

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.

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 prognostic 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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