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## Spotlight

## Is COVID-19 a Perfect Storm for Parkinson's Disease?

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**Three recent case reports (by Méndez-Guerrero *et al.*, Cohen *et al.*, and Faber *et al.*) describe the development of acute parkinsonism following coronavirus disease 2019 (COVID-19). We discuss possible underlying cellular and molecular mechanisms, and whether COVID-19 might be associated with elevated long-term risk of Parkinson's disease (PD).**

The COVID-19 pandemic has greatly impacted global health, with an estimated 39 million confirmed cases and 1.1 million deaths (as of October 16, 2020). Additionally, several COVID-19 patients have experienced long-term illness and residual symptoms even after the virus was no longer detectable. Here, we discuss whether COVID-19 is associated with an elevated risk of developing PD, either imminently after the viral infection or after several years.

The progressive neurodegenerative disorder, PD, is characterized by a range of motor and non-motor symptoms [1]. Years, or even decades, before the onset of the classical motor symptoms, the PD process is associated with a characteristic prodrome. The pathology in PD includes the loss of midbrain dopamine neurons, neuroinflammation, and development of intraneuronal protein aggregates (Lewy bodies, rich in  $\alpha$ -synuclein) in numerous brain regions [1]. Genetic studies suggest that ~5% of PD cases are familial, and the heritability in sporadic cases is believed to be ~25%. Aging is the most prominent risk factor, and analysis of genes

associated with PD risk has implicated multiple cellular dysfunctions, including immune system regulation and protein homeostasis. Biomarker studies also support an ongoing systemic inflammation in PD, and immune system disorders are associated with elevated PD risk. While the initial trigger(s) of sporadic PD are largely unknown, bacterial and viral infections have been implicated in some cases [2].

Notably, at least three published single-case reports indicate that patients with COVID-19 have developed clinical parkinsonism, either in isolation or with other neurological deficits, within 2–5 weeks of contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3–5]. They were aged 35, 45, and 58 years and all three had severe respiratory infection requiring hospitalization. Two of the three patients responded with reduced parkinsonian symptoms upon administration of traditional dopaminergic medication [4,5], and the third patient recovered spontaneously [3]. In all cases, brain imaging revealed reduced function of the nigrostriatal dopamine system, akin to PD. None of them had a family history of PD, or a history with signs of prodromal PD; one patient underwent genetic testing but did not carry any PD risk variants [4].

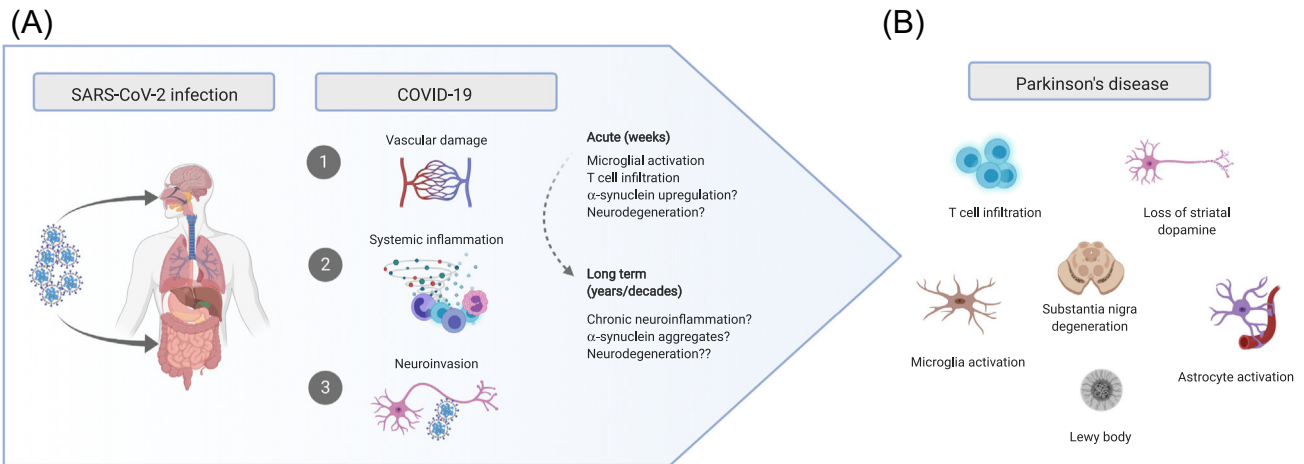
These cases do not prove a causal relationship between SARS-CoV-2 infection and the development of parkinsonism. Possibly, the reported patients were destined to develop PD, were on the cusp of losing the number of nigral dopamine neurons required for the emergence of motor symptoms, and the viral infection only accelerated an ongoing neurodegenerative process around a critical timepoint. However, the rapid onset of severe motor symptoms in close temporal proximity to the viral infection is still suggestive of a causal link. Furthermore, none of the reported patients exhibited signs of prodromal PD before contracting COVID-19. There are

no descriptions of neuropathology in patients who developed parkinsonism acutely following SARS-CoV-2 infection. However, perhaps something can be gleaned from a growing number of postmortem reports describing those dying with COVID-19 without parkinsonism. Notably, one such neuropathology study of 43 patients found evidence of microglial activation and invasion of cytotoxic T cells in the brainstem [6], which are neuropathological signs also associated with PD.

We propose three potential mechanisms for the rapid development of parkinsonism following SARS-CoV-2 infection (Figure 1). These mechanisms may operate either alone or in concert. First, vascular insults have been reported to develop in multiple organs, including the brain, in severe COVID-19 in conjunction with a hypercoagulable state [7]. This could conceivably directly damage the nigrostriatal system, akin to what is seen in vascular parkinsonism. However, the aforementioned recent autopsy study [6] did not report any bleeding or small vessel thrombosis in the brain.

Second, considering the association between inflammatory disorders and elevated PD risk, it is possible that marked systemic inflammation caused by severe COVID-19 could trigger neuroinflammation and demise of nigral dopamine neurons. Midbrain dopamine neurons are believed to be particularly susceptible to systemic inflammation. Several studies have demonstrated elevated interleukin (IL)-6 levels in COVID-19, and one report suggested that the kynurenine pathway is perturbed [8]. Interestingly, these are both mechanisms that have been associated with PD [2,9].

Third, SARS-CoV-2 may be a neurotropic virus, because viral RNA has been detected in postmortem brains of some patients with COVID-19. Furthermore, neuropathological studies using immunostaining for aggregated



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**Figure 1. Schematic Illustration of How Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection Might Lead to Increased Parkinson's Disease (PD) Risk.** (A) Initial viral infection of the respiratory tract and/or the gut in patients with coronavirus disease 2019 (COVID-19) could affect the brain in three ways: through vascular damage; systemic inflammation; and direct neuroinvasion (e.g., via the olfactory system or vagal nerve), which each might act alone or in concert. Possible acute brain changes that can develop as a consequence, as well as longer term ones, are listed. Three recent case reports [3–5] described the development of acute parkinsonism following COVID-19. These emerging findings suggest that SARS-CoV-2 infection leads to acute parkinsonism in certain cases, and raises the question of whether COVID-19 also elevates PD risk in the long term. Several of the brain changes that are commonly seen in PD (B) have also been observed following infection with SARS-CoV-2 or other related viruses, although fundamental questions remain regarding possible causal/mechanistic links. Figure created using Biorender (Biorender.com) with input from Gabriela Mercado and Sonia George.

$\alpha$ -synuclein have suggested that the PD process starts in the olfactory system or in enteric nerves and then propagates along neural pathways to additional brain regions [1]. Indeed, hyposmia and constipation are common features of prodromal PD, and  $\alpha$ -synuclein aggregates might contribute to their pathophysiology [1]. Strikingly, hyposmia (and dysgeusia) are common in COVID-19, and SARS-CoV-2 can infect the gastrointestinal tract, suggesting that the virus gains direct access to brain regions relevant to PD via these routes. Additionally, the respiratory tract is innervated by the vagus nerve, which may be yet another portal for viral entry into the brain. Furthermore, midbrain dopamine neurons express high levels of the angiotensin-converting enzyme 2 (ACE2) receptor, which is essential for viral entry, possibly making these cells vulnerable to SARS-CoV-2 attack [10]. An intriguing possibility is that the neuroinvasion of SARS-CoV-2 leads to an upregulation of neuronal  $\alpha$ -synuclein. Such an increase in  $\alpha$ -synuclein has been observed following

infection with West Nile virus [11] and Western Equine Encephalitis virus [12], and animals lacking neuronal  $\alpha$ -synuclein are more susceptible to West Nile virus encephalitis compared with those with this protein [11]. These findings suggest that  $\alpha$ -synuclein expression increases during viral infection of the nervous system and acts as a viral restriction factor. In COVID-19, it is possible that sustained elevated levels of intraneuronal  $\alpha$ -synuclein lead to the formation of aggregates, similar to the PD brain, possibly followed by neuronal death.

If this latter paradigm is correct, SARS-CoV-2 could predispose to the development of PD later in life. Experimental studies, and findings in families with  $\alpha$ -synuclein gene multiplications, indicate that sustained elevated  $\alpha$ -synuclein levels promote aggregation of the protein [1]. Superimposed on this, long-term systemic and/or neuroinflammation due to COVID-19, might be 'a perfect storm' for the development of PD.

Thus, while acute parkinsonism in conjunction with COVID-19 appears to be rare, spread of SARS-CoV-2 widely in society might lead to a high proportion of patients being predisposed to developing PD later in life, especially because they will also be affected by normal aging processes (Figure 1). Therefore, it is important to carefully follow large cohorts of patients affected by COVID-19, and monitor them for manifestations of PD. If patients with SARS-CoV-2 have an increased risk for PD, and potentially other related neurodegenerative disorders, it will be critical to identify treatments that mitigate such an elevated risk. A link between COVID-19 and PD would also imply that attaining 'herd immunity' by naturally infecting a large portion of the population could have disastrous long-term implications.

#### Acknowledgements

P.B. is supported by funding from Van Andel Institute and the Farmer Family Foundation on projects related to infections and PD. A.N. is supported by the Division of

Intramural Research, National Institute of Neurological Disorders and Stroke (NINDS). Finally, J.D.B. is supported by a VA Merit Award.

### Disclaimer Statement

P.B. has received commercial support as a consultant from Axial Biotherapeutics, Calico Life Sciences, CuraSen, Fujifilm-Cellular Dynamics International, Idorsia, IOS Press Partners, LifeSci Capital LLC, Lundbeck A/S, and Living Cell Technologies LTD. He received commercial support for grants/research from Lundbeck A/S and Roche. He has ownership interests in Acousort AB and Axial Biotherapeutics, and is on the steering committee of the NILO-PD trial.

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<https://doi.org/10.1016/j.tins.2020.10.009>

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## Spotlight

### This Is Your Brain on (Low) Glucose

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**Brain functioning and high-order cognitive functions critically rely on glucose as a metabolic substrate. In a recent study, Kealy *et al.* investigated the impact of glucose availability on sickness behavior and delirium in mice and humans. They identified disrupted brain carbohydrate metabolism as a key mechanistic driver of these behaviors.**

Metabolic processes support all biological functions. Various environmental constraints force organisms to prioritize certain metabolic programs over others to achieve optimal outcomes [1]. Abundant nutrients (e.g., glucose) drive growth and reproduction through anabolic processes, or energy production; by contrast, a lack of nutrients prioritizes catabolic processes, or energy breakdown. However, the metabolic processes that support immune responses are less straightforward. Inflammation is driven by the expansion of immune cells and biosynthesis of inflammatory mediators (anabolic processes) even though immune responses typically occur at the expense of organismal growth and reproduction [1]. Inflammation can manifest behaviorally as sickness behavior: anorexia, fatigue, loss of libido, and impaired cognition. These

behaviors reflect a diversion of metabolic resources from normal functioning toward pathogen defense. Indeed, cognition is barely a requirement for successful defense against pathogens at the organismal level.

Sterile inflammation can also perturb cognition. For example, patients with a hip fracture frequently experience delirium, which is characterized by impaired attention and reduced level of consciousness during the perioperative period [2]. However, whereas the specific cause of infectious inflammation is often well defined (i.e., a certain pathogen), delirium is a complex clinical state with multiple etiologies. In fact, delirium can arise from a range of precipitating factors, including trauma, major surgery, use of psychoactive drugs, and metabolic abnormalities [3]. Yet, not all major surgeries, to name one example, cause delirium. An individual's vulnerability to delirium depends on various predisposing factors, including pre-existing cognitive impairment, advanced age, history of stroke, and medication [3]. Despite this dizzying array of predisposing and precipitating factors, a recent paper by Kealy *et al.* [4] pegged disrupted carbohydrate metabolism as the proximate cause of delirium resulting from systemic inflammation in mice and humans.

Conventional wisdom dictates that inflammatory cytokines perpetrate sickness behaviors via actions at the blood–brain barrier and beyond it [5]. Kealy *et al.* [4] questioned whether inflammatory cytokines were in fact the proximate cause of these behaviors by exploring the glycemic and behavioral effects of systemic inflammation in mice using lipopolysaccharide (LPS) as an inflammatory stimulus. Intraperitoneal injection of LPS decreased glucose levels in the blood and cerebrospinal fluid (CSF), with kinetics that mirrored reductions in spontaneous behavior. The behavioral effect of LPS was also reduced by glucose supplementation and enhanced by 2-deoxyglucose, a glycolytic inhibitor. Interestingly, IL-1 $\beta$  alone