

REVIEW ON MULTIPLE SCLEROSIS MANAGEMENT IN TIMES OF SARS-COV-2 PANDEMIC

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ABSTRACT

The emergence of the novel coronavirus, SARS-CoV-2, has startled the entire world and created a genuine chaos inside the medical system. As the infection is spreading, the manifestations are becoming more diverse. The number of SARS-CoV-2-induced neurological cases described in the literature is increasing and the neurologists are experiencing disturbing times in managing their patients, especially those diagnosed with autoimmune diseases, namely multiple sclerosis (MS). Disease-modifying therapies (DMTs) seem to enhance the susceptibility of MS patients to develop severe form of infections. Therefore, their utilization during COVID-19 pandemic is controversial. This review aims to summarise the available recommendations regarding the neurological management of MS patients, with an emphasis on the changes this pandemic has brought in the MS treatment.

Keywords: multiple sclerosis, COVID-19, SARS-CoV-2, coronavirus, drug-modifying therapy

INTRODUCTION

The year 2020 will be remembered for a long time as a global challenge to survive SARS-CoV-2 invasion, which has brought a wave of huge changes inside the medical system in each country and unified the entire medical community in a battle against a unique enemy.

Coronavirus is a positive-sense RNA virus which has a crown-like appearance under electron microscopy [1]. It transmits through air-borne droplets or close personal contact and it manifests with fever, fatigue, headache, sore throat, dry cough, nasal congestion, arthralgia and myalgia [1-4]. Besides respiratory symptoms, a wider spectrum of manifestations has been reported, particularly in severe cases. The highest vulnerability belongs to the population with advanced age, underlying medical conditions (e.g. cardiovascular diseases) and immunosuppression [5,6].

Regardless of their field, all physicians are facing new challenges in the management of their patients, especially of those with chronic illnesses who require constant supervision. For neurologists, two main concerns have emerged during SARS-CoV-2 pandemic: first of all, the protection of the elderly who make up the majority of stroke or dementia patients and who are at risk of developing the severe form of infection, and secondly, the treatment of auto-immune diseases, such as multiple sclerosis, which might interfere with the evolution of infection [7]. While in the first case the implications are quite clear, in the second one the things are still controversial.

Multiple sclerosis (MS) is a chronic demyelinating and neurodegenerative auto-immune disease, generally affecting young adults, with an unpredictable evolution towards motor, sensitive, cognitive, visual and autonomic deficits. MS patients receiving disease-modifying therapies (DMTs) to

control the relapses are of particular interest in time of SARS-CoV-2 pandemic. It was previously demonstrated that people with MS are more prone to contracting different types of infections compared to general population [8,9]. Also, DMTs seem to increase their susceptibility [8,10]. Nevertheless, little is known about the influence DMTs have on the evolution of SARS-CoV-2 infections or about the precautions neurologists should adopt for MS patients during this pandemic. The purpose of this review is to summarise the relevant information about this topic that have been published so far and draw some valuable conclusions that could help the neurologists in the management of MS patients throughout these unprecedented times.

SARS-COV-2 INFECTION – NEUROLOGICAL INVOLVEMENT

There is a broad range of manifestations during COVID-19 infection with different grades of severity, depending on virus features, patients' risk factors and virus-host interaction. Primarily neurological symptoms could be easily ignored as they are thought to be complications of the treatment or secondary to other body homeostatic imbalances (e.g. metabolic, toxic). Thus, the real percentage of neurological involvement is still unknown. The clinical presentation comprises of rather non-specific symptoms – headache, myalgia, fatigue, nausea, taste and smell alteration, and more serious manifestations – disturbed consciousness, paralysis, epileptic seizures [11-18].

Most coronaviruses share common structural components and similar pathogenesis. Therefore, the previous SARS-CoV and MERS-CoV epidemics have allowed the researchers [19-21] to analyse the neurological involvement of coronavirus. They proved that neurotropism and neuroinvasion are characteristic to coronaviruses [20] and, therefore, to SARS-CoV-2 as well. Necropsy reports of deceased COVID-19 patients showed cerebral edema and neuronal degeneration [22] and researchers confirmed the viral presence in the cerebrospinal fluid by genome sequencing [18,23,24], which empower the belief that neurological lesions should be looked for in all hospitalized patients.

There are two direct ways for the viruses to reach the brain: haematogenous and neuronal pen-

etration. Because of the dimension of SARS-CoV-2, a neuronal spread via trigeminal or olfactory fibers seems more plausible [19]. It was already demonstrated a dissemination of coronavirus through the cribriform plate of the ethmoid bone into the central nervous system [25]. Anosmia and dysgeusia are common symptoms in SARS-CoV-2 infections and both could be caused by forebrain lesions [26,27]. On the other hand, coronavirus targets the receptor for angiotensin-converting enzyme 2 (R-ACE2) which is largely expressed throughout the body, including on the endothelium of the blood vessels in the brain. This would allow the virus to damage the blood-brain barrier and easily penetrate the central nervous system [23].

Breathing difficulties are prominent manifestations of SARS-CoV-2 infection and are explained by viral injuries in lung parenchyma. Some studies [18,28] also invoked central hypoventilation due to the loss of synapses between the cardio-respiratory centres in the brainstem and the corresponding receptors in the lungs. Turtle [29], however, disapproves, claiming that the pattern of breathing difficulties suits type 1 respiratory failure rather than type 2 which would occur in a central lesion. It is yet to be proven if this contributes to respiratory failure in SARS-CoV-2 infections.

Another important asset of coronavirus is its ability to activate the immune cells and trigger a powerful systemic inflammatory response syndrome which can eventually provoke multiple organs failure. By invading and activating the glial cells, the virus similarly induces an inflammatory state inside the brain, which results in neurological manifestations [23].

VIRAL INFECTIONS IN MS

MS is a debilitating neurological disease characterized by demyelination, neuronal inflammation and axonal loss, which eventually leads to invalidating deficits. The exact cause is still arguable, but several theories [30,31] have come up lately, among which a partially demonstrated etiological relationship between viral infections and multiple sclerosis. Nevertheless, it is generally stated that viral infections trigger the disease activity culminating in MS relapses, and COVID-19 makes no exception.

Although the neuroinvasion of coronavirus was already confirmed [23,24,32-34], it is still questionable if they persist inside the neuronal cells and trigger autoimmune neurological diseases in genetically vulnerable patients [13]. Salmi et al. [32] identified large titers of antibodies against coronavirus in the cerebrospinal fluid of MS patients. They concluded that either coronavirus has an important pathogenic role in developing MS, or the autoimmune nature of the disease leads to increased intratechal antibodies synthesis. Arbour et al. [33] described the presence of viral RNA inside the cerebral parenchyma, but they could not exclude an opportunistic infection rather than an etiological role in MS induction. Ding et al. [35] also found pathological evidence of SARS-CoV in the brain. Other researchers [36] have proposed a so-called “molecular mimicry” – a structural similarity between the myelin of the nervous system and the viral antigen, which triggers an autoimmune response.

As most of our information is based on studies of previous epidemics with kindred coronaviruses, further research is necessary in order to establish the genuine connection between SARS-CoV-2 infection and MS.

SARS-COV-2 INFECTION – DMTS

Regarding MS treatment, a series of precautions should be considered during the current epidemiological context. Because of the limited number of studies concerning the relationship between MS therapy and SARS-CoV-2 infection, most of them are merely recommendations. However, it was suggested that the MS immunomodulators could have a protective role by maintaining a quiescent immune status inside the body and, as a result, inducing a milder evolution of the infection [7,37,38].

Various neurological societies published consensus-based recommendations regarding the MS long-term treatment in order to facilitate the patients' follow-up in times of SARS-CoV-2 outbreak.

1. Interferon

Beta-interferon is an immunomodulator meant to slow the progress of the disease. There are no known contraindications for its introduction or maintenance in the treatment of MS patients diag-

nosed with active SARS-CoV-2 infection [26]. Together with glatiramer acetate, it is considered one of the safest drugs used in MS during pandemic, regardless of the patient's infectious status [39]. Moreover, inhaled treatment with interferon is currently explored for SARS-CoV-2 infection [8,26].

2. Glatiramer acetate

Glatiramer acetate, used to drop the number of MS relapses, modulates both innate and adaptive immune cells activity, resulting in an increase of anti-inflammatory cytokines. According to prior studies which have shown insignificant risk of acquiring viral infections during treatment, its use could be maintained in spite of active SARS-CoV-2 infection [26].

3. Teriflunomide

Teriflunomide inhibits the pyrimidine synthesis and, consequently, decreases the number of T and B cells. While there are no contraindications in free-coronavirus patients, when developing an active infection the treatment should be temporarily stopped until infection resolution. If initiating Teriflunomide, both the neurologist and the patient should be aware of the surveillance period with repeated blood tests [35,40], which might be problematic during pandemic.

4. Dimethylfumarate

Dimethylfumarate increases the level of anti-inflammatory cytokines, but decreases the level of pro-inflammatory cytokines [41]. It also produces lymphopenia. Therefore, in case of active SARS-CoV-2 infection, its use should be interrupted, at least temporarily [26]. If, however, the treatment continues, a regular lymphocyte count should be considered [35]. Similarly to the aforementioned drugs, it is recommended to use in times of SARS-CoV-2 pandemic, as the risk of MS relapse eclipses the probability of acquiring a viral infection [40].

5. Fingolimod

Fingolimod is a S1P immunomodulator which sequesters the lymphocytes inside the lymph nodes, thus preventing them to attack the nervous system. Its utilization requires a careful follow-up during pandemic, with a special attention being paid to lymphocyte count [35]. Moreover, it was demonstrated that fingolimod increases the risk of viral and opportunistic infections in MS patients [40,42-44]. It is advisable to delay its use at least until SARS-CoV-2 infection is excluded. If COV-

ID-19 infection is confirmed, it is advisable to avoid it while carefully observing the patient for possible relapses [26]. However, interestingly, Giovannoni et al. [45] mentioned clinical trials [46] that consider fingolimod a potential treatment for SARS-CoV-2 to prevent ARDS.

6. Cladribine

Cladribine induces the apoptosis of natural killer lymphocytes, while preserving B and T cells. In most cases, it does not lead to significant lymphopenia, but if it does, then the patients' prognostic during pandemic could worsen [26,47]. Therefore, repeated complete blood counts should be performed. It also augments the risk of reactivation of infections with DNA viruses [47]. Cladribine use is strictly forbidden in infected patients. For the rest of MS cohort, its administration could be delayed by six months depending on the disease activity [26].

7. Natalizumab

Natalizumab is a humanized monoclonal antibody against $\alpha 4\text{-}\beta 1$ integrin which prevents lymphocytes to penetrate the blood-brain barrier and, consequently, diminishes the immune surveillance of the central nervous system [26,45]. It is commonly associated with progressive multifocal leukoencephalopathy, viral meningitis and encephalitis after long periods of treatment [39,48-50]. It is appropriate to use Natalizumab during pandemic, but in case of active SARS-CoV-2 infection it is advisable to interrupt its use while constantly monitoring the patients for possible relapses [26]. If the risk of rebound is significant, expanding the dosing interval should be considered instead [35].

8. Ocrelizumab

Ocrelizumab is an anti-CD20 humanized monoclonal antibody. It was associated with a relatively high infection rate, mainly affecting the urinary and respiratory tracts [26]. Studies [50,51] linked Ocrelizumab with neutropenia and reduced level of Immunoglobulin M. According to Costa-Frossard et al. [26], it should be avoided in patients with active SARS-CoV-2 infection. If the benefits of continuing the treatment outweigh the administration's risks, the dosing interval should be extended [39]. In case the patient already received the first dose of the first cycle, it is desirable to complete the phase under careful supervision of the patient. In uninfected patients its use should relate to disease activ-

ity, patients' age and vulnerability to infection and likelihood of relapses consequent to the administration postponement [26].

9. Rituximab

Rituximab is an anti-CD20 chimeric monoclonal antibody. It is also associated with moderate infection of respiratory and urinary tracts, as well as with a decreased level of immunoglobulin G and neutropenia [52,53]. However, severe infections are infrequent. Rituximab approach is similar to that of Ocrelizumab [26,39,49,50].

10. Alemtuzumab

Alemtuzumab is an anti-CD52 humanized monoclonal antibody which destroys the lymphocytes, notably T and B cells [39,49,50]. It was correlated with severe fungal and bacterial infections and with reactivation of viral illnesses [54,55]. Therefore, alemtuzumab is forbidden in COVID-19 patients. Its use during pandemic depends on patients' comorbidities, disease activity, period of treatment [26].

SARS-COV-2 INFECTION – MS RELAPSES

It is already well-known that infections could enhance the disease activity and culminate in a temporary aggravation of patients' deficits. The neurologists should be extremely careful to differentiate between a genuine relapse and a pseudo-relapse due to underlying infection [26,39]. The latter does not need specific therapy, the deficits recover once the infection is cured. The recommended treatment for relapses is corticosteroid therapy. Nonetheless, it should be carefully managed because in SARS-CoV-2 infected patients it could have ambivalent effects depending on the moment of action [56]. If the steroids act when the virus replicates, they increase the risk of complications. But if they are administered in the hyperinflammatory stage, they might have beneficial effects. Unfortunately, in the clinical practice it is difficult to predict which viral phase is at a given moment, so the steroids avoidance is preferable. Nonetheless, it was established that steroids have little effect on the final functional recovery of the deficits, but mostly shorten the relapse period [26,39]. In MS, oral and intravenous corticosteroids are equally efficient, so the oral therapy is a convenient substitute to avoid hospitalization [39].

FURTHER IMPLICATIONS OF SARS-COV-2 INFECTION

SARS-CoV-2 pandemic has imposed changes in MS patients follow up. The access to MRI examinations and blood analysis is restricted. The patients should avoid as much as possible the contact with the hospital to diminish the risk of being infected with coronavirus. Therefore, hospitalization of MS patients should be done only in case of emergencies and, even so, for as little time as possible. Telemedicine is considered a valuable alternative to hospital visits for patients' follow-up [26,39,57]. Treatment initiation or switching in time of pandemic is challenging due to the aforementioned restrictions.

Last, but not least, people diagnosed with MS should follow the general recommendations of World Health Organization to reduce the transmission of SARS-CoV-2, such as: social distancing, frequent hand-washing with soap and water, respiratory hygiene, nose and mouth covering by masks if coughing/sneezing or when in contact with infected people. Furthermore, they should be familiar with the typical manifestation of COVID-19 infection and in case of presenting any relevant symptom they should immediately announce the authorities in charge. MS patients should be warned not to change their MS treatment without a prior discussion with their neurologists and to avoid any drugs that can jeopardize their health status (e.g. non-steroidal anti-inflammatory drugs – NSAIDs) [26,39,57,58].

CONCLUSIONS

COVID-19 pandemic has raised a series of uncertainties regarding the management of neurological patients, especially of those diagnosed with

MS. It is still unclear the precise influence of SARS-CoV-2 on the disease evolution, but the great susceptibility of MS patients towards severe forms of infections requires a special neurological monitoring. Apart from the general precautions that each person should respect in order to stop the transmission of the novel coronavirus, MS patients should receive and strictly obey special recommendations particularly concerning their treatment. The effect of disease-modifying drugs on the evolution of SARS-CoV-2 infection is still controversial. In non-COVID-19 MS patients, it is strongly advisable to continue the treatment with first generation DMTs (interferon, glatiramer acetate, teriflunomide, dimethylfumarate), Fingolimod and Natalizumab in order to avoid the repercussions related to its interruption. However, it is recommended to delay the start of lymphocytopenia-inducing DMTs (Alemtuzumab, Rituximab, Ocrelizumab, Cladribine) or to expand the dosing interval. Regarding COVID-19 positive patients, the main recommendation is to stop any treatment until infection resolution, but depending on the clinical status of the patient, extending the dosing interval or continuing with beta-interferon could be considered as alternatives. Initializing a new MS treatment is not desirable because of the restrictions to blood analysis or MRI investigations, which are necessary for patient surveillance. High dose steroids, usually utilized in case of relapse, could worsen the prognosis of the patients and, therefore, they ought to be avoided.

As there is no solid research to support the above recommendations due to the lack of longer follow-up, it is eventually the neurologist's decision how to handle each case, taking into consideration the patients features, disease characteristics and current treatment.

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