Exacerbation of motor and non-motor symptoms of Parkinson disease by severe acute respiratory syndrome-coronavirus-2 infection: Are there possible links?

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ABSTRACT

Background: Parkinson's disease (PD) is an ageing and progressive neurological disorder characterized by both motor (tremors, bradykinesia, rigidity) and non-motor symptoms (depression, GI disturbance, and cognitive decline). COVID-19 is a highly infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) with symptoms ranging from mild to severe cardiopulmonary dysfunction. Moreover, COVID-19 infection causes excessive release of pro-inflammatory cytokines and gut microbiome alterations and has been reported to cause neurological complications, all of which are more prevalent in PD.

Objective: This review sought to shed some light on several unanswered questions with respect to the possibility of reciprocity in pathological relationship between COVID-19 and PD, including the central issue as to whether the virus enters the neurons, astrocyte, brain vascular cells or microglia.

Methods: The review was carried out through PubMed search, using the following terms: 'COVID-19', 'Parkinson disease', 'coronavirus', 'Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)', 'gut disturbance'.

Results: There are no clear observations for human neuronal or astrocyte expression of angiotensin converting enzyme 2 (ACE2; main receptor for SARS-CoV2 viral entry) constitutively, but are induced by inflammation. Hence, the need for comparative study in both healthy and infected brains. Recent studies suggest that COVID-19 worsened both motor and non-motor symptoms in PD patients.

Conclusion: This finding showed the possibility of direct action of COVID-19 on motor/non-motor features of PD.

Keywords: Parkinson's disease; COVID-19; depression; motor symptoms; non-motor symptoms; neurotropism

Exacerbation des symptômes moteurs et non moteurs de la maladie de Parkinson par l'infection par le syndrome respiratoire aigu sévère Coronavirus-2 : Existe-t-il des liens possibles?

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RÉSUMÉ

Contexte : La maladie de Parkinson (MP) est un trouble neurologique progressif et vieillissant caractérisé à la fois par des symptômes moteurs (tremblements, bradykinésie, rigidité) et non moteurs (dépression, troubles gastro-intestinaux et déclin cognitif). Le covid-19 est une maladie extrêmement infectieuse causée par le coronavirus 2 du syndrome respiratoire aigu sévère (SARS-CoV-2), dont les symptômes vont d'un dysfonctionnement cardio-pulmonaire léger à un dysfonctionnement cardio-pulmonaire sévère. En outre, l'infection par le covid-19 provoque une libération excessive de cytokines pro-inflammatoires et des altérations du microbiome intestinal, et il a été signalé qu'elle provoque des complications neurologiques, qui sont toutes plus fréquentes dans la MP.

Objectif : Cette étude a pour but de faire la lumière sur plusieurs questions sans réponse concernant la possibilité d'une réciprocité dans la relation pathologique entre le covid-19 et la MP, y compris la question centrale de savoir si le virus pénètre dans les neurones, les astrocytes, les cellules vasculaires cérébrales ou la microglie.

Méthodes : L'étude a été réalisée à l'aide d'une recherche sur PubMed, en utilisant les termes suivants : " covid-19", " maladie de Parkinson ", " coronavirus ", " Coronavirus du syndrome respiratoire aigu sévère 2 (SARS-CoV-2) ", " trouble intestinal ".

Résultats : Il n'existe aucune observation claire sur l'expression neuronale ou astrocytaire humaine de l'enzyme de conversion de l'angiotensine 2 (ACE2 ; principal récepteur de l'entrée virale du SRAS-CoV2) de manière constitutive, mais elle est induite par l'inflammation. D'où la nécessité d'une étude comparative sur des cerveaux sains et infectés. Des études récentes entrevoient que covid-19 aggrave les symptômes moteurs et non moteurs chez les patients atteints de la maladie de Parkinson.

Conclusion : Cette découverte montre la possibilité d'une action directe de covid-19 sur les caractéristiques motrices et non motrices de la maladie de Parkinson.

Mots clés : maladie de Parkinson; covid-19; dépression; symptômes moteurs; symptômes non moteurs ; neurotropisme.

INTRODUCTION

Parkinson's disease (PD) is a progressive movement disorder characterized by motor symptoms (bradykinesia, tremor, rigidity, and postural instability) and non-motor symptoms including gastrointestinal disturbances, olfactory dysfunction, depression and cognitive decline.[1] The exact cause of PD is not clear, however, pathological findings have shown the degeneration of dopaminergic neurons in the substantial nigra pars compacta, alpha-synuclein aggregation, mitochondrial dysfunction, oxidative stress as well as neuro-inflammation to be linked with PD pathology.[2] It has also been hypothesized that PD originates from the gut and that non-motor symptoms of PD precede motor symptoms.[3-4] Findings from Braak's hypothesis suggest that the gut-brain axis plays a key role in PD development and exposure to pathogens via the nasal cavity could lead to gut-microbiome imbalance, thus leading to the severity of motor symptoms associated with PD.[3,5]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), commonly referred to as covid-19 is a global pandemic and has imposed great challenges on the public health sector. Early symptoms of covid-19 include fever, cough and breathing difficulty, but some persons present with neurological symptoms such as dizziness, seizures, inflamed brain and impaired sense of smell and taste[6]. Gut microbiome dysfunction/imbalance has also been reported to be associated with covid-19.[6] Interestingly, some of these neurological complications of covid-19, including gut microbiome imbalance, are also common in PD patients.[7] Furthermore, PD is more prevalent in the elderly, 60 years and above (the commonest risk factor for PD is ageing),[8] and during the pandemic in 2020, increased prevalence of covid-19 was seen in the elderly between the ages 60 to 90 years,[9] further suggesting that ageing could be a risk factor for covid-19 susceptibility. Literature findings have also reported that some of the pathways linked with PD, such as oxidative stress, inflammation, and protein aggregation are also implicated in covid-19 disease progression.[7,10] The induction of pro-inflammatory cytokines storm/neuroinflammation observed in both PD and covid-19 as well as the need for angiotensin-converting enzyme 2 receptor and dopamine decarboxylase enzyme for SARS-CoV2 cell entry (much talked about neurotropism of SARS-CoV2) and dopamine synthesis respectively, are co-regulated in non-neuronal cells.[11-12] Interestingly, overexpression of α-synuclein in PD patients may limit SARS-CoV-2 neuroinvasion and degeneration of dopaminergic neurons; conversely, SARS-CoV-2 can accelerate α-synuclein aggregation.[12] Moreso, studies have reported that covid-19 worsened motor and non-motor symptoms of PD.[7,13] Hence, the present review aims to shed light on possible link between COVID-19 and the risk of PD morbidity/mortality.

PD Pathology

PD could be inherited or sporadic, however, the exact cause of PD is unknown. The loss/degeneration of dopaminergic neurons in the substantia nigra pars compacta (SN) is linked to the motor symptoms of PD.[14] Moreover, the accumulation of alpha-synuclein (α-syn) is associated with Lewy body formation in the SN and leads to mitochondrial dysfunction.[15-16] Noteworthy, α-syn accumulation is also present in other parts of the brain including the heart and kidney. Moreover, studies have reported that α-syn spreads from the gut to the brain axis via the vagus nerve.[3] In addition, the decrease in mitochondrial complex 1 subunit of the respiratory chain and altered electron chain activity observed in the SN of PD patients are linked with mitochondrial dysfunction in PD pathology. The reduction in antioxidant enzymes; reduced glutathione, glutathione peroxidase, catalase and superoxide dismutase activities in the SN are also implicated in oxidative stress and neuroinflammation seen in PD pathology. Altogether, they have been shown to exacerbate non-motor complications of PD (cognition, depression, anxiety, and sleep disturbances).[17-18]

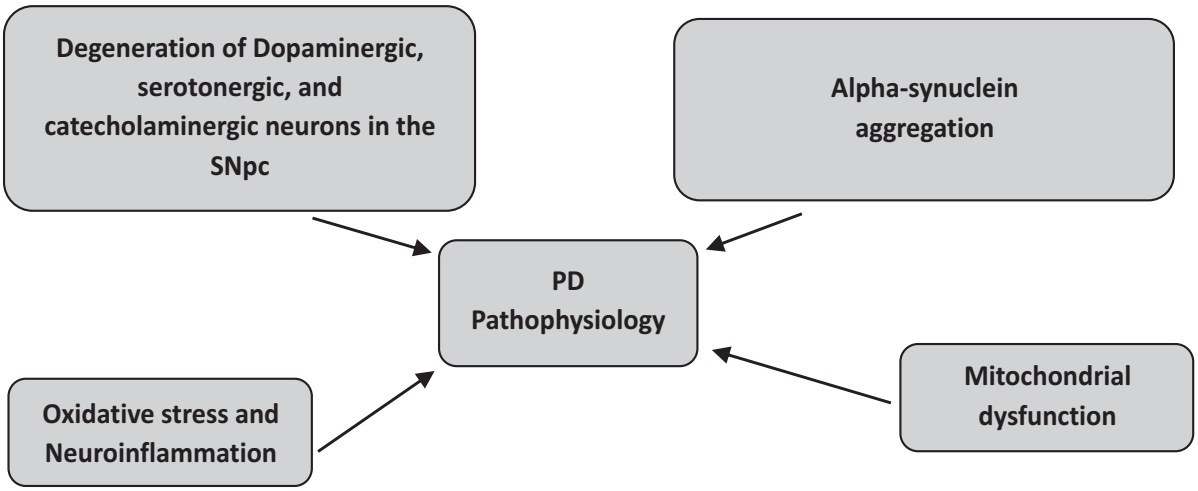

Figure 1: Pathophysiology of PD

Risk factors of PD and symptoms of PD

There are three major risk factors for PD and they include ageing, genetic and environmental factors.

Ageing: PD occurs in the elderly, especially above the age of 60, the SN also undergoes various molecular changes which affect/reduces the breakdown of protein and dopamine metabolism as well as decreased mitochondria function, thus, suggesting that PD symptoms progress/deteriorates with age.[19]

Genetic factor: Genetic contributors to Parkinson's disease exist across a continuum, ranging from highly penetrant DNA variants (i.e. causal) to variants that individually exert a small increase in lifetime risk of disease. Genetic risk is often divided into categories: rare DNA variants with high effect sizes, which are typically associated with monogenic or familial Parkinson's disease; and more commonly, smaller effect variants, which are usually identified in apparently sporadic Parkinson's disease.[19] Duplications, triplications, and mutations of the a-syn encoding gene SNCA are linked to familial PD suggesting that an increase in a-syn and/or the expression of mutational variants contribute to neurodegeneration.[7] Genome-wide associated studies have identified various genes which are involved in PD pathogenesis[20] including *SNCA, PRKN, UCHL1, PARK7, LRKK2, TREM2* etc.

Environmental factors: Exposure to heavy metals, herbicides, and pesticides plays a significant role in PD development. Exposure to pesticides/toxins such as MPTP, paraquat and rotenone have been shown to mimic key features of PD and as such these pesticides are used as validated models of PD in rodents and non-human primates.[21-22] They act by inhibiting mitochondrial complex-1 activities and through a cascade of mechanisms also lead to neuroinflammation, oxidative stress, loss of dopaminergic neurons in SN.[22] Similarly, heavy metals such as manganese and iron could accumulate in the brain resulting in oxidative stress and the production of free radicals.[23]

Symptoms/Signs of PD

Symptoms associated with PD are categorized into two: motor and non-motor symptoms.

Motor symptoms of PD: tremor, bradykinesia, rigidity and postural instability. These symptoms are the key/hallmarks symptoms of PD. Others include freezing, speech difficulty, swallowing difficulty, micrographia and reduced facial expression.

Non-motor symptoms: these include autonomic disturbances, cognitive impairment, neuropsychiatric disturbances, and olfactory loss often worsen the disease prognosis and further reduce the quality of life of PD patients as a patient can present with more than one non-motor complications.[24-25] PD drugs could also cause non-motor complications following long-term usage.[26] Gastrointestinal disturbances, which are one of the most common non-motor symptoms of PD, occur in more than 70% of people living with PD.[27]

Current Therapies used in the management of PD

There is currently no specific cure for PD, however, it can be managed pharmacologically and non-pharmacologically.

Pharmacological approach: these drugs are designed based on the different hypothesis that has been postulated in PD pathology. They proffer symptomatic relief, which makes the management of non-motor symptoms quite challenging because a patient could present with more than one non-motor symptom. Drugs used in the management of motor and non-motor symptoms of PD [8,28] include:

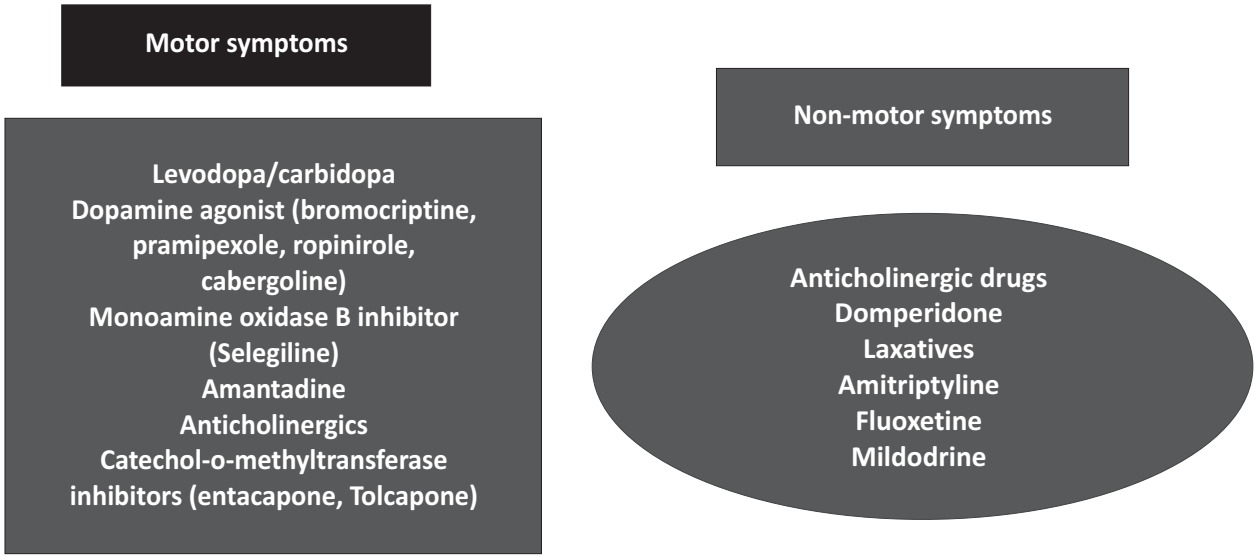

Figure 2: Drugs used in the management of motor and Non-motor symptoms of PD

The Non-Pharmacological approach used in PD management includes gene therapy, stem cell therapy, deep brain stimulation, and exercise.[29-30]

COVID-19

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), commonly referred to as covid-19, broke out in Wuhan (China) in 2019 resulting in morbidity and mortality globally.[31-32] and was declared an epidemic by WHO in March 2020. Covid-19 has affected more than 200 million people worldwide, with approximately 6 million deaths, mainly affecting elders and front-line workers.[31] The common signs and symptoms of covid-19 include fever, sore throat, cough, and lung infections. Others include acute respiratory distress syndrome, sepsis, neurological symptoms (seizure, loss of smell, cognitive decline, brain inflammation) and death.[7,31] Although SARS-CoV-2 majorly affects the lung, it can also affect other organs such as the brain, heart, and gastrointestinal system.[31] Studies have shown that dysregulation in the innate immune system/responses of the respiratory tract, could lead to clinical presentations of SARS Cov 2. [33] Furthermore, the severity of SARS-CoV-2 is linked with the excessive release of inflammasome and pro-inflammatory cytokines in the respiratory tract,[34-35] which further enhances lung injury and central nervous system (CNS) complication. Coronaviruses are associated with CNS diseases such as multiple sclerosis, Parkinson's disease, dementia, febrile seizures, and encephalitis epilepsy.[36] Literature reviews showed that human coronavirus SARS-CoV could invade the CNS through both the blood-brain barrier and olfactory bulb.[37-39]

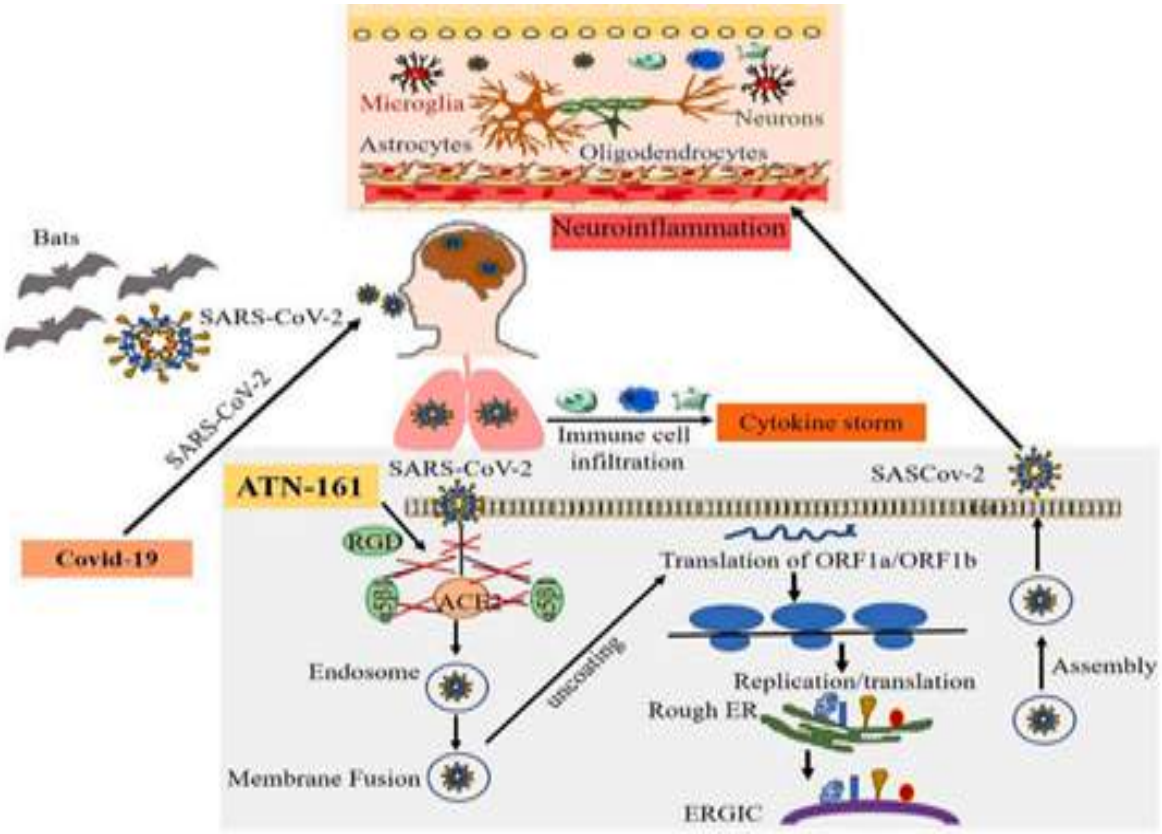

Figure 3: Showing transmission, replication, and CNS invasion of covid-19 virus in the human host. Adopted from [37]

COVID-19 is an RNA virus and risk factors that could predispose an individual to covid-19 infection include gender (increased incidence in males), age (aged 60 and above), staying/living in an overcrowded area, contact with an infected patient and comorbidity (diabetes, obesity, cardiovascular diseases, hypertension).[39-40]

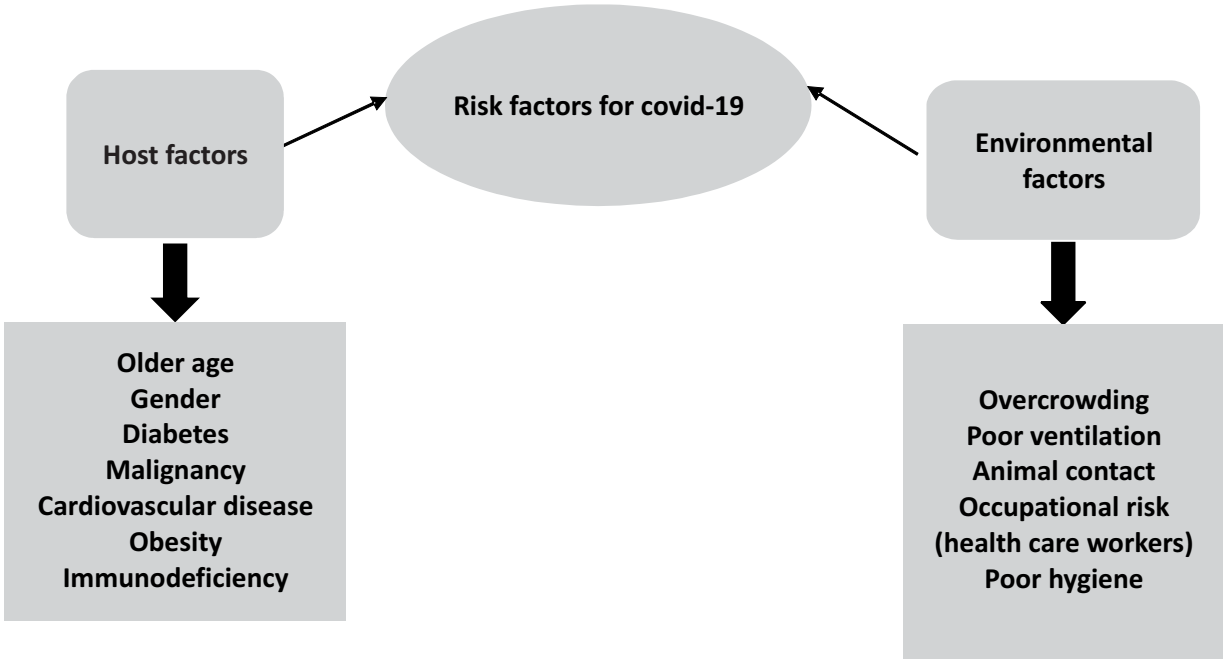

Figure 4: Showing Risk factors for covid-19 *Modified from* [39-40]

Utilized therapies for Covid-19

Pharmaceutical therapies that have been approved by the Food and Drug Administration (FDA) act by either inhibiting viral RNA replication, and viral assembly, or causing early termination of RNA transcription of the virus. Some also act to prevent the excessive release of proinflammatory cytokines, thus minimizing cytokine storm associated with covid-19.[37]

Table 1: Therapies used in the management of covid-19

Type of Therapy	Examples
Pharmaceutical therapies	Favipiravir, Chloroquine, Hydroxychloroquine, Remdesivir, Ribavirin, Tocilizumab, Vitamin D, Zinc
Vaccines	Pfizer BioNTech, Moderna (RNA-1273), Oxford-AstraZeneca (AZD1222), Johnson and Johnson (Ad26.COV2.S)
Home remedies	Saltwater gargles, hot teas, lozenges, Vaporizers, humidifiers, steam inhalers and herbal remedies
Others	Convalescent plasma

Adopted from[36]

PD and covid-19

Recent studies have shown that PD and RNA virus infection including covid-19 has similar underlining pathway mechanisms.[6,7] Knowledge of PD pathology has shown the involvement of oxidative stress, inflammation, mitochondrial dysfunction, α-synuclein protein aggregation, and exposure to heavy metals. Interestingly, RNA virus infection shows similar biochemical pathways.[6]

Also, some non-motor complications including cognitive decline, olfactory bulb dysfunction, GIT disturbances, and gut microbiome imbalance have been implicated in PD and are also present as neurological symptoms of covid-19.[6] This denotes that there could be an interplay/intersection between PD and COVID-19.

Table 2: Intersections between PD and RNA virus (covid-19)

Biochemical pathway	Parkinson's disease	RNA virus infection
Alpha-synuclein	Aggregation of alpha syn-associated Lewy bodies	a-syn expression is increased in response to neurons infected by RNA viruses
Dopaminergic pathway	Degeneration of dopaminergic neurons in the substantia nigra	Destroys the substantia nigra, which would prevent the production of dopamine
Oxidative stress	Increased expression of ROS and mitochondria dysfunction leads to neuronal cell death	Can cause ROS imbalance leading to DNA damage and cell death
Neuroinflammation	Excessive release of pro-inflammatory cytokines which exacerbates non-motor symptoms (cognition, depression) of PD	Triggers the excessive release of proinflammatory cytokines resulting in a cytokine storm (in COVID-19 patients).
Gut microbiome	GI disturbances, dysbiosis, and constipation are the common non-motor symptoms of PD	Reduced gut microbiota, resulting in the severity of the viral infection and GI disturbances
Olfactory tract	Olfactory dysfunction (non-motor symptom) is one of the early signs of PD	Olfactory dysfunction is also one of the early signs of COVID 19
Heavy Metal	Exposure to heavy metals (Manganese, iron) increases the risk of developing PD	A virus requires manganese and iron to replicate and heavy build-up could lead to neurodegeneration. SARS-CoV-2 virus replication is also dependent on mang anese and iron, and this could lead to the potential onset of PD

Adapted from[7].

The GUT, PD and Covid-19

In the human body, the community of microbiota is greatly dense and forms an absolute abundance of microorganisms. The gut microbiota is involved in immune systems, physiological processes, metabolism and even the development of various organs.[41-42] The Gut microbiota can change both in composition and activity throughout our lives and in response to host factors, such as age and genetics, and to changing environmental factors (diet and drugs). In addition, the intestinal microbiota is also involved in neurodevelopment and contributes to neurological disorders including PD.[43] In PD, pathological findings have revealed an imbalance in gut microbiota in PD patients and this could lead to GI disturbances associated with PD.3-4,[44] Viral infections including COVID-19 are common invading pathogens that affect the host microbiota causing dysbiosis and gastrointestinal disturbance.[45] Noteworthy is the fact that GUT microbiota reduces as one age and ageing is a risk factor for both PD and covid-19 infection.[45-46] Also, GI disturbances (constipation, diarrhoea) have been linked with covid-19 infection severity and as such could have a great impact on PD patients as GI disturbances are

common with PD patients.[7,47] Thus further reducing the quality of life or even resulting in mortality of PD patients.

The Olfactory tract in PD and covid-19

Olfactory dysfunction is one of the earliest non-motor symptoms of PD and is said to precede motor symptoms of PD. [48-49]Like in PD, olfactory dysfunction is one of the key symptoms of covid-19 infection characterized by loss of smell (Anosmia).[5,51] as the nasal cavity and olfactory epithelium are the major target sites for covid-19 virus. Studies suggest that the olfactory bulb is involved in the neuro-invasion of SARS-CoV-2 and this could be responsible for some neurological complications associated with covid-19 infection.[52-53] In addition, findings from the literature have shown that anosmia/olfactory impairment in PD could be due to the accumulation of α-Synuclein- associated Lewy bodies in the olfactory bulb.[54-55]

Impact of covid-19 on PD patients

During the heat of covid-19 outbreak where the global world was locked down, isolation was compelled for all. This isolation worsened some symptoms associated with PD, as some patients were more depressed and severe motor symptom was also observed.[56] Furthermore, severe symptoms of covid-19 were observed in PD patients that were infected with an increased mortality rate[36]. Covid-19 infection was reported to exacerbate motor and non-motor symptoms of PD, thus, further reducing the quality of life of PD patients as well as the increased burden of the caregiver [57-58]. Various studies have been carried out on the impact of isolation on PD, as well as the impact of covid-19 infection on PD. In a study carried out by Shalash *et al*.[56] they found that PD symptoms (motor and non-motor) worsened during the covid-19 pandemic evidenced by a decline in gait and balance, increased anxiety, depression over 6 months.[56] In PD management, regular exercise has been proven to have a positive effect on PD symptoms, as it helps to control the disease's progression,[59] but during isolation, there was an increased physical inactivity which could be responsible for the results observed. Similarly, other studies showed motor symptoms worsened and psychiatric symptoms (non-motor) of PD declined during isolation, which further suggests that the covid-19 pandemic had a negative effect on PD patients.[60-63] Findings from the study showed an increased prevalence of psychiatric symptoms (hallucination, irritability, apathy, depression, insomnia and delusion) associated with PD which could also be due to the increased level of stress and reduced physiotherapy/physical inactivity. Aside from the effect of the pandemic on PD patients resulting in a decline in motor activities as well as causing different mental issues, more complications could arise when a PD patient gets infected withcovid-19. It has been noted that PD occurs in the elderly and innate immune response is reduced in the elderly which makes them more susceptible to infections as such covid-19 could invariably worsen PD symptoms.

Other impacts of the infection on PD individuals include worsening of the disease prognosis. Several studies have reported that covid-19 infection exacerbated motor deficit in PD patients.[64-65] Brown *et al*.[65] showed that PD patients with covid-19 infection; showed new motor symptoms (18%), aggravated previous motor symptoms (at least one) (55%), decline in mood (51%), cognitive decline (7.8%) as well as exacerbated autonomic dysfunction (59%). Reports have suggested that inflammatory response and excessive release of pro-inflammatory cytokines associated with covid-19 infection could be partly linked to the aggravated motor and non-motor symptoms of PD.[66-67] In addition, PD patients are at a greater risk of covid-19-induced mortality relative to non-PD patients and the mortality rate has been reported to range from 19 to 50%.[68-69]

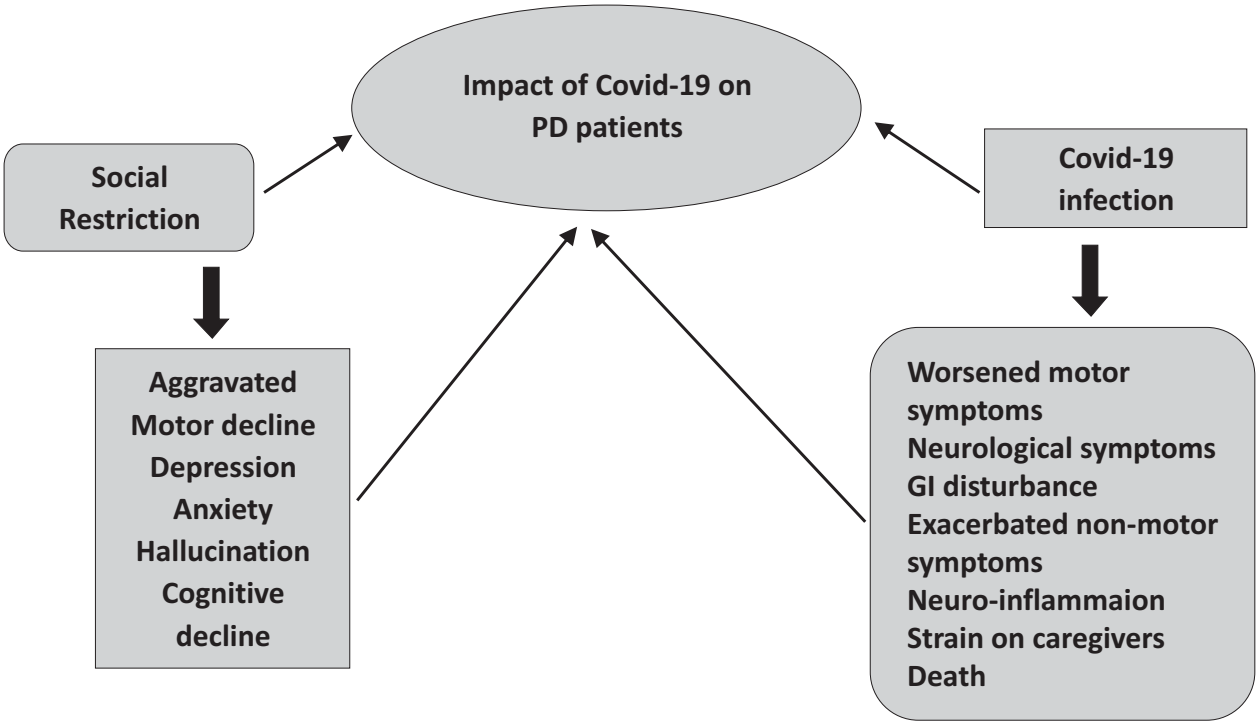

Figure 4: Impact of covid-19 on Parkinson's disease patient

Concluding Remarks/ Recommendations

Covid-19 is a worldwide pandemic that requires careful monitoring as it could impose many consequences on human health and well-being. Similarly, PD though not a pandemic, is one of the most common neurodegenerative diseases that imposes a great burden on the global health sector as the cause remains unclear and can only be managed symptomatically. It is important to note that covid-19 symptoms range from mild to severe in healthy individuals, however, In PD due to some comorbidity these symptoms could be severe. Also, the pandemic had a delirious effect on PD patients ranging from motor decline to psychiatric disorders. Even for healthy individuals, physical inactivity and isolation could affect mental health, leading to mood instability. It is therefore important that PD patients engage in simple activities that could help boost their mood and keep them busy even while at home[7,70]. Covid-19 infection also compounded PD symptoms, which could be due to the commonalities in their biochemical pathways (inflammation, oxidative stress, gut microbiomes) [7] and the less active state of the innate immune system in elderly individuals with PD. However, further research is needed to validate the underlining mechanism(s) involved.

ACKNOWLEDGEMENT

We are very grateful to the University of Lagos Library for their assistance in getting access to some of the literature materials.

We do not have any conflicting interest to declare.

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