Systematic Review / Meta-analysis

New-onset Parkinsonism as a Covid-19 infection sequela: A systematic review and meta-analysis

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Artic le Info

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Abstract:
Background: There remains a scarcity of literature regarding COVID-19 and its neurological sequelae. This study highlights Parkinsonism as a post-COVID-19 sequela and helps us understand a possible link between the two.

Methods: A literature search covering relevant databases was conducted for studies reporting the development of Parkinsonism in patients recovering from COVID-19 infection. A quality assessment tool developed by The Joanna Briggs Institute Critical Appraisal tools for the assessment of case reports was utilized. Fisher’s exact test was used to explore the factors associated with COVID-19 and Parkinsonism as its complication.

Results: Ten studies were included in our study. The median age of patients was 60.0, with an interquartile range of 42.5–72.0. There were 8 males (61.5%) patients, and 53.8% of cases were reported to have at least one comorbidity. Cogwheel rigidity was the most common symptom of Parkinsonism in 11 patients. While the most standard treatment modality used was Levodopa in 76.9% of cases. Using the Fisher’s exact test, it was identified that 10 patients (76.9%) with bradykinesia made a full recovery.

Conclusion: Despite presumed “recovery” from COVID-19, patients still face a wide range of neurological complications. One of these complications presenting as Parkinsonism requires health care professionals to be on the lookout for the long-term effects of COVID-19. Hence, our study provides information on the possible likely hood of a link between COVID-19 and the development of Parkinsonism as post-COVID neurological sequelae.

1. Introduction

Covid-19 (Corona Virus Disease) is a disease that is caused by a virus called SARS-CoV-2, which was discovered in December 2019 in Wuhan, China [1]. The virus belongs to the coronavirus family, the same family of the virus responsible for the epidemics of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and Severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 [2]. WHO(World Health Organization) declared it a global pandemic on March 11, 2020, and since then, it has been a public health care emergency [3]. As of April 29, 2022, there have been 599,531,232 confirmed cases of COVID-19, including 6,230,357 deaths reported to WHO since its onset [4]. The virus is reported to have a respiratory droplet and aerosol transmission-primarily through close contact when an infected person coughs or sneezes and an uninfected person inhales those liquid particles [5].

The disease presentation in COVID-19 varies in individuals, with some people presenting as asymptomatic/mild disease while others with a more severe illness and even death in some cases. Common symptoms include fever, cough, and shortness of breath [6]. Although Covid-19 primarily affects the respiratory system causing pneumonia, multi-organ failure and dysfunction have also been reported in more severe cases [7]. There is also evidence that SARS-CoV-2 can invade the neural tissue resulting in various neurological manifestations and complications [8,9]. Several theories regarding its route of entry and invasion into the CNS have been hypothesized. The first possible route for SARS-CoV-2 to enter the brain is across the blood-brain barrier (BBB). Several research reports show that the subunit S1 of SARS-CoV-2 S
protein reaches the brain across the BBB [10]. In addition to these reports, it has also been proposed that there is a route of viral entry from the olfactory mucosa into the brain. In the olfactory mucosa, endothelial tissue and neural tissue are near each other. Hence the virus may use this to invade the brain, which can be confirmed by the presence of S proteins in the olfactory mucosa [11]. A review article also suggests a possibility of transsynaptic transmission of SARS-CoV-2 from the peripheral nerve [8]. Several patients of COVID-19 developed neurological symptoms such as headache, dizziness, hypoguesia, and neuralgia [12–14]. While on a more severe side of complications, there have been reports of covid-19 induced Parkinsonism. There have already been well-documented reports about Parkinsonism after viral infections [15]. The first link of viral Parkinsonism comes from the possible relationship between lethargic encephalitis and the Spanish flu of 1918 [16].

Parkinsonism is an umbrella term used to describe symptoms of Parkinson’s disease, including bradykinesia, rigidity, tremor, and postural instability [17]. There have been several recent reports that support the notion that an increase in pro-inflammatory cytokines levels such as IL-6 and IL-1BETA may hasten the symptoms of Parkinson’s. Since COVID-19 can result in a cytokine storm in many cases, it may be postulated that there can be an increased incidence of Parkinsonism in those who recover from the infection in years to come [18]. Thus, our study aims to bring all the reports of such COVID-induced parkinsonism cases together to help understand a plausible link between the two in a better way. We investigate the disease pattern, signs and symptoms, treatment modalities, and outcomes in patients with COVID-19 infection and the development of Parkinsonism in these patients as a post covid neurological sequelae.

2. Methods

The protocol of this review is registered with The International Prospective Register of Systematic Reviews (PROSPERO) [19] CRD42022325061. This review is fully compliant with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 statement and also in line with the PRISMA criteria [20]. The AMSTAR-2 [21] checklist was also used to assess this study which determined this study to be a high-quality review.

2.1. Search methods

An extensive literature review was conducted on seven major databases online: PubMed, Cochrane library, Google Scholar, ScienceDirect, China National Knowledge Infrastructure (CNKI) Database, MedRxiv, and BioRxiv, covering a timeline of January 1, 2020 to January 1, 2022. The following keywords were used to search: COVID-19 along with its synonyms was made on the identification of a combination of some cardinal symptoms such as headache, dizziness, hypoguesia, and neuralgia [12–14]. While on a more severe side of complications, there have been reports of covid-19 induced Parkinsonism. There have already been well-documented reports about Parkinsonism after viral infections [15]. The first link of viral Parkinsonism comes from the possible relationship between lethargic encephalitis and the Spanish flu of 1918 [16].

The shortlisted articles were then extracted, independently and in duplicate, on a structured data form by two study authors. The information extracted from each study was as follows: the author’s name, country, year of publication, type of study, study population, data source, age, number of patients with Covid-19, Positive Sars-CoV-2 rRT-PCR nasal swab, Covid-19 symptoms (including anosmia, cough, respiratory symptoms, GIT symptoms, fever, and myalgia), Parkinsonism symptoms (including anosmia, bradykinesia, cogwheel rigidity, tremor, hypokinetic rigid syndrome, saccades hypomimia and hypophonia), treatment modalities, any other comorbidities and outcomes for both, covid-19 and Parkinsonism, (full recovery, partial recovery, treatment ongoing or death).

SPSS Version 26 (Chicago, IL: IBM SPSS Statistics) was used to analyze the data. Quantitative variables were represented as median and interquartile ranges, whereas frequency and percentages were used for qualitative variables. Fisher’s exact test was used to test for a significant relationship between the variables. The test results were considered statistically significant if the p-value was 0.05 or less.

2.3. Quality assessment

The authors evaluated individual study quality independently using The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic reviews [22]. The study quality was scored out of 8 by the author, based on the patient’s demographic description, patient history presentation, clinical condition presentation, diagnostic test results description, treatment description, post-intervention condition description, adverse events identification, and takeaway lessons. A study was good quality with a score of 6–8, fair quality with a score of 4–5, and poor quality with a score of <4.

3. Results

The comprehensive literature search yielded a total of 2555 studies from the databases. Overall, 10 studies were eligible according to our inclusion criteria [23–32]. The characteristics of these 10 included studies are shown in Table 1. The PRISMA flow diagram presents an overview of the detailed selection process (Fig. 1).

In terms of study type, of the included 10 studies, 9 (90%) were case reports, and only 1 study was case series (10%).

3.1. Demographics and epidemiology

13 patients with a median age of 60.0 and IQR (42.5–72.0) were included in this study. The gender of study cases was 61.5% males and 38.5% females. Of the 13 cases, 7 (53.8%) reported at least one comorbidity. Hypertension is the most prominent one with a frequency of 7(53.8%), then diabetes with a frequency of 4 (30.8%), and then asthma with a frequency of 1(7.7%), as shown in Table 1.

3.2. Clinical features, management, and outcome of COVID-19 infection

The commonest symptom during COVID-19 infection was respiratory symptoms (11 patients, 84.6%) which were followed by cough (9 patients, 69.2%) and fever (9 patients, 69.2%) while myalgia was the lowest presenting symptom (2 patients, 15.4%). Regarding management, the most administered treatment, according to our study, was mechanical ventilation (5 patients, 38.5%). At the same time, three patients (23%) received no treatment for COVID-19 infection. The two outcomes reported in our study were either death or full recovery (refer to Table 2).

3.3. Data extraction and analysis

The shortlisted articles were then extracted, independently and in duplicate, on a structured data form by two study authors. The information extracted from each study was as follows: the author’s name, country, year of publication, type of study, study population, data source, age, number of patients with Covid-19, Positive Sars-CoV-2 rRT-PCR nasal swab, Covid-19 symptoms (including anosmia, cough, respiratory symptoms, GIT symptoms, fever, and myalgia), Parkinsonism symptoms (including anosmia, bradykinesia, cogwheel rigidity, tremor, hypokinetic rigid syndrome, saccades hypomimia and hypophonia), treatment modalities, any other comorbidities and outcomes for both, covid-19 and Parkinsonism, (full recovery, partial recovery, treatment ongoing or death).

SPSS Version 26 (Chicago, IL: IBM SPSS Statistics) was used to analyze the data. Quantitative variables were represented as median and interquartile ranges, whereas frequency and percentages were used for qualitative variables. Fisher’s exact test was used to test for a significant relationship between the variables. The test results were considered statistically significant if the p-value was 0.05 or less.
Table 1  
Characteristics of included studies (N = 10).

| Study and year | Study design | country | Total Population | Age | Gender | Co-morbid | Covid-19 signs and symptoms | Covid-19 management | Parkinsonism signs and symptoms | Radiological investigations | Parkinson’s management | Recovery from parkinsonism symptoms |
|----------------|--------------|---------|------------------|-----|--------|-----------|-----------------------------|------------------|-------------------------------|------------------------|------------------|--------------------------------|
| Mikhal E Cohen 2020 | Case report | Israel | 1 | 45 | Male | Hypertension and asthma | Respiratory symptoms, anosmia, cough, fatigue, and myalgia | None. | Bradykinesia, cogwheel rigidity, tremor, hypophonia | F-DOPA-PET scan: decreases F-DOPA uptake in both putamen more apparent on left side | DaT scan: bilateral decrease in presynaptic dopamine uptake. EEG: diffuse mild and reactive slowing without any asymmetries or epileptiform discharges. | Partial recovery |
| Mendez Guerrero 2020 | Case report | Spain | 1 | 58 | Male | Hypertension and dyslipidaemia | Respiratory symptoms, anosmia, cough, GIT symptoms, fever, and fatigue | Steroids, protease inhibitor, mechanical 02 ventilation | Anosmia, cogwheel rigidity, hypokinetic rigid syndrome, vertical saccades and hypomimia | DaT scan: decreased dopamine transporter activity on left putamen | Levodopa and benserazide | Full recovery |
| Ingrid Faber 2020 | case report | Brazil | 1 | 35 | Female | None. | Respirator symptoms, anosmia, cough, GIT symptoms, fever, and myalgia, | None. | Anosmia, bradykinesia, cogwheel rigidity, hypokinetic rigid syndrome, hypophonia and hypomimia | DaT scan: bilateral decrease in presynaptic dopamine uptake. EEG: diffuse mild and reactive slowing without any asymmetries or epileptiform discharges. | Levodopa and benserazide | Full recovery |
| Mauro Morassi 2021 | Case report | Italy | 2 | 1) 70 | Female | 1) Hypertension | Respiratory symptoms, anosmia, cough, and fever. | 1) O2 supplementation, | 1) Bradykinesia, cogwheel rigidity, hypophonia and hypomimia | DaT scan: bilateral decrease in presynaptic dopamine uptake. EEG: diffuse mild and reactive slowing without any asymmetries or epileptiform discharges. | Levodopa and corticosteroid | Partial recovery |
|  | 2) 73 | 2) Hypertension and diabetes | 2) Hypertension, diabetes, and seizures. |  | 2) Female | 2) None. | Respiratory symptoms, anosmia, cough, and fever. | 2) O2 supplementation, Hydroxychloroquine, and protease inhibitor. | 2) Bradykinesia, cogwheel rigidity, hypokinetic rigid syndrome and hypomimia. | DaT scan: bilateral decrease in presynaptic dopamine uptake. EEG: diffuse mild and reactive slowing without any asymmetries or epileptiform discharges. | Levodopa and corticosteroid | Partial recovery |
|  | N/A | 3 | 1) Male | 72 | Male | None. | Respiratory symptoms, fever, and cough | Mechanical ventilation | Bradykinesia, cogwheel rigidity, hypophonia and hypomimia. | MRI: ventricular enlargement | None. | Levodopa and benserazide | Partial recovery |
|  | 722 | 2) Male | 2) Hypertension, diabetes, and seizures. |  | 2) Female | 2) None. | Respiratory symptoms, cough, and fever. | Mechanical ventilation | Bradykinesia, cogwheel rigidity, tremor. | MRI: gliosis in bilateral temporal lobes. | None. | Levodopa and benserazide | Full recovery |
|  | 66 | 3) Male | 3) None. |  | 3) Female | 3) None. | Respiratory symptoms, anosmia, cough, and fever. | 1) Steroids and oxygen supplementation. | 1) Anosmia, bradykinesia, cogwheel rigidity, hypophonia and hypomimia. | MRI: ischemic changes in paraventricular white matter. | None. | Levodopa and benserazide | Full recovery |
|  | 374 | 4) Male | 4) None. |  | 4) Female | 4) None. | Respiratory symptoms, and cough | Mechanical ventilation | Bradykinesia, cogwheel rigidity, tremor, resting tremor, hypomimia and hypophonia | MRI: basal ganglia and corona radiata stroke. | Levodopa and benserazide | Partial recovery |
|  | 60 | Male | Hypertension, diabetes, and hypercholesterolemia |  |  |  | Respiratory symptoms and cough | Mechanical ventilation | Hypokinetic rigid syndrome and hypophonia | MRI: Flair hyperintense lesion. | Levodopa and benserazide | Full recovery |
|  | 35 | Female | None. |  |  |  | Anosmia and fever | Mechanical ventilation | Bradykinesia, cogwheel rigidity, tremor, resting tremor, hypomimia and hypophonia | MRI: Flair hyperintense lesion. | None. | Full recovery |

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3.3. Clinical features, management, lab investigations, and outcome of Covid-19-induced Parkinsonism

All patients developed symptoms of Parkinsonism as post-COVID-19 neurological sequelae, but it took each patient a different number of days to develop Parkinson’s symptoms after contracting the COVID-19 infection, as shown in Table 1. The commonest symptom of Parkinsonism was cogwheel rigidity (11 patients, 84.6%) and bradykinesia (10 patients, 76.9%). While the least common symptoms were postural tremors (2 patients, 15.4%) and saccades (2 patients, 15.4%). The commonest management received were Levodopa (10 patients, 76.9%) and corticosteroid (3 patients, 23.1%). While Benserazide (1 patient, 7.7%), Dopaminergic therapy (1 patient, 7.7%), and Anticholinergic (1 patient, 7.7%) were the least administered treatment. (7 patients, 53.8%) patients fully recovered, and their symptoms fully resolved after treatment, while (6 patients, 46.2%) patients partially recovered, and symptoms persisted.

A set of different laboratory tests and investigations were run on the patients. The most common abnormal findings were reported on magnetic resonance imaging (MRI) which was abnormal in 64 (64.2%) cases, followed by electroencephalography (EEG) and fluorodeoxyglucose (FDG)-positron emission tomography (PET), both of which showed abnormal findings in 3(23.1%) cases (For the rest of the findings, refer to Table 3).

The odds between symptomatic presentation in COVID-19 and Parkinsonism, management, comorbid, and outcomes were measured using fisher’s exact test at a p-value less than equal to 0.05. It was identified that patients who had anosmia in covid-19 infection didn’t have diabetes as a comorbid (53.8%) at a p-value = 0.021. The rest of the findings are shown in Table 4.

3.4. Quality assessment of included studies

Three out of 10 studies were identified as good quality, while seven were of fair quality, as shown in Table S2. Studies were primarily downgraded for unclear patient’s demographic description [27], incomplete patient’s history presentation [24, 25, 27–32], inadequate diagnostic test results description [28, 30], unclear treatment description [25, 27, 28, 32], incomplete post-intervention condition description [23–25, 29], no proper adverse events identification [23–28, 30–32] and not enough takeaway lessons [23]. The most common cause for downgrading studies was no proper adverse events (harms) or unanticipated events being identified and described, which raised concerns if the treatment/intervention/drugs used has more benefit than risks and the if the benefits outweigh the risks.

4. Discussion

Both the developing and developed countries are still battling the spread of COVID-19. A major concern that needs to be addressed is what doctors are now calling the “Long COVID.” [14].

There have been several studies and enough data collection on complications in patients recovering from COVID-19 infection after 3 months, 6-months, and 1 year. Complications range from neurodegenerative diseases to impaired cognitive mental function [33–35]. Similar reviews on COVID-19 have previously been conducted with a broader agenda of tackling all the neurological complications, but none of the available literature focused on the grave dangers of long-term complications of Parkinsonism specifically. Hence our review provides extensive information regarding Parkinsonism associated with COVID-19 infection in terms of analyzing all the clinical features and presentations.

The median time since the development of parkinsonism symptoms in patients in our study was 14 days (IQR = 14.5 days). In a prospective observational study of 135 COVID-19 patients, new onset of neurological diseases was diagnosed after a 3-month follow-up who previously had not reported any such neurological manifestations, with
Parkinsonism being one of them [33]. In this study, bradykinesia, tremor, and rigidity were reported in $n = 7(5\%)$, $n = 13(10\%)$, and $n = 3(2\%)$, respectively, all of these being cardinal neurological presentations in Parkinsonism. These findings are in line with our study, where $n = 10(76.9\%)$ patients presented with bradykinesia, $n = 4(30.8\%)$ presented with tremors, and $n = 11(84.6\%)$ with rigidity. The primary neurological manifestation was anosmia/hyposmia in this observational study with a prevalence rate of 45% while in our study, anosmia was reported in 23.1% of patients. Anosmia/hyposmia was one of the most frequently occurring symptoms in COVID-19 patients. Anosmia is also one of the most common non-motor features of Parkinson’s disease [36]. This highlights the possibility of cerebral involvement in COVID-19, and it suggests that SARS-CoV-2 has the potential to invade the brain through olfactory pathways [37]. Several different hypotheses have been made on probable routes of entry for virus invasion into the CNS. One of the key pathways for neurotropic invasion is the olfactory pathway. The unique anatomical organization of the olfactory bulb and olfactory nerves in the nasal cavity and the forebrain can act as a channel for viruses to enter the brain compartments. SARS-CoV-2 is suggested to reach these brain structures using this pathway in the early stages of infection to cause inflammation and degenerative processes [38].

Another observation made in our review was that almost all patients with bradykinesia after COVID-19 showed a full recovery from parkinsonian symptoms. Showing that most of the cases showed a good response to Levodopa or a dopamine agonist. The DaT scans of both the patients (19, 20) showing decreased presynaptic dopamine uptake further suggest a possible virus invasion into the CNS. Angiotensin-converting enzyme-2 (ACE-2), which is widely expressed in various tissues, including the brain, could be another possible route of entry for the virus to enter the host brain cells and cause neuronal injury. SARS-CoV-2 could interact with ACE-2 in the capillary endothelium and cause parkinsonism was reported in two more patients [35]. In this study, bradykinesia was reported in $n = 5(6\%)$, tremors reported in $n = 2(2\%)$, and rigidity reported in $n = 5(6\%)$ patients. In another cohort study of 236,379 patients diagnosed with COVID-19, Parkinsonism was diagnosed in 0.11% of the patients after a 6-month follow-up [34]. These findings show how it makes each individual a different number of days to develop signs of parkinsonism and in some cases, it may even take up to a year. Hence, this highlights the importance of extensive follow-up that is required in patients recovering from COVID-19.

According to our study, anosmia/hyposmia was one of the most frequently occurring symptoms in COVID-19 patients. Anosmia is also one of the most common non-motor features of Parkinson’s disease [36].

Table 2

| Signs and symptoms | N(%) |
|--------------------|------|
| Respiratory symptoms | 11 (84.6) |
| Anosmia/hyposmia/dysgeusia | 7 (53.8) |
| Cough | 9 (69.2) |
| GI symptoms | 3 (23.1) |
| Fever | 9 (69.2) |
| Fatigue | 3 (23.1) |
| Myalgia | 2 (15.4) |
| Treatment | |
| Steroids | 4 (30.8) |
| Hydroxychloroquine | 2 (15.4) |
| Azyclor | 1 (7.7) |
| Remdesivir | 1 (7.7) |
| Protease inhibitor | 2 (15.4) |
| Mechanical ventilation | 5 (38.5) |
| Oxygen supplementation | 3 (23.1) |
| Outcome | |
| Hospitalisation | 12 (92.3) |
| Full recovery | 11 (84.6) |
| Death | 1 (7.7) |
blood-brain barrier destruction, which would promote virus entry into the CNS. Evidence shows mRNA is present in the brain of infected individuals of SARS-CoV, which also interacts with ACE-2. The high similarity between SARS-CoV and SARS-CoV-2 suggests an abundance of ACE-2 in epithelial tissues and theorized that it could be one of the reasons for the high prevalence of anosmia in patients with COVID-19. The extracellular domain of ACE-2 is the cellular receptor of SARS-CoV-2 spike proteins, which interacts with triggering endocytosis of the virus. The interaction seems to be increased in patients suffering from comorbidities [39].

Pinto and colleagues examined over 700 patients with comorbidities including hypertension, cardiac diseases, and diabetes having severe COVID disease. In these patients, they observed a high expression of ACE-2 in brain tissues promoting the entry of SARS-CoV-2 into the CNS and subsequently causing neuroinvasion [39].

To our knowledge, this study is the first study that highlights Parkinsonism as major neurological sequelae of COVID-19 infection. The findings of this study raise an alarming concern regarding the potential dangers that COVID-19 could present to the world in the future and how there needs to be more emphasis on what doctors have been calling the “Long COVID”. However, a more thorough analysis needs to be done before a causal link between the two can be made. This would require more extensive data collection and long-term follow-up of the studies, however, we did not find any studies that could meet our eligibility criteria.

5. Conclusion

To our knowledge, this study is the first study that highlights Parkinsonism as major neurological sequelae of COVID-19 infection. The findings of this study raise an alarming concern regarding the potential dangers that COVID-19 could present to the world in the future and how there needs to be more emphasis on what doctors have been calling the “Long COVID”. However, a more thorough analysis needs to be done before a causal link between the two can be made. This would require more extensive data collection and long-term follow-up of the
patients presenting with Parkinsonism as a post-COVID complication.

Ethical approval

This study did not need any ethical approval being a systematic review and meta-analysis of publicly available data.

Source of funding for your research

This study had no sources of funding.

Author contribution

SSA conceptualized the study design and objectives. AM, MAQ, and SSA drafted the study protocol, and conducted the literature search, study screening, selection, and data extraction. AM, MAQ, and SSA designed the data collection instrument, collected data, and carried out data analysis. SSA, AM, MAQ, SST, AP, and MB drafted the initial manuscript. AM, MAQ, SST, and AP critically reviewed and revised the manuscript. SSA is the guarantor and critically reviewed the manuscript. All authors approved the final manuscript as submitted for publication.

Registration of research studies

1. Name of the registry: International Prospective Register of Systematic Reviews (PROSPERO).
2. The unique identifying number or registration ID: CRD42022325061.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=325061.

Guarantor

Syed Sami Ali is the guarantor.

Consent

Not applicable.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

Data is available upon request to the corresponding author.

Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jamsu.2022.104281.

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