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REVIEW ARTICLE

Neuropathological Changes and Neurological Manifestations in COVID-19 Cases: A Narrative Review

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ABSTRACT

Background: Corona virus disease 2019 (COVID-19) has a lot of effects on the different tissues of human body particularly the respiratory system. Recently, there have been a lot of evidences that severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) has some effects on the nervous system especially brain tissues. In the early months of COVID-19 pandemic, the physicians focused on treating and dealing with lung damage and circulatory system support, but later the effects of neurological deterioration started to appear. In this review article we will discuss the different routes of administration of the virus into the central nervous system, neuropathological changes in the brain tissue, clinical neurological manifestations of the patients with COVID-19 and the histopathological changes in COVID-19 cases with neurological findings.

Conclusions: the brain tissue is affected by SARS-CoV-2 infection which causes a lot of neuropathological changes and manifests by different neurological signs and symptoms which are to be discussed.

Keywords: COVID-19; Neuropathology; SARS-CoV-2; Guillain Barre Syndrome; Neurological manifestations

INTRODUCTION

Corona virus disease 2019 (COVID-19) is a disease with a significantly broad spectrum of presentation and clinical symptoms caused by SARS-CoV-2. Infected patients have many common features such as fever, cough, and fatigue [1]. There are many possible dangers if these manifestations are not detected as early as possible which may cause serious complications of infected cases and this may lead to difficult management of these cases. Globally, as of 26 March 2022, there have been 476,374,234 confirmed cases of COVID-19, including 6,108,976 deaths, reported to WHO [2].
Patients come to hospital with fever, neck stiffness then diagnosed with encephalitis and further investigations showed positive COVID-19. There are a lot of recorded infected cases that suffered from neurological symptoms before their death. These patients were autopsied for examination of their brains and the findings were reported. This direct the attention to the danger of neuropathological lesions caused by COVID-19 and the importance to inform the neurologists and physicians dealing with suspected cases of COVID-19 about the recent findings of neurological manifestations, and the pathologists about the neuropathological features of suspected cases [1].
In this article, we aim to review the neurological manifestations, and the neuropathological changes of COVID-19 cases. We will present how the virus get into the brain, pathological findings and brain deformities in patients with COVID-19, neurological manifestation and effect of COVID-19 on both central and peripheral nervous system, and the spectrum of histopathological changes in COVID-19 cases.

Possible routes and mechanisms of CNS immersion in COVID-19

SARS-CoV-2 affects a variety of systems and cause many symptoms. Fever, dry cough, dyspnoea, and pneumonia are the most common symptoms of SARS-CoV-2 infection in the respiratory system. It's also linked to gastrointestinal symptoms (diarrhoea) and cardiovascular problems. SARS-CoV-2 has been linked to a variety of neurological symptoms, including loss of taste and smell, headaches, nausea, vomiting, and severe cerebrovascular

illness. There are many theories of how SARS-CoV-2 invades CNS but the exact cause is unknown [3, 4].

According to studies, there are several invasion routes such as the haematogenous pathway, peripheral neurological system and dysfunction of immune system. Although that SARS-CoV-2 is a novel virus, it has an ancient route of invasion. Angiotensin converting enzyme 2(ACE2) receptors have been found to interact with SARS-CoV-2 homotrimeric spike protein. ACE2 receptors are found all organs particularly in the endothelial cells. It`s presence in the general circulation provides a haematogenous route for CNS invasion. It binds to ACE2 receptors in the endothelium, then budding them off of capillary viral particles, causing damage and allowing access to the blood-brain barrier (BBB) ACE2 receptors in neurons interact with one other. Endothelial cell infection induces capillary rupture, resulting in bleeding or haemorrhagic infarction [3]. SARS-CoV-2 may enter the brain retrograding through cribriform palate after infection of the olfactory nerve as the olfactory nerve communicates both with the nasal epithelium and the olfactory bulb. It could potentially be through ACE2 receptors in the endothelium, which have access to the BBB. This can explain anosmia [3].

Immune cells play a role in SARSCoV-2's invasion of the CNS. After infection, cytokines and interferon are released and there is a state of war against the strange virus. The severe infection indicates overproduction of the pro-inflammatory cytokines. Prior studies provide that IL-6 and IL-8 affects the integrity of blood brain barrier. Recent studies on patients with CNS symptoms they found an elevation of IL-6 in CSF. So immune cells can infiltrate the BBB and cause inflammation along the brain and spinal cord. After infection, immune cells have to fight the virions, infecting them and allowing them to pass through the BBB [4].

Pathological changes in COVID-19 patients

To detect pathological changes in COVID-19 patients it is important to define the microscopical and macroscopical changes. For microscopical changes unfortunately the research that is conduct on brain autopsy for COVID-19 patients is limited to case series and retrospective studies. Examination of some patients of COVID-19 infection after their death revealed the characteristic changes of the brain. On microscopic examination of the brain fixed by formalin, several regions of the cerebral cortex were found thin, dark, and calcified. This was detected in the left frontal, left parietal and bilateral occipital cortices [5]. Microscopic examination of cerebral cortex in a study that was conducted in two patients with fetal covid-19 showed widespread multifocal infarcts. There was involvement of the whole cortical ribbon thickness by ischemic necrosis. The infarction was accompanied by extensive perivascular calcification. Subacute infarcts were detected with characteristic sheets of foamy macrophages and deposition of hemosiderin pigment. Cerebral amyloid angiopathies of moderate to severe forms were demonstrated in the cerebral cortex, cerebellum and leptomeninges. Many extramedullary megakaryocytes and sporadic platelet microthrombi were found in the infarcted areas. In addition, there was mild atherosclerosis with no sign of demyelination or infarction in the basal ganglia, thalamus and deep white matter [1].

In a study that was conducted in 146 patients, there were about 24 patients with nonspecific findings, 58 of the patients have mild to moderate acute hypoxic injury on the microscopic examination, 1 patient with sever hypoxic injury, and 22 of patients have focal ischemic necrosis. 23 patients with focal microhemorrhage and hemorrhage were found, 12 with microthrombus and 3 with neutrophilic plug. Infiltration of focal perivascular, parenchymal and T-cell predominant lymphocytic were also found. Activation of microglial especially in the brainstem was noted in some cases. A focus of extravasated blood over the lateral cerebellar hemispheres with a small subarachnoid hemorrhage was found in some cases. Axonal damage is less common. Acute and chronic inflammation in the olfactory epithelium and microglial activation [6].

And there was no evidence for SARS-CoV-2 RNA that indicates that all these changes may be as a result to host hyper immunity reaction. On a study that was conducted on 43 patients. Patients were grouped to 5 groups according their nervous system manifestations and a comparison on their neuroimaging finding was conducted as following; a group with 10 patients with encephalophagy group with neuroimaging within normal limits, 12 patients with CNS inflammatory syndrome with neuroimaging ranging between (normal - MRI abnormality - hemorrhagic changes), 8patients with stroke 4 of them have thrombus in large cranial vessels and the other 4 with pulmonary embolism (indication for hyper-coagulable state and increase in D-dimer) and the rest patients with peripheral nervous manifestations and miscellaneous symptoms has normal imaging [7].

To sum up, the most possible pathological findings in a COVID-19 patient including

hemorrhage, infarction, perivascular calcification and many extramedullary megakaryocytes.

Clinical picture and neurological manifestations of COVID-19

Even though COVID-19 affects both the respiratory and cardiovascular systems, many COVID-19 patients experience neurological symptoms such as headache, dizziness, hypogeusia, and neuralgia, as well as complications such as encephalopathy, acute cerebrovascular disease, and impaired consciousness. COVID-19 causes central and peripheral neurological signs and complications (Table 1) [8].

Headaches and dizziness: Despite the fact that headaches and dizziness are nonspecific and modest symptoms of many diseases, they have been linked to the presentation of COVID-19 in several publications. They are the most often reported symptom among patients [9].

The rate of occurrence varies between 3 and 12.1 percent [10, 11]. None of these papers go into detail about the details, mechanism, or pathology.

Encephalopathy: It was found that encephalopathy associated with headache was reported in 40% of patients [11]. Chen et al. reported evidence of hypoxic encephalopathy in 20 patients in a retrospective investigation of the clinical characteristics of 113 COVID-19 cases from China. Patients who have recovered had a much-reduced incidence [10].

The first verified case of COVID-19 related viral encephalitis from Japan was reported by Moriguchi et al [12]. A 24-year-old male presented with a fever, seizure, and loss of consciousness. He felt neck stiffness and had a normal CT scan of his brain. On the CT chest, there was patchy pneumonia. The PCR assay from the nasopharyngeal swab was negative, but the COVID-19 test from the CSF sample was positive. It was eventually determined that the symptoms were suggestive of right lateral ventriculitis and encephalitis [13].

Anosmia and ageusia: The most prevalent PNS signs of SARS-CoV-2 are anosmia and ageusia, which have previously been documented in prior coronaviruses (SARS-CoV (SARS), MERS-CoV) (MERS). These symptoms appear rapidly, and they are frequently accompanied by fewer nasal symptoms such nasal blockage or increased nasal discharge [14].

Some people with anosmia develop respiratory symptoms later in life, while others remain asymptomatic. In this context, even in the absence of other usual symptoms in the present pandemic, these symptoms should raise suspicion of COVID-19 infection [15]..

There were 24 investigations in total, providing data from 8438 patients of proven COVID-19 infection from 13 countries. They discovered the following:

Olfactory Dysfunctions: Only Six of the twenty-four research that looked at the prevalence of olfactory dysfunction used objective tests, whereas the rest relied mostly on self-reports. The prevalence of dysfunction was reported to range from 3.2 percent to 98.3 percent, with a combined incidence of 41.0 percent [16].

Gustatory Dysfunctions: The prevalence of gustatory dysfunctions was investigated in fifteen researches with 5649 patients. Only two out of fifteen used objective tests, while the remainder relied primarily on self-reports. The prevalence of dysfunctions was reported to range between 5.6 percent and 62.7 percent, with a combined incidence of 38.2 percent [16].

Another study indicated that the prevalence of smell and taste disorders is more prevalent in mild cases compared to moderate and sever cases and in female patients compared with males [17].

Seizures and status epilepticus: As COVID-19 patients may expert hypoxia, multiple organ damage and electrolyte disturbances that give the chance for clinical and subclinical seizures to occur especially in seriously ill patients. It is important to take in concern managing and treating these conditions [18].

The respiratory and cardiovascular systems are the primary targets of the COVID-19 virus. Neurological symptoms, on the other hand, are becoming increasingly common and can lead to major consequences if they are not identified and treated as soon as possible. Complications are clearly visible in seriously ill patients, and they might arise before or after respiratory symptoms, or they can be the sole symptoms in COVID-19 individuals. Considering that presenting with unexpected or unexplained neurological symptoms in young adult my make we suspect SARS-CoV-2 as a causative agent [19]. To improve therapy options and minimize chronic damage, we must first be more attentive when dealing with such scenarios. Second, it is recommended that data on short- and long-term neurological issues be collected consistently from various parts of the world, particularly in underdeveloped countries where competent medical services are rarely found.

Other manifestations: Researchers found that depression & anxiety (42%) and autoimmune diseases were identified to be the most common comorbidities (16%). The most common neurologic symptoms were "brain fog" (81%), headache (68%), numbness & tingling (60%),

dysgeusia (59%), anosmia (55%), and myalgias (55%) in SARS-CoV-2 patients, with only anosmia being more common in SARS-CoV-2 patients. In addition, 85% reported feeling tired. There was no link between the duration of time since the onset of the disease and the subjective perception of recovery. In the cognitive and tiredness domains, both groups had lower quality of life. When compared to a demographically matched US population, SARS-CoV-2 positive patients performed worse on attention and working memory cognitive activities [14].

Table 1: Central and peripheral neurological manifestations and complications [8].

Central nervous system (CNS) manifestations	**%**	**Peripheral nervous system (PNS) manifestations**	**%**
Headache & Dizziness	3-12	Hypogeusia	38
Impaired consciousness	Not reported	Hyposomia	41
Encephalopathy or Encephalitis	40	Neuralgia	60
Epilepsy – Ataxia	Not reported	Guillain Barre syndrome	Not reported
Transverse myelitis	Not reported	Skeletal muscle injury	55
Acute hemorrhagic necrotizing encephalopathy	Not reported		

The histopathological changes in COVID-19 cases

20 papers were reviewed including 184 patients with tissue-based neuro-histopathological analyses, including 101 cases examined by PCR for SARS-CoV-2 and 83 cases by immunohistochemistry, to explore the spectrum of COVID-19 neuropathology. The range of histologic findings reflects the heterogeneity of neurological features (Table 2). Microglial activation of microglial nodules in a probably underestimated subset; lymphoid inflammation including perivascular lymphocytosis, parenchymal lymphocytic infiltration, and leptomeningeal lymphocytic inflammation; hypoxic-ischemic changes astrogliosis; acute/subacute brain infarctions; primary hemorrhage; and microthrombi are the most common. It should be noted that papers with immunohistochemical studies have a higher prevalence of observed lymphoid inflammation and microglial nodules [20] (Table 2).

Table 2: Histopathological changes in brain tissue of COVID-19 cases. Some histologic results are likely to be under-reported as reviewed studies aren't constant in their focus [20].

Viral presence by PCR	**53.5% (54/101)**
Viral presence by IHC	27.7% (23/83)
Leptomeningeal	23.4% (43/184)
Acute Ischemic Changes	29.9% (55/184)
Astrogliosis	27.7% (51/184)
Acute/Subacute Brain Infarcts	21.2% (39/184)
Spontaneous Hemorrhage	15.8% (29/184)
Microthrombi	15.2% (28/184)
Alzheimer Type II	2.7% (5/184)
Neuronophagy	2.2% (4/184)
Neuronal Cell Loss	2.2% (4/184)
Hemorrhagic Transformation of Infarct	2.2% (4/184)
Foci of Demyelination	1.6% (3/184)
Vascular Neutrophilic Plugs	1.6% (3/184)
Perivascular Neutrophils	1.1% (2/184)
Parenchymal Neutrophilic Infiltration	1.1% (2/184)

Viral presence by PCR	**53.5% (54/101)**
Leptomeningeal Histiocytes	0.5% (1/184)
Acute Purulent Meningitis	0.5% (1/184)

CONCLUSIONS

In this review article, we discussed the neuropathological findings and clinical manifestations of COVID-19 depending on many research papers including cohort, clinical trial, case report studies... etc.

There are many mechanisms of involvement into the CNS such as; the peripheral nervous route, hematogenous route and Immune cell route and there were some evidences on the olfactory nerve route to brainstem as a possible route of invasion. Evidences of neuropathological changes of the brain tissue have been found on microscopic examination of the brain of dead cases infected by SARS-CoV-2. Some of these findings include infarction, calcification, ischemia, necrosis and micro-angiopathies.

As a result, COVID-19 patients can develop neuropathological central nervous system manifestations like headache, dizziness, encephalitis, acute hemorrhagic necrotizing encephalopathy, impaired consciousness, epilepsy and ataxia as well as peripheral nervous system manifestations like Hypogeusia, Hyposmia, Neuralgia, Guillain Barre Syndrome and myopathy.

RECOMMENDATIONS

Further research is still needed to support the management of neurological manifestations at an earlier stage to avoid further complications and deformities.

Conflict of interest

The authors listed above declare no conflicts of interest.

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