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CHAPTER ELEVEN

COVID-19: The cynosure of rise of Parkinson's disease

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Abstract

Parkinson's disease (PD) is one of the most common age-related disorders globally. The pathophysiological mechanisms and precipitating factors underlying PD manifestations, including genetic and environmental parameters, inflammation/stress and ageing, remain elusive. Speculations about whether the Coronavirus Disease 2019 (Covid-19) pandemic could be a pivotal factor in affecting the prevalence and severity of PD or triggering a wave of new-onset parkinsonism in both the near and distant future have recently become very popular, with researchers wondering if there is a changing trend in current parkinsonism cases. Could the current understanding of the Covid-19 pathophysiology provide clues for an impending rise of parkinsonism cases in the future? Are there any lessons to learn from previous pandemics? Our aim was to look into these questions and available current literature in order to investigate if Covid-19 could constitute a cardinal event affecting the parkinsonism landscape.

1. Introduction

The 20th century has been one of the greatest timelines in human evolution. The advancements in science have been unparalleled to any of the previous parts of human history. The conquest of various infectious disorders has been leading directly to one of society's greatest achievements: "increase in life expectancy." Indeed, we are at a cusp of science where every

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effort is made to increase life expectancy and quality of life. More specifically, life expectancy in the first half of the 20th century was less than 50 years, while now it has ascended beyond 70 years of age (The World Bank.IBRD.IDA, 2019). The leading causes of death have been shifting from infectious disorders to non-communicable and chronic conditions (World Health Organization, 2020), with the ever enigma of elixir of life hanging on winning over these age-related degenerative disorders, among which Alzheimer's dementia (AD) and Parkinson's disease (PD) are at the helm. There have been ongoing efforts to understand these disorders and factors affecting them, along with discovering early interventions to move past these hurdles.

Whether the Coronavirus Disease 2019 (Covid-19) could be a major spoke of the wheel in this race over degenerative disorders, can only be a soothsayer's predication. Can we only be retrospectively enlightened, or should we be taught by the past before facing the future? As George Santayana, an 19th century philosopher, quotes "Those who cannot remember the past are condemned to repeat it." There have been ample numbers of examples showing how prior medical outbreaks had an impact on life expectancy and chronic illnesses (Huremović, 2019). We will be covering on the lessons from the past to current available evidence to show what might be in hold for the future of new-onset parkinsonism due to the Covid-19 pandemic.

2. Lessons from the past

The past major epidemic and pandemic outbreaks have significantly contributed to the understanding of various disorders and have promoted scientific progress. Secondary parkinsonism developing in the context of or shortly after viral infections constitutes a well-established condition with a plethora of viruses acknowledged to be involved, including the West Nile virus (WNV), Herpes viruses, the Influenza A virus, the Human immunodeficiency virus (HIV) and others (Limphaibool, Iwanowski, Holstad, Kobylarek, & Kozubski, 2019; Valerio, Whitehouse, Menon, & Newcombe, 2021).

A peak into past pandemics, including outbreaks of the Coronaviruses (CoV) species, does give insight into potential future effects of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The pandemic of 1918 (Spanish Flu), 2003 (SARS-CoV-1) and 2012 (Middle East Respiratory Syndrome, MERS-CoV) have yielded a load of neurological

issues, some of which came to the forefronts after months or even years, in some cases up to seven decades, following the exposure to the pathogen (Weir, 2020).

Encephalitis lethargica (EL), also known as von Economo encephalitis, in 1916–17, has been one of the greatest mysteries in medical science, while its role in PD and parkinsonism cases has not been fully understood even nowadays (Reid, McCall, Henry, & Taubenberger, 2001). The acute phase of EL was characterized by intractable somnolence, oculomotor palsies and, occasionally, by hyperkinetic or hypokinetic movement disorders (Hoffman & Vilensky, 2017). Those who survived the acute phase were often left with long term sequelae, including parkinsonian-like signs such as severe bradykinesia, rigidity, tremor, and hypomimia (post-encephalitic parkinsonism). Such phenomena, along with associated lesions in the substantia nigra of these patients, have led to a deeper understanding of PD or parkinsonism pathology. However, this link of parkinsonism and EL was more widely accepted by the late 1930s, almost two decades from the initial outbreak of EL (Lutters, Foley, & Koehler, 2018), giving an insight that many times the acknowledgement of a potential association by a wider peer group might take decades from the occurrence of the relevant events and might remain under question for an extended time period (Estupinan, Nathoo, & Okun, 2013; Vilensky, Gilman, & McCall, 2010).

EL was soon followed by the Spanish flu outbreak (1918–20), which was triggered by the H1N1 influenza strain and affected more than 500 million people worldwide (Taubenberger & Morens, 2006). Prenatal exposure to this strain was associated with an increased risk of more than 20% in cardiovascular diseases in the age group of 60–80 years (Mazumder, Almond, Park, Crimmins, & Finch, 2010). These people would also experience growth retardations and were found to have a lower level of education and economic productivity over their lifetime. Interestingly, such associations imply that affected individuals would continue to suffer from long term implications during their life span due to exposure to an infectious agent in their antenatal lives.

The 2003 SARS-CoV-1 outbreak, which originated in China, affected 8422 people and caused 916 deaths (Institute of Medicine Forum on Microbial, 2004; O'Sullivan, 2021). A 15-year prospective study of 80 healthcare workers who were exposed to SARS-CoV-1, has revealed residual radiological lesions in the subjects' lungs with corresponding compromise of the respiratory function (Zhang, Li, et al., 2020). In a different

study, 22 individuals previously affected by SARS-CoV-1 were found to exhibit neurological symptoms in the long term, such as fatigue, myalgia, depression or poor sleep, leading the researchers to suggest a post-SARS-CoV-1 syndrome similar to fibromyalgia, with chronic fatigue and somnolence (Moldofsky & Patcai, 2011). The MERS-CoV, which emerged in Jeddah, Saudi Arabia in 2012 and infected about 2400 people worldwide (Donnelly, Malik, Elkholy, Cauchemez, & Van Kerkhove, 2019), has also left survivors who were diagnosed with chronic fatigue syndrome, depression and post-traumatic stress disorder (PTSD) (Elkholy et al., 2020; O'Sullivan, 2021). Given that some of these long-term effects, including neurological sequelae, were related to CoV species, it would not come as a surprise that any potential long-term complications of Covid-19 would be of mammoth proportions, taking into account the sheer volume of population affected by SARS-CoV-2 during the last 2 years.

3. Insights from the present

Covid-19 has been predominantly associated with a hyperinflammatory and hypercoagulable state (Fearon, Mikulis, & Lang, 2021; Nalbandian et al., 2021). The pathophysiologic mechanisms underlying SARS-CoV-2 effects include the following:

1. Direct viral toxicity.
2. Endothelial damage and microvascular injury.
3. Immune system dysregulation and stimulation of hyperinflammatory state.
4. Hypercoagulability with resultant in situ thrombosis and macrothrombosis.
5. Maladaptation of angiotensin converting enzyme 2 (ACE2) pathway.
6. Hypoxic injury.

These mechanisms might lead to acute and chronic sequelae, which may be broadly classified, based upon the prominence of underlying organs affected during the acute phase, as follows: pulmonary, hematologic, cardiovascular, neuropsychiatric, renal, endocrine, gastrointestinal, dermatologic, and multisystem inflammatory syndrome (in children) (Nalbandian et al., 2021).

84–88% of Covid-19 patients have been thought to exhibit some kind of neurological symptoms, including headache, dizziness, hyposmia, hypogeusia, encephalopathy/encephalitis (Helms et al., 2020; Mao et al., 2020), but also seizures, polyneuropathy, Guillain-Barre syndrome, and

vascular events (arterial and venous) (Frontera et al., 2021; Paterson et al., 2020; Peterson, Sarangi, & Bangash, 2021).

There have been various reports of exacerbation of pre-existing neurological symptoms, including those of PD. Cilia and colleagues have reviewed the effects of Covid-19 on 141 people with PD (PwP) and noted a significant worsening of both motor and non-motor parkinsonian features (Cilia et al., 2020). The postulation of this worsening has been attributed to the infection *per se*, along with possible drug interactions during the Covid-19 management. In another series of 27 PwP an aggravation of motor symptoms was noted in 51.9% of the patients, while an increased levodopa equivalent daily dose was found to be required in 48.2% of them (Leta et al., 2021). Antonini and colleagues have reviewed the effects of Covid-19 on 10 PwP, noting that individuals with advanced age and longer duration of PD were particularly susceptible to higher mortality rates (Antonini, Leta, Teo, & Chaudhuri, 2020). In a recent systematic review of the effects of Covid-19 on pre-existing neurological disorders ($n = 2278$, 26 articles), it was reported that about 59% of PwP experienced an exacerbation of their symptoms (Kubota & Kuroda, 2021).

Méndez-Guerrero and colleagues have reported the first case of a subject with Covid-19 who developed parkinsonism in the form of an asymmetric, hypokinetic—rigid syndrome with mild resting and postural tremor, vertical oculomotor abnormalities and hyposmia (Méndez-Guerrero et al., 2020). The dopamine transporter single-photon emission computerized tomography (SPECT) imaging with ioflupane I-123 injection (DaTscan) depicted an asymmetric loss of dopamine in the nigrostriatal pathway. Various case reports of new-onset parkinsonism in the context of Covid-19 have been reported since then, with some of them having a fairly good response to dopaminergic therapies (Boura & Chaudhuri, 2022). In most of these cases, the assumption of Covid-19 acting as a precipitating factor for parkinsonism has been based on the temporal association of the two conditions (parkinsonism manifesting during or shortly after Covid-19), the fact that patients belonged to a relatively younger age group without any family history of parkinsonism or pre-existing prodromal parkinsonian features, such as rapid eye movement (REM) sleep behavior disorder (RBD), hyposmia or gastrointestinal issues, or genetic evidence of known PD-related mutations in screened subjects, although there were exceptions and the heterogeneity of these cases is highlighted (Boura & Chaudhuri, 2022). Furthermore, case reports of parkinsonism following Covid-19 have shown functional imaging evidence of defects in the

dopaminergic pathway and a clinical benefit of dopaminergic therapies, mimicking typical PD (Cohen et al., 2020; Faber et al., 2020; Makhoul & Jankovic, 2021).

The possibility of Covid-19 causing parkinsonism could be based upon:

1. *The role of inflammatory mediators:* The pro-inflammatory cytokines may stimulate neuronal expression of alpha synuclein (α-syn) leading to cascading events with a final culmination to α-syn aggregation (Cheng, Fransson, & Mani, 2022). α-syn is the main protein component of the Lewy bodies and neuritis, which are considered the pathological trademark of PD (Poewe et al., 2017). Recently published data suggests that the innate expression of α-syn might confine viral transmission in the central nervous system (CNS) (Beatman et al., 2015; Massey & Beckham, 2016). However, whether a compromise of the above α-syn function might lead to a virus-induced over-production of intracellular α-syn, predisposing to PD, remains to be investigated. It has also been shown that a H5N1 infection might induce an aggregation of α-syn in various brain areas of rodents and a significant loss of dopaminergic neurons in their substantia nigra, thus, predisposing to synucleinopathies, including PD (Jang, Boltz, Webster, & Smeyne, 2009; Marreiros et al., 2020). More specifically, Marreiros and colleagues have reported that the infection of dopaminergic neurons with the H1N1 influenza virus resulted specifically in the formation of α-syn aggregates, indicating a highly selective process to develop parkinsonism.

   It is also of interest that there have been some case reports of post-Covid parkinsonism in the clinical practice where symptoms exhibited a good response to the administration of immunomodulatory/immunosuppressive therapies, like intravenous immunoglobulin (IVIg) and plasmapheresis, further highlighting the role of immune mechanisms in Covid-induced parkinsonism (Akilli & Yosunkaya, 2021; Tiraboschi et al., 2021).
2. *A direct neurotrophic invasion:* It has been shown that intranasal injections of either SARS-CoV-1 or MERS-CoV in animal models resulted in penetration of these viruses into the brain through the olfactory nerves, leading to an extensive spread of the virus in the CNS, including the thalamus and brainstem (Li et al., 2016; Netland, Meyerholz, Moore, Cassell, & Perlman, 2008). Song and colleagues have demonstrated a neuro-replicative potential and lethal consequences of SARS-CoV-2 infection in transgenic mice models expressing human ACE2 (Song et al., 2020). These preceding evidence, along with a high level of

genetic similarity between SARS-CoV-1 and SARS-CoV-2 (Williams et al., 2021), suggest a neuro-invasive potential of the latter in the CNS. SARS-CoV-2 has been thought to infect cells by interacting with the spike glycoprotein and ACE2 (Zhang, Penninger, Li, Zhong, & Slutsky, 2020). Cells with a high expression of ACE2, including airway epithelia, lung parenchyma, vascular endothelia, kidney cells and small intestinal cells, are believed to be highly susceptible to SARS-CoV-2 (Williams et al., 2021). In the brain, ACE2 are believed to be found in the striatum, the substantia nigra and the posterior hypothalamic area (Pavel, Murray, & Stoessl, 2020; Wan et al., 2021), although this has not been clarified.

It is also of interest that L-Dopa decarboxylase (DDC), an essential enzyme in the biosynthesis of both dopamine and serotonin, is the most significantly co-expressed and co-regulated gene with ACE2 in non-neuronal cell types, significantly affecting the dopamine blood levels (Nataf, 2020). A SARS-CoV-2 infection of monkey cell lines was found to induce downregulation of DDC, an effect which was also noticed with dengue and hepatitis C infections (Mpekoulis et al., 2021). These pathogens have also been associated with parkinsonism (Bopeththa & Ralapanawa, 2017; Tsai et al., 2016). Researchers showed that DDC levels rose in asymptomatic or mild severity Covid-19 patients, while an inverse relationship was noted between SARS-CoV-2 RNA levels and DDC expression (Mpekoulis et al., 2021). Whether a severe Covid-19 infection might lead to a dopamine depletion needs to be further investigated. Moreover, a dopamine D1 receptor agonist was found to suppress endoxin-induced pulmonary inflammation in mice, suggesting that a potential protective role of dopamine in inflammation needs to be further explored (Bone, Liu, Pittet, & Zmijewski, 2017).

In an autopsy study of 43 Covid-19 patients Matschke and colleagues confirmed the presence of SARS-CoV-2 in 53% of the subjects' brain (Matschke et al., 2020). It was also noted that microglia activation and cytotoxic T-cell infiltration was more pronounced in the brainstem and cerebellum. These preceding findings could be interpreted as indications that SARS-CoV-2 has the potential to directly invade the CNS.

3. *A part of multi-pathophysiological processes:* SARS-CoV-2 could also play a critical role by being part of multipronged pathophysiological processes. Up to now, many possible subjacent mechanisms have been speculated

to mediate the development of PD. Some possible hypotheses that might connect the dots between Covid-19 and parkinsonism would be the following: (1) the dual hit hypothesis (Hawkes, Del Tredici, & Braak, 2007; Klingelhoefer & Reichmann, 2015); (2) the multiple hit hypothesis (Meng, Shen, & Ji, 2019; Sulzer, 2007); and (3) the clustering of PD theory (Tsui, Calne, Wang, Schulzer, & Marion, 1999). Braak and colleagues have proposed that PD originates in the gut/ nasal cavity before affecting the brain (Rietdijk, Perez-Pardo, Garssen, van Wezel, & Kraneveld, 2017). This was further supported by loss of smell and gastrointestinal manifestations, appearing as prodromal symptoms in many PwP. Similar physiological processes might be replicated in the Covid-19 setting with many patients complaining of loss of smell and gastrointestinal issues; some of these symptoms might even persist in the long term (long COVID syndrome) (Leta et al., 2021).

4. The post Covid-19 future

The post-Covid-19 scenario varies from immediate changes noted in the near future to possible long term effects seen in Covid-19 patients, but also in antenatally exposed individuals, similarly to the Spanish flu. Some of these sequelae might be recognized early, while many might only be acknowledged decades later, as with EL. We need to learn from past experiences and undertake systematic follow-up assessments in the future in order to understand potential long term implications. The current pathophysiological understanding and research have given us some hints that Covid-19 might be a trigger for a parkinsonism wave in the next few decades, so vigilance is advised.

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