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Impact of the COVID-19 Pandemic on Parkinson's Disease and Movement Disorders

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The COVID-19 Pandemic

Human coronaviruses have classically caused mild respiratory infections. Two previous outbreaks caused by newly identified coronaviruses, SARS-CoV in 2002 and MERS-CoV in 2012, caused serious respiratory disease with increased mortality. The current coronavirus disease 2019 (COVID-19) pandemic is caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2).[1,2] The infection originated late 2019 in China, and in a few months disseminated to reach almost 200 countries, now affecting over 500,000 people with an overall estimated mortality of 4% (World Health Organization; March 27, 2020).

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Rate of transmission of the virus is measured by the reproductive number (R_0), which for SARS-CoV-2 is between 3.6 and 4 indicating high infectivity compared to influenza with R_0 1.4 to 1.6.[3,4] Importantly, transmission can occur during the presymptomatic phase of the infection and even after resolution. This occurs because virus shedding peaks early, usually at onset of symptoms, and continues for days or weeks following recovery.[4–6] The virus is an RNA (32KB genome) type, with a rate of recombination up to 25%, and covered by a crown of glycoproteins that can also mutate frequently.[7,8] These characteristics may explain the adaptability of the virus and its infectivity changes over time. The infection develops as the virus glycoprotein binds to ACE2 (angiotensin-converting enzyme 2) receptors that are abundantly expressed in the lung.[9] SARS viruses thus infect the cells of the pulmonary alveolus, causing acute diffuse alveolar damage, edema, and inflammation, which can evolve to acute respiratory distress syndrome (ARDS) in adults.[10] The disease is asymptomatic or milder in children and young adults. Symptomatic adult forms have increasing severity with age, although there have been notable exceptions to this age pattern, including in health care workers.[11] Symptoms may develop between 2 and 14 days after infection, with an average of 4 to 5 days, but cases of late onset of symptoms have been reported. COVID-19 can have a clinical presentation similar to influenza, typically with fatigue, fever, and nonproductive cough.[12] Diarrhea has been the initial symptom in fewer cases, indicating initial infection through the gastrointestinal tract. Neurological symptoms can occur and include headache and nausea. In addition, patients may report an intermittent or transient loss of smell and taste. Most infected patients (approximately 80%) experience a mild clinical form and recover without complications.[13,14] However, among patients with symptomatic forms, a proportion may require hospitalization (30% in Europe, European Centre for Disease Prevention and Control [ECDC] 3/25/2020), and, of those, 50% (5% of the overall infected patients as tested) need intensive care because of pneumonia and respiratory failure typically developing in 10 to 14 days, requiring a prolonged duration of care (usually more than 14 days; ECDC). Among the risk factors for presenting a severe form, age is the most important with a progressive rise starting at 50 years.[11] Also, COVID-19 severity increases with comorbidities, particularly hypertension, cardio- and cerebrovascular disease, diabetes, and immunosuppression.[10,14] These comorbidities, together with age, are important prognostic factors. Antiviral drugs, various antibodies, hydroxychloroquine, azithromycin, ACE2 inhibitors, and other experimental agents, including those aimed at mitigating the “cytokine storm” observed in severe cases, are among the COVID-19 treatments currently under study, but thus far none is proven or recommended for use outside of a controlled clinical setting. In addition, major research efforts are dedicated internationally to developing an effective vaccine.

Several recent publications provide in-depth details to assess the impact of the COVID-19 pandemic on the general population. In addition, it is hoped that it will soon be possible to deploy antibody assays for wide-spread testing for immunity in large populations, allowing us to assess more accurately the dissemination of the infection and mortality rate. Here, we will discuss the significance of this viral infection with respect to the central nervous system (CNS) and its relevance for patients with Parkinson’s disease (PD) or other movement disorders.

COVID-19 and Neurological Manifestations

From previous studies on SARS-CoV, we know that this virus infected the brain, including the brainstem, in both patients and experimental animals.[15] Following intranasal virus inoculation in mice, SARS-CoV or MERS-CoV entered the CNS, possibly through the olfactory nerves, and, importantly, the viruses were detected in the brain, but not in the lung, suggesting direct transfer to the CNS by olfactory nerves.[16] However, detection of high viral load in the brainstem after SARS-CoV infection is also indicative of infection spreading to the CNS from the respiratory tract, which is connected primarily by the vagus nerves to the ambiguus and solitary tract nuclei in the brainstem. Involvement of this brain region may also suggest that the cardiorespiratory center contributes to the severe respiratory distress caused by COVID-19.[17] Importantly, the extent of SARS-CoV-2 invasion of the CNS, and its role in the respiratory distress and failure caused by the infection, needs further investigation. A single study has reported enhanced antibody responses against different forms of coronaviruses in the cerebrospinal fluid of patients with PD compared to other neurological diseases and healthy controls.[18]

It is too early to know whether COVID-19 will have long-term neurological complications of exposure to SARS-CoV-2. The 1918 “Spanish” flu pandemic was caused by influenza A (H1N1). A viral etiology of encephalitis lethargica and postencephalitic parkinsonism, which followed temporally from the flu pandemic, has been suspected although is still not proven, with some evidence implicating an enterovirus.[19] Thus far, coronaviruses have not been linked to specific long-term neurological sequelae. Nonetheless, the observations of anosmia and ageusia are worthy of future study. The facts that hyposmia is a common feature of early PD (often even present in the prodrome) and that the olfactory system is an early predilection site for alpha-synuclein pathology might just be an intriguing coincidence.[20] However, it is notable that recent studies indicate that alpha-synuclein participates in the innate immune response to any viral infection, suggesting that these observations could be important.[21]

Is the PD Population Particularly Vulnerable During the COVID-19 Pandemic?

It is too early to know whether COVID-19 will have long-term impacts on patients with PD and movement disorders. The increased vulnerability of the elderly and those with comorbidities, coupled with the increased prevalence of PD with age, raises concerns about the potentially height-ened risks of COVID-19 in people with PD and other movement disorders. In addition, the ability to provide standard neurological care is being compromised by the strain on health care systems brought about by this pandemic.

There is currently insufficient evidence showing that PD by itself increases the risk of COVID-19. The experience in Lombardia, Emilia, and Veneto, the three most affected regions in Italy, does not show an apparent increased risk, although there are no systematic data available yet. A large population study[22] found that in individuals aged ≥55 years, patients with PD had more physical and nonphysical comorbidities than patients without PD. In this study, there were 12 physical comorbidities significantly associated with PD,

including coronary artery disease, cerebrovascular disease, and heart failure, which are known to render patients at increased risk for more severe forms of COVID-19. In addition, both PD and more severe forms of COVID-19, including higher mortality, show a clear preponderance of male sex.[12–14]

A retrospective cohort study conducted in Japan showed that, compared to age- and sex-matched patients, patients with parkinsonism hospitalized for pneumonia had a lower rate of in-hospital mortality, but a longer duration of hospitalization.[23] The study suggested that in-hospital mortality attributed to pneumonia is not higher in parkinsonian patients, but it is not clear that this applies to those who have developed advanced ARDS. Furthermore, patients with PD possess a higher risk of in-hospital complications, such as delirium, adverse drug reactions, syncope, aspiration pneumonia, falls, and fractures.[24] Therefore, strategies to prevent these complications are essential.

A Special Role of Telemedicine During the COVID-19 Pandemic

Patients with PD need routine visits to the hospital for physical assessment and medication adjustments by movement disorders specialists. However, hospital visits should be avoided where possible during this period. Fortunately, the validity of telemedicine to assess PD patients has been well documented in many studies, which is feasible because most physical examinations can be visualized.[25] Indeed, many core features of the disease, except rigidity and postural reflex impairment, can be videotaped or watched with video consultations. The International Parkinson and Movement Disorder Society has developed a practical step-by-step guide for how to implement telemedicine for a movement disorders clinic on their website, including the example of providers and some regional specifics (https://www.movementdisorders.org/MDS/About/Committees--Other-Groups/Telemedicine-in-Your-Movement-Disorders-Practice-A-Step-by-Step-Guide.htm).

Potential Medication Supply Issues for PD Patients During the Pandemic

The impact of the pandemic on global transport and supply chains, as well as manufacturing, has so far not been reported to affect medication supply for patients with PD. However, this situation needs to be monitored and communicated to clinicians in a timely manner so that they can work with their patients to make contingency plans.

Disruption to Research and Clinical Trials

Numerous academic- and industry-based laboratories investigating new therapies or diagnostics for PD have been forced to close or dramatically reduce their activities during the COVID-19 pandemic. Funding agencies are already discussing how to manage the situation where projects are delayed, sometimes coupled to inevitable increases in cost. Grant submission deadlines are being moved and the evaluation of proposed projects postponed. Furthermore, it is difficult to predict how the ongoing economic downturn will affect government and private sponsorship of research. Numerous conferences on PD and related disorders have already been cancelled. On a positive note, there is also a flurry of new activity using remote video conferencing to keep up the exchange of results and ideas in

PD research during the pandemic. Although it will take many months, or even years, before we can fully comprehend the impact of the pandemic on laboratory research on PD, we already know that it is and will remain significant.

Clinical research in PD is definitely highly impacted by the pandemic. Some jurisdictions or institutions have prohibited the initiation of new clinical trials and research. While this is understandable because of the potential impact of COVID-19 on hospital resources and out of concern for potential COVID-19 exposure to trial patients during their visits, there are many unmet clinical needs in people with PD and movement disorders. Delays in clinical trials investigating potential disease-modifying therapies in progressive neurodegenerative diseases, such as PD, or high-impact novel symptomatic therapies should be minimized. In addition, consideration should be given to evaluating studies on a case-by-case basis rather than uniform suspensions of research activity, which may cause a significant loss of scientific and economic investment in clinical research.

Concluding Remarks

Thus far, the comorbid diagnosis of PD itself or other movement disorders has not emerged as a specific risk factor for negative outcomes of COVID-19. The medical strategy for safety of patients with PD and the general elderly population is therefore not different and based on advising social distancing and testing whenever necessary. Currently, we should rely on scientific proof and testing as many people as possible among those involved in the care of our patients, followed eventually by the necessary containment measures.

Importantly, in any situation of unavoidable measures of triage attributed to lack of intensive care resources or ventilation equipment, there is no evidence that patients with PD or any form of parkinsonism or other movement disorders have less chance of survival from COVID-19 infection than patients with similar age and comorbidities.

Finally, countries have to face the reality that individual case containment might not be possible in the long term. As the health system moves from containment to mitigation, reintroduction of adequate management and care of patients with PD, as well as resumption of vital clinical and preclinical research, will be possible while still trying to control the COVID-19 outbreak critically blunting its peaks.[26] This global crisis, however, may significantly change the care for our patients with PD and other movement disorders toward better acceptance of telemedicine consultations and assessments.

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Recommendations and Priorities for Patients With PD and Movement Disorders

- All measures of social distancing currently in place for the general population almost globally must be strictly and carefully practiced.
- Patients should avoid or postpone in-patient hospital stay for nonemergency reasons, given that hospitals can unfortunately be a source of further infection.[27]
- Elective DBS surgeries may need to be postponed as well.
- Outpatient visits can be substituted by the available tools of telemedicine and should only be performed when direct contact is necessary for adjusting or checking DBS programming, for DBS battery failure, or pump treatments.
- Direct patient contact may be required for botulinum toxin therapy on a carefully considered, as-needed basis, ensuring adequate personal protective equipment.
- Quarantine may prevent patients with PD from an active lifestyle, which may already be impeded by pre-existing conditions, such as lack of motivation, physical disability, and mood problems. Virtual reality exercise games or home exercise instruments can be encouraged.
- In case of COVID-19 infection, the physician must ensure the maintenance of previous PD medications, especially the adequate dosages of L-dopa/DDCI, as recommended for any type of pneumonia in parkinsonian patients to avoid rigidity with contractures and respiratory impairment with reduced vital capacity and peak expiratory flow.[28]

The International Parkinson and Movement Disorder Society with this Viewpoint and other forth-coming communications will endeavor to provide updates and guidance for clinicians who care for PD and movement disorder patients.