View Point

The Challenge of Managing Parkinson's Disease Patients during the COVID-19 Pandemic

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Abstract

The 2019 novel coronavirus (nCoV) pandemic is rapidly developing across the globe and new information is emerging expeditiously and constantly, particularly in relation to neurological illnesses. Both central and peripheral nervous system involvement has been reported including headache, dizziness, hyposmia/anosmia, taste disturbances, seizures, stroke, alteration of the sensorium, and even acute hemorrhagic necrotizing leukoencephalopathy. Varying degrees of olfactory disturbances may pre-empt the diagnosis of COVID-19. Although no direct effect of 2019 nCoV has been reported yet on Parkinson's disease, there are enormous possible indirect effects and implications. We examine the potential effects and challenges posed by this pandemic to individuals with Parkinson's disease, particularly in the Indian context where telecommunication access or support group access may be lacking for these patients. Additionally, lockdown and social distancing may pose hurdles in the provision of optimum medical therapy, particularly if patients experience motor and non-motor deteriorations due to diverse reasons.

Keywords: COVID-19, India, movement disorders, Parkinson's disease

Introduction

In the early part of December 2019, health authorities recognized the emergence of several cases of a short febrile illness with respiratory features, including pneumonia in Wuhan, the capital of the Hubei province in China.[1] This was soon attributed to a beta coronavirus termed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) or 2019 novel coronavirus (2019-nCoV).[2] This virus was found to bear a close resemblance to the SARS-CoV-1 which led to the SARS epidemic in 2003. Another coronavirus called the Middle East respiratory syndrome (MERS) had led to a similar outbreak in 2012. Over the ensuing few months, this 2019 novel coronavirus swept across the globe, emerging as a pandemic with above 16,00,000 cases worldwide and above 100,000 mortality at the time of this article. In India, the curve is yet to flatten, with a number of new cases and deaths rising every day.

Some salient features from other studies reported so far are important from the perspective of Parkinson's disease (PD). In the previous SARS epidemic of 2003, which affected a smaller number of around 8,000 patients, neurological features were described including peripheral axonal neuropathy as well as muscle enzyme elevation, attributable to extensive vasculitis process triggered by the virus.[3,4] One patient was reported to have developed anosmia.[5] Additionally, the association with stroke was also reported in this epidemic.

Recent case series have described neurological features in association with the COVID-19 pandemic. In the series by Mao *et al*., out of 214 patients, 36.4% had associated neurological features.[6] The gamut of neurological manifestations ranges from olfactory disturbances (hyposmia/anosmia), headache, dizziness, and seizures to impairment of consciousness, stroke, and myopathy. One case of hemorrhagic encephalopathy has also been reported.[7] Compared to the SARS-CoV-1 in which neurological involvement was found to occur at 2–3 weeks into the illness, some of the symptoms reported in 2019-nCoV such as olfactory and gustatory disturbances have been found to occur earlier in the disease course.

There could be several pathophysiological manifestations underlying neurological manifestations. These could be a direct effect of the virus itself, secondary to an inflammatory cascade triggered by the virus, or even neurotropism and direct infiltration as has been reported in the brainstem.[8] The latter has been theorized to contribute to the respiratory failure that may accompany these patients. It is known that the virus enters the brain and binds to the enzyme angiotensin-converting enzyme (ACE)-2 receptors causing neuronal death.[9] Apart from the lungs, ACE2 receptors are importantly distributed in the medullary centers that control

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respiration and cardiovascular tone, and also, from the point of view of movement disorders, the striatal circuitry.[10] To date, a direct effect on the nigrostriatal pathway is not known, but considering an example from the H1N1 influenza virus, may be plausible. The Movement Disorders Society has recently published recommendations and priorities for patients with movement disorders during the COVD-19 pandemic.[11,12] From India, a case series of 21 patients have been recently published. Most (67%) of patients were males and in the 21–40 years age group. Although neurological features have not been focused on in this series, one person each had migraine, anxiety and obstructive sleep apnea.[13] Against this background, we explore the potential impact of the 2019-nCoV on patients with PD, particularly from an Indian perspective.

Burden of overlap

In 2016, it was estimated that 6.1 million people worldwide had PD. The prevalence in India was roughly 10% of the global burden, that is, 5.8 lakhs.[14] From India, crude prevalence rates (CPR) between 6 and 53/100,000 have been reported. Above the age of 60 years, the PRs were higher, being 247/100,000.[15] It is known to occur in 1% of people above the age of 65 years. As per WHO estimates, the highest mortality in COVID-19 is among older individuals, with the highest death rates in those above the age of 80 years. It is, therefore, reasonable to conclude that persons with PD affected by the COVID-19 pandemic in India form a particularly high-risk population since most PD patients are above the age of 60 years. There is also the possibility that stress, especially high during these times, unmasks latent PD.[16] Whether there is an increase in the incidence or prevalence of PD following the pandemic will only be answered by long-term longitudinal studies.

Lessons from the past

The 1918 Spanish flu pandemic was caused by H1N1 influenza A. post-encephalitic parkinsonism or encephalitis lethargica followed this pandemic and was believed to be of viral etiology, likely enterovirus.[17] Neurological features, albeit not parkinsonism, were reported following the SARS and MERS outbreaks.[18] Even in the current pandemic, smell impairment is reported in 5–7% of patients.[6] The fact that anosmia may precede overt alpha-synucleinopathies and is a premotor feature may suggest potential overlap between PD and COVID-19.[19]

Predisposing factors in PD

Persons with PD have significantly associated comorbidities including cardiac failure, coronary artery disease, cerebrovascular disease, diabetes all of which predispose to more severe forms of the COVID-19.[20] Additionally, both persons with PD as well as higher mortality groups among those afflicted with COVID-19 have larger male proportions.[21-23] Another contributory factor may be that the immune response in PD may be disrupted and this may also predispose this population to COVID-19. Microglia play an immune surveillance role and are mediators of the innate immune response.[24] Immune disbalance, triggered by putative infectious agents, may play a role in pathogenesis in PD.

Exacerbations due to intercurrent illness

In general, both motor and non-motor symptoms of PD may be exacerbated by intercurrent infections including viral infections. Patients may experience deterioration of bradykinesia, rigidity as well as tremor following systemic infection. Possible mechanisms that underlie these exacerbations include altered brain metabolism of dopamine, changes in drug pharmacodynamics or effects of inflammatory changes secondary to infections or the direct effect of endotoxins triggered by the infectious agent.[25]

As a result, persons with PD infected with SARS-CoV-2 are likely to have a motor and non-motor deterioration. Clinicians must assess these patients for worsening in PD from baseline status and up-titrate the dopaminergic drugs as necessary. Motor deterioration may be in terms of both the cardinal features (tremor, rigidity and bradykinesia) but also falls. Non-motor worsening may include sleep disturbances, anxiety, and depression.

Ventilatory issues

Severe respiratory issues occur in COVID-19 which may necessitate ventilation. This is an important factor to consider because persons with PD already have some form of restrictive lung disease, characterized by respiratory muscle bradykinesia, rigidity and dystonia of the trunk. Loss of chest wall compliance may occur due to camptocormia. Even a severe obstructive pattern of airflow has been reported in advanced PD.[26] Dystonia of the neck may make intubation challenging. Per se, dyspnea is also reported by persons with PD and is considered to be an underestimated symptom, which may be associated with motor fluctuations or even anxiety.[27] Additionally, the COVID-19 virus has the potential to inhibit cough reflex and potentiate swallowing dysfunction in these patients, predisposing them to aspiration and aspiration pneumonia.

Drug-related issues

The interactions between drugs used for PD and coronavirus are unclear. We do not know whether the drugs used in PD management could have an impact on the virus. Conversely, whether the virus will influence drug effects is also not known. Foremost among PD drugs is the potential role of amantadine. Amantadine was used in the management of the influenza A virus. It acts by interfering with virus uncoating inside the cell. It blocks the M2-protein which forms an ion channel on the viral membrane which is required for virus transport inside the cell. However, its use was associated with the emergence of drug-resistant mutants and hence, it is no longer favored for this indication. Whether this drug blocks a protein on the 2019 novel coronavirus is not clear although this has been previously reported for the SARS coronavirus.[28]

Another concern relevant to drugs is their administration in a PD patient who is ventilated for COVID-19. Oral drug administration in this condition would be via nasogastric tube of a percutaneous enterostomy tube. Options to maintain

smooth dopaminergic drugs and avoid dopaminergic withdrawal states in such a situation include liquid levodopa, transdermal rotigotine patches as well as apomorphine subcutaneous intermittent injections or apomorphine pump. In India, the option of apomorphine is available although costly.

Psychological aspects

Half of the patients with PD experience fatigue.[29] Dopamine depletion in the nigrostriatal pathway has been associated with motor and cognitive inflexibility in PD patients.[30] A role of dopamine has also been hypothesized in optimal coping mechanisms, the depletion of which may lead to increased stress and a sense of loss of control in PD patients.[31] Hence, almost 40–50% also have clinically significant anxiety and depression[32] which may further worsen, either on receiving a diagnosis of COVID-19, or even self-isolation. These issues comprise 'hidden sorrows' in PD patients.[33] Post-viral asthenia may exacerbate fatigue. Increased stress in these patients may not only exacerbate motor symptoms such as dyskinesias and freezing of gait but also reduced the efficacy of dopaminergic medications.[34] This may even lead to uncovering of a latent akinetic-rigid state.[16] PD patients should be encouraged to join peer support groups via social media services as well as various societies so that they may be able to interact with other peers during these trying times. These strategies may encourage PD patients to be resilient even in times of crisis.

Rehabilitation

As a result of social distancing, immobilization, and lockdowns necessitated by COVID-19, exercise, as well as physiotherapy or other rehabilitative services, maybe interrupted for PD patients. This lack of physical activity may lead to a worsening in the motor as well as non-motor symptoms such as constipation. Patients should be advised to follow a light yoga program at home and maintain stretching and exercises that they would have been encouraged to learn earlier. The recent Park-in-Shape trial showed that home-based aerobic activity (30–45 min of stationary cycling using a home trainer thrice weekly over 6 months) compared to stretching may help attenuate the off-state motor signs in PD patients and may be encouraged.[35] Mindfulness strategies are known to reduce depression and anxiety levels.[36] Such home-based exercised and relaxation techniques may promote coping during the lockdown period. Many mindfulness applications may be used for practice. These programs may be accessed via applications on smartphones or online platforms.

Providing medical advice during COVID-19 times

The social distancing norms that have found widespread advent in these times pose enormous challenges to medical consultation and it is the need of the hour for clinicians as well as patients to be well versed with teleconsultation/video consultation techniques. There are obvious disadvantages including lack of patient proximity for examination as well as an inability to manage some problems such as deep brain stimulation device-related issues. Nevertheless, valuable advice, as well as medical support, can be provided to PD patients using these services. The challenges to these solutions in India are obviously, lack of awareness or access to telecommunication methods. Additionally, there may be medicolegal concerns about advice delivered through these mechanisms although guidelines are in place to safeguard against the same.

Persons with PD may hence not only be a vulnerable population in COVID-19 times but also a high-risk population. Such patients must be encouraged to particularly follow the principles of hand hygiene and social distancing while simultaneously organizing social support groups and medical access via telecommunication services. This would prevent these persons, already isolated by the disease to some extent, from further feeling isolated and bereft of medical support.

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Conflicts of interest

There are no conflicts of interest.

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