

The Portrait of a Killer; SARS-CoV-2 Potential Mechanisms For Neuronal Damage

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The betacoronavirus SARS-CoV-2 or COVID-19 [1] was first reported in Wuhan, China in December 2019 [2]. Since then, it has rapidly swept through the globe, resulting in a pandemic [3] of the twenty first century. SARS-CoV-2 still tenaciously persists and rages through many parts of the world. It ravages the human population leaving illness and death in its wake. As of June 3rd 2021, the WHO COVID-19 dashboard has reported 171 million cases of SARS-CoV-2 in 220 countries and 3.686 million deaths.

Although, SARS-CoV-2 primarily causes an acute respiratory syndrome, it can damage the heart and also induce brain dysfunction, neuropsychiatric and neurological manifestations [4]. Furthermore, post mortem evidence shows signs of multi-organ (lungs, heart, kidneys, brain and liver) dysfunction and failure [5,6]. This is probably related to inflammatory volatile “cytokine storm” and coagulation abnormalities ascribing for the malevolent and potentially lethal actions of the virus.

Similarly, one of the two viruses that was responsible for influenza pandemic of 1918 [7] has also been reported to be neurovirulent [8]. The virus caused encephalitis lethargica, delirium and cycloplegia [9]. Epidemiologists postulate that post-encephalitic parkinsonism was about twice more likely after infection with this virus. Additionally, infections with other viruses such as West Nile [10], Coxsackie [11], St Louis [12], Japanese encephalitis [13] and HIV [14] are also known to produce parkinsonian motor features. A perplexing feature is that the neurological sequelae occur after many years following the viral infection. Interestingly, mice infected with H5N1 virus exhibited neuropathological changes similar to Parkinson’s disease such as alpha-synuclein aggregation, microglial activation and destruction of dopaminergic substantia-nigra neurons [15]. These viruses are said to be neurotropic and gain access to the brain resulting in encephalopathies, which in turn initiate parkinsonian features.

SARS-CoV-2 infections has been associated with non-specific neurological symptoms such as dizziness, headache, and more specific manifestations such as, encephalitis, seizures, Guillain-Barre syndrome, hypercoagulable states that lead to acute cerebrovascular disease [16]. Encephalopathy may occur para or post infection and are a relatively common occurrence. Although, SARS-CoV-2 related encephalitis is self-limiting relating to the clearance of the virus [17], nevertheless, the brain infection may result in delayed and permanent neurological damage in patients that have recovered, particularly for those that were acutely affected.

Thus, SARS-CoV-2 is neurotropic and is able to manifest neurological symptoms [18]. Although the precise neurotropic pathways are unclear, it has been suggested that it may involve direct (neuronal retrograde or haematogenous dissemination) or indirect mechanisms. Ageusia and hyposmia are commonly associated with SARS-CoV-2 and they may be present in the absence of other clinical features. Perhaps, SARS-CoV-2 invades the olfactory bulb to gain entry to the brain. Indeed, this phenomenon has been observed in transgenic mice that express transmembrane angiotensin 2 (ACE 2) receptors [19]. Additionally, gene expression databases demonstrate a high expression of ACE 2 receptors in human olfactory mucosa. Thus, the nasal olfactory epithelium may be a likely candidate for the entry of the virus, it can then get access to the brain via the nerves. The infected olfactory receptor neurons probably ascribes for the hyposmia and ageusia

Generally, it seems that two major modes of cellular damage are executed by SARS-CoV-2, inflammation and thromboembolic events. Using high resolution magnetic resonance imaging (MRI) on post-mortem brain tissue, activated microglia were found in some SARS-CoV-2 patients in the olfactory bulb, substantia nigra, dorsal motor nucleus of the vagal nerve and the medulla [20]. Microgliosis is indicative of neuroinflammation and is also reported in the substantia nigra in Parkinson's disease [21]. In addition, hyposmia is observed in over 80% of the SARS-CoV-2 infected patients and about 65% parkinsonian patients [22]. Hyposmia is a premotor symptom in Parkinson's disease. Although to date only a few reports of SARS-CoV-2 infected patients exhibited nigrostriatal abnormalities coupled with acute onset parkinsonian like motor features in the absence of any genetic predisposition [22,23]. Nevertheless, this should not rule out the possibility that some of the SARS-CoV-2 surviving patients may have a propensity to develop neurodegenerative disorders (such as, Parkinson's disease), particularly since ageing is a known risk factor.

It appears that inflammation is the primary mode of cellular carnage employed by SARS-CoV-2. Evidence suggests that aged patients with chronic illness are particularly susceptible to the severe form of the SARS-CoV-2 infection with a high mortality rate. This is perhaps due to, the modest age related elevation of systemic pro-inflammatory cytokines, excess production of free radicals, changes in ACE 2 receptor expression and alterations in autophagy [24]. Incidentally, the production of reactive oxidative species and accumulation of unwanted protein due a dysfunctional autophagic system are hallmarks of alpha-synucleinopathies such as Parkinson's disease [25]. Therefore, there is a possibility that if these older patients were to survive the acute SARS-CoV-2 infection that they may develop a neurodegenerative disease in the future.

Interestingly, post-mortem studies do not exhibit an abundance of the virus in the brain, thereby supporting indirect organ damage via immune mechanisms and platelet aggregation leading to brain dysfunction. Viral particles were found in brain endothelial, thereby demonstrating them as a focal point of attack [26]. Although, the virus can also gain entry by binding to neuropilin and CD209L receptors [27], it appears that SARS-CoV-2 mainly binds to ACE 2 expressing endothelial cells of the blood vessels. This binding is crucial for its mode of action as it allows the virus to infect the host causing inflammation and blood vessel damage [28].

The binding of the virus SARS-CoV-2 to endothelial cell triggers the inflammatory cascade and results in the release of pro-inflammatory cytokines (interleukin 1 β , 6, 10; tumor necrosis factor- α) also known as a 'cytokine storm', nitric oxide and free radicals [29,30]. This may cause dysregulation of the immune system. Alternatively, the virus may induce the release of the cytokines resulting in endothelial damage. The endothelial dysfunction may be a direct consequence of SARS-CoV-2 invasion leading to inflammation.

Both mechanisms appear to be possible. The peripheral cytokines can damage the blood brain barrier, thereby allowing the virus to enter the brain and attach to the endothelial cells and trigger neuroinflammation. In addition, the virus may enter the central nervous system via the nerve pathway. Nevertheless, the increase in cytokines may trigger a host of cellular deleterious events including; neuronal apoptosis, activation of microglia, which in turn can increase production of glutamate and depletion of dopamine and 5-hydroxytryptamine (5-HT). Consequently, the disruption in brain neurotransmitters levels can lead to neuronal malfunctions.

The elevation in glutamate, aspartate and cytokine coupled with the reduction of the inhibitory transmitter γ -aminobutyric acid may account for the occurrence and the onset of seizure pathogenesis in severely affected SARS-CoV-2 patients [31]. Additionally, the cytokines and free radicals produced in the brain, particularly in the hippocampus also contribute to the onset of epilepsy. Additionally, a leaky blood brain barrier may allow the entrance of blood proteins that disturb the osmotic balance in the brain thus provoking seizures [32].

The nigrostriatal disturbances reported in the SARS-CoV-2 infected patients could cause reduction brain dopamine. Furthermore, the "cytokine storm" can also initiate the production of cytotoxic free radical species. Indeed, cytokines interleukin 1 β , 6, and tumor necrosis factor- α can generate the free radical nitric oxide and nitric oxide synthase [33]. Nitric oxide free radical can react with superoxide radicals to producing highly cytotoxic and reactive peroxynitrite species [34]. Thus, a possible nigral dopamine reduction coupled with production of free radicals and mitochondrial malfunction may trigger neuronal destruction [35] via initiating processes such as free radical

mediated oxidative stress resulting in the manifestation of some parkinsonian features [36]. Since these biochemical changes are similar to those observed in the neurodegenerative disorder.

The neuropsychiatric complications and impairment of cognitive functions that are related to the SARS-CoV-2 infection may be attributed to the depletion in 5-HT. The role of 5-HT to effectively treat depression is well established [37]. Also, it has been suggested that brain 5-HT plays a protective role during systemic inflammation [38]. This notion is supported by the reduction in cytokine (interleukin 1 β , 6, 10; tumor necrosis factor- α) surges, a reduction in plasma nitric oxide following intracerebroventricular administration of 5-HT prior to lipopolysaccharide administration in a model for inducing sepsis related immune response in rats [39]. It employs central and peripheral mechanisms to dampen the inflammatory response. Furthermore, although central 5-HT pathways can modify systemic inflammation, it can also be affected by it, particularly in the anteroventral region of the hypothalamus. This is a principal area for the maintenance of body temperature.

This supports the rationale for the advocacy of selective 5-HT reuptake inhibitors, that would amplify the central 5-HT levels, consequently this may diminish some of the SARS-CoV-2 induced deleterious immune responses and also reduce the associated neuropsychiatric manifestations [40]. Indeed, SARS-CoV-2 infection generates cytokine-mediated neuroinflammation, which can result in a neuropsychiatric syndrome known as immune effector cell-associated neurotoxicity syndrome [41]. The elevated 5-HT levels may act both peripherally on 5-HT receptors and indirectly centrally through anti-inflammatory vagal reflex [39].

The virus induced inflammation in blood vessels, may damage the vessel walls and make them leaky and allow access of the protein fibrinogen from the vessels into the brain areas. Vascular injury to the endothelial cells can result in platelets aggregation and which couples with fibrin to triggering coagulation cascade and the formation of fibrin clots. Additionally, the activated platelets may prompt the release of thromboxane A₂, which promotes platelet aggregation. These clots have the propensity to occlude blood vessels and result in acute cerebrovascular events, pulmonary embolisms, and deep vein thrombosis [42].

Many studies furnish evidence for abnormal coagulation parameters such as high levels of D-dimer in SARS-CoV-2 infected patients [43]. Like many other viral infections, SARS-CoV-2, can also cause small blood vessel thrombosis leading to catastrophic microvascular damage [44]. The presence of microscopic clots in small blood vessels would reduce the perfusion rate of blood at a cellular level in the brain and peripheral organs. This contention is supported by MRI studies demonstrating small blood vessel damage, but only marginal damage to nerves [20]. Consequently, this would exacerbate the severe hypoxemia that is characteristic of SARS-CoV-2, infection [28]. This deficient state of oxygen may improve in time as the infection clears, however that does not negate the viable possibility of cellular damage and subsequent long-term effects. For instance cerebral microvascular disturbances may ascribe for the modest cognitive impairment such as the 'brain fog' associated with SARS-CoV-2 infections and more importantly in acute cases this may precipitate Alzheimer's disease subsequently in later years [46].

Finally, the emergence of new SARS-CoV-2 strains may also suggest evolving patho-mechanisms, this may prove to be a challenge in the battle against this formidable virus.

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