# COVID-19 and De Novo Movement Disorders: Lessons Learned So Far

Since the emergence of the COVID-19 pandemic in the month of December 2019, there has been a substantial upsurge in publications addressing its association with various movement disorders. While initial data was discrete and sketchy, recent systematic reviews have unfurled a better understanding of the impact.[1-3] As the disease appears to linger on for some time, more research is needed in the upcoming years to address the gaps and controversies emerging from the data assimilated so far. Moreover, the data heralds an inevitable analogy to the encephalitis lethargica that swept the world in the 1920s. A study published in this issue of the journal has reviewed the papers published in the last 3 years (December 2019 to December 2022) and explored the data from 82 studies encompassing 133 patients.[4] The study has reconnoitered some of the unanswered questions in this regard like the impact of patient's age, comorbidity and severity of infection, and latency of onset of movement disorders and their outcome.

Myoclonus-ataxia was the most commonly reported movement disorder followed by varied combinations of myoclonus, ataxia, opsoclonus, and tremor. While post-hypoxic etiology was suspected in a few patients based on cortical or brainstem lesions in neuroimaging, post-infectious autoimmune response targeting cerebellar and brainstem neurons was surmised in most of them, supported by improvement at the time of discharge with immunotherapy.[5] The majority of patients had generalized or multifocal myoclonus, while focal myoclonus was noted in a few. Stimulus-sensitivity, action inducibility, and beneficial response to levetiracetam or clonazepam support cortical origin in most cases. Abnormal excitation of either the corticospinal tract from hyperactivation of cerebello-thalamo-cortical circuitry or the reticulo/rubrospinal tract from excitation of brainstem nuclei directly or indirectly from cerebellar projection likely plays the major role in the generation of myoclonus and its association with other hyperkinetic movement disorders.[6] The predilection of older age with variable onset latency for myoclonus can be explained by the time required to spawn an autoimmune response (autoimmune) and reorganization of neuroplasticity after an insult (post-hypoxic) in a predisposed brain network. Comparable onset latency for ataxia or opsoclonus along with response to immunotherapy indicates a shared autoimmune pathophysiology.[7] However, the development of later entities with mild infection and ataxia in younger populations reflects more vulnerability of the Purkinje cells and GABAergic synapses in the cerebellum.

Post-COVID Parkinsonism is the next most highlighted movement disorder in all the recent papers published on this topic, bringing back the memoir of encephalitis lethargica, described by Von Economo after the 1918 flu pandemic. However, the causal relationship is still debatable. SARS-CoV2 may play the "initial hit," while some multifactorial events with or without genetic predisposition may end up in the development of long-term Parkinsonism. Possible pathophysiology proposed in the studies include SARS-CoV2-related hypersensitivity vasculitis (endothelitis), neuroinvasivity of the virus affecting substantia nigra pars compacta (SNpc) and striatum through ACE2 receptor tropism, and subsequent local and systemic pro-inflammatory response and SARS-CoV2 N protein-mediated alpha-synuclein aggregation.[8-10] Three major post-COVID Parkinsonism groups have also been identified so far based on etiopathogenesis—(1) inflammatory or hypoxic insult in the backdrop of encephalopathy, (2) unmasking of non-symptomatic Parkinson's disease, and (3) structural or functional damage to the nigrostriatal dopaminergic pathway based on imaging findings.[8] This systematic review highlighted a delayed onset latency for de novo Parkinsonism along with variable levodopa responsiveness and a tendency to persist for a long period in most cases. The findings strengthen the possibility of post-COVID nigrostriatal dysfunction in predisposed individuals. The time required to unleash such a response consists of a multistep interplay of different direct and indirect pathophysiological factors as discussed, which may explain the longer latency. A similar trend was noted in post-COVID isolated postural or action tremor as well, indicating a possible role of dopaminergic dysfunction in tremor pathophysiology.

Other de novo hyperkinetic movement disorders reported were dystonia and rarely chorea, stereotypies.[2] Dystonia was commonly noted as a part of mixed phenomenology with myoclonus or Parkinsonism. Interestingly, the review noted shorter onset latency for dystonia in contrast to the usual longer latency in secondary dystonia as seen in post-stroke cases. This indicates simultaneous affection of multiple other brain networks as a result of SARS-CoV2, apart from the typical pallidothalamic involvement. Chorea and arm-lifting stereotypic movements resembling "Lazarus sign" were also reported mainly from structural damage to cortico-striatal circuitry subsequent to the infection.[6] Apart from them, functional tics and tremors were reported in a few studies as a part of post-COVID neuropsychiatric complications.[2]

The review also highlighted some studies indicating overlapping phenomenology with typical autoimmune movement disorders. The finding of positive anti-NMDA, anti-GAD, anti-GFAP, and anti-GlyR antibodies in some of them further indicates the role of SARS-CoV2 in flaring up a systemic autoimmune response.[2]

Finally, the review summarized the neuroimaging findings of these patients with de novo movement disorders. MRI hyperintensities involving cerebellum in ataxia and putamen in chorea indicate possible structural involvement of cerebello-thalamo-cortical and cortico-striatal network in post-COVID movement disorders. Similarly, TRODAT positivity in patients with de novo Parkinsonism suggests affection of either the nigrostriatal dopaminergic pathway or involvement of the striatum itself as discussed previously. Factors responsible for preferential involvement of direct or indirect striatal pathways leading to hypo or hyperkinetic movement disorders need to be elucidated in future studies. Functional neuroimaging with FDG-PET revealed some exciting pathophysiological clues.[9] Hypermetabolism in the cerebellum along with hypometabolism of the frontal cortex indicates affection of cerebellar brain inhibition (CBI), while cortical hypometabolism in Parkinsonism represents involvement of cortical network, beyond basal ganglia. The findings pave the way for future studies with transcranial non-invasive brain stimulation in SARS-CoV2-related movement disorders.[11]

As we are now delving deeper into the enigma of de novo movement disorders after COVID-19, there is an unmet need to integrate the facts, filtering out the fantasies.[12] More importantly, we need to be cognizant of the movement disorders that are directly virus-mediated, in contrast to the associations that are mere chance findings or as a result of confounding factors. The data currently available in this regard lay the foundation for future studies to explore the complex relationship between the virus and interlaced brain networks that phenotypically result in a spectrum of movement disorders.

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