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Research Report

Parkinsonism as a Third Wave of the COVID-19 Pandemic?

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Abstract. Since the initial reports of COVID-19 in December 2019, the world has been gripped by the disastrous acute respiratory disease caused by the SARS-CoV-2 virus. There are an ever-increasing number of reports of neurological symptoms in patients, from severe (encephalitis), to mild (hyposmia), suggesting the potential for neurotropism of SARS-CoV-2. This Perspective investigates the hypothesis that the reliance on self-reporting of hyposmia has resulted in an underestimation of neurological symptoms in COVID-19 patients. While the acute effect of the virus on the nervous system function is vastly overshadowed by the respiratory effects, we propose that it will be important to monitor convalescent individuals for potential long-term implications that may include neurodegenerative sequelae such as viral-associated parkinsonism. As it is possible to identify premorbid harbingers of Parkinson's disease, we propose long-term screening of SARS-CoV-2 cases post-recovery for these expressions of neurodegenerative disease. An accurate understanding of the incidence of neurological complications in COVID-19 requires long-term monitoring for sequelae after remission and a strategized health policy to ensure healthcare systems all over the world are prepared for a third wave of the virus in the form of parkinsonism.

Keywords: Parkinson's disease, parkinsonism, COVID-19, SARS-CoV-2

> "*For too long medical science has tended to relegate the 1918 influenza/encephalitis lethargica/parkinsonism puzzle to an intellectual ash heap – apparently on the assumptions that these pandemics are past and of little and dwindling importance to current and future health. But failure to identify the 1918 influenza virus as the cause of encephalitis lethargica and parkinsonism has crippled progress towards the understanding of influenza pathology and epidemiology needed to fuel and guide prevention of these elusive yet exceedingly important diseases.*"
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> Reimert Ravenholt, 1982 [1].

In December 2019, pneumonia caused by a novel coronavirus, SARS-CoV-2, was reported for the first time in Wuhan, China [2]. On March 12, 2020, the World Health Organization (WHO) officially declared coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, a pandemic. At the time of preparing this manuscript, 23.7 million people had been infected, and >800,000 people had died from COVID-19 according to data from the WHO [3]. The

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presentation and nature of symptoms in COVID-19 appear to be ever-increasing, with new case-reports appearing daily. Extrapulmonary complications have been reported in many instances of infection, including neurological symptoms.

THE NEUROTROPISM OF VIRUSES

Several viruses are known to be neurotropic (capable of invading nerve cells), including herpes simplex virus, poliovirus, influenza Type A virus, and the coronaviruses [4–8]. In order to understand the pathogenesis of these viruses within the central nervous system, it is critical to understand the mechanisms of entry into the CNS. There are many ways in which viruses are hypothesized to enter the brain, including viremia, infection of the endothelial cells, and retrograde axonal transport [9]. The virus that has been studied the most, with a view to understanding CNS penetration and the subsequent neurotropism, is influenza. It has been reported that intranasal infection with H1N1 (swine flu) and H5N1 (avian flu) resulted in infection of the olfactory epithelium and transmission through the axons into the olfactory bulb of wildtype mice [10, 11]. Importantly there is a significant body of literature illustrating that the coronaviruses are neurotropic [12–19], and recent findings suggest dopaminergic neurons are permissive to SARS-CoV-2 infection [20].

NEUROINFLAMMATION AND PARKINSONISM

Chronic neuroinflammation is thought to play a role in the pathogenesis of Parkinson's disease (PD)/parkinsonism. In the brain, increases in complement protein pathways and activated microglia are seen in regions with degeneration [21]. The primary insult may be idiopathic, traumatic, or environmental, but inflammation is ubiquitous in areas of neurodegeneration. The question remains does inflammation result in neurodegeneration or does the underlying disease drive inflammation. For instance, epidemiological examinations involving non-steroidal anti-inflammatories shows that they are largely not effective in preventing PD [22, 23]. One recent proposal that PD may be initiated following continuous gut aggravation is gaining significant attention. The initiator of neuroinflammation may be the bacterial endotoxin, lipopolysaccharide (LPS) from the outer membrane of gram negative bacteria that are present in the mouth and gastrointestinal tract [24]. It is proposed that a level of endotoxin causes an 'cytokine storm' and parkinsonism [25]. Animal models show that a single injection of LPS can trigger neuroinflammation and subsequent loss of nigral cells [26, 27]. As such, early gastrointestinal dysfunction in people with PD may be more than a prodromal symptoms of PD but additionally represent an early environmental inflammatory trigger.

ENCEPHALITIS

Infection by neurotropic viruses as well as the local induced immune response that result can irreversibly disrupt the complex structural and functional architecture of the central nervous system. Infectious pathogens (viral or bacterial) can trigger neuroinflammation via induction of pro-inflammatory cytokines in microglia, the principal immune cells of the CNS [11, 28]. This immune response of microglial activation and hypercytokinemia can induce further microglial activation. It has been reported that the dopaminergic neurons of the substantia nigra pars compacta are particularly susceptible to an environment of continual chronic inflammation and neuronal damage contributing to the neurodegeneration in PD and parkinsonism [29, 30] (reviewed in [31]). Neuroinflammation of this nature is one of the connecting phenomena that link infectious diseases and neurodegeneration. Besides immediate and direct effects, there are several neurological disorders often associated with autoimmune mechanisms that are assumed to be delayed virus-induced disorders: multiple sclerosis, Guillain-Barré syndrome, narcolepsy, and encephalitis lethargica. The clinical presentation of acute inflammation of the brain is also linked to delayed neuropathological manifestations later in life, such as parkinsonism [9, 32].

VIRUSES AND PARKINSONISM

The etiology of PD and parkinsonism is yet to be fully understood and studying the underlying pathomechanisms may be important for the efficient development of preventative interventions. A single pathogen is unlikely to be responsible for the entire pathogenesis of PD, but there is some evidence that certain viral infections may increase the susceptibility of PD and parkinsonism. Acute parkinsonism is associated with neurotropic viruses, including coxsackievirus, St. Louis encephalopa-

thy, and human immunodeficiency virus [33]. The first link between viruses and parkinsonism comes from the possible relationship between encephalitis lethargica and the 1918 Spanish Flu. In the acute form, encephalitis lethargica presented with annual, mostly winter peaks of varying size and severity that was most prevalent in the early 1920s [34]. In the acute stage the post-mortem histological appearances of the encephalitis lethargica brain were usually normal, but more advanced cases showed varying degrees of vascular congestion and perivascular lymphocytic cuffing. In chronic encephalitis lethargica there was less inflammation, but signs of degeneration in the midbrain, especially of the oculomotor nuclei and the substantia nigra. Subsequently, there was an was an increased 2-3 fold risk of parkinsonism reported in people born between 1888–1924 [1]. The aetiology of encephalitis lethargica is widely debated as advanced virological techniques were not available in the 1920s—but plausibly considered to be caused by another neurotropic virus epidemiologically comparable to polioencephalomyelitis. Other possibilities are also considered to be either environmental, parainfectious, auto-immune, or a combination of these insults (reviewed in: [35]). Temporally, an influenza causation provides a convenient explanation due to the disappearance of encephalitis lethargica after 1940 and the cessation of the 1918 influenza strain in humans after 1933 [36]. To date, evidence for influenza-induced encephalitis lethargica is inconclusive, however, as stated by McCall "an open mind about the influenza hypothesis avoids complacency about the potential for another encephalitis lethargica-like epidemic accompanying a new influenza pandemic" [36].

There is no evidence that these viruses are causally linked to parkinsonism or PD, however, there is a proposed hypothesis that "an unknown pathogen" results in a neuronal insult and is the first 'hit' in a dual 'hit' hypothesis of PD [37, 38]. This hypothesis proposes that there is an initial insult from a neurotropic pathogen that enters the brain through the nasal or gastric pathways and induces long-lived activation of the glial cells that predisposes the brain to oxidative insult in later life or alternatively may become primed to react abnormally to stimuli in the aging brain and to become neurotoxic and destructive during neurodegeneration. As such, the second 'hit' is pathogenic and deleterious due to an already primed neural system. It is for this reason that the current COVID-19 pandemic could provide valuable insights into the effect of viral infections/inflammation in neurodegenerative conditions to neurologists and neuroscientists, as there are many case reports of severe neurological complications in hospitalized patients, as well as sensory loss in many patients.

References for the following review of neurological symptoms in COVID-19 were identified by searches of PubMed between December 2019 and June 2020, and references from relevant articles. The search terms "SARS-CoV-19", "COVID-19", "neurological", "encephalitis", "hyposmia", "anosmia", and "olfaction" were used. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this review.

NEUROLOGICAL SYMPTOMS ASSOCIATED WITH COVID-19

To date, there have been a number of case reports and demonstrating the presence of neurological symptoms in COVID-19 (Table 1) and three major case series with neurological reports have been published. Mao et al. performed a retrospective case study on 214 hospitalized patients in China and demonstrated that 78 (36.4%) patients presented with varying neurological symptoms including headache, dizziness, hyposmia, and skeletal muscle symptoms [39]. Helms et al. evaluated 58 hospitalized patients in France, 8 (13.8%) had neurological symptoms upon admission into the intensive care unit (ICU), and a further 39 (67.2%) demonstrated neurological symptoms when sedation and neuromuscular blockers were withheld [40]. Romero-Sanchez analyzed the medical history of patients on the Spanish ALBACOVID registry [41]. Of the 841 patients in this study, 483 (57.4%) developed neurological symptoms and of the 197 people who died, neurological complications were determined to be the cause of death in 8 (4.1%). The neurological symptoms reported to date, range from severe, such as encephalitis (Table 1) in hospitalized patients to mild (e.g., hyposmia; Tables 2 and 3). It is important to note that there are no control groups associated with these reports, and it will be of great value to understand the prevalence of these neurological symptoms in non-COVID-19 pneumonia and acute respiratory distress syndrome induced by other infectious and non-infectious causes.

Even though severe cases of neurological symptoms are relatively rare, there is evidence that the virus can affect the nervous system. This is reflected

Table 1
Neurological manifestations in COVID-19

Symptom	n (study/review)	n symptom (%)	Study type
Acute cerebrovascular disease	11069	332 (3.0)	Systematic review [70]
Dizziness	2236	151 (6.8)	
Headache	16446	3308 (20.1)	
Hypogeusia	846	430 (50.8)	Systematic review [71]
Impaired consciousness	2890	146 (5.1)	
Guillain-Barre syndrome		23	Case reports [72]
Neuralgia		1	Case report [73]
Epilepsy		1	Case report [74]
Ataxia		2	Case report [75, 76]
Encephalitis		26	*Table 2*
Hyposmia	16530	9728 (58.9%)	*Table 3 and 4*

Table 2
Case reports of encephalitis in COVID-19

Author	Country	Patient age (y), sex	Diagnosis
Benameur [60]	USA	31, F 34, M 64, M	Encephalitis
Bernard-Valnet [77]	Switzerland	64, F 67 F	Viral meningoencephalitis
Dogan [78]	Turkey	53 ICU patients	6 (11.3%) meningoencephalitis
Efe [79]	Turkey	35, F	Encephalitis (confirmed in a lobotomized sample)
Huang [58]	USA	40, F	Encephalitis
Karimi [80]	Iran	30, F	Encephalitis
Lu [81]	China	304 (hospitalized)	8 (2.6%) encephalopathy
Moriguchi [59]	Japan	24, M	Convulsive encephalopathy
Pilotto [82]	UK	60, M	Encephalitis
Poyiadji [83]	USA	56, F	Acute necrotizing hemorrhagic encephalitis
Wong [84]	UK	40, M	Rhombencephalitis

Table 3
Hyposmia in COVID-19 (self-reported questionnaire)

Author	Country	*N* (SARS-CoV-2 pos)	*N* (olfactory disturbance)	%	Females (%)	Age, y (mean ± SD)
Abalo-Lojo [85]	Spain	131	77	58.8	57.4	50.4
[a]Beltran-Corbellini [86]	Spain	79	56	70.9	39.2	61.6 ± 17.4
[a]Gelardi [87]	Italy	72	42	58.3	*NR*	*NR*
[a]Giacomelli [44]	Italy	59	31	52.5	32.2	60
Gudbjartsson [88]	Iceland	1221	118	9.7	44.1	44.3
Haehner [89]	Germany	34	22	64.7	54.6	41.3
[a]Hornuss [90]	Germany	45	22	48.9	44.4	56 ± 16.9
[a]Lechien [43]	Multiple	417	357	85.6	63.1	36.9 ± 11.4
Lee [91]	Korea	3191	855	26.8	63.6	44.0
[a]Levinson [92]	Israel	42	15	35.7	45.2	34.0
[a]Mao [39]	China	214	11	5.1	59.3	52.7 ± 15.5
Menni [93]	UK/USA	7178	4668	65.0	71.9/78.1	41.3 ± 12.2/44.7 ± 14.3
Paderno [94]	Italy	508	283	55.7	44.0	55 ± 15
Speth [95]	Switzerland	103	63	31.2	51.5	*NR*
Spinato [45]	Italy	202	130	64.4	52.0	56 (med)
[a]Vaira [96]	Italy	72	44	61.1	62.5	49.2 ± 13.7
Wee [97]	Singapore	154	35	22.7	*NR*	*NR*
Yan [98]	USA	59	40	67.8	49.2	Range 18–79
[a]Yan [99]	USA	128	75	58.6	52.2	53.5 (hospitalized), 43 (ambulatory)

[a]denotes studies performed on hospitalized patients; *NR*, not reported.

Table 4
Hyposmia in COVID-19 (clinical olfactory tests)

Author	Country	*N* (SARS-CoV-2 pos)	*N* (olfactory disturbance)	%	Clinical olfactory test	Females (%)	Age, y (mean ± SD)
[a]Hornuss [90]	Germany	45	38	84.4	Sniffin' Sticks	44.4	56.0 ± 16.9
Lechien [100]	Multiple	2013	1754	87.1	Sniffin' Sticks	67.5	38.9 ± 11.6
Lechien [101]	Belgium	86	53	61.6	Sniffin' Sticks	65.1	41.7 ± 11.8
[a]Moein [102]	Iran	60	35	58.3	UPSIT	33.4	46.6 ± 12.2
Vaira [103]	Italy	345	244	70.7	OTT (ethyl-OH)	57.7	48.5 ± 12.8
[a]Vaira [96]	Italy	72	60	83.3	CCCRC	62.5	49.2 ± 13.7

[a]Denotes studies performed on hospitalized patients; CCCRC, Connecticut Chemosensory Clinical Research Centre test; OTT, olfactory threshold test; UPSIT, University of Pennsylvania Smell Identification Test.

in the numbers of patients presenting with olfactory complications, with a variety of studies reporting that COVID-19 patients have concurrent hyposmia. However, given the imprecise nature of the methods used to evaluate olfactory performance the incidence of hyposmia associated with COVID-19 is likely to be under-reported. Published studies (Table 2), relying on self-reporting of olfactory alterations demonstrated a prevalence that ranged from 5.1–85.6% (mean ± SD; 49.6 ± 21.77%). These studies suggest that roughly half of the patients with clinically confirmed COVID-19 present with an olfactory deficit (or deficits in olfaction *and* taste). Self-assessment is notoriously unreliable, as people may not recognize a reduction in their sense of smell if it is not severe, or the patient has respiratory difficulties. To date, six studies have been performed that utilize clinical olfactory tests, including the Sniffin' Sticks, University of Pennsylvania Smell Identification Test (UPSIT), and Connecticut Chemosensory Clinical Research Centre Test (CCCRC), that can quantify the degree of hyposmia and anosmia in patients (Table 2). These data demonstrate a range of olfactory disruption prevalence from 58.3–87.1%, (mean ± SD; 74.2 ± 12.47%), which is substantially higher than self-reported studies.

The problematic nature of self-evaluation of hyposmia has been reported in other disease cohorts [42] and is highlighted in two COVID-19 studies that compared self-reported with measured olfaction performance. In a study by Hornuss et al., 22 out of 45 COVID-19 patients (48.9%) self-reported a change in their sense of smell; however, using the "Sniffin' Sticks" it was determined that 38 of the 45 COVID-19 patients had hyposmia or anosmia (84.4%). Vaira et al. found similar findings in that of 72 COVID-19 participants, 44 people reported olfactory deficits (14 olfactory deficits alone, 30 olfactory and taste deficits; 61.1%), however, using the CCCRC it was determined that 60 had either hyposmia or anosmia (83.3%). These data suggest that the number of studies relying on self-reporting of hyposmia results is unreliable and likely results in an under-estimation of olfactory deficits, and therefore neurological symptoms, in COVID-19 patients. Importantly, there are reports that hyposmia/anosmia precede other symptoms [43–45], and in some cases these are the only symptoms of COVID-19 [46, 47]. The reported recovery period is varied, with majority of people recovering between 1–28 days, and very few people showing no recovery in follow-up after one month [48]. Olfactory dysfunction may therefore go unrecognized by the individual affected by COVID-19—a phenomenon called olfactory anosognosia. In community studies, olfactory awareness is negatively related to age, cognitive decline, especially concerning memory and executive control such as attention, and male sex [49].

Viral and post-viral olfactory disorders usually occur after an upper respiratory tract infection (URTI) associated with a common cold or influenza. Estimates of its prevalence vary widely. Women are more often affected than men and post-UTRI disorders usually occur between the fourth and either decade of life [50]. The diagnosis is made according to the history, clinical examination, and olfactory testing. The exact location of the damage in post-UTRI is not yet known even though biopsies suggest direct damage of the olfactory receptor cells is likely. Further, central mechanisms may also be important. There is limited information on the viruses responsible that include influenza viruses, parainfluenza viruses, coronaviruses, respiratory syncytial virus, coxsackie virus, adenoviruses, poliovirus, enteroviruses, and herpesviruses. Spontaneous recovery may occur but there is no effective therapy except specific olfactory training. Olfactory anosognosia has not previously been described in cases of viral olfactory dysfunction. However, the high prevalence of olfactory anosognosia reported in COVID-19 here raises the

possibility that this could reflect involvement of the central nervous system in COVID-19 infections.

One of the commonest causes of impaired olfactory function are the neurodegenerative disorders of Alzheimer's and Parkinson's disease. Hyposmia was first recognized as a possible symptom of PD well after James Parkinson's descriptions of motor phenomenology and well after the encephalitis lethargica pandemic [51]. It has subsequently been found to be one of the earliest prodromal symptoms of PD and is present in up to 90% of patients with early-stage PD [52]. Intracellular aggregates of α-synuclein, the pathologic hallmark of PD, involve the olfactory bulb and anterior olfactory nucleus at Braak stage I [53]. While olfactory dysfunction is independent of cognitive impairment at baseline [54], patients with PD who exhibit decreased olfactory ability appear to have a significant increase in their risk of progression in the disease [55]. The percentage of olfactory anosognosia ranged from 63 to 80% in non-demented PD, significantly higher than that in healthy individuals [54, 56]. Furthermore, olfactory anosognosia accompanied by olfactory deficits in the *de novo* state can be a predictor of cognitive decline and conversion to dementia in PD [57].

EVIDENCE OF CNS INFILTRATION IN COVID-19: VIRAL PARTICLES

The presence of neurological symptoms is evidence of the neurotropic potential of SARS-CoV-2. There are several reports of virus found in the CSF of patients [58–60], and there has also been one incidence of viral particles in the frontal lobe of a deceased COVID-19 patient [61]. Although parkinsonism linked to viruses is often considered post-encephalopathy, there is evidence that even in the absence of encephalitis, the brain is undergoing SARS-CoV-2-related changes [62]. The report by Politi et al. described a case of a 25-year-old female with a mild dry cough and persistent severe anosmia. This patient was positive for SARS-CoV-2 but had no fever and a negative chest and maxillofacial computerized tomography scan. MRI demonstrated the anosmic patient had cortical alterations in the right gyrus rectus, and subtle alterations in the olfactory bulbs, both of which resolved within 28 days. This case highlights the possibility of cerebral involvement in mild cases with only hyposmia as the sole neurological symptom. Although these changes were not found in two other anosmic COVID-19 patients, it suggests that SARS-CoV-2 has the potential to invade the brain through the olfactory pathways. Indeed, this has been demonstrated with SARS-CoV *in vivo* in which the virus was able to disseminate across the cribriform plate during infection and lead to a cerebral invasion [16]. Although there is a reasonable focus on the severe neurological symptoms in COVID-19 for the short-term management of these patients, the high prevalence of hyposmia, especially in mild cases, should be of concern due to the known correlation between neurotropic viruses and Parkinson's disease/parkinsonism.

THE THIRD "WAVE" OF THE COVID-19 PANDEMIC

There may be a myriad of potential long-term neurological and neuropsychiatric complications secondary to SARS-CoV-2 infection including a potential link to worsening parkinsonism in patients with PD and possibly even delayed neurological effects including parkinsonism. It remains to be seen whether COVID-19 viral infections will be later linked to parkinsonism as is the case in other viruses. Also, unlike many neurological conditions, such as neuropathy, there are emerging tools available to identify parkinsonism *early* in the disease process. As such, this review serves as a 'call to arms' for the neurology community in preparation of a potential wave of parkinsonism to come.

There is insufficient data at this stage to quantify the increased risk of developing parkinsonism associated with COVID-19. The high prevalence of anosmia combined with a suspicion about a link between an encephalitis lethargica-type association with a historic influenza pandemic leads us to question whether history is repeating. Fortunately, this time we are more informed about the features of prodromal PD/parkinsonism and we are able to test the hypothesis that COVID-19-related neurological features may relate to neurodegenerative sequelae. At face value it is attractive to equate the hyposmia and anosmia in COVID-19 to the hyposmia and anosmia in parkinsonism, however this determination cannot be made without extensive studies. We are proposing there may be an increase in the risk profile of individuals with neurological complications associated with SARS-CoV-2 infection, as demonstrated by symptoms such as hyposmia or encephalitis that may reflect a neurological injury. Furthermore, individuals who have more severe symptoms may have a more

dramatic change in their risk profile. History suggests that this may be problematic as PD/parkinsonism is the fastest growing neurological syndrome, predicted to affect more than 12 million people by 2040 [63]. This number alone is going to have significant social and economic consequences as it is a disease that progresses slowly, is very costly, and has no disease-modifying treatments. Spanish flu-induced encephalitis saw a latent interval between "recovery" and onset of parkinsonism of 5 years in half of the survivors of the encephalopathy [32]. Even if this number is an overestimation, with more than 23 million people infected with COVID-19 worldwide, the potential increase in the number of cases of parkinsonism in the coming years is going to have serious ramifications for the health care systems of many countries, and a well-considered proactive response should be implemented. Importantly, strategies involving herd immunity that require an infection rate of 60–70% need to be very carefully considered, although they may represent a short-term fix from the acute infection, there may well be disastrous long-term consequences.

Population-based studies of the neurological symptoms of COVID-19 that include appropriate COVID-19 controls with no neurological complications would be needed in order to study the susceptibility of population groups. Furthermore, it would be of great benefit to patients who present with neurological symptoms to undergo short-term studies that include quantitative analysis of olfaction, as well as studies for signs of neuroinflammation, microhemorrhages, cerebral alterations, and neuronal loss [64]. In terms of screening for parkinsonism, it is well understood that significant progression of the neurodegenerative process occurs prior to diagnosis. The current diagnosis of PD and parkinsonism relies on the clinical presentation of a movement disorder, that already reflects late-stage disease as 50–70% of dopaminergic neurons have already perished [65, 66]. By relying on the spontaneous observation of manifestation of neurological problems in recovered patients affected by COVID-19, the response to the potential long-term consequences of COVID-19 may therefore also prove 'too little, too late, too flawed' [67]. The best way to identify populations that are likely to develop parkinsonism will be to create a health registry of COVID-19 patients that undergo regular long-term neurological follow up for the signs of prodromal PD/parkinsonism, as well as blood tests for neurofilament light chain for signs of neurodegeneration [68]. The Movement Disorder Society research criteria for prodromal Parkinson's disease identifies and assigns likelihood ratios to various prodromal symptoms associated with PD, including hyposmia, REM sleep behavior disorder, and constipation, and may help to guide the neurological follow up of COVID-19 patients [69]. This strategy will allow for the stratification of patients likely to develop parkinsonism and refer individuals for diagnostic dopamine neuroimaging studies. However, this risk assessment is designed for use in a research setting and requires further refinement before implementation into clinical practice. As such, now is the time for substantial investment in the early identification, diagnosis, and treatment of PD and parkinsonism to help arm clinicians with the best tools available to handle a potential influx of parkinsonism over the next half-century.

The world was caught off guard by the first wave of COVID-19, will we be ready for the third wave of neurological sequelae such as parkinsonism?

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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