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COVID-19 and the Risk of New-Onset Parkinson's Disease and Multiple Sclerosis: A Systematic Review of the Evidence

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Abstract

Background: Emerging evidence suggests COVID-19 may increase the risk of long-term neurological complications, including Parkinson's disease (PD) and multiple sclerosis (MS). This review examines the potential association between COVID-19 and new-onset neurodegenerative diseases to clarify risks and guide future research and clinical care.

Materials and Methods: This systematic review searched multiple databases-including Medline/PubMed, Embase, PsycINFO, SciELO, Web of Science, ProQuest, Scopus, CINAHL, and the WHO COVID-19 database-as well as grey literature from January 2020 to December 2024 for studies reporting confirmed COVID-19 followed by new diagnoses of PD or MS. Two reviewers independently screened and extracted data on demographics, clinical features, diagnostics, and outcomes, assessing study quality with a standardized checklist.

Results: Twenty-one studies met inclusion criteria, including 18 case reports and 3 cohort studies, mostly from Europe and the Americas, with participants aged 21–76 years. Among 279,911 individuals, 0.14% developed PD and 0.007% developed MS after COVID-19 infection. Diagnoses were confirmed clinically and through imaging, often with elevated inflammatory markers or genetic predispositions. Neurological symptoms appeared from a few days to one year post-infection, including motor deficits, cognitive decline, and sensory disturbances. Proposed mechanisms involved viral neurotropism, immune dysregulation, and persistent inflammation. Most patients received disease-specific treatments, with outcomes ranging from full recovery to persistent deficits. Although study quality was generally good, the predominance of case reports and moderate certainty of evidence require cautious interpretation.

Conclusion: This review suggests a possible increased risk of neurodegenerative diseases such as MS and PD following COVID-19, likely linked to immune and inflammatory processes. Well-designed, large-scale longitudinal studies are essential to confirm these findings and better understand the long-term neurological consequences.

Key Words: COVID-19, Multiple sclerosis, Neurological complications, Parkinson's disease.

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1- INTRODUCTION

Global health has been profoundly affected by the COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). While COVID-19 is primarily recognized for its acute respiratory effects, coronaviruses-including SARS-CoV, SARS-CoV-2, and MERS-CoV-are also associated with a wide range of neurological complications due to their capacity to invade the nervous system (2, 3). Evidence suggests that certain neurodegenerative and immune-mediated diseases, such as Parkinson's disease (PD) and multiple sclerosis (MS), may be triggered or exacerbated by viral infections (4–6). Viral particles and nucleic acids have been detected in brain tissue in various neurological conditions, supporting the role of viruses in neurological pathology. For example, higher concentrations of human coronavirus 229E have been observed in post-mortem brain tissue of MS patients (7), although the significance of these findings for disease causation remains complex and sometimes inconclusive. In some cases, viral particles are found in specific cell types, such as astrocytes in Creutzfeldt-Jakob disease (8), while in others, like PD, no direct viral presence is detected in brain tissue (9). Overall, the relationship between viral infections and neurodegenerative diseases is multifaceted, involving direct viral invasion, immune-mediated injury, and persistent inflammation.

Viruses' neuroinvasive potential can trigger neuroinflammation and cytokine storms, which may accelerate α-synuclein aggregation-a hallmark of Parkinson's disease-and contribute to the immune dysregulation observed in multiple sclerosis (10). These pathological effects may result either directly from the virus through the host's initial immune response or indirectly via antibodies and immune-mediated mechanisms (1, 10). Viral infections can significantly amplify neuroinflammation by activating immune cells such as microglia and astrocytes, leading to the release of pro-inflammatory cytokines and chemokines. This inflammatory cascade can cause degeneration of dopaminergic neurons in the substantia nigra, a key event in PD progression (11). Chronic activation of microglia, the central nervous system's primary immune cells, sustains the release of pro-inflammatory cytokines, resulting in neuronal damage, impaired synaptic function, and cognitive decline, thereby promoting neurological disease pathogenesis (12, 13). Astrocytes also act as crucial immune regulators and potential viral reservoirs; by detecting viral particles through specialized receptors, they initiate inflammatory signaling cascades that exacerbate neuroinflammation and contribute to long-term neurological symptoms (13, 14).

The impact of COVID-19 on neurological health is increasingly evident, with growing literature suggesting it may worsen symptoms in patients with Parkinson's disease (PD) and multiple sclerosis (MS), while also raising concerns about new-onset Parkinsonism or MS following infection. Neurological symptoms in COVID-19 patients-such as loss of taste and smell, stroke, and brain inflammation-highlight the virus's neurotropic and neuroinflammatory effects (15–17). SARS-CoV-2 can directly invade neural tissues or trigger inflammatory responses that affect the nervous system, with studies showing a higher frequency of neurological disorders among COVID-19 survivors. Notably, COVID-19-positive outpatients have an increased relative risk of developing PD compared to those without infection (18). Research indicates that in susceptible individuals, the inflammatory response to SARS-CoV-2 may initiate persistent autoimmune and

neurological disorders, including PD and MS (19, 20). However, not all patients develop neurological complications, indicating a complex interplay of genetic and environmental factors.

Understanding the link between COVID-19 and Parkinson's disease (PD) or multiple sclerosis (MS) is essential for improving early diagnosis and patient management. This study systematically reviews existing evidence to clarify the potential association between SARS-CoV-2 infection and the subsequent risk of developing PD or MS. By synthesizing current data, we aim to enhance understanding of viral impacts on long-term neurological health and provide guidance for future research and clinical practice, emphasizing the importance of ongoing investigation and vigilant monitoring (1, 4, 6, 7, 15–20).

2- MATERIALS AND METHODS

2-1. Study Protocol, Registration, and Ethics

This systematic review was conducted in accordance with a pre-registered protocol (PROSPERO CRD42022346649) and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21). Ethical approval was not required, as the study involved analysis of publicly available articles only. The research adhered to ethical standards by respecting copyright laws and maintaining transparency in methods and sources.

2-2. Literature Search

A comprehensive literature search was conducted covering the period from January 2020 to December 2024 across multiple databases, including Medline/PubMed, Embase, PsycINFO, SciELO, Web of Science, ProQuest, Scopus, CINAHL, the WHO COVID-19 Database, grey literature sources (OpenGrey, GreyNet International, institutional repositories), and Google Scholar. No restrictions were applied regarding study design, geographic location, sex, race, disease severity, or other demographics.

The search strategy was developed based on the PECO framework (Population, Exposure, Comparator, Outcome) (22):

- Population: Individuals of all ages, sexes, ethnicities, and geographic locations from the general population.
- Exposure: Laboratory-confirmed or clinically diagnosed COVID-19 infection.
- Comparator: None required, as the primary objective was to assess outcomes following COVID-19 exposure without comparison to non-infected individuals.
- Outcome: Incident cases of Parkinson's disease (PD) or multiple sclerosis (MS) following COVID-19 infection.

Standardized search terms combined keywords and Medical Subject Headings (MeSH) related to COVID-19 and neurological conditions. For example, searches in Medline included terms such as ("COVID-19" OR "SARS-CoV-2" OR "coronavirus" OR "2019 novel coronavirus") AND ("Parkinson's disease" OR "Parkinsonism" OR "Multiple sclerosis" OR "Neuroinflammation"). Boolean operators and truncations were applied to optimize sensitivity and specificity, with appropriate adaptations for each database.

2-3. Eligibility

2-3-1. Inclusion Criteria:

- Studies reporting new-onset Parkinson's disease (PD) or multiple sclerosis (MS) following COVID-19 confirmed by RT-PCR, antigen, or antibody tests.
- Studies categorized by design,

participant characteristics, neurological outcomes, COVID-19 severity, and geographic location.

- Studies including incident PD or MS cases or post-COVID symptoms indicative of these diseases.
- Preference given to larger cohorts and adjusted analyses when overlapping data were present.

2-3-2. Exclusion Criteria:

- Studies focusing on general or acute neurological symptoms unrelated to PD or MS.
- Participants with pre-existing PD or MS.
- Abstracts, preprints, or studies lacking sufficient data for analysis.

2-4. Quality Assessment

Two reviewers (SS and MI) independently evaluated the methodological quality of the included studies using the Joanna Briggs Institute (JBI) critical appraisal tools (23). The JBI checklist for cohort studies consists of 11 items (maximum score: 22), while the checklist for case reports includes 8 items (maximum score: 16). Each item was scored as 2 (done), 1 (unclear), or 0 (not done). For cohort studies, quality was classified as good (16–22), fair (9–15), or poor (below 9). For case reports, scores of 11–16 indicated good quality, 5–10 fair quality, and below 5 poor quality.

A risk of bias table was created in Excel, using color coding (green: done/low risk; yellow: unclear/medium risk; red: not done/high risk) to visually summarize methodological strengths and weaknesses. Both reviewers also independently assessed the diagnostic criteria for COVID-19 and neurological outcomes (PD and MS). Any discrepancies were resolved through consensus.

2-5. Data Synthesis

Two authors (SS and MI) independently extracted key data from the included studies using a standardized template that captured study characteristics (author, year, design, sample size), patient demographics, COVID-19 diagnostic methods, neurological diagnoses, time to symptom onset, clinical manifestations, proposed mechanisms, treatments, and follow-up outcomes. Any discrepancies were resolved by consensus.

Due to significant heterogeneity in study design, participant selection, sample sizes, methods, and outcome measures, statistical pooling was not feasible. Consequently, the data were unsuitable for reliable meta-analysis. Instead, a narrative synthesis was performed, grouping studies with comparable neurological outcomes to facilitate cross-study comparisons and highlight data limitations. Heterogeneity was summarized by comparing participant characteristics, management approaches, and outcomes (**Table 1**).

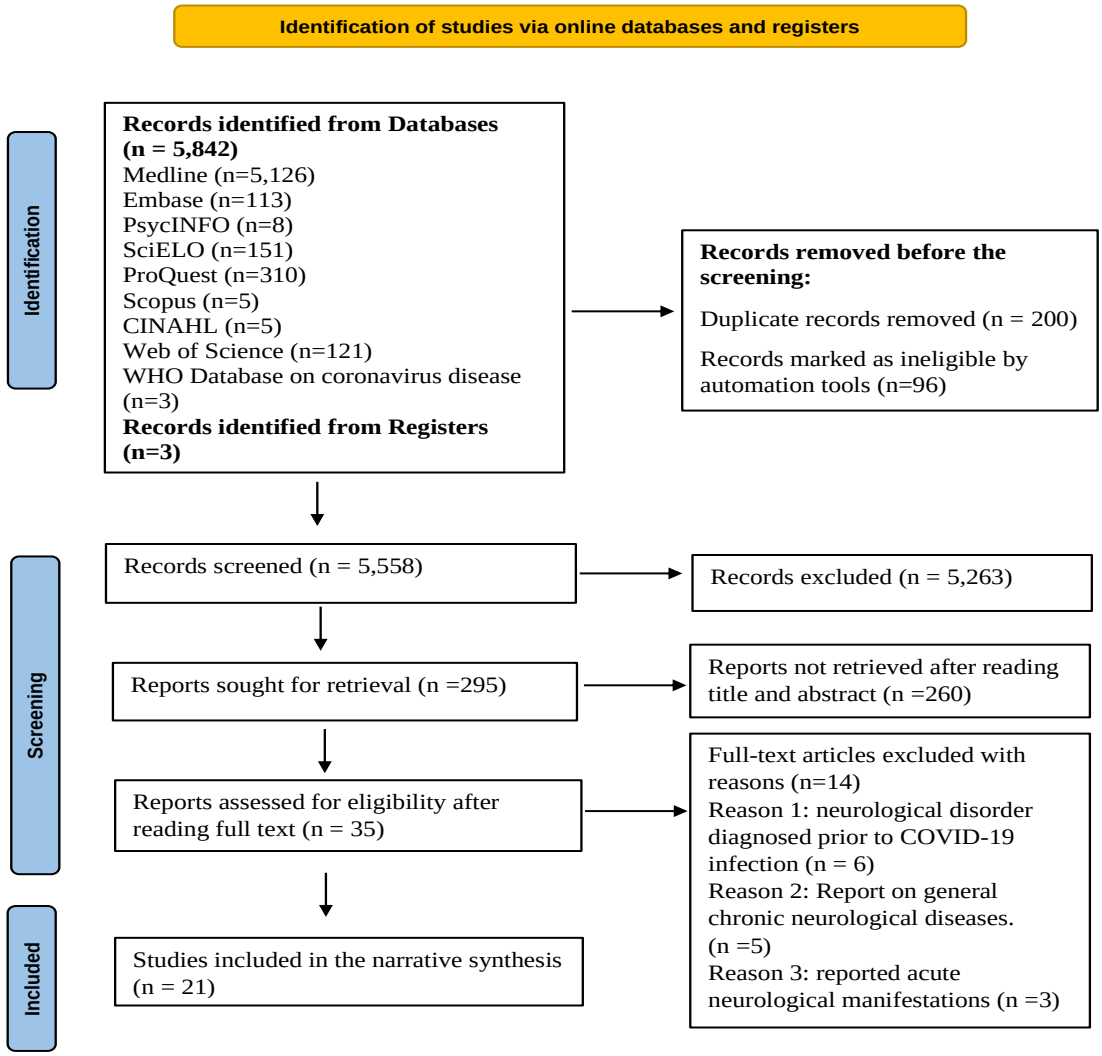
The overall certainty of evidence was assessed using the hierarchy of evidence. Cohort studies, considered moderate-level evidence, were evaluated using the GRADE approach to determine confidence in the findings (24). Case reports, lower in the evidence hierarchy, were appraised narratively with a focus on completeness and relevance, guided by the JBI critical appraisal checklist (23).

3- RESULTS

3-1. Study Selection

The literature search results were imported into Covidence to facilitate efficient management, including duplicate removal, blinded title and abstract screening, full-text review, and conflict resolution among reviewers (25). Two reviewers (SS and MI) independently conducted a two-stage screening process. Initially, 5,854 studies were identified through database and registry searches.

After removing 200 duplicates and 96 ineligible records, 5,558 studies underwent title and abstract screening. Of these, 5,263 were excluded, leaving 295 full-text articles for detailed assessment. Applying the predefined inclusion and exclusion criteria, 21 studies comprising 279,911 participants met the eligibility criteria and were included in the final review. The study selection process is summarized in the PRISMA flow diagram (**Figure 1**).



Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

Fig.1: PRISMA flow chart for the study selection process.

3-2. Risk of Bias Assessment

All included studies were rated as "good quality" using the JBI critical appraisal tools for cohort and case reports (23; **Table 2**). However, the overall certainty of the evidence was tempered by factors such as study design limitations, risk of bias, indirectness, inconsistency, imprecision, and potential publication bias (26, 27). The majority of included studies were case

reports (n=18), with a smaller number of cohort studies (n=3), placing the evidence at a moderate level within the hierarchy (28). Despite these limitations, the consistently low risk of bias across studies strengthens confidence in the findings. While conclusions should be interpreted with caution due to the observational and descriptive nature of the data, the quality and coherence of the evidence provide meaningful insights. These results are considered reliable within the current evidence framework and underscore the urgent need for further rigorous, high-quality research to validate and expand upon these findings.

3-3. Characteristics of Included Studies

A total of 21 studies were included in this review, comprising three cohort studies and 18 case reports, with a combined total of 279,911 participants. Sample sizes ranged from single case reports to large cohorts of up to 236,379 individuals. The studies covered multiple regions, including North and South America (n=7), Europe (n=9), Africa (n=1), the Middle East (n=3), and Asia (n=1) (**Table 1**). Participants' ages ranged from 21 to 76 years, with a median age of 52. COVID-19 diagnoses were confirmed in 19 studies using RT-PCR, antigen, or antibody testing, and neurological outcomes were established through clinical evaluation, imaging, and laboratory investigations. Comorbidities were reported in ten studies, and 14 studies described COVID-19 severity, with ten specifically noting severe cases. The interval between COVID-19 diagnosis and neurological symptom onset ranged from days to one year in 19 studies.

Parkinson's disease was reported in 15 studies. Of these, two cohort studies documented 336 incident cases of PD/parkinsonism among 236,514 participants (29, 30), while 13 case reports described 17 individual cases. New-onset multiple sclerosis was reported in five case reports, each involving a single participant. One study reported both PD and MS, identifying 26 PD and 14 MS cases among 43,375 participants. Case reports provided detailed accounts of clinical presentation, diagnostic imaging, management, and potential mechanistic links between COVID-19 and the onset of PD or MS (**Table 1, Table 2**).

3-4. Parkinson's Disease

3-4-1. Pathophysiologic Mechanisms:

The association between Parkinson's disease (PD) and COVID-19 appears multifactorial, involving heterogeneous causal pathways. Proposed mechanisms for new-onset PD following COVID-19 infection include viral neurotropism, immune dysregulation, inflammatory responses, hypoxic–ischemic injury, and neurotoxicity. Evidence suggests that SARS-CoV-2 may promote α-synuclein aggregation through sustained neuroinflammation and oxidative stress, potentially accelerating PD pathogenesis (1, 2, 4, 5).

3-4-2. Clinical Presentations/Neurological Examination Findings:

This review identified both motor and non-motor symptoms characteristic of PD among patients in 13 studies. Reported symptoms included tremor, bradykinesia, rigidity, postural instability, gait disturbances, cognitive impairment, autonomic dysfunction, mood disorders, fatigue, and speech difficulties (31–40).

3-4-3. Diagnostics and Findings:

Imaging modalities used in 12 case reports included MRI, CT, F-DOPA PET, SPECT, DaTscan, FDG-PET, and EEG (31–42). Findings varied but commonly showed basal ganglia atrophy, white matter changes on MRI, reduced dopamine uptake on F-DOPA PET, and asymmetric uptake on DaTscan, all suggestive of PD. Clinical assessment tools such as the Movement Disorder Society-Unified

Parkinson's Disease Rating Scale (MDS-UPDRS), Montreal Cognitive Assessment (MoCA), Sniffin' Sticks olfactory test, Luria test, and Mini-Mental State Examination (MMSE) were reported in eight studies, revealing motor symptoms alongside cognitive and olfactory dysfunction (30, 32–37, 39).

3-4-4. Laboratory Investigations:

Laboratory analyses included cerebrospinal fluid (CSF) studies and genetic testing. Elevated inflammatory markers-such as cytokines, C-reactive protein, and interleukins-were frequently observed. Genetic mutations in the GBA gene, a known PD risk factor, were also reported in several cases (31, 33–35, 37, 39, 40, 43, 44).

3-4-5. Treatment and Outcomes:

Nine case reports described PD-specific treatments, including levodopa-carbidopa, pramipexole, benserazide, biperiden, and amantadine, with varying therapeutic responses (32, 34–37, 39–41, 44). Two studies reported management with non-PD-specific regimens (31, 43). In ten studies, patients did not receive PD-targeted treatment but showed variable improvements in motor and non-motor symptoms and functional status.

3-5. Multiple Sclerosis

3-5-1. Pathophysiologic Mechanisms:

This review highlights diverse causal mechanisms suggesting a multifactorial etiology for multiple sclerosis (MS) following COVID-19. Proposed mechanisms include viral neurotropism, virus-induced demyelination, autoimmune reactions, and inflammatory responses, as reported in several case reports (42, 45–48). Neurodegeneration was also observed in one cohort study, where among 43,375 participants, 26 (0.06%) were diagnosed with Parkinson's disease and 14 (0.03%) with MS during a twelve-month follow-up after COVID-19 infection (18).

3-5-2. Clinical Presentations:

Clinical Presentations
The onset of MS symptoms after COVID-19 infection varied from two weeks up to one year. Common presenting symptoms included paraesthesia, nystagmus, binocular diplopia, paraparesis, visual disturbances, fatigue, drowsiness, limb weakness, and, in some cases, fulminant demyelination requiring hospitalization. These symptoms were documented in four case reports (42, 45, 47, 48).

3-5-3. Diagnostics and Findings:

Five studies utilized MRI, T2-FLAIR, and CT scans to detect and characterize MS lesions and exclude other conditions (42, 45–48). MRI findings included characteristic demyelinating lesions and new or enhancing lesions in the brain and spinal cord consistent with MS pathology. Diagnostic confirmation also involved McDonald's criteria, fundoscopy, limb strength evaluation, visual acuity assessments, and electromyography (42, 45–48).

3-5-4. Laboratory Investigations:

Laboratory analyses in these case reports included cerebrospinal fluid (CSF) analysis, viral serology, complete blood count (CBC), and vitamin B12 measurement. CSF findings revealed oligoclonal bands and elevated inflammatory markers, while blood tests showed increased C-reactive protein (CRP), cytokines, and erythrocyte sedimentation rate (ESR) following COVID-19 infection (42, 45–48).

3-5-5. Treatment and Outcomes:

Three case reports described MS-specific treatments such as corticosteroids and disease-modifying therapies (DMTs), with outcomes ranging from complete symptom resolution to significant improvement (45–47). In contrast, two untreated patients also exhibited significant improvement within three to four weeks of follow-up (42, 48).

Table-1: Summary of Included Studies Assessing the Association between COVID-19 and the Development of PD and MS (n=21).

Author, Year, (Reference)	Study Design / Population	COVID-19 Diagnostics	Neurological Diagnosis (Imaging/Exam)	Time to Onset of Neurological Symptoms	Condition / Outcome Studied	Treatment / Management	Outcome / Duration of Follow-up
Akilli and Yosun-kaya, 2021, (31)	Case report (n=1)	RT-PCR	MRI: Unremarkable. Exam: Cogwheel rigidity, bradykinesia, anteflexion gait.	3 days after COVID-19 diagnosis	Acute Parkinsonism	Convalescent plasma	Complete recovery after 2 months; improved orientation/cooperation.
Ayele et al., 2021, (32)	Case report (n=1)	RT-PCR	MRI: Bilateral pallidal T2/FLAIR hyperintensity. Exam: GCS 13/15, right-hand resting tremor, bradykinesia, jaw-closure oromandibular dystonia, facial hypomimia, hypophonia, drooling.	Not reported (N/R)	Parkinsonism	Levodopa/carbidopa	Significant improvement on follow-up.
Cavallieri et al., 2022, (33)	Case report (n=2)	RT-PCR	MRI: Mild microvascular changes. SPECT DaT: Mild bilateral reduction in presynaptic dopaminergic uptake. Exam: Right hand tremor, slight bilateral bradykinesia/rigidity, reduced right arm swing (MDS-UPDRS-III: 12/132).	4 months after COVID-19 diagnosis	Probable Parkinson's disease	N/R	N/R
		RT-PCR	MRI: Unremarkable. SPECT DaT: Decreased dopamine transporter in both putamen. Exam: Left leg tremor, slight left hand bradykinesia (MDS-UPDRS-III: 4/132).	1 month after COVID-19 diagnosis	Probable Parkinson's disease	N/R	N/R
Cohen et al., 2022, (34)	Case report (n=1)	RT-PCR	Brain CT, MRI, EEG: Unremarkable. 18F-FDOPA: Increased uptake in both putamen, more apparent on left side. Exam: Hypomimia, hypophonic speech, cogwheel rigidity, moderate bradykinesia, slow gait, MCA-28 of 30.	9 days after COVID-19 diagnosis	Probable Parkinson's disease	Methylprednisolone, pramipexole, biperiden	Improvement in tremors after 3 months
Faber et al., 2020, (35)	Case report (n=1)	RT-PCR	MRI & FDG-PET: Unremarkable. Exam: Decreased facial expression, eyelid retraction, hypometric saccades, hypophonia, bradykinesia, cogwheel rigidity, stooped posture, reduced arm swing, MDS-UPDRS-III: 49, Sniffin' Sticks: 9/16.	4 weeks after COVID-19 diagnosis	Akinetic-rigid parkinsonism	Levodopa/benserazide	Symptoms improved after 4 days; no further follow-up
Fearon et al., 2021, (36)	Case report (n=1)	N/R	CT: Bilateral globus pallidus edema with hemorrhagic foci. MRI: Resolution	1 year after COVID-19	Post-infectious parkinsonism	Levodopa	Unresponsive to levodopa

			of edema with tissue loss. Exam: Severe hypophonia, hypomimia, asymmetric rigidity/bradykinesia, freezing of gait, postural instability, positive grasp reflex, impaired Luria test.	diagnosis			
Ghosh et al., 2022, (37)	Case report (n=1)	N/R	MRI: Symmetrical hyperintense signals in bilateral caudate nucleus and putamen. Chest CT: COVID-19 severity score 8/25. Exam: Generalized bradykinesia, hypomimia, monotone speech, axial/appendicular rigidity (MDS-UPDRS: 60), akinetic mutism.	5 days after COVID-19 diagnosis	Parkinsonism with akinetic mutism	Levodopa/carbidopa, pramipexole, sertraline	Improvement after 2 months
Makhoul and Jankovic, 2021, (38)	Case report (n=1)	RT-PCR	DaT scan: Decreased uptake in right putamen. Exam: Minimal hypomimia, mild left-sided bradykinesia and rigidity.	5 days after COVID-19 diagnosis	Parkinsonism	N/R	N/R
Méndez-Guerrero et al., 2020, (43)	Case report (n=1)	RT-PCR	EEG: Diffuse mild reactive slowing. Exam: Bilateral myoclonic jerks, moderate hyposmia, slight up-gaze, tetraparesis, brisk reflexes, loss of spontaneous movement, moderate cogwheel rigidity, hypomimia.	23 days after COVID-19 diagnosis	Parkinsonism	Non-specific treatment	Symptoms improved without specific treatment
Morassi et al., 2021, (39)	Case reports (n=2)	RT-PCR	EEG: Bilateral theta-delta slowing with bitemporal epileptiform discharges. MRI: Acute alterations. FDG-PET/CT: Diffuse cortical hypometabolism. MMSE: 28/30. Exam: Generalized hypertonia, cogwheel rigidity, loss of spontaneous movements (right limbs), bradykinesia, hypomimia, hypophonia, ophthalmoparesis.	6 weeks after COVID-19 diagnosis	SARS-CoV-2-related encephalitis with prominent Parkinsonism	Carbidopa/levodopa	After 9 months: walking with aid, severely affected ADL (3/6), late-day confusion
Morassi et al., 2021, (39)	Case reports (n=2)	RT-PCR	EEG: Bilateral theta-delta slowing with bitemporal epileptiform discharges. MRI: Acute alteration or contrast-enhanced areas. FDG-PET/CT: Diffuse cortical hypo-metabolism. MMSE: 28/30. Exam: Generalized hypertonia, cogwheel rigidity, loss of spontaneous movements of right limbs, bradykinesia, hypomimia, hypophonia, ophthalmoparesis.	6 weeks after COVID-19 diagnosis	SARS-CoV-2-related encephalitis with prominent Parkinsonism	Carbidopa/levodopa	After 9 months: walking with aid, severely affected ADL (3/6), late-day confusion (sundowning)

		RT-PCR	EEG: Generalized theta slowing with sharp waves over right frontotemporal region. MRI: Acute alteration or contrast-enhanced areas. FDG-PET/CT: Diffuse cortical hypo-metabolism (sensorimotor sparing). Exam: Anarthria, vertical gaze limitation, bilateral hypokinetic-rigid syndrome, loss of spontaneous movements, cogwheel rigidity, hypomimia, diminished blinking, glabellar tap sign.	3 days after COVID-19 diagnosis	SARS-CoV-2-related encephalitis with prominent Parkinsonism	Amantadine, levodopa/carbidopa neurological sequelae	No improvement; died 30 days post-discharge from complications
Rass et al., 2021, (30)	Cohort study (n=135)	RT-PCR	Sniffin' Sticks test, MoCA for cognitive deficit	3–6 months after COVID-19 diagnosis	Parkinsonism	N/R	76 presented with Parkinsonism
Rao et al., 2022, (44)	Case reports (n=3)	RT-PCR	Loss of smell, cogwheel rigidity, postural instability, bradykinesia	5 days after COVID-19 diagnosis	Parkinsonism	Levodopa	Complete resolution after 4 months
		RT-PCR	MRI: Gliosis in bilateral temporal lobes, periventricular white matter changes. Exam: Right limb rigidity, severe bradykinesia	5 days after COVID-19 diagnosis	Parkinsonism	Levodopa	Symptoms resolved after 1 month
		RT-PCR	MRI: Ischemic changes in periventricular white matter. Exam: Rigidity, postural instability, motor slowing	7 days after COVID-19 diagnosis	Parkinsonism	Levodopa-carbidopa	Complete resolution after 8 months
Roy et al., 2021, (41)	Case report (n=1)	RT-PCR	MRI: Basal ganglia and corona radiata stroke. Exam: Encephalopathy, quadriplegia, left hemiparesis, hypokinetic-rigid state, poor mental status	N/R	Parkinsonism	Carbidopa/levodopa	Continued improvement on follow-up
Taquet et al., 2021, (29)	Cohort study (n=236,379)	RT-PCR	N/R	6 months after COVID-19 diagnosis	Parkinsonism	N/R	260 (0.11%) developed Parkinsonism
Tiraboschi et al., 2021, (40)	Case report (n=1)	RT-PCR	CT: Unremarkable. EEG: Bilateral slow waves, epileptiform discharges. MRI: Unremarkable. PET/CT: Increased mesial temporal and subthalamic metabolism. Exam: Confused, agitated, seizures, bradykinesia, postural/action tremor left upper limb	2 months after COVID-19 diagnosis	Parkinsonism/immune-mediated SARS-CoV-2–related encephalitis	IV immunoglobulin	Full recovery after 2 months

Zarifkar et al., 2022, (18)	Cohort study (n=43,375)	RT-PCR	N/R	12 months after COVID-19 diagnosis	Parkinson's disease, Multiple sclerosis	N/R	26 (0.06%) Parkinson's disease, 14 (0.03%) multiple sclerosis
Domingues et al., 2020, (42)	Case report (n=1)	RT-PCR	Brain/cervical MRI: Unremarkable. Chest CT: Unremarkable. Exam: Hypoesthesia left upper limb/hemithorax	3 weeks after COVID-19 diagnosis	Multiple sclerosis/CNS demyelinating disease	N/R	Full recovery after 3 weeks
Moore et al., 2021, (45)	Case report (n=1)	RT-PCR	MRI: Juxtacortical, periventricular, infratentorial lesions. Cervical/thoracic MRI: Unremarkable. Exam: Vertical nystagmus, internuclear ophthalmoplegia	2 weeks after COVID-19 diagnosis	Multiple sclerosis	IV methylprednisolone, prednisone	Improvement in nystagmus, double vision
Palao et al., 2020, (46)	Case report (n=1)	Antibody testing	Orbital MRI: Right optic nerve lesion. Brain MRI: Periventricular demyelinating lesions. Spine MRI: Unremarkable. Exam: Papillitis, visual acuity 20/200, hyperreflexia, clonus, plantar/Hoffmann signs	3 weeks after COVID-19 diagnosis	CNS demyelinating disease	IV/oral methylprednisolone	Full recovery at discharge
Yavari et al., 2020, (47)	Case report (n=1)	RT-PCR	Brain MRI: Multiple plaques. Exam: Facial paresis, paraesthesia, anosmia, facial nerve involvement, normal limb power	2–3 months after COVID-19 infection	Multiple sclerosis/Demyelinating disease	Subcutaneous interferon-beta-1a, escitalopram, clonazepam	No follow-up data
Zoghi et al., 2020, (48)	Case report (n=1)	RT-PCR	Chest CT: Ground-glass opacities. Spinal MRI: LETM, intramedullary lesion. Brain MRI: Bilateral corticospinal tract lesions. Exam: Upper limb 4+/5, lower limb 2/5, sensory impairment, absent abdominal reflex	3 weeks after COVID-19 diagnosis	ADEM, Multiple sclerosis	Plasma exchange, antibiotics	Improvement after 3 weeks

Abbreviations:

ADEM: Acute disseminated encephalomyelitis; DaT-SPECT: Dopamine transporter-single-photon emission computed tomography; CT: Computed tomography; FDG: 18-F-fluorodeoxyglucose; PET: Positron emission tomography; MRI: Magnetic resonance imaging; FDOPA: Fluorodopa; MDS-UPDRS: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; FLAIR: Fluid-attenuated inversion recovery; MoCA: Montreal Cognitive Assessment; LETM: Longitudinally extensive transverse myelitis; EMG: Electromyography; T8: Eighth thoracic vertebra; EEG: Electroencephalogram; N/R: Not reported.

Table-2: Patient Demographics, Clinical Presentation, Comorbidities, Pathophysiologic Mechanism, and Study Quality.

Author, Year, (Reference)	Age / Gender	Comorbidity / Predisposing Factors	Clinical Presentation / COVID-19 Severity	Potential Mechanism of Association with COVID-19	Risk Rating / Study Quality
Akilli and Yosun-kaya, 2021, (31)	72 / Male	Diabetes mellitus, hypertension, peripheral artery disease	Altered consciousness, slowed movements, tremors. Severe infection	Neurotropism	High risk of bias (case report). Good quality
Ayele et al., 2021, (32)	35 / Female	None reported	Fluctuating mentation, abnormal behavior, fever, visual hallucinations. Severe infection	Viral-mediated neuroinflammation, α-synucleinopathy	High risk of bias (case report). Good quality
Cavallieri et al., 2022, (33)	67 / Male	GBA gene variant (genetic PD susceptibility)	Progressive finger dexterity impairment, mild right hand tremor, nightmares. Severe infection	Neurodegeneration	High risk of bias (case report). Good quality
	45 / Male	PRKN gene variant (genetic PD susceptibility)	Resting tremors. Mild infection	Neurodegeneration	High risk of bias (case report). Good quality
Cohen et al., 2022, (34)	45 / Male	Hypertension, asthma	Speech and writing difficulties, tremor episodes.	Immunologically mediated mitochondrial injury, oxidative stress	High risk of bias (case report). Good quality
Faber et al., 2020, (35)	35 / Female	None reported	Paraesthesia, right arm weakness, lower voice tone, rigidity, slowness, gait unsteadiness. Mild infection	Post-infectious neuroinflammation	High risk of bias (case report). Good quality
Fearon et al., 2021, (36)	46 / Male	None	Freezing of gait, postural instability, positive grasp reflex. Severe infection	Hypoxemia and virus-specific endothelial mechanisms	High risk of bias (case report). Good quality
Ghosh et al., 2022, (37)	65 / Female	Type 2 diabetes mellitus	Vomiting, drowsiness. Severe infection	Autoimmunity	High risk of bias (case report). Good quality
Makhoul and Jankovic, 2021, (38)	64 / Female	None reported	Resting tremors, 10-year history of constipation. Mild infection	Autoimmunity, hypoxia	High risk of bias (case report). Good quality
Méndez-Guerrero et al., 2020, (43)	58 / Male	None reported	Severe infection	N/A	High risk of bias (case report). Good quality
Morassi et al., 2021, (39)	70 / Female	Hypertension, mixed anxiety–depressive disorder	Depression, fever, cough, dysgeusia. Moderate infection	Inflammation and neurodegeneration	High risk of bias (case report). Good quality
	73 / Female	Diabetes mellitus II, hypertension, mixed anxiety–depressive disorder with psychotic symptoms	Fever, depression. Moderate infection	Inflammation and neurodegeneration	High risk of bias (case report). Good quality

Rass et al., 2021, (30)	Median 56 (IQR 48–68), Female 39, Male 53	Cardiovascular disease, hypertension, pulmonary disease, endocrinological disease, chronic disease, liver disease, diabetes mellitus II, hypercholesterolemia, malignancy	N/A	Direct virus-associated pathology, inflammatory reaction	Low risk of bias (cohort study). Good quality
Rao et al., 2022, (44)	72 / Male	None reported	Fever, chills, cough, breathlessness (4 days)	Neurotropism	High risk of bias (case report). Good quality
	66 / Male	Diabetes, hypertension, seizure disorder	Cough, hoarseness (2 weeks), generalized tonic-clonic seizure	Neurotropism	High risk of bias (case report). Good quality
	74 / Male	None reported	Decreased mobility	Neurotropism	High risk of bias (case report). Good quality
Roy et al., 2021, (41)	60 / Male	Hypertension, diabetes, hypercholesterolemia	Worsening shortness of breath. Severe infection	N/A	High risk of bias (case report). Good quality
Taquet et al., 2021, (29)	Mean 47 / Male 10,401, Female 131,460	Variable	Variable severity of infection	Viral CNS invasion, immune response	Low risk of bias (cohort study). Good quality
Tiraboschi et al., 2021, (40)	40 / Female	Overweight	Agitation, confusion, tonic-clonic seizures. Severe infection	Immune-mediated encephalitic process	High risk of bias (case report). Good quality
Zarifkar et al., 2022, (18)	Mean 66 / Female 24,480, Male 18,896	Cerebrovascular risk factors (hypercholesterolemia, diabetes II, hypertension, obesity, smoking)	Not available (N/A). Variable severity of infection	Neurodegeneration	Low risk of bias (cohort study). Good quality
Dominguez et al., 2020, (42)	42 / Female	Paraesthesia (left upper limb, hemithorax, hemiface, 3 years prior)	Paraesthesia (left upper limb, hemithorax, hemiface)	Autoimmunity	High risk of bias (case report). Good quality
Moore et al., 2021, (45)	28 / Male	Glaucoma, right retinal hole, oscillopsia	Binocular diplopia	Neuroinflammation	High risk of bias (case report). Good quality
Palao et al., 2020, (46)	29 / Female	Asthma, rhinoconjunctivitis	N/A	Neurological autoimmunity	High risk of bias (case report). Good quality
Yavari et al., 2020, (47)	24 / Female	None reported	Sore throat, low-grade fever, myalgia (1 month)	Neurotropism	High risk of bias (case report). Good quality
Zoghi et al., 2020, (48)	21 / Male	None reported	Loss of appetite, vomiting, malaise, weakness, paraesthesia, urinary retention, paraparesis, drowsiness. Severe infection	Immune reaction	High risk of bias (case report). Good quality

N/A: Not available; PD: Parkinson’s disease.

4- DISCUSSION

This systematic review rigorously evaluated the potential association between COVID-19 and the onset of Parkinson's disease (PD) and multiple sclerosis (MS). By synthesizing findings from both cohort and case reports, the review examines the clinical presentations, diagnostic approaches, underlying pathological mechanisms, and patient outcomes associated with these neurological sequelae.

Cohort studies provided observational evidence supporting a possible link between COVID-19 infection and the emergence of neurodegenerative symptoms. Meanwhile, case reports illustrated a broad spectrum of clinical presentations, including motor dysfunction, demyelinating lesions, and rapid neurological decline following COVID-19 infection.

Although the findings are heterogeneous, they collectively offer preliminary insights into the neurological consequences of COVID-19. These results highlight the need for further research to clarify the mechanisms by which SARS-CoV-2 may contribute to long-term neurological dysfunction and to guide future clinical management and public health strategies.

4-1. Interpretation of Findings

4-1-1. Parkinson's Disease:

The association between viral infections and parkinsonism has historical precedent, most notably following the 1918 Spanish flu pandemic, during which encephalitis lethargica-a condition characterized by Parkinsonian symptoms-was observed after influenza virus infections (49, 50). This historical context continues to inform ongoing research into the role of viral infections in the pathogenesis of PD. Multiple viruses, including influenza, Epstein-Barr virus, HIV, and now SARS-CoV-2, have been implicated in triggering neuroinflammation, immune dysregulation, and direct neural injury, all of which may contribute to the loss of dopaminergic neurons in the substantia nigra, a hallmark of PD (51).

The onset of both motor and non-motor PD symptoms-such as tremor, bradykinesia, rigidity, postural instability, and gait disturbance-following COVID-19 suggests that SARS-CoV-2 infection may induce or exacerbate these symptoms. The mechanistic pathways identified in this review, including viral neurotropism, immune dysregulation, inflammatory responses, hypoxic–ischemic injury, and neurotoxicity, align with current literature on PD pathophysiology. These pathways, combined with genetic vulnerability and environmental triggers, can lead to the progressive loss of dopaminergic neurons (52–54). Brundin (55) further highlights three possible routes: COVID-19 may cause brain pathway damage similar to vascular parkinsonism; immune-mediated inflammatory processes triggered by COVID-19 can induce parkinsonism; and COVID-19 may elevate interleukin-6, a protein linked to PD.

Diagnosis of PD primarily relies on characteristic motor symptoms, with imaging and clinical assessment tools providing supportive evidence. Studies in this review utilized various imaging modalities (MRI, DaTscan, CT, F-DOPA PET, SPECT, FDG-PET, EEG) and clinical assessments (MDS-UPDRS-III, MoCA, Sniffin' Sticks, Luria test, MMSE) to evaluate dopaminergic function, detect structural abnormalities, and clarify ambiguous cases (31–42). Imaging findings, while variable, often demonstrated changes consistent with PD pathology, supporting the view that COVID-19 may influence a neurodegenerative process. Elevated inflammatory markers (e.g., interleukins, C-reactive protein) in cerebrospinal fluid and blood samples of patients with

Parkinsonian symptoms post-COVID-19 further suggest that SARS-CoV-2 infection may trigger PD through inflammatory pathways (6, 31, 33–35, 37, 39, 40, 43, 44, 54). Recent studies indicate that SARS-CoV-2 can activate microglial inflammasomes, promoting neuroinflammation and neurodegeneration similar to that seen in PD (6, 8).

The identification of genetic mutations associated with PD (e.g., LRRK2, GBA) raises the possibility that COVID-19 acts as an environmental trigger in genetically susceptible individuals (33). However, while these findings support the role of neuroinflammation in PD development, elevated inflammatory markers are not exclusive to PD and may reflect a general immune response to acute viral infection. Moreover, genetic mutations alone do not establish causation without longitudinal studies or pathological confirmation. The inflammatory hypothesis, while plausible, requires further robust evidence to distinguish between transient post-viral reactions and the onset of true neurodegeneration. Finally, the varied responses to dopaminergic treatments among patients highlight the complexity of managing PD, especially in cases with atypical parkinsonism or treatment-resistant variants.

4-1-2. Multiple Sclerosis:

Multiple sclerosis (MS) is characterized by inflammation, demyelination, and neuroaxonal degeneration within the central nervous system (CNS), and is widely considered to have an autoimmune basis (54, 56). The causal mechanisms identified in this review support the hypothesis that COVID-19 may act as a trigger for MS through immune dysregulation and neuroinflammatory processes (42, 45–48).

The symptoms observed in the reviewed studies-such as paraesthesia, nystagmus, binocular diplopia, paraparesis, visual disturbances, fatigue, drowsiness, and limb weakness-closely align with the classic heterogeneous presentations of MS described in the literature (57, 58). All five case reports included symptoms consistent with established MS clinical guidelines, reinforcing the biological plausibility of an autoimmune-mediated demyelinating disease.

Neuroimaging, particularly MRI, is central to MS diagnosis and provides critical insights into lesion distribution and disease activity (57). In the reviewed studies, MRI frequently revealed demyelinating patterns typical of MS, including multiple plaques in various brain regions, optic nerve lesions, periventricular white matter lesions, and infratentorial involvement (45–48). These findings are consistent with the revised McDonald diagnostic criteria for MS (59), supporting both the accuracy of the diagnosis and the possibility of a post-COVID-19 association.

Immunological and inflammatory biomarkers further strengthen the diagnostic picture. Oligoclonal bands in cerebrospinal fluid-a hallmark of MS found in 85–95% of patients-as well as elevated C-reactive protein and pro-inflammatory cytokines, were detected in the reported cases (42, 45–48). These biomarkers are critical for confirming MS and indicating underlying immune activity and disease progression. Neurological findings in the reviewed studies, including optic neuritis, limb paraesthesia, and motor weakness, are consistent with focal demyelinating lesions in the CNS and the asymmetric neurological deficits typical of MS (57, 58).

While the evidence is suggestive, it is important to recognize that a direct causal link between COVID-19 and MS cannot be established at this time. Viral infections-including measles, poliomyelitis, varicella, and meningitis-have long been implicated in the pathogenesis of neurological disorders (12,

60–62). Notably, Epstein-Barr virus has been associated with MS (63). The immune dysregulation observed in COVID-19 patients is not specific to MS and can mimic other post-infectious or autoimmune neurological syndromes. The improvement of symptoms in some cases may indicate acute demyelinating events or post-infectious inflammatory syndromes rather than definitive MS. In classic MS, symptoms may remit, but the disease process is chronic, and full recovery is rare. The favorable response to treatment in some cases may reflect an immune-mediated, monophasic reaction to viral infection rather than the onset of a chronic autoimmune disease, although follow-up data are lacking.

The fundamental pathophysiology of MS involves demyelination, whereas Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons (11, 64). The reviewed studies indicate that COVID-19's neurological effects are diverse, including direct viral damage, immune-mediated injury, inflammatory reactions, and vascular damage. These findings suggest that COVID-19 can provoke acute autoimmune reactions, but the long-term implications for MS or PD remain unclear.

The absence of longitudinal data, particularly in case reports, makes it difficult to determine whether the demyelinating events meet the diagnostic threshold for MS as outlined in the McDonald Criteria, or whether parkinsonian features meet the criteria for PD, especially regarding the hallmark of progressive motor decline over time. It is therefore plausible that COVID-19 may act as a transient trigger for neurological symptoms rather than a direct initiator of MS or PD pathogenesis (65–68). These observations highlight the complex interplay between COVID-19, the immune system, and the nervous system, and underscore the need for further research to clarify the long-term neurological impacts of COVID-19.

5- CONCLUSION

This systematic review provides a comprehensive synthesis of current evidence regarding the potential association between COVID-19 infection and the new onset of Parkinson's disease (PD) and multiple sclerosis (MS). Across 21 studies-including three cohort and 18 case reports-with a combined sample of 279,911 participants from diverse global regions, rare but documented cases of new-onset PD and MS following COVID-19 infection were identified. The proposed pathophysiological mechanisms, including viral neurotropism, immune dysregulation, inflammatory responses, and neurotoxicity, are biologically plausible and supported by clinical and laboratory findings.

While the majority of patients responded to established disease-specific treatments, the predominance of case reports and the limited number of high-quality cohort studies restrict the overall strength of the evidence. Although the risk of bias was generally low, the observational and descriptive nature of the data, along with potential publication bias and study design limitations, necessitate cautious interpretation.

In summary, current evidence suggests a possible link between COVID-19 infection and the development of PD and MS in a small subset of patients, but causality cannot be definitively established at this stage. These findings underscore the importance of heightened clinical vigilance for neurological symptoms in patients recovering from COVID-19 and highlight the urgent need for robust, large-scale prospective studies to clarify the relationship, elucidate underlying mechanisms, and inform both preventive and therapeutic strategies.

6- AUTHORS' CONTRIBUTIONS

Study conception or design: SS, and MJI; Data analyzing and draft manuscript preparation: MJI and OFA; Critical revision of the paper: SS, and MJI; Supervision of the research: SS; Final approval of the version to be published: SS, MJI, and OFA.

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