

## The Management of Neurological Disease during the COVID-19 Pandemia

### COVID-19 Pandemi Sürecinde Nörolojik Hastalıklara Yaklaşım

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#### ABSTRACT

In this current pandemic period, neurological disorders are the most devastating disease group among all disease groups considered which created the highest health burden for patients, their relatives, and healthcare workers which keeps increasing with aging world population. COVID-19 directly invades lungs, it also involves the nervous system. However, it is too early to know whether COVID-19 will have long-term impacts on patients with neurologic disease. The COVID-19 pandemic has changed people's daily routines, and it all happened in a short period. Neurologists are affected negatively by the COVID-19 pandemic in a few key ways, including: a reduced ability on admission or transfer of critically ill neurologic patients. During these exceptional times, a huge need arose for neurologists in the frontline and expected to be aware of and conscious for diagnosing neurological complications of COVID-19. In this process, the use of telemedicine (teleneurology) in the field of neurology is a significant approach to evaluate patients. Telemedicine has been used as a platform for rehabilitation, neurological examinations, neuropsychology and other specialty services. Management of neurological diseases such as Parkinson disease, multiple sclerosis, intracranial infections, epilepsy, dementia, headache, neuromuscular diseases, and stroke had been affected in this process. In this review article, the main goal is to discuss how the diagnosis, proper management of people with existing neurological disease during pandemia period.

**Key Words:** COVID-19, pandemia, neurology, management, telemedicine

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#### ÖZET

Nörolojik bozukluklar; pandemi döneminde hastalar, yakınları ve sağlık çalışanları için en yüksek sağlık yükünü yaratan hastalık grupları arasındadır ve bu durum yaşanan dünya nüfusu ile birlikte artmaktadır. COVID-19 hastalığı direkt olarak akciğer tutulumu yapmasının yanı sıra, sinir sistemini de etkilemektedir. Ancak, COVID-19'un nörolojik hastalığı olan hastalar üzerinde uzun vadeli etkileri olup olmayacağını bilmek için henüz çok erkendir. COVID-19 salgını, insanların günlük yaşantılarını değiştirdi ve bunların hepsi çok kısa bir sürede içinde gerçekleşti. Nöroloji uzmanları, COVID-19 pandemi sürecinde önemli durumlardan olan kritik nörolojik hastalıkların kabulü ve bu hastaların sevk edilmesi konularında, karar verme konusunda olumsuz yönde etkilendiler. Bu olağanüstü dönemde, nörologların hastalıkla mücadele ve yönetiminde ön safhada yer almaları ve COVID-19'un nörolojik komplikasyonları açısından dikkatli olmaları gerekecektir. Bu dönemde nöroloji alanında teletıpın (telenöroloji) kullanımı, hastaları değerlendirmek için önemli bir yaklaşım olarak gündeme gelmektedir. Teletıp rehabilitasyon, nörolojik muayeneler, nöropsikoloji ve diğer uzmanlık hizmetleri için bir platform olarak kullanılmaktadır. Parkinson hastalığı, multipl skleroz, intrakranial enfeksiyonlar, epilepsi, demans, baş ağrısı, nöromusküler hastalıklar ve inme gibi nörolojik hastalıkların yönetimi bu süreçte etkilenmiştir. Bu makalede COVID-19 döneminde nörolojik hastalığı olan kişilerin tanısı, tedavisi ve yönetimi tartışılmaktadır.

**Anahtar Sözcükler:** COVID-19, pandemi, nöroloji, yönetim, teletıp

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**INTRODUCTION**

While the viral pandemic starting from Wuhan city of China and spreading all over the world which caused by the virus named SARS-CoV-2 and the disease named coronavirus disease 2019 (COVID-19), World Health Organization (WHO) along with all ministries of health worldwide has also being informed about the symptoms of the disease, methods of diagnosis, and treatment approaches for the evaluation of patients with neurological disease or new neurological complaints (1).

The World Federation of Neurology (WFN) (2), the European Academy of Neurology (EAN) (3), The American Academy of Neurology (AAN) (4) and Turkish Neurological Society (5) has published several reports on the neurological findings along with COVID-19 prevention and treatment approaches in neurological diseases that may arise from COVID-19 itself. Older adults are at a significantly increased risk of developing severe disease following SARS-CoV-2 infection. We know that over 95% of these deaths occurred in those older than 60 years. More than 50% of all deaths were reported on people aged 80 years or older. Several papers also reported that 8 out of 10 deaths has occurred in individuals with at least one underlying co-morbidity, in particular those with cardiovascular diseases/hypertension and diabetes, but also with a range of other chronic underlying conditions (6). Especially considering that the group of patients with neurological disease is over 65 years old which generates most affected group by the pandemic, the event may be adversely affected not only in the pandemic period but also in the post-pandemic period. During this period, especially when restrictions on leaving home considered, problems arise in the regulation of the treatment of the patients who previously diagnosed neurological diseases, in the management of patients who wish to consult a doctor with new neurological complaints. How should neurologists manage these issues during a pandemic? In our country, very few number of patients over 60 years of age live in elderly nursing homes unlike other countries, often alone or with their families. The prevalence of neurological diseases is not fully known during the pandemic period, since patients do not go to health centers with the concern of COVID-19 transmission and neurological symptoms are not taken seriously by individuals. In this review article, we shared our experience on approach to the management of patients who already have neurological diseases or newly diagnosed during the pandemic process and present our recommendations on the management of patients with neurological symptoms originating from COVID-19 in the course of the COVID-19 pandemic, which is also important in our country.

Although neurological involvement is rare in patients with COVID-19, neurological manifestations such as acute cerebrovascular diseases, unconsciousness, and encephalopathy may occur in patients with advanced systemic effects of infection (7). The disease may begin with neurological symptoms or the patients may develop neurological complications during treatment. Neurologists can examine patients infected with COVID-19 in the outpatient clinic, the emergency room, and in-patient ward. For this reason, the staff need to wear favourably disposable personal protection equipment such as work caps, surgical masks, work clothes such as scrubs, face shields/goggles, gloves properly, and use hand sanitiser that contains ethanol, hydrogen peroxide or sodium hypochlorite. For patients with neurological symptoms which suspected COVID-19, it is recommended that the patient's evaluation completed on COVID-19 designated clinic and then consult a neurologist. Infected patients may show neurological symptoms initially (8). Another concern for neurologists is the vulnerability of patients with neurological disease when combined with COVID-19. This is also the desirable approach for patients receiving disease-modifying therapies and immunosuppression. Many neurological patients are at risk due to diabetes, heart disease or COPD (chronic obstructive pulmonary disease) among with being old (9). There are no clear data on the outcomes or treatment of patients with pre-existing neurological diseases, and in particular, the effects of immunosuppression (10, 11).

The number of neurologists are not enough to serve the patients with critical illness or chronic disease due to the high number of patients due to COVID-19 pandemics; reduced routine follow-up; risk of individual exposure when neurological diseases are increasing with the aging world population considered.

We know that corona viruses are not primarily neurotropic viruses. The primary targets of the virus are respiratory epithelium. The target receptor for cell binding and subsequent internalization is angiotensin converting enzyme-2 receptor (ACE2). ACE2 receptors are also found in glial cells in the brain and spinal neurons.

For this reason, it can adhere to neuronal tissue and cause damage. As another way, during the viremia stage of the disease, the virus can enter the brain with the breakdown of the blood brain barrier. Another estimated mechanism is the invasion of peripheral nerve terminals by the virus which then gains entry to the CNS through the synapse connected route. Neuropathological mechanism of CNS damage likely by hypoxic brain injury and an immune mediated damage to the CNS. Immune mediated damage is due to the cytokine storms with activation of T lymphocytes and macrophages and endothelial cells, and increased levels of inflammatory cytokines, more release of Interleukins 6 causes vascular leakage, activation of complement and coagulation cascade, disseminated intravascular coagulation and finally end organ damage (12).

The important neurologic manifestations of SARS-CoV-1 associated disease, vary from fairly specific symptoms (eg, loss of sense of smell or taste, myopathy, and ischemic or hemorrhagic stroke, transverse myelitis, acute hemorrhagic necrotizing encephalopathy, ataxia, encephalitis, Guillain Barre syndrome, Miller-Fisher syndrome, neuralgia) to more non-specific symptoms (eg, headache, reduced level of consciousness, dizziness, or seizure, agitation, delirium, confusion, or executive dysfunction (7, 11-22). Neurologists should also keep in mind the potential risks for postinfectious disorders.

Management of neurological diseases such as Parkinson Disease (PD), multiple sclerosis (MS), intracranial infections, epilepsy, dementia, headache, neuromuscular diseases, and stroke is affected in this process. In this review article, it is discussed how the diagnosis, treatment and management of people with existing neurological disease should be during global COVID-19 pandemic period.

**Neurological manifestations of COVID-19**

The neurological manifestations and complications of COVID-19 can be divided into central and peripheral categories. Central nervous system manifestations including headache and encephalopathy, acute cerebrovascular disease related symptoms, intracranial infection related symptoms, peripheral nervous system symptoms and neuromuscular symptoms.

*Stroke*

COVID-19 pandemic has been so large and widespread. However, under such extreme situations, there has been no previous experience that can be used to develop plans for the emergency management of acute stroke treatment. Therefore, the control of the COVID-19 is very important, at the same time the management of stroke must not be neglected (23). Stroke remains a medical emergency even during a pandemic period. Management of the patients with stroke for hyper acute treatments such as thrombolysis and thrombectomy impacts have functional outcomes and mortality. These patients should avoid entering the neurological intensive care unit and be treated in a private room (24). Factors that affect outcomes in patients with stroke can include exposure to in-hospital pathogens; acute treatment, and post stroke care such as rehabilitation. During a pandemic period, stroke protection and provide a framework for key considerations including screening, personal equipment, and crisis resource management. Considerations and suggested algorithms can be utilized and adapted for local practice (25). If acute ischemic stroke patient with suspected or unverified diagnosis of COVID-19 is accepted, neurologists and infectious disease specialists are collectively urgent treatment. In this case, Chest CT shows very high sensitivity for new corona infection findings (> 95%) (26). Although specificity is also important to initiate the procedure, in case of doubt, the patient is treated as COVID-19 positive.

Prophylactic anticoagulated therapy is recommended for ischemic stroke patients with a high D-dimer level. These patients should be transferred to the isolation ward, and neurologists should assist in the management (8). In acute ischemic stroke, the team that will administer IV tPA must use full personal protective equipment and employ maximum compliance with contact safety rules (25, 27). The use of Telestroke must be maximized in the pandemic period because all aspects of acute stroke evaluation can be performed.

*Intracranial Infection*

Some patients infected with COVID-19 have had symptoms similar to those with intracranial infections such as headaches, seizures and impaired consciousness. In some patients, central nervous system symptoms can be observed before pulmonary symptoms are seen. Therefore, neurologists should be alert when viewing COVID-19 infected patients, and patients with suspected status should be performed head MRI with or without contrast should be seen.

It is recommended to search for SARS-CoV-2 nucleic acid using PCR by performing lumbar puncture. Treatment strategies such as reducing cerebral edema, treating and preventing seizures should be considered for these COVID-19 patients with intracranial infection, and guidelines should be followed (8).

#### *Parkinson's Disease and Movement Disorders*

The risk of Parkinson's patients catching COVID-19 is not different from other individuals. However, older adults are at the highest risk of developing a serious case of COVID-19, and since most patients with Parkinson's disease (PD) are typically older, the disease may be severe if the virus is caught. Patients with parkinsonism hospitalized for pneumonia had a lower rate of in-hospital mortality, but the length of hospital stay (28). In addition, patients with PD have a higher risk of intra-hospital complications such as delirium, adverse drug reactions, syncope, aspiration pneumonia, falls and fractures (29). Therefore, strategies to prevent these complications are important.

Increased psychological stress and social isolation due to pandemic may temporarily worsen various motor symptoms in patients (e.g. tremors, freezing of walking or dyskinesia), reducing the effectiveness of dopaminergic drugs. In addition, increased stress can possibly unmask a hidden hypokinetic severe syndrome by consuming its compensatory mechanisms (30). In case of COVID-19 infection, neurologists should ensure that adequate doses of previous PD medications, especially L-dopa, are recommended for any pneumonia in Parkinson's patients, as recommended to avoid stiffness and reduced vital respiratory failure (31).

Self-management strategies that reduce stress, increase coping or increase physical exercise will play an increasing role in PD treatment (30). However, this universal crisis can significantly change the care of patients with PD and other movement disorders towards better acceptance of telemedicine consultations and evaluations (32). In fact, apart from stiffness and postural reflex disorder, many basic features of the disease can be recorded or watched on video by video consultations (33). The International Parkinson's and Movement Disorder Association has developed a step-by-step practical guide on how to apply telemedicine for a motion disorders clinic on its website (34).

#### *Myasthenia Gravis /Lambert-Eaton Myasthenic Syndrome*

Most of our patients with myasthenia gravis (MG) / Lambert-Eaton Myasthenic Syndrome (LEMS) constitute a greater potential risk group for COVID-19 related complications. Patients with myasthenia gravis must comply with hand washing, masking and social distance measures. First of all, patients should not abandon existing drugs without consulting their doctor. In addition, there is no evidence that symptomatic treatments such as pyridostigmine put the patient at any increased risk. Therefore, the treatments they use should not be interrupted unless there are other clinical reasons. Immunosuppressive therapy increases the risk of infections, exacerbation and treatment of the disease or stop the risk of worsening the transition only symptomatic treatment is important. If a patient is stable under immunotherapy, treatment should continue unchanged. There is no evidence that infusion therapies such as intravenous immunoglobulin or plasma exchange increase the risk of COVID-19. However, unless necessary to be seen as an emergency, telehealth visits are recommended to all of our patients. Some of neuromuscular patients use oral steroids (cortisone) or another immunosuppressant drug (e.g. azathioprine, methotrexate, etc.). Since these drugs suppress the immune system, our patients are considered to be at risk for infections. However, in case of discontinuation of the drugs used, the diseases may recur or worsen. There is no information that COVID-19 infection is more severe in patients taking these drugs yet. For this reason, we do not recommend discontinuing or reducing their medication. The decision on whether to initiate a B cell depletion therapy needs to be taken into account in particular, as the risk of viral disease complications is higher, and should be postponed to a later date. When changing or stopping an existing immunosuppressive therapy that carries a potential risk for increasing disease activity and/or MG exacerbation or crisis, people with MG and their MG healthcare providers should consider specific side effects and benefits (35).

#### *Epilepsy*

The effects of COVID-19 on epileptic patients and the prevalence of new epilepsy cases remain uncertain. There is no evidence that the use of seizure medications (also called antiepileptic drugs (AEDs) or antiseizure medications or drugs) increases the risk of coronavirus infection except ACTH, steroids, and immunotherapies.

People with seizures and epilepsy should make sure they take their medication regularly and always as prescribed. The problem is that going to emergency department owing to increased or uncontrollable seizures could expose the patient to coronavirus. Epilepsy foundation does not recommend going to emergency room unless there is a real emergency. It is very important to maintain the control of seizures, besides the prevention of COVID-19. Some societies do not recommend changing AEDs of patients with well-controlled seizures, as seizure exacerbations or status epilepticus may increase the risk of COVID-19 infections (36,37).

#### *Migraine*

Headaches can be a symptom of systemic viral infections and are no exception for COVID-19 (39). The presence of a headache is not helpful for the diagnosis or prognosis of COVID-19 infection, and 8% of patients may have headaches. Headache in COVID-19 infection is likely to be associated with fever and may be related to it (15). Patients with primary headaches, especially migraines, should follow the recommended treatment and pay attention to dietary triggers, especially alcohol consumption, which can be increased under isolation. Maintaining regular sleep and eating habits and managing stress is important because they are common migraine triggers. Under social isolation conditions, anxiety and depression disorder can worsen and adversely affect chronic headaches and excessive drug use. Medication intake for acute treatment for migraine should be limited to less than twice a week. According to treatment guidelines, NSAIDs, especially ibuprofen, naproxen, diclofenac, has proven efficacy and safety in clinical trials of the symptomatic treatment of migraine and is therefore recommended for acute treatment. In addition, indomethacin is the only treatment available for some Trigeminal autonomic cephal(al)gias (TACs). In general, NSAIDs have great therapeutic value in headaches. FDA has new recommendations for the use of NSAIDs (38,39).

Neurologists are working to keep individuals with migraine out of the emergency department and hospital, while also foregoing or at least minimizing face-to-face visits and procedural treatments. Moreover, telehealth provides an important opportunity to continue to care for vulnerable population and, help avoid urgent care visits that put patients at risk and burden the over-whelmed healthcare system (38).

#### *Alzheimer's disease and related dementias*

Patients Alzheimer's disease and related dementias (AD/ADRD) are among the patients with which this virus can be transmitted. These patients are at greater risk than the rest of the society because they have many additional diseases such as diabetes and high blood pressure and are mostly of advanced age. Due to the risk of Covid-19 contamination, patients should not apply to the hospital for check-up or report renewal and prescribing, except for new neurological complaints and urgent reasons (shortness of breath, high fever, chest and abdominal pain, and so on). Therefore, patients, except for complaints that may be, and bringing them to the hospital for reasons such as routine check-ups or renewing reports increase the risk of virus transmission. COVID-19 pandemic further exacerbates AD/ADRD patient's vulnerability, due to both the morbidity and mortality from COVID-19. The indirect effects of the pandemic on the social supports and the health care system on which they depend. Initiating a new medication during the pandemic may be associated with higher risk, especially if components of routine screening are disrupted such as in-person clinical assessments, blood work, or electrocardiogram, or the ability to follow up on adverse events just in time (40).

Symptoms of dementia, such as motor agitation, wandering, or intrusiveness may undermine efforts to maintain isolation (41). Creative ideas to incorporate alternative social physical activities safely within the home are needed. The pandemic and its consequences may also be experienced as a trauma, followed by post-traumatic stress disorder (42). Stress and trauma can accelerate cognitive deterioration (43). Whereby people are turning to technology to stay socially connected and access areas including health care. Some individuals with AD/ADRD may have trouble using technology due to cognitive impairment. They may need instruction and support to use these tools.

The COVID-19 pandemic crisis may facilitate the development of non-pharmacological interventions that can be delivered at the home of the participants or that use small portable devices that can be easily used in private homes (44).

**Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder**

People with multiple sclerosis (MS) are at increased risk COVID-19 or may be develop severe COVID-19. If there is something clearly that, any decision to start a disease modifying therapy (DMT) during the COVID-19 pandemic will need to be taken carefully. Patients have active MS they need to be treated based on the clinical evidence and hence may need to be treated with higher efficacy DMTs. When treatment is delayed and deescalated therapy by switching to immunomodulatory DMTs, such as interferon- beta, glatiramer acetate or teriflunomide, or interrupting dosing of DMTs to wait for a vaccine will delay the adequate treatment of MS (45).

Some patients treated their MS and controlled may be more important than the potential danger of being exposed to and acquiring a more severe COVID-19 infection. Therefore, treatment should be individualized and discussed with patients. For instance, both cladribine and anti-CD20 therapies are relatively safe to use during the COVID-19 pandemic based on their profiles defined in phase 3 trials. Patients on sphingosine 1-phosphate receptor modulators should be at relatively low risk of complications from COVID-19 infection and why it may be safe to continue these treatments during the pandemic (46).

People with MS and related disorders should be advised not to make changes to their MS treatment without discussion with their neurologist. MS relapses are frequently treated with a short-course of high-dose intravenous methylprednisolone. During the COVID-19 pandemic, neurologists should take into consider having a higher threshold for offering steroid treatment. Patients should be carefully evaluated for symptoms of active COVID-19 infection before receiving corticosteroid treatment. It is safe to initiate treatment with interferon, and glatiramer acetate. High-efficacy treatment is required for patients with severe, or breakthrough disease then starting or switching to natalizumab is preferable to alemtuzumab, cladribine or ocrelizumab. Because of the systemic immunosuppression risk is lower and prolonged lymphocyte depletion does not occur. Some immunotherapies may increase the risk of more severe infection and taking into account the immunosuppressive effects of the treatment, as well as other patient factors (e.g. age, physical disability, comorbidities) (47).

Management of NMOSD patients without COVID-19 infection relapses in patients with NMOSD may be devastating. Patients should be provided to continue their attack prevention treatments such as corticosteroids, azathioprine, mycophenolate mofetil, rituximab, tocilizumab and eculizumab. Moderate dose corticosteroids can be used to prevent relapses in a short time, as clinical needs to stop or delay treatment in patients with NMOSD (47).

**A Special Role of Telemedicine During the COVID-19 Pandemic**

Recently, it has been aimed to avoid unnecessary hospital visits of patients by using telemedicine in the COVID- 19 period. It is known that telemedicine has previously been validated as a tool for assessing disability in MS. It is preferable to make the visits of MS patients through telemedicine or telephone due to the risks during the pandemic period (48). Telemedicine within neurology (teleneurology) is growing as an approach for evaluating patients (e.g. stroke, Parkinson's disease, MS and epilepsy). It has been used as a platform for rehabilitation, neurological examinations, neuropsychology and other speciality services. Telemedicine provides doctors' consultation by keeping patients away from the crowd. Thus, prevents the spread of COVID-19 among patients (49).

As a result, COVID-19 is a highly contagious disease that has become a worldwide pandemic. Infected patients may show neurological symptoms in the early stages. Neurologists should pay close attention to these symptoms and have a high index of suspicion when evaluating patients in an endemic region. However, this global pandemic could deliver an advantage of screening and evaluating for remote learning and supporting processes including all health-care workers among with neurologists and promise a faster organization skill for national health-care services.

**Conflict of interest**

No conflict of interest was declared by the authors.

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