INFLUENCE OF NOVEL CORONAVIRUS DISEASE (COVID-19) ON PARKINSON’S DISEASE: SYSTEMATIC REVIEW

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1. Abstract

Background:
The novel Coronavirus (COVID-19) infection has affected the population with various medical issues including the underlying neurological comorbidities such as Parkinson disease. COVID – 19 is found to bind with the host angiotensin-converting enzyme 2 (ACE2) receptors for viral entry. ACE2 receptors are normally expressed in various body surfaces as well as in the neurons and glial cells where they act as an entry port to SARS-CoV-2 infection to invade the central nervous system (CNS). ACE2 are also highly expressed in dopamine neurons which might worsen the outcome in terms of motor symptoms in PD with the treatment course. It may lead to an indirect response via immune-mediated cytokine storms and propagate through CNS leading to damage. Parkinson’s disease has also been noticed due to certain post-viral infections apart from COVID-19 such as, HSV, Influenza virus A, Measles virus, Cytomegalovirus and Mumps (Olsen et al, 2018). We aim to provide a thorough review on neurological outcomes and impact of COVID-19 in Parkinson disease.

Methods: A systematic review was conducted to analyze the impact of COVID-19 in patients with Parkinson disease (> 21 yo). Systematic literature search was done using PubMed, Science Direct, Google Scholar and Cochrane databases. PRISMA guidelines were followed summarized in Fig. 3 for study acquisition.

Results:
Of the Parkinson's patients that were tested positive for SARS-CoV-2, worsening of motor symptoms were reported along with other COVID-19 symptoms (Fig. 4 and 5). These symptoms include bradykinesia, tremors, gait disturbances, delirium and dementia and severe spasms of arms and legs. Encephalopathy was also one of the main symptoms presented in two of the studies. Increased mortality rates were identified for those who were hospitalized due to COVID-19 and PD when compared to other patients.

Conclusion: Parkinson's disease may experience substantial worsening of motor and non - motor symptoms during COVID 19. Due to the novelty of the virus, studies were reported from recent years and further extensive studies are needed to explore more about the disease severity and neurological outcomes when compared to other non-PD patients. Authors identify this as a limitation for this paper. Additional studies are needed to understand the role of ACE2 in increasing vulnerability to viruses and role of ACE inhibitors as treatment modality.

Keywords: COVID-19, Parkinsons, SARS-CoV-2, Pandemic
2. **INTRODUCTION:**

During the time of December in 2019 a new virus outbreak occurred in Wuhan City, China. It was causing pneumonia-like symptoms and belongs to a Novel member of the coronaviridae family named SARS-CoV-2 (severe acute respiratory coronavirus 2 syndrome) [1]. This virus emerged as a global pandemic and threat to life of humans due to its accelerated exponential spreading capability. As of 30 April 2021, there have been 14,99,10,744 confirmed cases of COVID-19, including 31,55,168 deaths reported globally[2]. Coronavirus are enveloped positive single stranded RNA viruses and their 3’ terminal contains structural proteins. The Spike (S) protein in this virus allow them to fuse between host cell membrane and virus and also between infected and surrounding uninfected cells [3]. There is a surge in the levels of cytokines (TNF-α, IL-6, IL-8, and IL-10) leading to suppression of T-cell response. Not many studies were focused on the ACE2 role in increasing vulnerability of viruses and role of ACE inhibitors in treatment of these PD patients. Moreover, COVID-19 was found to invade the host cells or escape detection due to spike proteins [4].

COVID-19 has posed challenges in the healthcare system in terms of its unpredictable and novel manifestations on pulmonary, neurology, cardiovascular, gastrointestinal and hematological systems. Published data showed evidence of the presence of SARS-CoV-2 in CSF, in addition to respiratory, fecal and blood samples. In about 36.4% of cases, neurological findings have been identified ranging over dizziness, headache, hyposmia, hypogeusia, dysphagia, muscle pain, seizures, loss of consciousness, etc[5]. Novel Coronavirus has imposed additional concerns with social factors such as, the surge in isolation, limited social activities which authors hypothesize might accentuate neuro-psychological problems like depression and impairment of cognition.

With the availability of limited studies, the authors have tried to provide a comprehensive and analytical review to understand the effect of COVID-19 on Parkinson’s disease. Through this paper, we aim to study the impact of novel coronavirus on Parkinson disease by performing a systematic literature review.
3. METHODOLOGY:

A systematic literature search was performed from December 2019 to July 2020, using the keywords such as, “COVID19”, “SARS-CoV-2”, “Parkinson’s disease”, “Pandemic” and “Mortality”. We did an extensive search on databases namely PubMed central, Google Scholar, Cochrane, Science Direct and EMBASE for open access studies.

Inclusion criteria: (For studies and the target population)
- COVID-19 patients with Parkinson's disease
- Patients diagnosed with Parkinson's disease before COVID-19 infection
- Age group > 21 years old
- Both genders
- Available articles in English language only

Exclusion Criteria:
- Non-COVID-19 PD patients
- Articles on Pregnant women
- Articles on pediatric population
- Randomized control trials, crossover studies design.
Study selection:
We included studies with COVID-19 positive patients with a history of Parkinson's disease, studies published in English and with open access. A total of 250 articles were generated from our initial search. Authors scanned the abstract independently which led to inclusion of 154 articles. After the initial full articles screening process, 125 articles did not meet the inclusion criteria and were removed. Finally, 16 articles were added and analyzed in detail by all the authors. Relevant demographic and clinical information were extracted from the selected studies such as age, gender, clinical manifestation, comorbid conditions, diagnostic tests, treatment and outcome. This was then added into the MS-EXCEL spreadsheet for analyses and cumulative result interpretation. (PRISMA guidelines Figure 2).

Figure 2. Prisma Chart
4. RESULTS:

Of the 16 articles, 7 (43.8%) were case reports and case series, 4 (25%) case-control studies, 2 (12.5%) cross-sectional, 2 (12.5%) cohort and 1 (6.25%) retrospective study (Figure 3) [6-21]. All Together describing a total of 1290 Parkinson's patients with COVID-19. Male gender was predominant in 10 studies [6–15] and female gender was predominant in 6 studies [14] [16–20]. Of the patients whose data was available, Average mean age was 76.9 and average disease duration was 11 years. Almost most of the patients reported to have other comorbidities, most common were hypertension [6][10][12][13][17][18][20][21], diabetes [7][9][13] [15-18], obesity [6], dyslipidemia[18], cardiovascular disease[6][7][11][12][16-18][21], immunocompromised[6][12][21], COPD[6][10][11][15], asthma[15], chronic renal and liver diseases[15][16][21].

Of the Parkinson's patients that were tested and positive for infection with SARS-CoV-2, worsening of motor symptoms [6–8] [11–13] [15,16][18][20] including bradykinesia, tremors, gait disturbances, delirium and dementia [10][16] and severe spasms of arms and legs [19] reported, with individual study percentage ranging from 19% to 100%, along with other COVID-19 symptoms. Encephalopathy was also one of the main symptoms presented in 2 of the studies [17][20]. Mortality rates for those who were hospitalized ranged from 5.7% to 100% [6-13 ][15-19][21].

![Types of Study in systematic review](image)

Figure 3 Types of study in systematic review
| No | Author | Study design | Sample (N) PD | male gender % | Age Mean | Comorbidities % | Disease duration mean (years) | Outcomes | PD related symptoms: With COVID % |
|----|--------|--------------|---------------|---------------|----------|----------------|-------------------------------|----------|----------------------------------|
| 1  | Cilia R et al., 2020 | case-control | 12 cases 36 control | 41.7 % cases 41.7 control | 65.5 Cases 66.3 control | 8.3% COPD 33.3 HTN 8.3% Obesity 8.3% Cardiopathy 16.7% cancer 8.3% immunocompromised | 6.3 y cases 6.1 y control | 50% affected by COVID-19 (cases group) 0% affected by COVID-19 in control group 8.3% hospitalized | Worsening of motor symptoms |
| 2  | Del Prete, Eleonora, et al.2020 | case-control | 7 cases 14 control | 57.2 % cases 57.2 % control | 75.7 cases 75 control | cases: 71.5% HTN 42.8% Diabetes 28.5% cardiomyopathy 14.2% malignancies | 9.29 y cases 8.93 y control | 13% mortality 14% case fatality | 30% worsening |
| 3  | Hainque E et al., 2020 | Case report | 2 | 50 % | 77.5 | HTN | 22y | 100% | 100% worsening |
| 4  | Lo Monaco MR et al., 2020 | Case series | 5 | 66.6 % | 74.2 | 20% Chronic Renal failure 20% Diabetes hypertension | NA | 20% case fatality | 60% Worsening |
| 5  | Fasano, Alfonso, et al. 2020 | Case-control survey | 105 | 52.4% | 70.5 | Obesity 18.1% HTN 41.9% COPD 5.6% Diabetes 7.6% Cancer 9% | 9.9 y | 17.1% hospitalized 5.7% mortality | |
|   | Filatov, Asia, et al. 2021 | Case report | 1 | 74 | atrial fibrillation cardioembolic stroke | COPD | NA | Icu hospitalization Poor prognosis | Encephalopathy |
|---|-----------------------------|-------------|---|----|------------------------------------------|------|----|-------------------------------|----------------|
| 7 | Brown EG, et al, 2020 | Cross sectional | 51 | 47 % | 65 | Immunocompromised 22% Heart Disease 20% HTN 25% Lung disease 14% | 0-3y: 21 3-6y: 12 6-9y: 9 >9y: 9 | 9.8% Hospitalized 3.9% ICU 2% Ventilator | 55 % worsening 18 % new PD symptom |
| 8 | Kobylecki C et al 2020 | Cohort, observational | 58 | 62.5 % | 78.3 | Diabetes 8% HTN 38% | 9.5 | 22.4% Mortality rate | 69% Delirium 54% Dementia |
| 9 | Lo Monaco MR et al, 2020 | Case report | 1 | Female | 58 | NA | 8 y | NA | severe spasms of arms and legs. |
| 10 | Antonini et al 2020 | case series | 10 | 60 % | 78.3 | Diabetes Orthostatic hypotension CHF, COPD Asthma IHD, CKD, dementia, osteoporosis anxiety disorder | 12.7 y | 40% mortality rate | Worsening of mobility with fall Worsening of motor symptoms Worsening of anxiety |
| 11 | Vignatelli et al, 2020 | cohort | 696 PD 184 Parkinsonism control 8590 | 58.8 & PD 58.2 control | 57.1 Parkinsonism control | 75 PD 80.5 PS Contro 176.0 | PD and PS 22.6% cardiomyopathy 14.6% Cerebrovascular disease 8.5% Chronic pulmonary disease 3% Liver disease | NA | Hospitalization 0.6% PD 3.3% PS 0.7% control | PD: 72.8% Tremor 80.4% Bradykinesia 81.6% Clinical features onset unilateral |
|   |                            |             |    |     |                               |      |    |                               | PS: 52.5% Tremor 89.2% Bradykinesia 52.5% Clinical features onset unilateral |
| # | Reference | Study Type | Sample Size | Male/Female (%) | Sample Details | 5% Renal Disease | 10% DM | 8.5% Malignancies | 12.2 y | 75% Mortality Rate | 50% Worsening of PD Symptoms |
|---|-----------|------------|-------------|----------------|----------------|-----------------|---------|------------------|--------|----------------|----------------------------|
| 12 | Artusi CA, et al, 2020 | Multiple Case Reports | 8 | 62.5% | HTN Diabetes, Depression, Lung Neoplasm, A Fib | NA | 26.7% HTN | 20% DM | 64.3% Dyslipidemia | 13.3% Cardiomyopathy | 6.7% Valvular Cardiomyopathy | 20% Cardiac Arrhythmia | 6.7% Cardiac Insufficiency | 14.3% Pulmonary Disease | 6.7% Smoking | 12.5% Mortality Rate | 50% Worsening of PD Symptoms |
| 13 | Diego Santos-Garcia et al, | Cross-Sectional | 15 | 47.1% | 76.3 | 26.7% HTN | 20% DM | 64.3% Dyslipidemia | 13.3% Cardiomyopathy | 6.7% Valvular Cardiomyopathy | 20% Cardiac Arrhythmia | 6.7% Cardiac Insufficiency | 14.3% Pulmonary Disease | 6.7% Smoking | 33.3% Hospitalized | 65.7% Worsening of Symptoms | 47.7% Bradykinesia | 41.4% Sleep Problems | 40.7% Rigidity | 34.5% Gait Disturbances | 31.3% Anxiety | 28.5% Pain | 28.3% Fatigue | 27.6% Depression | 20.8% Tremor |
| 14 | R Sainz Amo et al, 2020 | Case Control | Case: 33 | 59 | Case: 7 | 5.9 | 36% Dementia | 20% Stroke | 6.7% Dyslipidemia | 20% Cardiac Arrhythmia | 6.7% Valvular Cardiomyopathy | 20% Cardiac Insufficiency | 14.3% Pulmonary Disease | 6.7% Smoking | 54% Hospitalization | 21% Mortality Rate | NA | 66.7% Worsening Motor Symptoms | Encephalopathy |
| 15 | Jing li et al, 2020 | Case Report | 1 | Female | 85 | HTN Stroke | 6 y | 26.7% HTN | 20% DM | 64.3% Dyslipidemia | 13.3% Cardiomyopathy | 6.7% Valvular Cardiomyopathy | 20% Cardiac Arrhythmia | 6.7% Cardiac Insufficiency | 14.3% Pulmonary Disease | 6.7% Smoking | 33.3% Hospitalized | 65.7% Worsening of Symptoms | 47.7% Bradykinesia | 41.4% Sleep Problems | 40.7% Rigidity | 34.5% Gait Disturbances | 31.3% Anxiety | 28.5% Pain | 28.3% Fatigue | 27.6% Depression | 20.8% Tremor |
| 16 | De Marcaida et al, 2020 | Retrospective | 36 | 64% | 74.5 | HTN Cardiovascular Disease | Renal Disease, Diabetes | Chronic Lung | 16.2 y | 67% Hospitalization | 36% Mortality | 75% Alteration Mental Status | 19% Worsening of the Movement Abnormalities | 31% Worsening Mobility |
5. Discussion:

A wide variety of neurological consequences have been reported by a large number with COVID-19 positive [22-32]. Neurological symptoms including those associated with core dysfunction (fatigue, headache, confusion, stroke [33], dizziness, syncope[34], seizure, anorexia, and insomnia) [35-38], central-peripheral mixture (Guillain Barre syndrome)[39], enteric, or peripheral nervous systems dysfunction (anosmia, ageusia, myoclonus[40], neuropathic pain, and myalgia)[41].

The increase in the hospital admission and mortality rates in the PD and other chronic neurological diseases during Covided 19 pandemic needs to be addressed to understand the exact effects. Most neurological diseases including Parkinson's are highly dependent on prescribed medications to control their symptoms, with social isolation and some of the clinical practices forced to shut down, which led to irregular visits might be one of the reasons for worsening of the symptoms [42].

In this Systematic Review, We included studies with COVID-19 positive patients with a history of Parkinson's disease. The most common manifestation related to COVID 19 in PD is Motor dysfunction. Most of the study shows a common domain that is motor neuron deficit, in the range of moderate to severe. Some of the patients show delirium, dementia, encephalopathy among other covied-19 complications. This can be related to the ACE2 mechanism of the brain. When SARS-CoV-2 enters the cell, it increases the activity of T cells, causing vasodilation, thrombosis, and hypoxemia, which then leads to stroke and seizures. Exact mechanism is still unclear. Some theory shows the effect is due to the virus attacking the ACE 2 receptors of the brain. Another theory shows the presence of new receptors in the corona virus including sialic acid residues [43]. How SARS- COV2 affects the brain is still questionable.

The median age is 76.9 with male predominance and average disease duration is 11 years. Almost most of the patients reported to have other comorbidities, most common were hypertension, diabetes, obesity, dyslipidemia, cardiovascular disease, immunocompromised, COPD, asthma, chronic renal and chronic liver diseases.

The major limitation for this systematic review is the presence of confounder factors as the majority of the Parkinson's diseases patients are elderly with other comorbidities. Also the duration of the diseases and the severity of the symptoms may influence the clinical outcome of
covid-19 infection. Important information including patients medication compliance which might affect the coveted 19 infection outcome were lacking as well.

6. Conclusion:
Covid-19 has become the most prevalent infectious disease that extensively affects multiple body systems. The Central Nervous System is substantially susceptible to this infection, which can lead to deteriorating neurological findings, particularly in patients with PD. Some of these findings are motor dysfunction, delirium, dementia, severe spasms of arms and legs and encephalopathy. These signs observed in Covid-19 positive patients with a history of PD are mostly elderly male with longer duration of illness and other comorbid conditions. It is still unclear how Sars-CoV2 affects the nervous system in such patients, which is why future research is encouraged to provide more concrete information to diminish neurological outcomes, hospital stay and mortality on PD patients.

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