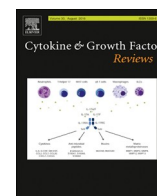




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COVID-19 infection may increase the risk of parkinsonism – Remember the Spanish flu?



The recent outbreak of coronavirus disease 2019 (COVID-19) has resulted in a global pandemic. Crucially, most of the damage in patients dying from the COVID-19 infection appears to be mediated by their own immune responses rather than by the virus. The viral infection culminates in a surge in signaling protein molecules that elicits massive inflammation, a “cytokine storm”, -which targets the lungs, attacking different tissues culminating in acute respiratory distress syndrome (ARDS), multiorgan failure and death [1]. The very high level of pro-inflammatory cytokines i.e. the cytokine storm, or cytokine release syndrome (CRS), may be pivotal in the severe pathology of COVID-19. The cytokine storm is not unique to COVID-19 but is also associated with influenza virus, human immune deficiency virus and some other viruses. Recent studies suggest a link between the cytokine storm, and speeding up the onset of parkinsonism [2–4]. Whether COVID-19 induced cytokine storm would spur the onset of parkinsonism in vulnerable patients is currently unclear. Herein, based on recent reports connecting COVID-19 and cytokine storm, we briefly present an intriguing hypothetical model connecting COVID-19-infections, the subsequent runaway inflammation reactions and the possible surge of vulnerability to parkinsonism. These activations in pro-inflammatory cascades might bear opportunities for therapeutic intervention before the onset of neurodegeneration.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen for COVID-19, targets mainly the lung and other organs, culminating in organ damage via binding angiotensin-converting enzyme 2 (ACE2) receptor [5], a highly expressed protein on the outer surface of cells within the lung, kidney and heart [6]. Notably, the massive release of inflammatory cytokines and chemokines during the “cytokine storm” may be crucial in mortality from COVID-19. Several inflammatory cytokines, such as interleukin-6 (IL-6) and interleukin-1 β (IL-1 β), are significantly elevated in COVID-19 patients, with some chemokines observed more in severely ill patients. Postmortem pathology, in COVID-19 patients with upregulated inflammatory chemokines, reveals necrosis and monocyte infiltrations in the lung, heart and gastrointestinal mucosa [7,8]. Besides, severe lymphopenia with hyperactivated proinflammatory T cells [8] is widely observed in critically sick patients, suggesting a potent trigger of cytokine storm and dysfunctional immune responses.

Although SARS-CoV-2 virus may mediate neurological damage by eliciting immune cytokines storm, alternatively, it also directly infects the brain. Indeed, recent studies demonstrate the presence of the novel coronavirus in the post-mortem brain tissues of fatal cases of COVID-19 [9]. It has been suggested that infection of endothelial cells may facilitate the viral passage from the respiratory tract to the blood thereby crossing the blood-brain barrier into the brain [23].

Often confused as one, Parkinson's disease (PD) is considered the most common kind of Parkinsonism, accounting for more than 80% of all cases [24]. PD is a progressive neurodegenerative condition characterized by motor symptoms, like Parkinsonism's, including tremor, rigidity, and impaired balance [25]. In addition, PD is cellularly characterized by gradual loss of dopaminergic neurons in the substantia nigra [10]. The exact

molecular cause of neuronal loss in PD remains unknown [11]. Only about 10-20% of patients have an identifiable genetic link, while the cause in the other 80-90% is not completely understood [26]. It is widely appreciated that genetic factors and environmental factors (including heavy metals and pesticides) may play a role in the causation of PD [12,13].

The hypothesis that a viral infection may trigger the onset of parkinsonism stems from a few previous observations [14]. First, the incidence of parkinsonism after the Spanish flu pandemic in 1918 increased significantly with people born during the pandemic having 2 to 3-fold risk to develop parkinsonism than those born before 1888 or after 1924 [14]. Notably, many of the patients who survived Spanish flu exhibited viral encephalitis - brain swelling, inflammation and damage due to viral infection of the central nervous system, ultimately infecting the brain, a scenario that can be fatal [15]. Indeed, almost every Spanish Influenza patient who had an acute episode of encephalitis within the infection course from the influenza virus later developed the so-called viral parkinsonism. Viral parkinsonism has been linked to other viral infections, including other viruses such as the West Nile Virus and HIV.

Second, the H5N1 virus when administered in the nose of mice can infect the alpha-synuclein (the major component of Lewy bodies, the hallmark of PD) and elicit dopaminergic neuronal loss in the substantia nigra. Finally, experimental H1N1 infection in mice sensitizes dopaminergic neurons to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin in experimental models for parkinsonism that leads to dopaminergic neuron loss. Interestingly, vaccinating the animals against the flu or treating them with Tamiflu at the time of infection protects the animals from dopaminergic neuronal loss [12,13,27].

Interestingly, the dengue viral infection, which is an arbo viral infection transmitting by *Aedes* mosquitoes [16] and affects over 300 million infections per year with millions of severe cases, has been reported to progress to ultimately culminate in massive cytokine storm in severe dengue viral infection cases. While some patients recover from primary severe dengue-viral infection, the dengue viral-mediated cytokine storm and its potential complication i.e. post-encephalitic parkinsonism continue to exist after the dengue viral infection [17].

Although viral parkinsonism might bear similar features with idiopathic parkinsonism, it seems unlikely that the pathophysiology is due to abnormal Lewy bodies accumulation and neurofibrillary deposition in brain tissue [14,18]. Whether the dengue viral-mediated cytokine storm and the resultant augmented inflammatory reaction underlie the molecular events leading to dengue-linked parkinsonism is far from clear.

Intriguingly, given that several recent reports support the notion that elevation of pro-inflammatory cytokines levels including IL-6 and IL-1 β may hasten the onset of Parkinson's symptoms [2,3,19,20] and, concomitant intake of non-steroidal anti-inflammatory medication is inversely associated with a later diagnosis of Parkinson's disease [21]. Immunosuppression with steroids such as methylprednisolone may help in attenuating parkinsonism progression in selected patients [28].

Since COVID-19 results in cytokine storm in many cases [22], it is

plausible that it may lead to an increased incidence of parkinsonism in those who recover from the infection. Future investigations and longitudinal studies are crucially advisable in this patient population to discern this possible risk.

Declaration of Competing Interest

None

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