moderate to severe bilateral forehead, periorbital or temporoparietal headache with pulsating or pressing quality, exacerbated by neck flexion. Moreover, a large number of COVID-19 patients complain of a sudden onset disabling headache due to the infection, with no previous history of recurrent cephalalgy (3)a novel coronavirus, is responsible for the outbreak of coronavirus disease 19 (COVID-19.

2.2. Dizziness

Dizziness is a prevalent symptom in COVID-19, after fever, cough, fatigue, dyspnea and headache. A case report presented a SARS-CoV-2 infected patient with nervous system onset consisted of dizziness and also dry throat, with no other typical respiratory or systemic symptoms (7). This should draw attention of clinicians to dizziness in infectious diseases, especially in the absence of common respiratory symptoms.

2.3. Altered mental status, confusion, delirium

Altered mental status can be a primary manifestation of COVID-19 and reflects the disease severity. Impaired consciousness with acute confusion is a reversible brain dysfunction based on septic encephalopathy, systemic inflammatory response and hypoxia caused by acute pulmonary infection (3). The most susceptible people are the elderly patients, especially those with neuropsychiatric comorbidities, such as vascular dementia or Alzheimer's disease (1).

Furthermore, patients may also experience agitation and delirium. The presence of comorbidities during the viral infection can facilitate the onset of the delirium (hypertension, other cardiovascular diseases, cerebrovascular diseases, diabetes, hepatitis B infection, chronic obstructive pulmonary disease, chronic kidney diseases and malignancy) (8). Hyperactive delirium may require aggresive management, including haloperidol, risperidone, olanzapine or quetiapine. Benzodiazepines can also be administered in cases with prevalent anxiety and agitation, but doses should be kept as low as possible to avoid adverse effects (1).

In addition to the manifestations in acute stages, COVID-19 patients may also develop depression, anxiety, fatigue and post-traumatic stress disorder (9).

2.4. Cerebrovascular diseases

Patients with COVID-19 may have multiple vascular risk factors that can predispose to ischemic, hemorrhagic stroke and cerebral venous thrombosis. Guan et al. indicated that cerebrovascular disease was present in 1,4% of 1099 patients with laboratory-confirmed COVID-19 from 552 hospitals in 30 provinces (10). In another Spanish study cerebrovascular diseases were identified in 14 (1,7%) of 841 COVID-19 patients including 11 patients with ischemic strokes and three patients with intracerebral hemorrhage (11).

COVID-19 cerebrovascular disease is predominantly ischemic and involves large vessels and multiple vascular territories. The stroke patients are usually older and have more comorbidities such as hypertension, diabetes, prior history of stroke and elevated inflammatory markers. In older individuals cerebrovascular disease seems to be a result of the hyper-inflammatory state and endothelial dysfunction and it is correlated with the severity of the systemic disease (12). A review of six consecutive COVID-19 patients with stroke showed that all patients had a highly pro-thrombotic state with increased values of D-dimer and ferritin and five of them had detectable lupus anticoagulant. The strokes occured 8-24 days after the disease onset (13).

In younger patients, the infectious cerebrovascular disease appears to be due to sepsis-induced coagulopathy, with elevated prothrombin time and thrombocytopenia without hypofibrinogenemia (12). Oxley et al. published a report of five younger adults with COVID-19 (aged 33-49) presenting with a large vessel stroke. The infarcts involved the middle cerebral artery (three patients), posterior cerebral artery and internal carotid artery. In two of five cases, the stroke was the first clinical manifestation, with no other COVID-19 related symptom (14).

Therefore, laboratory monitoring of coagulation markers (fibrinogen, D-dimer, CRP, IL-6) can be performed to assess an underlying prothrombotic or inflammatory response and to guide treatment (3).

The prothrombotic state associated with COVID-19 can also cause cerebral venous (sinus) thrombosis, a rather rare complication. Initial symptoms consists of progressive headache, visual disturbances, focal neurologic deficits, altered consciousness and seizures. Deep cerebral vein thrombosis can be complicated by hemorrhagic venous infarction with large necrotic areas. Treatment with low molecular weight heparin or unfractionated heparin is necesarry (3).

2.5. Meningoencephalitis

There have been reported cases of meningitis and encephalitis over the course of the pandemic, without clearly drawing the line to the exact mechanism: direct infection, or parainfectious immune mediated disease. (1) The typical clinical presentation which includes headache, fever and sudden onset seizure, prompts rapidly a diagnosis. The cases reported were managed appropriately, performing both clinical and paraclinical investigations including cerebral CT, a routine EEG recording and lumbar puncture with CSF analysis. In most of the cases, the results of the investigations were inconclusive.

Despite that, the innability to detect SARS-CoV2 RNA in CSF doesn't exclude a CNS infection. There are some hypotheses proposed, the first being that the virus is thought to be cell-bound without actually entering the CSF or accomplishing at concentrations beneath the testing techniques. Moreover, the detection of hem products as a result of erythrocytes destruction in the CSF can affect the accuracy of the PCR tests used for identifing SARS-COV-2. The viremia can also be on a persistent low-level. Evidence showed that SARSCoV-2 RNA can only be identified in blood in 1% of the infected cases. (3)

2.6. Seizures

There is information which points out that COVID-19 can induce seizures in patients with no previous report of epilepsy.

Moreover, in patients with balanced cases of epilepsy it can disturbe the fragile equilibrium and precipitate a seizure. Well known factors that contribute are first of all hypoxia, as it can potentiate a hypoxic encephalopathy, fever and hyperpyrexia (over 40 degrees). Hyperthermia and brain damage induces the activation of glial cells and permeabilizes the blood brain barrier, along with disturbance of electrolites. It is widely shown that post-ischemic stroke as a result of hypoperfusion, has implicatons in the development of seizures in acute onset. (15) In chronic cases, mechanisms such as gliosis, chronic inflammation, angiogenesis, and eventually apoptosis and neuronal death, *neurogenesis, synaptogenesis, and loss of synaptic plasticity* are thought to play an important role. In cases of hemorrhagic strokes, the resorbtion of blood components can result in a state of hyperexcitability, which is known as seizure-provoking. (3) (16)

Once the virus penetrates the central nervous system, it determines the release of cytokines like TNF-alfa, IL-6, IL-1B which have been linked to both the inducing and perpetuating seizures. (16) It has been proven that IL-IB leads to the accumulation of glutamate in synapses, that can perpetuate a state of hyperexcitability. Furthermore, TNF-alfa leads to a greater number of glutamate receptors, while lowering the number of GABA receptors which translates also into an increasing neuronal excitability. Another cytokine favouring epilepsy is IL-6 which influences long term potentiation (LTP) and the neurogenesis of the hippocampus, in this way inducing and affecting the severity of epilepsy.

Another fact worth mentioning is that during the pandemic, in order to protect the medical personal from exposure, there have been concerns to the usage of routine EEG due to the risk of contaminations. Therefore, a limitation of possible studies can be the fact that a number of unidentified non-convulsive seizures could have passed unnoted. (1)

2.7. Neurogenic respiratory failure

One peculiar finding that has led to the belief that the respiratory failure characterizing COVID-19 has not only pulmonary cause but also a neurological one is the fact in many cases reported, patients actually had no respiratory complaint whatsoever but X-rays and other investigations performed showed poor lung performance. This developed into the theory that a “happy or silent hypoxemia” may be present. The disruption of BBB is believed to happen via retrograde trans-synaptic dissemination from receptors in the lung to the brainstem centers.

The effects of SarsCov2 at the level of gas exchange causing severe alveolar damage is well noted, however difficult to manage compared to typical cases of viral pneumonia. The involvement of CNS in the breathing process is involuntary imposed with the help of the pacemaker cells in the pre-Bötzinger complex (pre-BÖTC), situated at the level of the medulla oblongata, connected to the phrenic nerve motor neurons. This speculation is of great concern for the management of Covid19, as it has been shown that many patients cannot be withdrawn from mechanical ventilation event though signs of recovery from pneumonia are present. The neurogenic contribution to the involuntary breathing mechanics is of future interest. (17) (18)

Conclusions

At present, most data focuses on the respiratory consequences of SarsCov2 shown during the pandemic. Many neurological manifestations have been reported, though more data is necessary and it prevents us from making conclusions of its prevalence and characteristics. This paper managed to primarily draw attention to the symptoms pointing towards the neurotropism of the virus.

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