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Relationship Between Coronavirus Disease 2019 and Parkinson's Disease

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Abstract:

New literature shows that Covid 19 has negative effects on patients with Parkinson's Disease. Covid 19 is known to produce neurological manifestations and infects the central nervous system. Similarly, the virus also causes neuromuscular complications and involves the peripheral nervous system. Studies show PD patients with a severe Covid 19 infection have a higher mortality rate, worsening in symptoms, and require an increase in drug dosage. These studies suggest that Covid 19 may lead to a more rapid onset of PD, or may increase the risk of developing PD. Furthermore, researchers observed that Motor and nonmotor symptoms significantly worsened in PD patients with Covid compared to PD patients.

Introduction

The Coronavirus disease 2019 (Covid 19) pandemic has led to over 3 million deaths worldwide and has caused permanent damage in many more. Covid 19 has also exacerbated many underlying conditions, specifically ones that involve cardiopulmonary and neurological complications. In this review paper, we will be discussing the connection between Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2) and the acceleration of the onset of Parkinson's Disease (PD). As previous research has shown, SARS-COV-2 is known to infect the nervous system and manifest in neuromuscular diseases. SARS-COV-2 has shown that similarly to SARS-COV, this virus can invade tissues by binding to the angiotensin-converting enzyme 2 (ACE2) receptor on certain host cells. This binding is mediated by the spike protein found on the surface of SARS-COV-2 and was found to have up to 20 times the binding affinity of SARS-CoV [37]. Additionally, during previous coronavirus epidemics (SARS-CoV and MERS-CoV), animal studies on transgenic mice showed that both of these viruses were able to reach the brain when introduced intranasally [37,38].

SARS-COV-2 also is able to infect the peripheral nervous system, and Myalgia is a common symptom of the disease. Myopathy or myositis can occur as a late manifestation of COVID-19 and is associated with multi-organ damage [39]. Direct damage is implicated by the presence of ACE-2 receptors in skeletal muscle. Critical illness myopathy is associated with multi-organ damage. A case report from Wuhan describes a patient with leg weakness and pain 9 days into his COVID-19 illness, which was treated with aggressive hydration, PLEX, then IVIG with rapid improvement [39, 40]. COVID-19 induced a significant worsening of motor performance, motor related disability and experiences of daily living [19]. Worsening of levodopa-responsive motor symptoms and increased daily OFF-time, caused either by the effects of acute systemic inflammatory response or by changes in pharmacokinetics, was so pronounced in one-third of cases to prompt neurologists to increase dopaminergic therapy [19].

Understanding the neurological bases of PD can help us see the connection with Covid 19. Selective loss of dopaminergic neurons in the striatum causes impairment of motor control in persons with PD [9]. The motor circuit of PD consists of corticostriatal projections from the primary motor cortex, supplementary motor area, cingulate motor cortex and premotor cortex, terminating on the dendrites of the striatal medium spiny neurons. The direct pathway is a monosynaptic connection between the medium spiny neurons that express dopamine D1 receptors and GABAergic (gamma amino butyric

acid-ergic) neurons in the globus pallidus internus (Gpi) and the substantia nigra pars reticulata (SNpr)[9]. Changes in cerebellar activity and in the interaction between the basal ganglia and cerebellum contribute to the pathophysiology of tremor in PD. Abnormalities of balance and gait are due to dysfunction of the basal ganglia output via projections into the midbrain locomotor region (pedunculo-pontine and cuneiform nuclei) [9].

Furthermore, Covid 19 can induce a cytotoxic aggregation of proteins, including α-synuclein which are pathognomonic of PD. 10 clinical cases collected from the experience at the Parkinson and Movement Disorders Unit in Padua, Italy, and the Parkinson's Foundation Centre of Excellence at King's College Hospital in London, UK, showed that PD patients of older age (mean, 78.3 years) with longer disease duration (mean, 12.7 years) are particularly susceptible to COVID-19 with a substantially high mortality rate (40%)[20]. Antibodies against coronavirus were found in the cerebrospinal fluid of PD patients more than 2 decades ago, suggesting a possible role for viral infections in neurodegeneration. Angiotensin-converting enzyme 2 (ACE2) receptors are highly expressed in dopamine neurons, and they are reduced in PD because of the degenerative process; therefore, SARS-CoV-2 related brain penetration may cause additional harm and worsen symptoms and may increase the requirement of dopamine replacement therapy [20].

Although SARS-COV-2 is a relatively new virus, there are many research papers documenting the short term effects, and a significant amount of papers are being published daily. By providing case studies that studies the effect of Covid on PD, we hope that we can encourage further research to be done. Many people around the world suffer from Parkinson's Disease, and the first step to determining any treatment is to study this connection. As we begin to see the long term effects of Covid we can determine the extent of the damage done to the population.

Methods

In this paper, we analyzed all published reports on COVID-19-associated Parkinson's Disease (PD) in hopes of shedding light on potentially overlooked, yet significant, neurologic complications of the virus. Published literature was compiled using Pubmed, Google Scholar, and Scopus as search engines. We identified isolated case reports, case series, and cohort studies. COVID-19, Parkinson's Disease, Sars Cov 2, and Neurology were used as keywords in the search. Studies lacking the focus on neurology were excluded in our search. The last search was done on 10th of june 2021, however new information about the virus is being added to the literature continuously.

Covid-19 And the Nervous System

It has been shown that in addition to common pulmonary clinical manifestations of covid-19, it has a role in neurological manifestations as well. In a retrospective observational study that was done at 3 centers (Main District, West Branch, and Tumor Center) of Union Hospital of Huazhong University of Science and Technology (Wuhan, China), it was shown that 36.4% of patients with severe covid-19 infections had neurological manifestations [1]. Of the 214 patients in this study (mean [SD] age, 52.7 [15.5] years; 87 men [40.7%]) with COVID-19, 126 patients (58.9%) had nonsevere infection and 88 patients (41.1%) had severe infection according to their respiratory status. Overall, 78 patients (36.4%) had neurologic manifestations [1].

Compared with patients of nonsevere infection, patients with severe infection were older, had more underlying disorders such as hypertension, and showed fewer typical symptoms of COVID-19, such as fever and cough [1]. Patients with more severe infection had neurologic manifestations, such as acute cerebrovascular diseases (5 [5.7%] vs 1 [0.8%]), impaired consciousness (13 [14.8%] vs 3 [2.4%]), and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]) [1].

Given high rates of COVID-19 infection in the general population, coincidental occurrence of neurologic events is likely. However, currently there is convincing evidence that SARS-COV-2 can involve the nervous system, and its neurotropic potential is increasingly well established [2].

In May of 2020, a Japanese team reported on a case that describes the first case of a 24 year old male patient, who was brought in by the ambulance due to a convulsion accompanied by unconsciousness which was later diagnosed with aseptic encephalitis with SARS-COV-2 RNA in cerebrospinal fluid [3].

Further studies have elaborated the indirect mechanism of injury of SARS-COV-2 and the nervous system. SARS-Cov-2 binds to ACE2 receptors with a higher affinity compared with SARS-COV [4]. ACE2 is known to be a cardio cerebral vascular protection factor, which plays a major role in regulating blood pressure and anti atherosclerosis mechanisms. When bound to ACE2 receptors, SARS-COV-2 viruses may cause abnormally elevated blood pressure and increase the risk of cerebral hemorrhage and ischemic stroke [2]. In addition, when the virus replicates and proliferates in pneumocytes, it causes diffuse alveolar and interstitial inflammatory exudate, as well as the formation of membranes in the most severe forms. This, in turn, leads to alveolar gas exchange disorders causing hypoxia in the CNS, increasing the anaerobic metabolism in brain cells, inducing cellular and interstitial edema, obstructing cerebral flow blood, as well as ischemia and vasodilation in the cerebral circulation [2].

Furthermore, the immune response can also play a role in the indirect mechanism of injury of SARS-COV-2 and the nervous system. Some patients with COVID-19 have died from hyperinflammatory syndrome (cytokine storm) and multiorgan failure. Coronaviruses also have the ability to infect macrophages and glial cells. Experimental models have shown that glial cells are capable of secreting proinflammatory factors, such as interleukin-6, interleukin-12, interleukin-15, and tumor necrosis factor alpha, after coronavirus infection [5-6].

In addition to the indirect mechanism of injury between SARS-COV-2 and the nervous system, published literature suggests that there may even be a direct link between SARS-COV-2 and central nervous system invasion. Altered sense of smell and/or taste in uncomplicated early-stage COVID-19 patients is suggestive of a movement of the virus to the brain via the olfactory bulb, which enables the virus to reach and affect the brain [2]. SARS-Cov-2 has been shown to use the ACE2 receptor for cell entry. This receptor has also been detected over glial cells and neurons, which make it a potential target for COVID-19. Moreover, SARS-CoV-2 spike protein could interact with ACE2 expressed in the capillary endothelium; the virus may also damage the blood-brain barrier and enter the CNS by attacking the vascular system [7-8]. Ultimately, we see that there is a link between severe COVID-19 cases and neurological manifestations that can be caused by direct and indirect effects of SARS-COV-2.

Neuromuscular Manifestations of Covid-19

SARS-COV-2 also involves the peripheral nervous system. Myalgia is one of the common early symptoms of the disease. Guillain-Barrè syndrome and Miller-Fisher syndrome are increasingly being described in patients with preceding or concomitant COVID-19 disease [23]. This points towards the involvement of peripheral nerves either by direct infection of nerves or by the mechanism of "molecular mimicry". There are also reports of myositis and rhabdomyolysis secondary to COVID-19 disease. Since muscle also expresses ACE-2 receptors, direct muscle involvement by SARS-CoV-2 is postulated in addition to immune-mediated muscle damage [23].

A cohort study conducted in Denmark analyzed 20 consecutive patients from a Long-term COVID-19 Clinic referred to electrophysiological examination with the suspicion of mono- or polyneuropathy. The team performed examinations from 77 to 255 (median: 216) days after acute COVID-19. None of the patients had received treatment at the intensive care unit. Of these 20 patients, 10 of them were not hospitalized. Conventional nerve conduction studies (NCS) and quantitative electromyography (qEMG) findings from three muscles were compared with 20 age- and sex-matched healthy controls [21]. qEMG showed myopathic changes in one or more muscles in 11 patients (55%). Motor unit potential duration was shorter in patients compared to healthy controls in biceps brachii (10.02 ± 0.28 vs 11.75 ± 0.21), vastus medialis (10.86 ± 0.37 vs 12.52 ± 0.19) and anterior tibial (11.76 ± 0.31 vs 13.26 ± 0.21) muscles. All patients with myopathic qEMG reported about physical fatigue and 8 patients about myalgia while 3 patients without myopathic changes complained about physical fatigue [21].

Myopathy may be an important cause of physical fatigue in long-term COVID-19 even in non-hospitalized patients [21].

Comprehensive examinations of the published literature show that 9 patients with COVID-19-related myositis/rhabdomyolysis were reported [23]. 8 patients presented with generalized or limb weakness. Myalgias were present in four patients. One patient who did not have muscle weakness presented with myalgia, fever, and dyspnoea [23]. One patient presented with repetitive muscle twitching along with tingling and numbness in the legs [24]. 3 patients passed red blood cells in the urine. All patients had elevated CPK levels [24, 25]. One patient who presented with dark-coloured urine had the most elevated CPK level of 427,656 IU/L. All patients had elevated levels of CRP, LDH, and serum ferritin [23]. Six patients had abnormalities on chest imaging like ground-glass opacities, pneumonia, pleural effusion, or multifocal opacities [23]. Two patients required mechanical ventilation [26, 25]. 5 patients improved with conservative management [23].

In addition to myositis and rhabdomyolysis, there is a report of six COVID-19 patients with critical-illness myopathy. All six patients had acute flaccid quadriparesis [23]. Electrophysiological tests revealed a myopathic pattern. They had mildly elevated creatine kinase and all patients had a good outcome [27]. Cachexia and sarcopenia have also been described in patients affected by COVID-19 [28].

Conclusively, the published literature indicates that Covid 19 has also been shown to induce neuromuscular manifications.

Pathophysiology Of Parkinson's Disease

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterized by early prominent death of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and widespread presence of alpha synuclein (aSyn), an intracellular protein.[9] Intraneuronal inclusions of α-synuclein (αSyn) protein, are commonly referred to as Lewy bodies (LB)[33]. It is important to note that the loss of dopaminergic neurons leads to motor deficiencies.

Clinical manifestations of PD include the presence of bradykinesia in combination with at least one more manifestation: muscular rigidity, rest tremor or postural instability (the latter being a feature of the more advanced form of the disease)[9]. These symptoms are often unilateral in nature. A non motor symptom associated with PD is hyposmia. Hyposmia, identified as reduced sensitivity to odor, is a common non-motor symptom of Parkinson's disease (PD) that antedates the typical motor symptoms by several years. It occurs in ~90% of early-stage cases of PD.[11].

There are many treatments that are used to manage PD and most of these treatments target the dopaminergic pathway. Conventional pharmacological treatments for PD are dopamine precursors (levodopa, l-DOPA, l-3,4 dihidroxifenilalanina), and other symptomatic treatments including dopamine agonists (amantadine, apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, ropinirole, rotigotine), monoamine oxidase (MAO) inhibitors (selegiline, rasagiline), and catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone[12].

Age and genetics are risk factors for PD : the incidence and prevalence of PD increases with advancing age, being present in 1% of people over the age of 65 years[9] and genetic markers for parkinsonism include LRRK2, SNCA, VPS35, Parkin, PINK1, and DJ1[10].

Other Potential risk factors include environmental toxins, drugs, pesticides, brain microtrauma, focal cerebrovascular damage, and genomic defects.[12]. However it is interesting to note that a number of viruses have been associated with both acute and chronic parkinsonism: these viruses include influenza, Coxsackie, Japanese encephalitis B, western equine encephalitis, herpes and those that lead to acquired immunodeficiency disorder (HIV) [13].

Parkinson's Disease Associated with Covid-19

As already established, there are certain viruses that are associated with PD. It should come as no surprise that with the newly emerging literature about covid-19, it is apparent that there may be a connection between covid-19 and PD. As previously stated alpha synuclein bodies are pathognomonic of PD. This is especially interesting with the fact that covid-19 could prompt cytotoxic aggregation of proteins, including α-synuclein: this hypothesis is supported by evidence in animal models that viral infections can trigger α-synucleinopathies in the CNS [14].

Furthermore, as previously mentioned, aggregating shreds of evidence suggests that Olfactory dysfunction (OD) is one of the most common signs of COVID-19.[15,16]. This in relation with the fact 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 [17,18].

Cases have also shown that covid-19 might exacerbate the symptoms of PD requiring increased drug dosages and increase in overall mortality: Of 141 PD patients resident in Lombardy, changes in clinical features in the period January 2020 to April 2020 were compared with those of 36 PD controls matched for sex,

age, and disease duration using the clinical impression of severity index for PD, the Movement Disorders Society Unified PD Rating Scale Parts II and IV, and the nonmotor symptoms scale: it was observed that Motor and nonmotor symptoms significantly worsened in the COVID-19 group, requiring therapy adjustment in one third of cases[19].

10 clinical cases collected from the experience at the Parkinson and Movement Disorders Unit in Padua, Italy, and the Parkinson's Foundation Centre of Excellence at King's College Hospital in London, UK, from the beginning of March to the current period showed that most patients requiring additional levodopa dosing following covid-19 infection: anxiety and other nonmotor features, such as fatigue, orthostatic hypotension, cognitive impairment, and psychosis, also worsened during the infection: fatigue was a dominant symptom during the SARS-COV-2 infection in all cases on advanced therapies and three patients died from COVID-19 pneumonia[20]. These findings suggest that PD patients of older age (mean, 78.3 years) with longer disease duration (mean, 12.7 years) are particularly susceptible to COVID-19 with a substantially high mortality rate (40%) [20].

Clinical information of 117 community-dwelling PD patients with COVID-19 followed in 21 tertiary centres in Italy, Iran, Spain, and the UK was gathered, and showed Overall mortality was 19.7%, with a significant effect of co-occurrence of dementia, hypertension, and PD duration [22].

Furthermore, there has been an established link in the acceleration of PD and severe covid-19. Immune responses and excessive inflammation in COVID-19 may also accelerate the progression of brain inflammatory neurodegeneration [42]. There is no question the viral neurotropism is important along factors intrinsic to the host, including genetics, innate immunity, the hyperactivation of the immune system, and the development of cytokine storm syndrome along with the immune previous status of the host to the COVID-19 encounter [41]. Long-term neurodegenerative diseases ought to be in the mind of every neurologist across the world, with aberrant proteostasis, neuroinflammation, and abnormal immune responses being key factors for accelerating PD pathology [41].

There does seem to be a association between COVID-19 and the PD, this may be due in part to the fact that both diseases have been identified to be neuroinvasive, however it is clear that more research needs to be done to verify and ascertain the exact nature of the relationship between COVID-19 and PD.

Similarities between SARS-COV-2 infection and PD in the brain

Although it is commonly thought that the neuropathology of PD is characterized solely by dopaminergic neuron loss, the neurodegeneration extends well beyond dopaminergic neurons: neurodegeneration and lewy body formation are found in noradrenergic (locus coeruleus), serotonergic (raphe), and cholinergic (nucleus basalis of Meynert, dorsal motor nucleus of vagus) systems, as well as in the cerebral cortex (especially cingulate and entorhinal cortices), olfactory bulb, and autonomic nervous system [32]. Furthermore, Oligomeric forms of alpha-synuclein are emerging as key mediators of pathogenesis in Parkinson's disease: these oligomers are often localized, in the absence of Lewy bodies, to neuroanatomical regions mildly affected in Parkinson's disease [36]. In a blinded study with post-mortem brain tissue from patients with Parkinson's disease (n = 8, age range 73–92 years, four males and four females) and age- and sex-matched controls (n = 8), diffuse alpha-synuclein proximity ligation assay signal is significantly more abundant in patients compared to controls in regions including the cingulate cortex (1.6-fold increase) and the reticular formation of the medulla (6.5-fold increase) [36]. This could mean that the medulla is implicated in PD.

COVID-19 on the other hand is not as well studied however, with newly emerging data, we can try to understand and theorize the mechanism of neuroinvasion. In a post mortem case series of 43 patients, SARS-CoV-2 was detected by qRT-PCR or immunostaining in the brains of 21 (53%) of all tested patients: furthermore, immunohistochemical analysis revealed viral proteins in the cranial nerves (either glossopharyngeal or vagal) originating from the lower medulla oblongata and in single cells within the medulla oblongata [34].

From this, we see that PD and COVID-19 both have implication and effects on the vagus nerve/nucleus as well as the medulla oblongata. This just means that more research needs to be done to ascertain the exact degrees of similarities between the two diseases. It is important to note that COVID-19 reports of detailed neuropathological examinations have lagged behind general autopsy series, in part due to the initial focus on lung pathology combined with the longer (2–3 weeks) formalin fixation time preferred by most neuropathologists before cutting brains as well as the fact that some institutions are reluctant to perform brain removal in COVID-19 cases due to concerns over electric bone saw generated aerosols, which can be effectively contained through the use of vacuum filters or hand saws[35].

As mentioned above, PD has already been implicated with certain viruses, therefore with all the similarities between COVID-19 and PD, it is very plausible to theorize that SARS-COV-2 can also be implicated with PD. However, it is clear that more research needs to be done to further elucidate this connection.

Discussion and Conclusion

After an extensive analysis of currently published literature in regard to COVID-19-associated PD our team have discovered a potentially overlooked, yet significant, neurologic complication of SARS-COV-2. A study conducted in Wuhan China documents that out of 214 covid 19 patients, 78 (36.4%) had neurologic manifestations [1]. This study also found that patients with a more severe infection are significantly more likely to develop said neurologic manifications. For example, a comparison of patients with more severe infections vs patients with less severe infections shows- acute cerebrovascular diseases (5 [5.7%] vs 1 [0.8%]), impaired consciousness (13 [14.8%] vs 3 [2.4%]), and skeletal muscle injury (17 [19.3%] vs 6 [4.8%]) [1]. Furthermore, it's been revealed in the literature that SARS-COV-2 can involve the nervous system, and its neurotropic potential is increasingly well established [2].

Case reports such as the one written by Moriguchi Et al, indicate that there may be a direct infection of SARS-COV-2 and the nervous system. In this specific report a 24 year old male patient, who was brought in by the ambulance due to a convulsion accompanied by unconsciousness, was later diagnosed with aseptic encephalitis with SARS-COV-2 RNA in cerebrospinal fluid [3]. Possible mechanisms of direct SARS-COV-2 involvement in the nervous system include but are not limited to: A)the olfactory bulb, altered sense of smell and/or taste in uncomplicated early-stage COVID-19 patients is suggestive of a movement of the virus to the

brain via the olfactory bulb [2], B) Glial cells and neurons, SARS-Cov-2 has been shown to use the ACE2 receptor for cell entry. This receptor has also been detected over glial cells and neurons, which make it a potential target for COVID-19 [7], C) Capillary endothelium, SARS-CoV-2 spike protein could interact with ACE2 expressed in the capillary endothelium; the virus may also damage the blood-brain barrier and enter the CNS by attacking the vascular system [8].

Indirect mechanisms of injury that can lead to neurologic complications due to covid-19 have also been proposed. SARS-Cov-2 binds to ACE2 receptors with a higher affinity compared with SARS-COV [4]. ACE2 is known to be a cardio cerebral vascular protection factor, which plays a major role in regulating blood pressure and anti atherosclerosis mechanisms. When bound to ACE2 receptors, SARS-COV-2 viruses may cause abnormally elevated blood pressure and increase the risk of cerebral hemorrhage and ischemic stroke [2]. In addition, when the virus replicates and proliferates in pneumocytes, it causes diffuse alveolar and interstitial inflammatory exudate, as well as the formation of membranes in the most severe forms. This, in turn, leads to alveolar gas exchange disorders causing hypoxia in the CNS, increasing the anaerobic metabolism in brain cells, inducing cellular and interstitial edema, obstructing cerebral flow blood, as well as ischemia and vasodilation in the cerebral circulation [2].

Furthermore, published literature indicates that Covid 19 has also been shown to induce neuromuscular manifications, as shown in a cohort study conducted in Denmark. In the study, a qEMG analysis showed myopathic changes in 55% of the patients, and a noticeable decrease in motor unit potential duration [21]. Even more so, published literature shows 9 patients with COVID-19-related myositis/rhabdomyolysis were reported [23]. 8 patients presented with generalized or limb weakness. Myalgias were present in four patients. One patient who did not have muscle weakness presented with myalgia, fever, and dyspnoea [23]. One patient presented with repetitive muscle twitching along with tingling and numbness in the legs [24]. Six patients had abnormalities on chest imaging like ground-glass opacities, pneumonia, pleural effusion, or multifocal opacities [23]. Two patients required mechanical ventilation [26, 25].

It has already been established in the literature that a number of viruses have been associated with both acute and chronic parkinsonism. These viruses include influenza, Coxsackie, Japanese encephalitis B, western equine encephalitis, herpes and those that lead to acquired immunodeficiency disorder (HIV) [13]. It should come as no surprise that with the newly emerging literature about covid-19, it is apparent that there may be a connection between covid-19 and PD. As previously stated alpha synuclein bodies are pathognomonic of PD. This is especially interesting with the fact that covid-19 could prompt cytotoxic aggregation of proteins, including α-synuclein: this hypothesis is supported by evidence in animal models that viral infections can trigger α-synucleinopathies in the CNS [14]. Furthermore, as previously mentioned, aggregating shreds of evidence suggests that Olfactory dysfunction (OD) is one of the most common signs of COVID-19.[15,16]. This in relation with the fact 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" [17,18].

Case reports have shown that covid-19 might exacerbate the symptoms of PD requiring increased drug dosages and increase in overall mortality:

Of 141 PD patients resident in Lombardy, changes in clinical features in the period January 2020 to April 2020 were compared with those of 36 PD controls matched for sex, age, and disease duration using the clinical impression of severity index for PD, the Movement Disorders Society Unified PD Rating Scale Parts II and IV, and the nonmotor symptoms scale: it was observed that Motor and nonmotor symptoms significantly worsened in the COVID-19 group, requiring therapy adjustment in one third of cases[19]. 10 clinical cases collected from the experience at the Parkinson and Movement Disorders Unit in Padua, Italy, and the Parkinson's Foundation Centre of Excellence at King's College Hospital in London, UK, from the beginning of March to the current period showed that most patients requiring additional levodopa dosing following covid-19 infection: anxiety and other nonmotor features, such as fatigue, orthostatic hypotension, cognitive impairment, and psychosis, also worsened during the infection: fatigue was a dominant symptom during the SARS-COV-2 infection in all cases on advanced therapies and three patients died from COVID-19 pneumonia [20]. Clinical information of 117 community-dwelling PD patients with COVID-19 followed in 21 tertiary centres in Italy, Iran, Spain, and the UK was gathered, and showed Overall mortality was 19.7%, with a significant effect of co-occurrence of dementia, hypertension, and PD duration [22].

Furthermore, there has been an established link in the acceleration of PD and severe covid-19. Immune responses and excessive inflammation in COVID-19 may also accelerate the progression of brain inflammatory neurodegeneration [42]. There is no question the viral neurotropism is important along factors intrinsic to the host, including genetics, innate immunity, the hyperactivation of the immune system, and the development of cytokine storm syndrome along with the immune previous status of the host to the COVID-19 encounter [41]. Long-term neurodegenerative diseases ought to be in the mind of every neurologist across the world, with aberrant proteostasis, neuroinflammation, and abnormal immune responses being key factors for accelerating PD pathology [41].

There does seem to be an association between COVID-19 and the PD, and this may be due in part to the fact that both diseases have been identified to be neuroinvasive.

For example, with the research that has already been done on PD, it has been found that Lewy body formations are observed in the dorsal motor nucleus of vagus[32]. Moreover, as already mentioned above, it has also been shown in a blind study that diffuse alpha-synuclein proximity ligation assay signals are significantly more abundant in patients compared to controls in regions such as the medulla (6.5-fold increase) [36].

In a post mortem case series of 21 patients (in which SARS-CoV-2 was detected by qRT-PCR), immunohistochemical analysis revealed viral proteins in the cranial nerves (either glossopharyngeal or vagal) originating from the lower medulla oblongata and in single cells within the medulla oblongata [34].

This shows that both PD and covid-19 have implication and effects on the vagus nerve/nucleus as well as the medulla oblongata and this might explain some aspects of the unclear association between PD and COVID but it is clear that more research needs to be done to verify and ascertain the exact nature of the relationship between COVID-19 and PD.

In conclusion, it is evident that Covid 19 has also been shown to induce neuromuscular manifestations such as myositis rhabdomyolysis, critical-illness myopathy and acute flaccid quadriparesis as mentioned above. As already stated Parkinson's

disease (PD) is a chronic progressive neurodegenerative disorder which may be exacerbated by covid-19. For example, clinical information of 117 community-dwelling PD patients with COVID-19 followed in 21 tertiary centres in Italy, Iran, Spain, and the UK was gathered, and showed overall mortality was 19.7%, with a significant effect of co-occurrence of dementia, hypertension, and PD duration[22] It is important to note that there seems to be an association between these two diseases and that it could be due to the fact that they are both neuroinvasive as well as the fact that both of their disease processes are implicated at the medulla, and the vagus nucleus/nerve.

The authors of this paper contributed equally.

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