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Neurological Manifestations of COVID-19: A review of the impact on chronic neurological conditions

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Abstract

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by SARS-CoV-2 infection and is associated with both acute and chronic disorders affecting the nervous system. This comprehensive review aims to summarize the current knowledge on the impact of COVID-19 on the nervous system, including epilepsy, Parkinson's disease, Alzheimer's disease, multiple sclerosis, ischemic stroke, and Guillain-Barré syndrome. The review highlights the increased risk of neurological complications in patients with pre-existing neurological conditions, such as epilepsy, Parkinson's disease, and multiple sclerosis. Additionally, COVID-19 infection has been linked to a range of neurological symptoms, including headaches, seizures, encephalitis, and stroke. The pathophysiology of COVID-19-related neurological manifestations is complex and multifactorial, involving direct viral invasion, immune-mediated mechanisms, and systemic inflammation. The review discusses the potential therapeutic strategies for managing COVID-19-related neurological complications, including antiviral medications, immunomodulatory therapies, and supportive care. The review also emphasizes the importance of telemedicine and remote monitoring in managing patients with chronic neurological conditions during the COVID-19 pandemic. Furthermore, it highlights the need for ongoing research to better understand the long-term neurological consequences of COVID-19 infection and to develop effective strategies for prevention and treatment.

Keywords: Covid-19; Neurological disorders; Parkinson's disease; Neurological Manifestations; Multiple Sclerosis; Guillain-Barre Syndrome

1. Introduction

Since its discovery in Wuhan, China in late 2019, coronavirus disease 2019 (COVID-19), disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in over 3 million deaths and placed unprecedented pressure on social, economic and health care systems worldwide. Many survivors of the acute infection experience persistent and incapacitating neurological symptoms, which can have socioeconomic and personal consequences [01]. Recent research connects the coronavirus 2019 (COVID-19) pandemic, which disrupted our lives and changed the world from December 2019 to the present, to brain diseases [02]. In approximately 200 million cases of infection and 4 million fatalities as of August 2021, coronavirus disease 2019 (COVID-19) has spread over the world and caused almost a decade's worth of lost life expectancy [03].

With the COVID-19 pandemic spreading across the globe, reports of a range of mild to severe mental syndromes, such as headache, anosmia, seizures, encephalitis, coma, and acute cerebrovascular events like ischemic stroke and hemorrhage, among patients infected with SARS-CoV-2 are starting to surface [04]. There have been several instances of central and peripheral neurological disease linked to the infection since the beginning of the epidemic [05]. It indicates that approximately one-third of COVID-19 cases experience neurological symptoms [06]. Scientists are working to learn more about this unique virus's impact on the central nervous system (CNS) and the connection

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between neurological problems and acute respiratory distress in infected people. More recently, they have noticed neurological indications of the virus [07]. Following their release from the intensive care unit and recovery from their respiratory symptoms, patients may be more susceptible to long-term residual neuropsychiatric and neurocognitive disorders, such as depression, obsessive-compulsive disorder, Parkinson's disease, and Alzheimer's disease [08]. Coronaviruses are linked to conditions affecting the central nervous system (CNS), including multiple sclerosis, disseminated encephalomyelitis, convulsions, and epilepsy [09].

2. Impact on Neurological Disorders

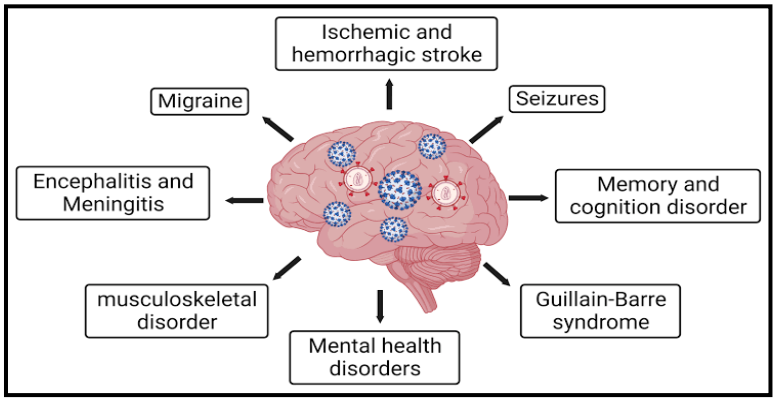

Figure 1 Covid-19 Impact on neurological diseases [09]

2.1. Epilepsy

Chronic epilepsy is a neurological condition with a high frequency and incidence that is frequently accompanied by psychiatric comorbidities [10]. There is no proof that having epilepsy increases your risk of getting COVID-19. It is recommended that neurologists provide guidance to patients, families, and caregivers regarding how to administer emergency treatment to patients and when to bring them to the emergency department in case of seizures [11]. Although there have been case reports of patients with COVID-19 having seizures with no history of epilepsy, it is not clear if this is directly due to SARS-CoV-2 infection or an unmasking of a seizure disorder due to other factors [12].

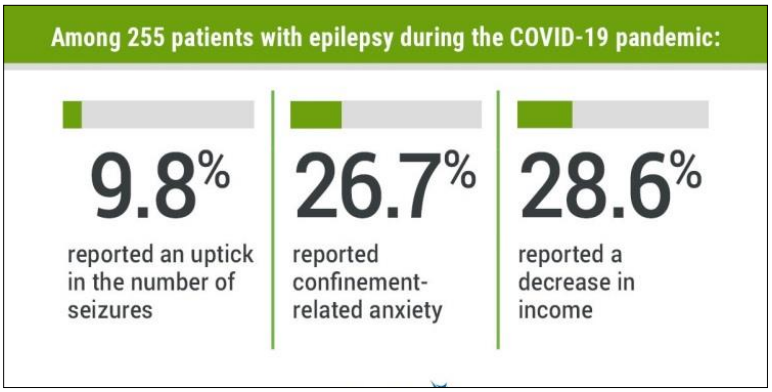

Figure 2 Epilepsy ratio during covid-19 [13]

Individuals who suffer from an underlying seizure disease may be more vulnerable to COVID-19-related breakthrough seizures. While case reports exist of COVID-19 patients experiencing seizures without a prior history of epilepsy, it is unclear if this is a direct result of the SARS-CoV-2 infection, or the seizure disorder being revealed because of other causes [14]. During the COVID-19 pandemic, epilepsy patients (PWE) encountered some significant challenges that require management and clarification. Telemedicine issues, psychological distress, and disruptions in clinical services during visits to medical centers have all been thoroughly researched. Only a small number of research, meanwhile, have examined changes in the frequency of seizures in PWE with COVID-19 infection [13]. Despite mostly causing respiratory symptoms, COVID-19 can also impact other organs, such as the brain, and result in neurological problems. Due to a variety of causes, people with epilepsy (PWE) have been disproportionately affected by the pandemic, experiencing

worsened seizures in up to 22% of cases, increased stress, and restricted access to care [15]. Seizures have been reported to occur in COVID-19 patients in case reports. Individuals may exhibit encephalopathies associated with metabolic disruptions, hypoxia, and renal or hepatic dysfunction because of COVID-19 disease sequelae, or seizures because of viral encephalitis [16].

2.1.1. Diagnosis

To avoid inducing seizures, epileptic patients with COVID-19 (or any other type of feverish sickness) should also be advised to have a low tolerance for using an antipyretic (ideally paracetamol rather than aspirin) [17].

2.2. Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease (AD), with a prevalence of 0.3% in the general population. PD is a highly age-related brain disorder, affecting 1.0% of those over 60 and 3.0% of those over 80 [18]. In patients with complex devices, patients check the battery charge of their deep brain stimulation device and adjust the settings, which can be controlled remotely by their neurologist [19]. The second most prevalent neurodegenerative disease is Parkinson's disease (PD), which is progressive and chronic in nature. Nonmotor symptoms such as dementia, psychosis, and autonomic dysfunction can also be present along with tremors, stiffness, and bradykinesia [20].

It is too early to determine the long-term impact of COVID-19 on patients with Parkinson's disease and movement disorders. Concerns over the possibly elevated risks of COVID-19 in individuals with Parkinson's disease and other movement disorders are raised by the aging population's increasing susceptibility and the prevalence of comorbidities [7]. Parkinson's disease (PD) patients, or at least specific PD populations (e.g., advanced stage), may be at potential risk for severe COVID-19 because both PD patients and reported COVID-19 patients share common characteristics regarding age, comorbidities, and a risk of respiratory dysfunction [21].

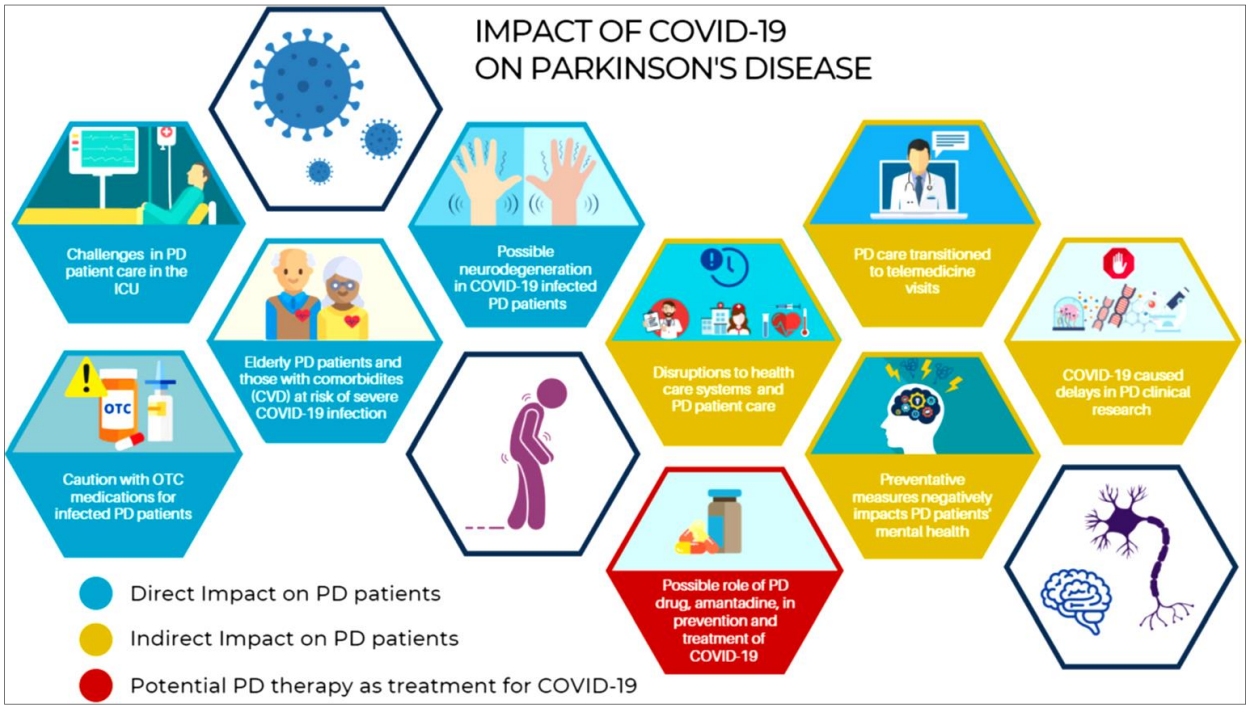

Figure 3 Covid-19 Impact on Parkinson Disease [20]

The unpredictable nature of coronavirus (2019) and its distinct symptoms in (a) respiratory, (b) neurological, (c) cardiovascular, (d) gastrointestinal, and (e) hematological systems have created numerous obstacles for worldwide healthcare systems [22]. Numerous of these investigations have concentrated on the connection between Parkinson's disease (PD) and SARS-CoV-2 and COVID-19. It seems sense that elderly individuals with advanced Parkinson's disease are more susceptible to a sudden respiratory epidemic [19]. Review the relationship between PD and COVID-19 to outline the current state of knowledge and inspire more research considering the global outbreak of COVID-19 cases and the many neurological manifestations of the disease [23].

2.2.1. Diagnosis

Patients with Parkinson's disease are receiving less in-person medical attention result of the COVID-19 epidemic. It is advisable to support digital rehabilitation techniques, such as virtual rehabilitation platforms, as a substitute for providing rehabilitation services at the community level [24]. The problem is exacerbated by the possibility that these individuals are receiving non-oral treatments for advanced Parkinson's disease (PD), such as deep brain stimulation (DBS), intrajejunal levodopa infusion, and subcutaneous apomorphine [25].

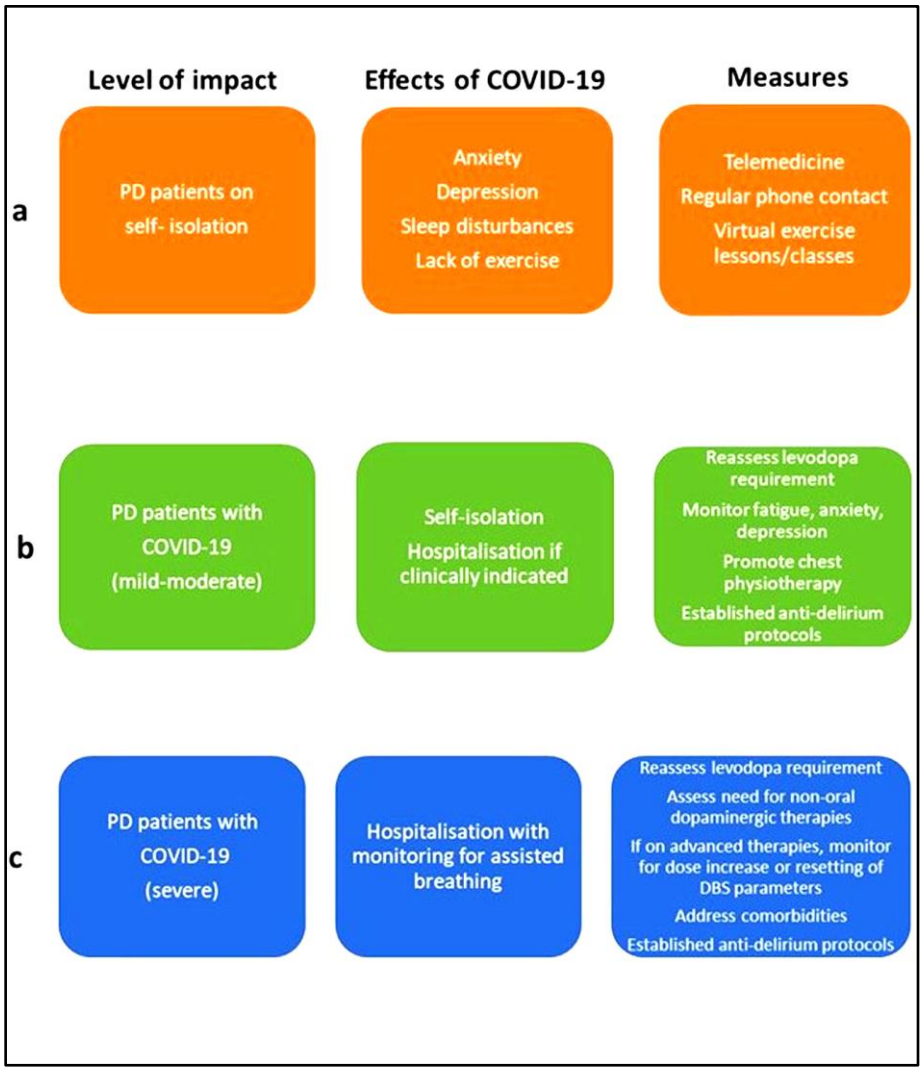

Figure 4 Flowchart identifying potential management issues in Parkinson's disease patients [23]

2.3. Alzheimer's Disease

For dementia, Alzheimer's disease (AD) is the most prevalent type. It is a terminal disease that is degenerative and incurable. While most cases are identified in those over 65, an early-onset variety, which is less common, can manifest considerably earlier [26]. Since Alzheimer's disease (AD) is a well-known degenerative condition that typically affects the elderly, it is unknown if COVID-19 infections in AD patients are likely to progress to severe stages [27]. Lockdowns and social isolation are important ways to stop the COVID-19 virus from spreading, but they may be harmful to the elderly's bodily or emotional well-being [28].

Alzheimer's disease (AD) is a neurodegenerative disease that gradually impairs neurological and cognitive functions [19]. The finding of pathogens such as Chlamydia pneumoniae, Borrelia spirochetes, Helicobacter pylori, and herpes simplex virus (HSV) in the postmortem brain of AD raises questions about the connection between infectious theory and Alzheimer's disease [17]. A "cytokine storm" of intense inflammation is frequently linked to severe outcomes from SARS-CoV-2 infection [29].

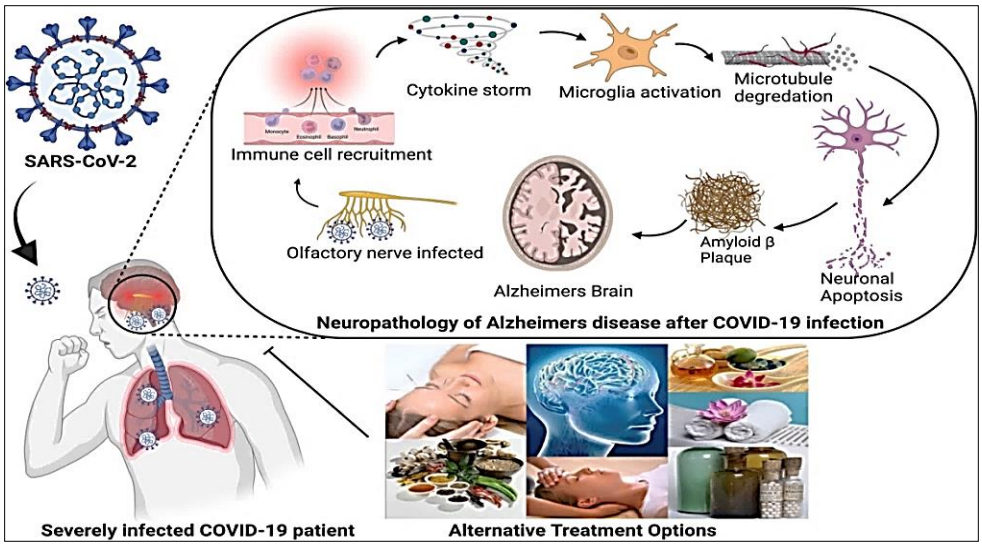

Figure 5 Covid-19 Impact on Alzheimer's disease [24]

Even though majority of AD patients begin to exhibit symptoms in their mid-60s, the disease is not regarded as a normal aspect of aging. In some rare cases, people between the ages of 30 and 60 may experience the symptoms. The Alzheimer's Association estimates that 200,000 Americans under 65 have AD [30]. Staying at home creates a "de-stimulation environment" for AD patients in which further limits their options for social connection, physical activity, and cognitive stimulation [31].

2.3.1. Risk Factors:

- Conjectures, three etiological hypotheses about the development have been described, with moderate to high support, based on epidemiological studies, neuroimaging techniques, and neuropathology research [22].
- Psychological
- Vascular
- Genetic
- The hypothesis, which states that amyloid protein precursor (PP) cleavage or buildup of PP in the brain causes the development of neurotoxic pathogenic oligomers and senile plaques, is one of the most extensively researched theories about AD [6].

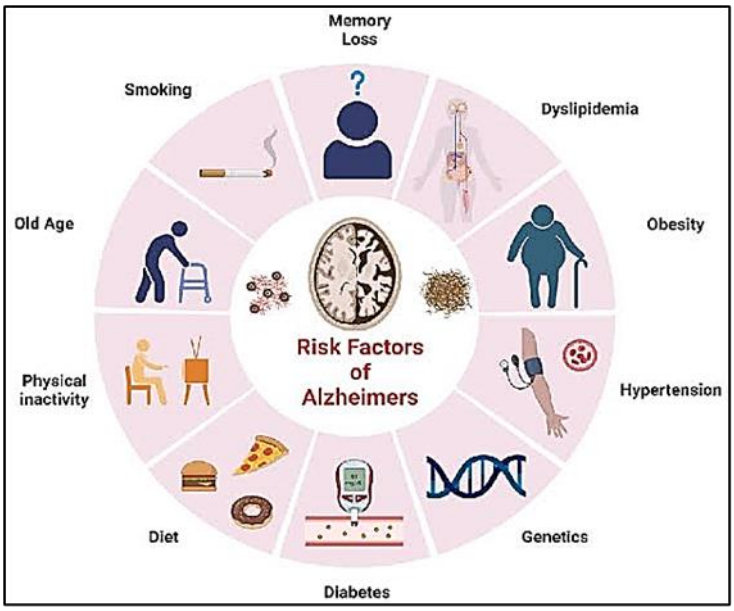

Figure 6 Risk factors of Alzheimer's disease in Covid-19 [22]

2.3.2. Diagnosis

Additionally, there are strategies to lower the likelihood that an elderly COVID-19 patient may get Alzheimer's. First, anti-inflammatory treatment may be administered. Memantine and anticholinesterase inhibitors are commonly used in Alzheimer's patients infected with COVID-19 [32]. In addition, significant difficulty arises in the treatment of hospitalized COVID-19 patients who already have AD or another type of dementia, as prolonged isolation in a single room in an unfamiliar environment without the assistance of family or relatives increases the likelihood of delirium [24]. Frequent exercise is linked to a delay in AD and dementia onset in older adults who do not have cognitive impairment [29]. Crucially, certain anti-PD drugs may be advantageous in the fight against SARS-CoV-2. The Food and Drug Administration (FDA) has authorized amantadine, a PD drug, as a treatment for influenza A virus. Because of its antiviral qualities, it may also be used to treat COVID-19 [38]. In 2019, the estimated annual incidence of AD was 148.1 patients per 100,000 population (95% CI 147.0–149.2), but in 2020, the estimated incidence was 118.4 patients per 100,000 population. The remaining patients were taking combination therapy, with the most prevalent combination being rivastigmine and memantine (266 patients, or 6.8% of the total), followed by donepezil and memantine (216 patients, or 5.4% of the total). Regarding treating Alzheimer's, the combination of galantamine and memantine accounted for 56 cases, or 1.4% of the total [33].

3. Other Neurological Manifestations

While other neurological conditions do not raise the chance of contracting SARS-CoV-2, the treating neurologist should take their morbidity into account [25]. Individuals with migraines, for example, may experience higher morbidity and greater use of medical resources, while individuals with cognitive impairment may find it more difficult to withdraw socially [34]. Shortness of breath, fever, chills, exhaustion, and a severe cough are among the early symptoms of this virus. Hypogeusia and hyposmia are also present, along with neuro invasion by SARS-CoV-2, which causes excruciating headaches, disorientation, and brain fog. Complications with motor movement are also noted [33]. Encephalitis, cerebral venous thrombosis, and ischemic stroke are a few of the cerebrovascular consequences of COVID-19 infection. Multiple sclerosis, headaches, mental confusion, and Guillain-Barre syndrome (GBS) [35].

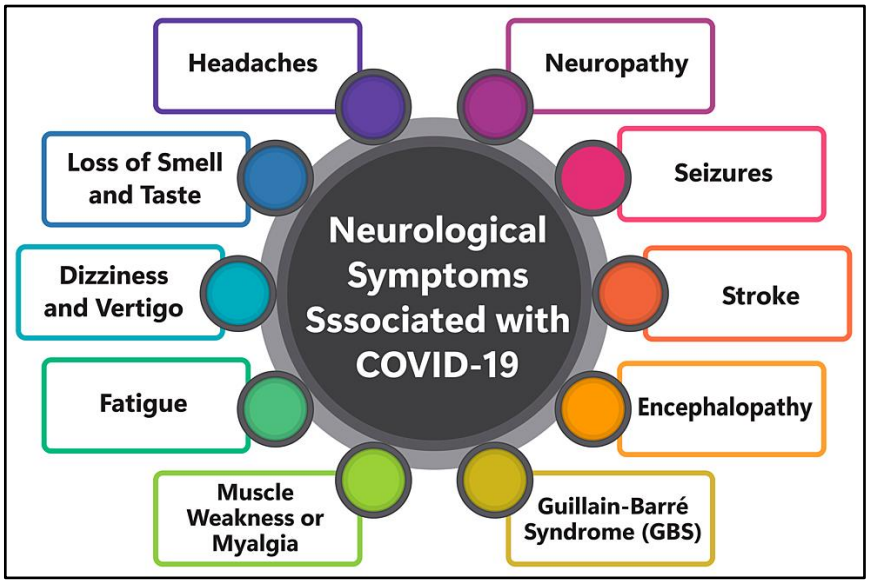

Figure 7 Other Neurological Symptoms in time of COVID-19 infection [21]

The COVID-19 vaccine has number of local and systemic neurological side effects, ranging from minor to severe, according to reports found in the VAERS database. These side effects are contingent upon a person's age, sex, medical history, and level of pre-existing immunity [36]. While majority of COVID-19 infected people do not have any severe side effects that necessitate medical attention, a small percentage do Cerebrovascular events, which cause neurological impairments, are one of the more common severe neurological consequences observed in COVID-19 patients [37].

3.1. Dementia

Dementia encompasses a broad range of conditions marked by widespread, persistent, and typically irreversible cognitive decline. This decline can cause progressive changes in various functions, including memory, orientation,

personality, and behavior, ultimately jeopardizing the individual's autonomy in day-to-day life [18]. Using a magnifying glass, examine the effects of SARS-CoV-2 virus infection on patients suffering from dementia and mobility difficulties [38].

A significant risk of unfavorable outcomes during a COVID-19 infection is dementia, and those with cognitive impairment have a greater mortality rate and more severe clinical symptoms than those without cognitive impairment [34]. More than merely increased mortality is one of the consequences of having COVID-19 in dementia patients as compared to COVID-19 individuals without dementia [27]. Research has also indicated declining clinical outcomes, such as a 30%–50% rise in hospitalization and ICU admission risk among individuals with COVID-19 dementia [40]. Compared to COVID-19 patients without dementia, COVID-19 dementia patients also showed five times higher risks of experiencing early, late, and progressive cognitive deterioration [39].

3.2. Multiple Sclerosis

It is not unexpected that Multiple Sclerosis (MS) may be a population of special interest given the immunological nature of illness and the therapeutic management of disease-modifying treatments (DMTs), which might change immune functioning and hence raise susceptibility of COVID-19 [2].

3.3. Ischemic Stroke

The most prevalent severe neurological condition linked to COVID-19 is stroke, which is more common in older people and men. The range of stroke risk is 0.5% to 1.6% [40]. Between the beginning of COVID-19 symptoms and stroke, the time gap ranged from 1 to 27 days (mostly 6–10) [10]. Furthermore, older, hypertensive, with higher levels of D-dimer and C-reactive protein, and with a more severe clinical course of COVID-19 infection were associated with a higher risk of strokes [41].

When there is an interruption in the blood supply to the brain, a stroke occurs [26]. The most frequent kind of stroke is an ischemic stroke, sometimes referred to as brain or cerebral ischemia, which is brought on by an obstruction in the arteries that surround the brain [35]. Most studies on pandemic-related stroke care found that patients had to wait a long time to begin therapy and had restricted access to interventional treatment alternatives like thrombolysis or thrombectomy [37]. The patients who are young and middle-aged (30–45 years old) are the age group most frequently afflicted by ischemic stroke. One of the main cardiovascular conditions that impair brain function and cause insufficient blood flow to the brain is stroke [42].

3.4. Guillain-Barre Syndrome

Peripheral nerve demyelinating disease (GBS) is a rare immune-mediated condition that typically follows viral infections [3]. Majority of patients had lower extremity weakness and paresthesias when they first had neurological symptoms, which usually appeared five to ten days after the start of viral symptoms [17]. In comparison to the previous year, found a 2.6-fold rise in March–April 2020. Additionally, found that the GBS prevalence was higher in the SARS-CoV-2 positive group (0.15 versus 0.02%) than in the non-SARS-CoV-2 group visiting the emergency department [43].

In roughly 0.4% of COVID-19 patients, Guillain-Barré syndrome (GBS) appears 5–10 days after the virus first appears. Within one to four days, the majority of COVID-19 and GBS patients manifest with increasing limb weakness [37]. Nonetheless, there are increasing instances of GBS in COVID-19 patients. A case series from Italy revealed five incidences of GBS following COVID-19 infection [41]. While there is still uncertainty regarding the recurrence risk of COVID-19 vaccination in patients with a history of GBS, several research findings indicate a safety signal. Only 3.5% of patients had relapsed following immunization, according to research [44].

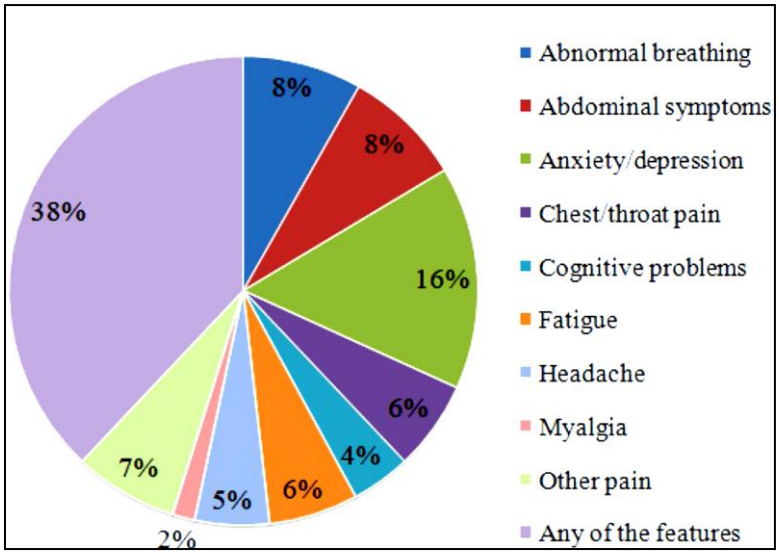

Figure 8% Rate of Patient's in Covid-19 Neurological symptoms [35]

Table 1 Summary of the impact of COVID-19 on chronic neurological conditions and recommendations for their management [37,40,42]

Non-acute neurological condition	**Impact of COVID-19 infection/crisis**	**Recommendations/guidelines for management by professional bodies/health authorities**
Epilepsy	Overrepresentation in LMIC Risk of fever-triggered seizures Possible mobility and cognitive disabilities	Do not cease antiepileptic medications Discussions with physicians about any current immunosuppressants Epilepsy Foundation guidelines
Parkinson's Disease and other movement disorders	Often elderly, vulnerable population Possible bulbar and respiratory issues Cognitive impairments could impact compliance Infections may lead to sudden motor and behavioral changes	Healthcare workers must have knowledge on PD and be prepared for delirium Masks and eye protection should be worn during Botox® procedures
Multiple sclerosis	Reduced availability of services in the COVID-19 crisis Risk due to an immunocompromised state	Guidelines by some Multiple Sclerosis associations released on disease-modifying treatments (DMTs)
Stroke	Residual impairments including dysphagia May be elderly with the comorbid disease Pneumonia risk	FAST protocol Protected-code stroke
Guillain-Barré Syndrome	Possible parainfectious profile Post-infection complication Potential for life-long disability and CIDP Maybe immunosuppressed	GBS and CIDP patients are only deemed at higher risk if on immunosuppressants
Migraine and severe headache	Require frequent outpatient consultations	Use Telemedicine

4. Treatment

The first course of action for a patient suffering with COVID-19 should be bed rest and water consumption order to reduce the danger of dehydration and conserve calories. When a patient has a high fever (more than 38.5 °C), antipyretic medications such as acetaminophen or ibuprofen are advised, as needed [45]. General practitioners (GPs), psychiatrists, geriatricians, internists, and other medical specialists diagnosed a total of 1037 patients (21.8%) [34]. The National Health Commission of China (NHC) has launched number of antiviral medications for the prevention, identification, and management of COVID-19. Interferon α (IFN-α), lopinavir/ritonavir, arbidol, ribavirin, and chloroquine phosphate are the quintessential medications of this type [46].

According to recent studies showing the effects of SARSCOV-2 on different organs, people with COVID-19 are frequently diagnosed with cognitive issues such brain fog and motor movement impairments [47]. SARS-Cov-2 infection and its complications may be more common in patients with neuromuscular disorders (such as myasthenia gravis) and neurodegenerative conditions (such as dementia, Parkinson's disease) [48]. As a result, the pandemic has prompted a swift restructuring of clinical care delivery, incorporating telemedicine and telephonic contacts [40]. Various strategies for the care of individuals with long-term neurological disorders have been investigated globally an effort to preserve patient continuity during COVID-19 [49].

An overview of the overall hazards associated with chronic neurological patients as well as the risk stratification of specific disorders has been made available by the Association of British Neurologists [50]. The primary adverse effects of these therapies on the nervous system should be known to neurologists as the COVID-19 treatment continues to change in response to new evidence of efficacy and clinical studies [51]. The care of these severely ill patients would become challenging, and the fatality rate would rise a few weeks later if the virus was still spreading [46]. A growing body of research indicates that SARS-CoV-2 infection has detrimental effects on the central nervous system (CNS), which may cause neurological and psychiatric symptoms in those who are afflicted [52].

Routine follow-up visits were not possible during lockdown due to safety precautions. Thus, telemedicine plays a critical role in maintaining patient care and preventing symptom exacerbation [36]. The findings revealed that 88.1% of neurologists and 37.6% of PD patients had opted for alternatives to in-person consultations, while 40.5% of neurologists and 13.7% of PD patients had employed telemedicine [53]. Within 14 days of exposure, or if there is a history of contact with suspected or confirmed cases, doctors should inquire with patients and their companions about any characteristic COVID-19 symptoms, such as fever, sore throat, and so on [51]. Prioritizing the adoption of effective bedside delirium prevention and management during the COVID-19 pandemic has been advised [54]. Some locations have tried to alter their treatment plans to lower the chance of developing severe COVID-19. Some of them preferred to utilize other very successful medications, including natalizumab, in place of anti-CD20 treatment while others were successful in using individualize docrelizumab treatment based on B-cell CD19 levels and extended anti-CD20 dose intervals [52].

Table 2 Potential impact of Neuro Disease therapies on COVID-19 clinical course and stratification risk and treatment [48,50,51,].

Medication	**Potential benefit in COVID-19**	**Potential adverse effect in COVID-19**
Interferon β	Reduced viral replication. Inhibition of proinflammatory cytokines	Unknown
Natalizumab	May interfere with SARS CoV-2 host cell entry	Reduced SARS-CoV-2 clearance from the CNS and gut
Dimethyl fumarate	Reduced innate immune response to virus	Lymphopenia-related increased risk of infection and impaired viral clearance
Teriflunomide	Anti-viral effect	Lymphopenia-related increased risk of infection and impaired viral clearance

Hematopoietic stem cell therapy	Unknown	Unknown
Cladribine	Reduced innate immune. response to virus	Lymphopenia-related increased risk of infection and impaired viral clearance
Rituximab/ocrelizumab/ Ofatumumab	Unknown	Increased risk of infection and impaired viral clearance
Glatiramer acetate	Counteract proinflammatory responses	Unknown
Fingolimod/Siponimod/ Ozanimod	Lymphopenia may be beneficial for pneumonia and ARDS	Lymphopenia resulting in reduced viral clearance

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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