

CNS Manifestations in COVID19: Symptoms Suggest Involvement, its Manifestations and Future Course

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Corona Virus Disease- 19 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as an alarming global pandemic since the first reported cases in December 2019 in Wuhan city, a populated area of the Hubei province in China. It was initially known as Novel Coronavirus. Previous outbreaks caused by Coronaviruses include severe acute respiratory syndrome (SARS) in 2003 and Middle East respiratory syndrome (MERS) in 2012. Both Coronaviruses originated from bats, which infected secondary host such as civet cats (SARS) and dromedary camels (MERS). Coronavirus usually cause upper respiratory tract infections and are associated with gastroenteritis and necrotizing enterocolitis in Children [1,2].

Although SARS-CoV-2 mainly targets the respiratory tract because of plenty of ACE-2 receptors by its spike-like protein on its surface, but other organ systems such as the renal, liver and cardiovascular systems are also affected. Additionally, neurological symptoms are commonly seen in COVID-19 and include ageusia and anosmia, non-specific symptoms such as headache, prominent agitation, convulsions, impaired consciousness, change in mental status and dizziness, and severe conditions such as hemorrhagic encephalopathy, ischemic stroke, and posterior reversible encephalopathy syndrome with epileptic seizures. Furthermore, research and clinical work-up of patients, suggest that meningitis, encephalitis, polyneuritis cranialis and Guillain-Barré, Miller Fisher syndromes and perivascular acute disseminated encephalomyelitis (ADEM)-like appearance might also be associated with COVID-19 [1-6]. With the onset of various neurological symptoms, the common view holds and suggests CNS involvement by COVID19. The appearance of anosmia, as a fairly common symptoms, suggested very early in the course of the pandemic a consistent neurological involvement.

Jason Netland., *et al.* in their experimental study conducted on transgenic mice, showed that the entry of SARS-CoV virus into the brain occurred by the olfactory bulb, further leading to trans-neuronal spread. They observed significant fraction of neurons to be expressing viral antigen by day 4 and suggested that the death of the mice occurred due to the death of infected neurons, particularly the neurons located in the cardiorespiratory centres of the medulla [7].

A histopathological examination of 06 patients who died of COVID19 in Germany, revealed meningitis, lymphocytic panencephalitis and localized perivascular inflammation, in all the cases examined. Also, they observed that all the younger aged cases (< 65yrs) exhibited diffuse petechial haemorrhages owing to massive intracranial haemorrhage due to COVID-19 associated coagulopathy. Hence, in the younger cases, they attributed CNS haemorrhage to be a fatal complication. However, they attributed none of these changes to be due to COVID19 induced hypoxia [8]. On the other hand, Isaac H. Solomon., *et al.* suggested only hypoxic induced injury in the cerebrum and cerebellum, with no evidence of meningitis, encephalitis or olfactory bulb abnormality. They also found no cytoplasmic viral staining on immunohistochemical examination [1].

The post-mortem brain examination of a 71-year-old male who died of COVID19, revealed widespread haemorrhagic white matter lesions distributed throughout the cerebral hemisphere. Histopathology showed a perivascular acute disseminated encephalomyelitis (ADEM)-like appearance, along with features of axonal damage. Also, observed were clusters of macrophages at the periphery of the lesions. Only scant CD3 positive perivascular lymphocytes were observed. Hence, this case report highlighted that the postulated mechanism for this type of insult could be due to para-infectious post viral autoimmune response apart from primary vascular disease [9]. Another case study, reported a case of Acute necrotizing encephalopathy in patient with COVID19, who showed symmetric hypoattenuation within the bilateral medial thalami on Non-contrast CT imaging. MRI showed haemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions suggestive of Acute necrotizing encephalopathy [10].

In a study by Matschke J., *et al.* they investigated the brain tissue of 43 patients who died from COVID-19 for glial responses, inflammatory changes, and the presence of SARS-CoV-2 in the CNS, they concluded that SARS-CoV-2 RNA and proteins can be detected in the CNS. The brain showed mild neuropathological changes with marked neuroinflammation in the brainstem being the most common finding. However, the presence of SARS-CoV-2 in the CNS was not associated with the severity of neuropathological changes [11].

The neurological symptoms so commonly appearing in patients with COVID-19 infection, could be due to various reasons. Some of the few explanations include direct cytopathic effect by the virus, hypoxia induced changes, cerebrovascular insults due to coagulopathy and also metabolic changes [8].

Specifically, the effect and impact of SARS-CoV-2 on the CNS and brain tissue could be (i) direct neurological alterations in infected individuals, (ii) worsening of an already existing neurological conditions and damages, and/or (iii) increased susceptibility or accelerated damage caused by other insults. In patients younger than 65 years, CNS haemorrhage was a common fatal complication of COVID-19.

Given the global dimension of the current pandemic and the high transmissibility of SARSCoV-2, the evidence discussed earlier raises concerns regarding the potential long-term CNS consequences of COVID19 too.

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