

Commentary

COVID-19 and Parkinson's Disease: Are We Dealing with Short-term Impacts or Something Worse?

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We read with great interest the commentary by Helmich and Bloem [1] in which the authors suggested that patients with Parkinson's disease (PD) may not only face a greater risk of developing worse coronavirus disease 2019 (COVID-19)-related respiratory outcomes, but also a variety of “hidden sorrows” of the pandemic. The authors argue that PD patients may suffer from chronic stress and lack of physical activity associated with social isolation. As the COVID-19 continues snaking its way around the world (as of April 29, 2020, global cases topped 3 million), we would like to further highlight several impacts that the ongoing COVID-19 pandemic may induce on the global burden of PD.

Preliminary studies suggested that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is the etiologic agent of the COVID-19, may have a potential neurotropism in humans though such feature has not been conclusively demonstrated yet [2, 3]. Similar to other respiratory viruses, the SARS-CoV-2 may gain access to the Central Nervous System (CNS) by the hematogenous route or axonal transport along with the olfactory neuroepithelium [4, 5]. The olfactory pathway hypothesis for SARS-CoV-2 neuroinvasion is supported by the fact

that several patients with COVID-19 infection have experienced hyposmia/anosmia and dysgeusia [6–9]. Indeed, the interesting aspect of such a route (from the nasal cavity to the olfactory bulb, then to the piriform cortex, and finally to the brainstem) is the potential presence of the virus in the brainstem, which contains the respiratory nuclei responsible for breathing rhythm [5, 10]. In fact, more than half of the patients with COVID-19 infection showed respiratory distress [3, 11, 12].

In the clinical scenario, nearly 50% of all emerging viruses present neurological symptoms in the acute phase [13]. Such feature does not seem to be different for COVID-19, since several patients reportedly showed neurologic manifestations [3, 11, 14]. For example, patients with the severe form of the COVID-19 infection were more likely to develop acute cerebrovascular disease, consciousness disturbance, and skeletal muscle injury [6]. In addition, an evidence of encephalopathy and intracerebral haemorrhage was found on brain imaging scans of patients with the SARS-CoV-2 infection [15–17]. Finally, a case of COVID-19-related meningitis/encephalitis and a case of COVID-19 infection associated with Guillain-Barré syndrome have recently been reported [15, 18]. It would be of interest to further investigate cerebrospinal fluid (CSF) samples as well as post-mortem brain and spinal cord tissue from deceased COVID-19 patients (whenever possible) to probe for any direct evidence of CNS infection [19].

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On other hand, the burden of the long-term neurological morbidity from neuroinfectious diseases is largely unknown [13]. A growing body of evidence suggests that the pathological process of PD may be modulated (or initiated) by viruses or other pathogens [20–25]. An early evidence of a potential link between viruses and PD stems from an epidemic of Encephalitis Lethargica (EL), following the 1918 influenza outbreak. In that occasion, nearly all patients who had an acute episode of EL developed post-encephalitic Parkinsonism, a condition that closely resembled the clinical picture of PD [26]. Although the evidence linking influenza to the PD pathogenesis was correlational, it readily prompted the scientific community to further investigation. For example, Jang et al. showed that the administration of nonlethal doses of the highly pathogenic H5N1 influenza virus into mice noses induced microglia activation as well as α -synuclein phosphorylation and aggregation in brain areas infected by the virus, which persisted long after the infection was resolved [22]. The study also showed a significant long-lasting loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [22]. A later study that examined the neurotropic and inflammatory potential of the A/California/04/2009 (CA/09) H1N1 virus showed that, although no evidence of a viral neurotropism was found, CA/09 H1N1 virus robustly increased microglial activity in the SNpc of the mice [23]. In addition, an altered expression of several neurotrophic factors and cytokine-related genes was detected, following the CA/09 H1N1 infection [23]. Finally, the hypothesis that viral infections may contribute to PD pathogenesis is not limited to the influenza virus, since some of the cardinal motor symptoms and histological features of PD have been also associated with other viruses (e.g., coxsackie virus, West Nile virus, Japanese encephalitis B virus, Saint Louis encephalitis virus, and HIV) [20, 27].

We acknowledge that further research is needed to better elucidate the role of viruses in the pathogenesis of PD. Nevertheless, the above findings have significant clinical implications as they suggest a potential contribution of both neurotropic and non-neurotropic viruses to the initiation of PD neurodegeneration, either directly (by the physical presence of the virus in the CNS parenchyma) or indirectly (by inducing a long-lasting inflammatory process in the brain). However, triggers *per se* may be, in most cases, insufficient for PD to develop [28]. Thus, ‘facilitators’ have been suggested to play a role in PD pathogenesis, either by acting concomitantly with the triggering event

(e.g., a viral infection) or after it. Such processes usually take place in the prodromal or asymptomatic phase of PD [28]. Among the several ‘facilitators’ that may affect the progression of PD, the aging and cellular senescence have by far the most recognized impact. For example, the global prevalence of PD was 2–3% of the population aged > 65 years in 2017, and such number is set to reach over 14 million cases worldwide by 2040, which makes PD the fastest growing disorder among all neurological disorders [29]. Such exponential growth is sustained by the continuously aging of the population [30]. Independently of PD, global life expectancy has increased by approximately six years in the past couple of years [31]. As longevity increases, so does the number of persons living with PD, which may lead to greater financial and social burdens [29]. In fact, estimates suggest that a PD pandemic is on the rise [29, 32].

Although it is too early to suggest what long-term neurological outcomes the survivors of COVID-19 infection may face, some evidence may come from previous pandemics of respiratory viruses. First, given that SARS-CoV-2 may induce a cytokine storm syndrome and hyperinflammation in patients with severe COVID-19 infection [33], is it possible to hypothesize that SARS-CoV-2/COVID-19 infection could be a triggering event of the neurodegenerative cascade underlying PD [19]? In addition, previous studies showed that other human coronaviruses may remain latent in leukocytes and thus may be prone to producing latent or persistent infections of the CNS [34]. While clinical signs of Parkinsonism and PD have not been associated with previous outbreaks of coronaviruses, anti-coronavirus antibodies were detected in the CSF samples of persons with PD [35]. Second, could COVID-19 survivors represent a disproportionately large fraction of the future PD patient population? Although the extant evidence is still inconclusive, previous studies reported that persons who were born or were young at the time of the 1918 influenza outbreak had a 2- to 3-fold higher risk of developing PD than those born prior to 1888 or after 1924 [36, 37]. Finally, could the future burden of PD be affected by the COVID-19 pandemic?

The scientific community can also offer a glimmer of hope amid COVID-19 pandemic. Sadasivan and colleagues previously showed that prophylactic treatment with either vaccine or antiviral therapy was effective in protecting mice against the synergistic effects of H1N1 influenza virus and MPTP (a neurotoxin used to model PD in animals) on SNpc dopaminergic neuronal loss [24]. Driven by the

COVID-19 pandemic's spread, a worldwide effort is now underway to find vaccines and viable therapies against SARS-CoV-2.

In conclusion, COVID-19 pandemic has disrupted modern society on an unprecedented scale. The long-term link between viruses and neurodegenerative disorders is difficult to demonstrate, but we should not cast aside the long-lasting impacts that the growing COVID-19 pandemic may have on the pandemic of PD. In fact, such concern has been widely shared by the scientific community [38–40]. It would be of interest to adopt strategies to closely follow up COVID-19 survivors. For example, health systems should keep accurate medical records (clinical and imaging biomarkers) to aid specialists and researchers to address the long-term deleterious effects of SARS-CoV-2 on CNS (and their potential association with neurodegenerative disorders such as PD) in the coming years [19, 39, 40]. As other global pandemics in the past, the COVID-19 pandemic will likely last for a limited length of time. Yet, it is about time we recognize that the pandemic of PD is not going away anytime soon.

ACKNOWLEDGMENTS

DBV is currently funded by postgraduate fellowship from São Paulo Research Foundation (FAPESP #2016/17746-3). FAS is currently funded by São Paulo Research Foundation (FAPESP #2018/18568-7). The National Council for Scientific and Technological Development (CNPq) and the Coordination for the Improvement of Higher Education Personnel (CAPES) also supported our studies.

DISCLOSURE

The authors report no conflicts of interest.

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