SARS-CoV-2 and the dopaminergic system

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A significant portion of COVID-19 survivors exhibit neurological deficits, and upon close examination also display pathological changes in the nervous system. Recent reports describe three patients hospitalized with severe COVID-19 who developed clinical parkinsonism, in isolation or with other neurological deficits, within 2-5 weeks of contracting SARS-CoV-2 [1-3]. In all three cases, brain imaging revealed reduced function of the nigrostriatal dopaminergic system. Two received dopaminergic drugs and experienced clinical benefit [2,3], while the third patient spontaneously recovered from the parkinsonism [1]. These cases do not definitely prove a causal relationship between SARS-CoV-2 infection and acute parkinsonism, but the rapid onset of severe motor symptoms shortly after the viral infection is suggestive. None of the patients had a family history of Parkinson's disease (PD), or showed signs of prodromal PD. One patient underwent genetic testing and did not carry any of the major PD risk variants [2].

What might be the underlying mechanisms of the acute onset of parkinsonism following COVID-19? While the initial trigger(s) of sporadic PD are not known [4], bacterial and viral infections have been implicated [5, 6]. There are three potential mechanisms for the rapid development of parkinsonism that may occur either alone or in concert [7]. First, vascular insults occur in multiple organs, including the brain, in severe COVID-19 [8]. One neuropathology study emphasized microvascular lesions in different brain regions including the substantia nigra [9] and microglial activation as well as invading cytotoxic T cells have also been observed in the brainstem [10]. Second, the systemic inflammation that occurs in severe COVID-19 could possibly trigger neuroinflammation and demise of nigral dopamine neurons. Midbrain dopamine neurons are believed to be particularly susceptible to systemic inflammation. In COVID-19, the level of IL-6 is elevated, and the kynurenine pathway is perturbed [11], changes that both are relevant to PD [12]. Third, SARS-CoV-2 RNA has been detected in brain tissue, indicating that it is neurotropic. The neuropathology and clinical features of prodromal PD suggest that the disease process in PD might be triggered in the olfactory system (causing hyposmia) or in enteric nerves (leading to constipation) and then propagates to, for example, the substantia nigra [4] . Strikingly, hyposmia (and dysguesia) are common in COVID-19, and SARS-CoV-2 can infect the olfactory epithelium [13], possibly using Neuropilin-1 receptors to gain entry to the cells [14]. Notably, in COVID-19 there are microvascular lesions specifically in the olfactory system and dorsal motor nucleus of the vagal nerve [9] that innervates the

digestive and respiratory tracts which both are favored sites of attack of SARS-CoV-2. Midbrain dopamine neurons express high levels of the ACE2 receptor which is essential for SARS-CoV-2 entry [15]. Upregulation of neuronal alpha-synuclein can occur following invasion of other viruses [16, 17], and elevated alpha-synuclein is associated with Lewy body pathology. Thus, it is conceivable that people infected with SARS-CoV-2 might end up being predisposed to PD later in life.
While the development of acute parkinsonism following COVID-19 is a rare event, the three case studies might tell us something fundamentally important about underlying disease mechanisms in sporadic PD, and they highlight the need to be vigilant of changes in the incidence of PD in the post-COVID-19 era.

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