

Neurological implications of SARS-CoV-2 infection: review of literature

Implicações neurológicas da infecção por SARS-CoV-2: revisão da literatura

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ABSTRACT

The infection caused by the new coronavirus had its first case described in December 2019, in Wuhan, China, and reached a pandemic status in March 2020. Since then, knowledge about the different aspects of this infection has evolved, as well as increased reports concerning related neurological manifestations. Thus, the neurologist assumes a fundamental role in the care of these patients, who may have a clinical phenotype that goes beyond respiratory aspects. In the present study, we highlight the data available in the literature so far regarding the main neurological implications related to COVID-19 infection, in addition to calling attention for some aspects related to patients with previous neurological diseases who contract this infection.

Keywords: coronavirus, infection, neurology.

RESUMO

A infecção causada pelo novo Coronavírus teve seu primeiro caso descrito em dezembro de 2019, em Wuhan, China e alcançou o status de pandemia em março de 2020. Desde então, o conhecimento sobre os diferentes aspectos da referida infecção evoluiu assim como aumentam relatos de manifestações neurológicas relacionadas. Assim, o neurologista assume papel fundamental na assistência desses pacientes, que podem ter um fenótipo clínico que ultrapassa os aspectos respiratórios. No presente estudo, destacamos os dados disponíveis na literatura até o presente momento no tocante às principais implicações neurológicas relacionadas à infecção pelo COVID-19, além de destacar alguns aspectos relativos aos pacientes com doenças neurológicas prévias que contraem a referida infecção.

Palavras-chave: coronavirus, infecção, neurologia

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INTRODUCTION

It has now been over 5 months since the first recognized case of Coronavirus Disease 19 (COVID-19) in Wuhan, China and almost 3 months since the World Health Organization (WHO) categorized this outbreak as a pandemic¹ - which grew to become one of the most devastating public health and economic crisis.

Following exposure to the new coronavirus named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), with an incubation period of approximately 14 days, symptoms similar to the common cold virus (e.g. fever, cough, myalgia, fatigue) ensue, with several degrees of anosmia and altered sense of taste frequently reported². Some patients, for reasons still not known, will remain asymptomatic, nevertheless shedding virus and spreading the disease³.

On the other hand, some patients will progress to more severe and critical conditions, developing viral pneumonia that can lead to severe acute respiratory syndrome (SARS) and require mechanical ventilation⁴.

In Brazil alone, to this day, the death toll is at 20.000 deaths (still rising)⁵ and reports of several systemic complications, such as cardiovascular/thromboembolic

events^{6,7}, acute kidney failure⁸, among others, are emerging around the world.

Here, we focus on the neurological aspects of COVID-19 and its complications reported to date.

EPIDEMIOLOGY

The new coronavirus originated in China in December 2019. In March 2020, the infection caused by this virus was classified as a pandemic and in April it already affected more than 2.3 million people with approximately 162,000 fatal cases⁹.

Neurological manifestations are more common in severe cases and can be central such as headache, encephalopathy, dizziness and peripheral ones such as hyposmia and hypogeusia. These were the most common manifestations described so far. Other manifestations and complications are described in Table 1⁹.

In a retrospective study conducted by Mao et al. involving 214 SARS-CoV2 patients, the average age of the affected patients was 52.7 years, 40.7% were men, 58.9 had non-severe infection and 36.4 had neurological symptoms¹⁰.

Table 1: Main Neurological manifestations and complications of COVID-19 infection⁹

CENTRAL NERVOUS SYSTEM	PRIPHERAL NERVOUS SYSTEM
Dizziness	Hypogeusia
Headache	Hyposmia
Acute cerebrovascular disease	Neuralgia
Impaired consciousness	
Transverse myelitis	
Acute hemorrhagic necrotizing encephalopathy	
Encephalopathy	
Encephalitis	
Epilepsy	
Ataxia	

Adapted from: Ahmed I, Rathore FA.9

PATHOPHYSIOLOGY

The pathophysiology of the symptoms and neurological complications associated with SARS-CoV-2 is not completely known^{9,11}. As there are not enough experimental studies on COVID-19, it is believed that this virus behaves similarly to the Severe Acute Respiratory Syndrome and Middle East Respiratory (SARS-MERS) syndrome since it arose from a mutation of this virus. The target receptor, with which the virus binds and is internalized in the cell, is the angiotensin converting enzyme-2 receptor (ACE 2). Once inside the cell, the

viral RNA is released into the cell cytoplasm, translated, replicated and, after the formation of the protein envelope, the virus is released into the bloodstream. ACE 2 is found in the glial cells of the brain and medullary nerves⁹.

It is postulated that the virus spreads to the nervous system in four ways: nasopharyngeal epithelium, lung, blood circulation and peripheral nerve. From the nasopharyngeal epithelium, dissemination occurs to the olfactory nerve, olfactory bulb and then to the brain and brainstem^{9,11}.

Another hypothesis involves the high viral load in the airways and dissemination through the vagus nerve to the

dorsal nucleus from this nerve justifying the dysautonomic signs (nausea, vomiting, diarrhea, heart rate and breathing) involved in the infection. The third hypothesis is that the virus can spread through the bloodstream through the blood-brain barrier³. A fourth entry mechanism occurs through the peripheral nerve endings⁹. The nerve dissemination is facilitated by proteins known as kinesin e dinein¹².

Once inside the body, damage to the nervous system occurs as a result of cerebral hypoxia and / or immune damage. Cerebral hypoxia can occur as a consequence of pulmonary involvement that leads to a systemic reduction of circulating oxygen. As a result of anaerobic metabolism there is formation and accumulation of toxic metabolites causing malfunction and cerebral edema. The immune system imbalance caused by the viral presence also contributes to the malfunction of the nervous system. The unregulated production of inflammatory cytokines, activation of T lymphocytes, macrophages and endothelial cells play an important role in the neurological consequences. One of the cytokines involved is interleukin 6, which causes vascular leakage, complement activation, disseminated intravascular coagulation and organic damage^{9,13}.

After the initial understanding of these mechanisms, some of the neurological manifestations resulting from COVID-19 infection will be described below.

NEUROLOGICAL COMPLICATIONS ASSOCIATED WITH COVID-19:

General aspects

Using SARS and MERS as examples, the literature review does not suggest that these coronaviruses are direct causes of neurological complications. The associated cases described were neuromyopathy of the critical patient, Guillain-Barré syndrome and strokes, the latter attributed to hypercoagulability, vasculitis and/ or sepsis^{14,15}. Despite this, there is pathological evidence through autopsy studies on the presence of coronavirus in the brain, but at much lower levels than in the lungs¹⁶.

In this context, a recent retrospective study with 214 patients from Wuhan, China showed neurological complications in 78 (36.4%) of them. Neurological symptoms described were specially headache and impaired consciousness, six patients had cerebrovascular disease (ischemic/hemorrhagic), 23 patients had "muscle damage", defined by elevated levels of creatine phosphokinase (CPK); other findings described were

ataxia, seizures, hyposmia, hypogeusia and neuralgias¹⁷. These data suggested that patients with more severe systemic presentations were more likely to have neurologic findings, in comparison with those with milder forms of the infection, such as acute cerebrovascular diseases (5.7 % vs. 0.8 %), impaired consciousness (14.8 % vs. 2.4 %) and skeletal muscle injury (19.3 % vs. 4.8 %)¹⁸.

Considering the aspects described above, we will expose two representatives of the possible neurological complications described in the literature in association with infection by COVID-19: Guillain-Barré syndrome (GBS) and cerebrovascular diseases, besides other neurological manifestations.

Guillain-Barré syndrome

GBS is an acute immune-mediated disease of the peripheral nerves and roots (polyradiculoneuropathy) that is usually elicited by various infections in 60% cases, most frequently with gastrointestinal or respiratory symptoms^{19,20}. During the pandemic COVID-19, GBS has been reported in several countries around the globe^{21,22,23}.

The first case of COVID-19 and GBS has been described in Shanghai, China. A 61-year-old woman, who had returned from a trip to Wuhan, developed severe fatigue, acute weakness and areflexia.

Fever and respiratory symptoms developed 7 days after the neurological symptoms, when the chest computed tomography showed ground-glass opacities in both lungs and the oropharyngeal swabs were positive for SARS-CoV-2 on RT-PCR assay. Cerebrospinal fluid (CSF) testing (day 4) showed an increased protein level. Nerve conduction studies (day 5) showed a demyelinating neuropathy. She was treated with intravenous immunoglobulin (IVIG), with good recovery²².

It was still uncertain whether COVID-19 was really the cause of the syndrome²¹. Could GBS associated with SARS-CoV-2 follow the pattern of a parainfectious profile, rather than the classic post-infectious profile, as reported in GBS associated with Zika virus? Ottaviani et al. had the same question while reporting a case with early onset of neurological symptoms²⁰.

nating pattern, with a chronology undoubtedly in favor of a complication of COVID-19 infection in Paris²⁴. The same pattern was reported by Galán et al. in Madrid²⁵.

In northern Italy, from February 28 through March 21, 2020, it was reported five patients with GBS after coronavirus symptoms. Neurological symptoms started after

5 to 10 days. Four patients began with lower-limb weakness and paresthesia and one patient had facial diplegia followed by ataxia and paresthesia. None of the patients had dysautonomic features²¹. On CSF analysis the RT-PCR for COVID-19 was negative in all patients. Two patients had a normal protein level (3 to 10 days). On electromyography, the findings were generally consistent with an axonal variant of GBS in three patients and with a demyelinating process in two patients¹⁹. Magnetic resonance imaging, with gadolinium, showed enhancement of the caudal nerve roots in two patients, enhancement of the facial nerve in one patient, and was normal in two patients. Patients were treated with IVIG; two received a second course of IVIG and one had plasma exchange²¹.

Sedaghat et al. reported a case of acute progressive symmetric ascending quadriparesis associated with bilateral facial paresis. COVID-19 was diagnosed two weeks before. Electrodiagnostic findings were consistent with acute motor-sensory axonal neuropathy¹⁹.

Two cases in Madrid highlight the rare occurrence of Miller-Fisher syndrome and cranial polyneuritis during the pandemic. The first patient presented 5 days after COVID-19 symptoms, with anosmia, ageusia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, areflexia, albuminocytologic dissociation and positive testing for GD1b-IgG antibodies. The second patient presented ageusia, bilateral abducens palsy, areflexia and albuminocytologic dissociation²³.

Another clinical picture was observed in a 61 year old male after 10 days of COVID-19 pneumonia. He had bilateral facial nerve palsy, without another neurological symptoms. CSF demonstrated mildly elevated levels of proteins (44 mg/dL). He was treated with low dose oral prednisone with good recovery²⁶. Isolated facial diplegia is a rare variant of GBS with only few cases described so far²⁷.

Scheidl et al. described a case with typical GBS clinical and electrophysiological manifestations with positive PCR for SARS-CoV-2, in a patient that had only transient loss of smell and taste three weeks prior to onset of the neurological symptoms. It shows that there is no connection between the severity of the respiratory syndrome and further neurological phenotype²⁸.

In COVID-19 scenario, GBS should be distinguished from critical illness neuropathy and myopathy, which tends to appear later in the course of critical illness^{21,29}.

In summary, GBS is associated with COVID-19 infection. Involvement of cranial nerves is common, with a case report of exclusive facial palsy. CSF PCR has been negative in all reported cases to date. The electrophysiological pattern is variable. Mild initial symptoms of COVID-19 do not rule out the possibility of severe neurological complications. The treatment of choice was intravenous human immunoglobulin. Cases of GBS may be underestimated by the difficulty of evaluating these patients due to sedation, isolation and absence of neurologists in intensive care units, causing a possible worse prognosis.

CEREBROVASCULAR DISEASES

Epidemiology

Cerebrovascular diseases are one of the most important neurological complications of COVID-19. In fact, stroke may be the clinical presentation of the disease. In one Chinese study, ischemic stroke occurred in 3% of the patients with COVID19 and it was more common in those with severe infection¹⁰. Hemorrhagic strokes and cerebral venous thrombosis are far less common than ischemic strokes, but some cases have been reported^{30, 31}.

Mechanisms

Many patients with COVID-19 have cerebral ischemia secondary to classical mechanisms, e.g. atherosclerosis, atrial fibrillation. However, ischemic stroke was reported in COVID-19 patients without vascular risk factors³². Three main mechanisms appear to be responsible for the occurrence of ischemic strokes in COVID-19: a hypercoagulable state, vasculitis and cardiomyopathy³³. The SARS-CoV2 evokes a systemic inflammatory response, with the production of proinflammatory cytokines (cytokine storm) that manifests as elevated levels of inflammatory biomarkers (interleukin-6, ferritin, lactate dehydrogenase, D-dimer). It also produces an acquired hypercoagulable state with hyperviscosity and the production of antiphospholipid antibodies that predisposes to venous and arterial thrombosis. The coronavirus surface spike protein binds to ACE2 receptor on human vascular endothelial cells and smooth muscle, invades the host cells and causes vasculitis, that may lead to symptomatic cerebrovascular occlusion (ischemic stroke) or rupture (hemorrhagic stroke), or a coronary vasculitis resulting in acute coronary syndrome and subsequent cardioembolic ischemic stroke. Finally, cardiac involvement may be caused by direct invasion by the virus, causing a myocarditis, with resultant

injury and even death of cardiomyocytes.

Prognosis

A study performed in Lombardy, Italy, compared the characteristics of 43 patients with COVID-19 related stroke with 68 patients with stroke but without COVID-19³⁴. Interestingly, the distribution between transient ischemic attacks, ischemic and hemorrhagic stroke was similar within groups, as well as vascular risk factors. However, the outcome was worse in patients with COVID-19 related stroke than in those with stroke but without COVID-19. It is not clear if the worse outcome is due to the pulmonary disease or to different stroke characteristics, such as subtype or size.

Therapy

The COVID-19 should not change the indications for acute ischemic stroke reperfusion therapies. In eligible patients for intravenous thrombolysis and/or mechanical thrombectomy usual care should be performed according to local/regional protocols³⁵.

Stroke patients with common initial symptoms of COVID-19 (fever, cough, dyspnea, anosmia, etc), those enzyme receptor, also located in the glia and neurons (2). As far as a potential target for the virus, the literature shows that neurological manifestations are present in more advanced or severe cases of the disease, probably due to hypoxemia or encephalopathy and in selected cases encephalitis^{38,39}. Despite seizure threshold reduction in infected patients is not describe a recent paper showed a case SARS-CoV-2 infection with the first clinical presentation through focal status epilepticus in an elderly patient with previous structural epilepsy and more data is need⁴⁰.

Treatment is another crucial matter in the association of SARS-CoV-2 infection and epilepsy. Symptomatic medications for respiratory tract infections, like pseudoephedrine, are contraindicated in patients with epilepsy, and they need to avoid that. Regarding medications proposed for the treatment of SARS-CoV-2, we must pay attention to pharmacodynamic interactions between the several drugs and also be aware of the summation of adverse effects between them⁴¹. A brief consideration of these interactions with the most commonly used anti-seizure drugs (ASDs) is described as follows.

- **Chloroquine/hydroxychloroquine**

There is no known interaction with chloroquine and the

who had contact with a confirmed case during the previous 14 days and those unable answer screening questions, should be considered a suspected case of COVID-19. Guidelines recommend proceeding with usual COVID-19 safety precautions until the screening can be reliably completed or infection had been excluded by formal testing³⁵.

A hypothetical consideration is that perhaps DOACs (which target only one clotting factor) might be less effective than heparin or warfarin, which targets many clotting factors³⁶.

PATIENTS WITH PREVIOUS NEUROLOGICAL DISORDERS

Another area of concern for neurologists is the vulnerability of patients with pre-existing neurological diseases. There are still no clear data on outcomes in patients with underlying neurological conditions, as well as the impact of their treatments in the context of COVID-19 infection.

We highlight below the aspects of COVID-19 infection in patients with the following previous neurological conditions: epilepsy, central nervous system (CNS) demyelinating disorders and neuromuscular disorders.

Epilepsy

Epilepsy is a prevalent chronic condition, and the susceptibility of this population in times of pandemic by SARS-CoV-2 is an apprehension. We must consider the possible consequences of the infection and create strategies to keep them safe during the interruption of clinical services.

There is no evidence that epilepsy would increase the risk of contamination by SARS-CoV-2 or that the infection would evolve more seriously³⁷. However, we must not forget that people with epilepsy may have associated comorbidities, including asthma, cardiovascular disease, being elderly, or immune-deficiency that increase their risk. Within this context, patients with autoimmune epilepsies like Rasmussen's Encephalitis need more attention due to the risk of infection by the use of immunosuppressive drugs. Epileptic syndromes in which fever and infection would be an important trigger like Dravet's Syndrome is another critical issue; however, there is no evidence that this occurs³⁷.

Considering the neurological consequences of SARS-CoV-2, as previously seen, the virus penetrates the host through the binding of the angiotensin-converting 2

main ASDs. However, due to the risk of arrhythmias, it is recommended to avoid the associating of ASDs with the same potential risk, especially some sodium channel blockers⁴².

- **Lopinavir / Ritonavir**

Carbamazepine, phenytoin, phenobarbital, primidone, and valproic acid reduce the serum levels of these antivirals. Besides that, there is an increase in blood levels of carbamazepine, cannabidiol, clonazepam and clobazam and a reduction of lamotrigine, phenobarbital, primidone for them⁴².

- **Ribavirin**

There are no reported drug interactions, but the intravenous route can cause seizures⁴².

- **Remdesivir**

It is not yet approved for clinical use by regulatory agencies, so there is little information about drug interactions.

- **Tocilizumab**

There are also no reports of interactions with ASDs.

Finally, patients should be away from health services as much as possible due to the higher risk of contamination and overload the system. Therefore, it is essential to organize a home seizure rescue program and the hospitalization only in cases of prolonged seizures, longer than 5 minutes or in a cluster, trauma, and seizures in the water.

Psychiatric comorbidities are very frequent in people with epilepsy, and keeping them oriented helps to reduce anxiety and fear.

CNS DEMYELINATING DISORDERS

The current pandemic of COVID-19 is leading people with autoimmune diseases, especially those undergoing immunomodulatory or immunosuppressive treatment, to question whether their bodies are competent to deal with a possible infection with this dreaded virus. The same panorama is present when we talk about patients with multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD).

People with MS or NMOSD should follow the same preventive recommendations as the general population, which is already so widespread, and be educated to be aware of possible symptoms. In general, they must maintain good hygiene, avoid crowding, restrict interper-

sonal contact and unnecessary travel. Masks must be used if the patient is in the window of a high potency immunosuppressive treatment, or according to local health authorities' recommendations^{43,44}.

We have no data, so far, that simply having these diseases is a risk factor for contamination by COVID-19⁴⁴. However, people with mobility limitations are known to be at higher risk for more severe respiratory syndromes, regardless of the causative agent, and should pay extra attention to preventive measures. As well as elderly patients and with other comorbidities, such as hypertension, diabetes, heart disease, obesity, among others^{43,44}.

Another major worry concerns immunomodulatory and immunosuppressive treatments. In general, the recommendation in demyelinating diseases is: maintain treatment regularly, regardless of which one it is^{43,44,45,46}. One-off cases may require temporary interruption, or postponement, but the decision is always made in consensus of the neurologist with the patient. If you are going to start a new therapy in this period, discuss it openly with your patient about the best options within the current context^{43,44,46}. Even with all care, our patients are subject to developing COVID-19 infection. In this context, the temporary suspension of the medication in use may even be considered, depending on the severity of it, or which drug is in use^{43,45,46}.

Some points are worth mentioning in relation to the treatments available in our country:

- Interferon-beta, glatiramer acetate, teriflunomide and dimethyl fumarate do not significantly increase risk of infection, as these drugs do not suppress the immune system when monitoring is done correctly. Greater care and immediate contact with the neurologist is recommended for patients who are using dimethyl fumarate and have a significant decrease in the number of lymphocytes^{43,45,46}.
- In case of treatment with natalizumab, keep it normally, despite being a medicine with a powerful influence on the immune system, its action is directed to the central nervous system, and not to the lungs and airways. As COVID-19 does not seem to predominantly affect the central nervous system, a topic still under investigation, the use of natalizumab can be considered carefully at the moment. Extended doses regimen may be considered in some cases^{43,45,46}.

- Fingolimod can increase the chances of the patient having a viral infection, however, interrupting the treatment can lead to a rebound of the disease, thus expanding the attention to preventive measures and making social isolation. Similar to dimethyl fumarate, greater care and immediate contact with the neurologist is recommended for patients who have a significant decrease in the number of lymphocytes^{43,45,46}.
- Alemtuzumab, mitoxantrone and possibly cladribine: so-called immune reconstitution therapies would be the most at risk, especially during lymphocyte depletion. For this reason, the precautions related to preventive measures must be redoubled at this time, and additional measures can be discussed with your patient, such as be temporarily away from your activities. However, after the lymphocyte count returns to normal, the risk of viral infections is likely to be similar to the general population. In this context, cladribine has an advantage, due to a less marked depletion of T lymphocytes^{43,45,46}.
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- Ocrelizumab and Rituximab, anti-CD20 therapies, have less impact on T lymphocytes, therefore not being associated with serious viral infections; however there is an increased risk of contracting certain infections, predominantly mild to moderate^{43,45,46}.
- Azathioprine, mycophenolate and continuous oral prednisone, in doses above 20mg per day: because of being immunosuppressive medications, they can increase the risk or severity of viral infections. However, the abrupt interruption of its use or dose reduction can lead to a reactivation of the disease, therefore, another situation in which preventive measures must be intensified^{43,45}.

Last, but not least, at this period, in case of a relapse occurrence, one should consider risk versus benefits of intravenous pulse therapy. Still first you must discard pseudo-relapse due to a possible infection. Oral corticosteroid pulse therapy may be an alternative, with proper guidance from the specialist^{43,45,46}.

NEUROMUSCULAR DISORDERS (NMD)

The literature is scarce on neuromuscular complications associated with coronavirus infections, including

COVID-19. It is possible that neuromuscular complications (NM) occurred in previous coronavirus infections, but were masked by the systemic manifestations of the infections.

The risks of severity related to COVID-19 infection in patients with NMD will vary according to some factors, including: type of NMD (including specific phenotype), age of the patient, associated comorbidities and use of immunosuppressants²⁹. Thus, the risk assessment must be done with an individualized approach, remembering that in patients with bulbar/respiratory involvement, autonomic dysfunction, musculoskeletal deformities (scoliosis), for example, the risks will be greater (Table 2). Regardless of the risk estimate, all patients and their caregivers should be guided and encouraged to practice measures to reduce contagion, such as social distancing, handwashing and, preferably, stricter isolation in patients who are most at risk.

Table 2: Factors increasing risk of contracting COVID-19 or having more severe disease²⁹.

1) Immunosuppression with multiple agents
2) Additional factors:
High doses of immunosuppressive therapy of cell/antibody-depleting therapies.
Multiple immunosuppressive therapies, concurrently or sequentially.
Highly active immune-mediated neuromuscular disease.
Bulbar involvement.
Respiratory muscle weakness
Musculoskeletal deformities (scoliosis).
3) Other medical comorbidities:
Pulmonary disease.
Renal disease.
Liver disease.
Diabetes mellitus.
Older age.
Ischemic heart disease

Adapted from: Guidon AC, Amato AA.²⁹

Initially, during the pandemic, we need to be vigilant for NM complications that may, directly or indirectly, be related to the infection. We can stratify the potential neurological complications related to COVID-19 infection in patients with NMD in 4 groups²⁹:

- Risk of infection to cause neuromuscular disease (GBS, myositis, among others).
- Risk of infection exacerbating previous neuromuscular disease, especially autoimmune and neurodegenerative ones.
- Risk related to immunosuppressive and/or immunomodulatory therapies in patients with autoimmune/immune mediated neuromuscular diseases.
- Risk of therapies used for COVID-19 infection (chloroquine and hydroxychloroquine can cause toxic neuropathy and myopathy).

Risk of infection to cause neuromuscular disease

So far, we have no evidence of direct viral invasion, with consequent inflammation and neurodegeneration of motor neurons and peripheral nerves, as seen in other viral infections (cytomegalovirus, poliovirus, varicella zoster virus).

Coronavirus infections can be associated with myopathies. About a third of patients infected with other coronaviruses developed myalgia and increased CPK^{47,48}, and rhabdomyolysis^{49,50}. In a recent Chinese cohort, myalgia/fatigue was described in 44-70% of hospitalized patients, and CPK elevation by up to 33%^{51,52}. Such evidence suggests that coronavirus infections can cause viral myositis.

Risk of exacerbation of pre-existing NMD

Viral infections are known to be common triggers for exacerbations or progression of NMD. To date, we do not have data related to the magnitude of the risk of exacerbating NMD by COVID-19 or previous coronavirus. However, it is possible that we observe exacerbations, progression or even the appearance of new presentations of NMD associated with the infection by COVID-19.

An updated review of consideration by disease has been compiled⁵³.

In general, the risk of exacerbation of acquired or

hereditary NMD by COVID-19 will be primarily defined by the presence and severity of the patient's cardiac/respiratory dysfunction, pre-existing bulbar involvement, previous comorbidities, and pathophysiology of the underlying disease, among others factors.

Risk of using immunosuppressants/immunotherapies

Immune-mediated NMD patients undergoing immunosuppressive therapies are at increased risk of COVID-19 infection and a more severe course of infection. To date, published data from Wuhan, China, have not evaluated neuromuscular comorbidities and use of immunosuppressants in the studied cohorts^{51,52}. Regarding the approach to immunosuppressive therapies, consensus is being developed until we have robust data on outcomes. Table 3 outlines and summarizes initial recommendations, based on recent published expert opinion²⁹.

Most outpatients with outpatient DNM and without evidence of COVID-19 infection should continue taking their usual medications. If there are symptoms suggestive of COVID-19 infection, patients should contact their neurologist, who should guide the continuity of treatment or switch (if possible and indicated) to another immunosuppressant, always considering the risks and benefits individually. Abrupt interruption of any immunosuppressive therapy should be avoided, as it could result in an acute worsening of the underlying DNM, with the possible need for high doses of corticosteroids, hospitalization and / or the start of another immunosuppressant. Avoiding initiation and suspension of corticosteroids will not be necessary in most cases.

Some treatments are not expected to cause an increased risk of COVID-19 infection or associated serious illness. Among these, immunoglobulin therapy (intravenously / subcutaneously), plasmapheresis, and complement inhibitory therapy (such as eculizumab) stand out. In the case of these therapies, care should be taken with the need to go to infusion centers, preferring, if possible, adjustment for home infusion.

In the future, knowledge about the patient's immunological status, as well as the availability of effective vaccination, may be incorporated into risk stratification and therapeutic decision with regard to immunosuppressants.

Table 3: Patients with neuromuscular disease without COVID-19: treatment-specific guidance²⁹.

Treatment type	Disorders	Recommendations
Corticosteroids	CIDP, MG, inflammatory myopathies, DMD, others	Lowest possible effective dose. Avoid abrupt cessation in chronic previous use. Continue steroids unchanged in DMD.
Immunosuppressive therapies (azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, cyclosporine)	CIDP, MG, inflammatory myopathies, others	Continuation of therapy typically recommended; consider reduced dose, if possible. Consider to delay initiation in stable patients, if possible.
Immunosuppressive/cell depleting therapies (Rituximab, ocrelizumab, cyclophosphamide)	CIDP, MG, inflammatory myopathies, MMN, others	Consider postponing infusions, spacing dosing interval, or switching to a different therapy.
Immunomodulatory therapies (immunoglobulin, plasma exchange)	GBS, CIDP, MG, inflammatory myopathies, others	Likely do not increase risk of virus. Careful with infusion centers, consider home infusion if possible.
Nonimmunomodulatory infusion and intrathecal therapies, gene therapies (edaravone, nusinersen/zolgensma, patisiran/inotersen, myozyme, others)	ALS, SMA, FAP, Pompe disease	Careful with infusion centers, consider home infusions if possible.
Multidisciplinary care (physical therapy, occupational therapy, speech therapy, clinical swallow evaluation)	All	Consider telemedicine, if possible.

Abbreviations: ALS=amyotrophic lateral sclerosis; CIDP=chronic inflammatory demyelinating polyneuropathy; DMD=Duchenne muscular dystrophy; FAP= familial amyloid polyneuropathy; MMN=multifocal motor neuropathy; SMA=spinal muscular atrophy.

Adapted from: Guidon AC, Amato AA.²⁹

CONCLUSIONS

The emergence and evolution of the SARS-CoV-2-related pandemic has enabled knowledge about potential neurological complications related to this virus. In this context, the main role of the neurologist will be a careful assessment of the neurological clinical characteristics manifested by patients with COVID-19 infection. An important aspect to be considered is the distinction between the direct neurological effects of viral infection and the systemic effects of the disease on the nervous system. In addition, it is prudent to consider the possible neurotoxic effects of medications used, as well as morbidities that result from the critical condition. Some doubts still remain unanswered. What will be the neurological effects of COVID-19? Case reports in the world literature will be essential, as well as *postmortem* studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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