COVID-19 and management of neuroimmunological disorders

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The importance of reported neurological manifestations of coronavirus disease 2019 (COVID-19) is still unclear. Nevertheless, an immediate and ongoing neurological challenge posed by the COVID-19 pandemic is the management of patients who are undergoing immunotherapy for existing neuroimmunological disease.

In December 2019, an endemic acute respiratory infection that causes bilateral pneumonia and acute respiratory distress was first reported in Wuhan, China. The pathogen was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease — coronavirus disease 2019 (COVID-19) — has caused the first recorded non-influenza pandemic. Approximately five million cases have been verified and the global death toll is >320,000 (20 May 2020, Johns Hopkins University & Medicine Coronavirus Resource Center). Severe COVID-19 can cause progressive respiratory failure and death. Susceptibility is increased by older age, comorbidities, recent surgery and intrinsically or iatrogenically compromised immunity[1] (BOX 1).

Various neurological complications of COVID-19 have been reported (BOX 1), though their true incidence remains elusive[2–5]. Direct invasion of neural parenchyma by SARS-CoV-2 is a possibility; the virus could access the CNS via the nasal mucosa, lamina cribrosa and olfactory bulb or via retrograde axonal transport. In the CNS, it could travel to the brainstem and contribute to dysregulation of breathing and pulmonary and cardiac functions[6].

Alternatively, the neurological manifestations could be indirect effects mediated by host cytotoxic $CD8^+$ T cells, postinfectious cross-reactive immune responses or vigorous inflammatory responses in the wake of a cytokine storm[7]. For example, many proinflammatory cytokines can destroy endothelial cells or induce a hypercoagulative state, changes that could account for cerebrovascular manifestations of COVID-19, though a chance association cannot be ruled out. Encephalopathy could result from multi-organ failure, sepsis or the COVID-19-associated cytokine storm. Whether emerging associations with rare conditions, such as Guillain–Barré syndrome[5], suggest causative relationships or chance associations remains unclear.

Several autoimmune neurological diseases — most notably multiple sclerosis (MS) — have previously been related to viral infections, though unequivocal evidence that viral infections are associated with disease activity is lacking. Whether MS increases the risk of contracting COVID-19 or COVID-19 increases MS disease activity is unclear. Similarly, no consistent data are yet available for neuromyelitis optica spectrum disorders (NMOSDs), myasthenia gravis, Guillain–Barré syndrome or chronic dysimmune neuropathies.

The greatest concern with COVID-19 in all neuroimmunological diseases is the consequences of immunotherapies. For patients with these diseases, the risks and benefits of their treatments must be assessed and the extent to which disease-modifying therapies limit antiviral host immunity must be considered. The risks vary across immunotherapies available for various neuroimmunological disease[8].

Different classes of drugs for MS are associated with different levels of risk. On the basis of their presumed mode of action and evidence from their use in patients, β-interferons, glatiramer acetate and teriflunomide are safe in COVID-19 because they do not cause relevant immunosuppression or increase the risk of viral infections. Similarly, dimethylfumarate only moderately affects the functions of memory B cells, plasmablasts and plasma cells and few patients develop persistent lymphopenia with low levels of $CD8^+$ T cells that would compromise anti-viral immunity. Overall, therefore, viral infections are not a major risk with dimethylfumarate.

Immunotherapies with higher efficacy in MS have more pronounced effects on immune function, so could pose higher risks. Sphingosine 1-phosphate receptor modulators retain lymphocytes in lymphoid tissue but the innate immune response is only slightly affected. The risk of viral infections (herpes, varicella zoster) is modestly increased with these drugs. By constrast, cladribine tablets cause rapid depletion of B cells and T cells. Levels of T cells and natural killer cells remain within the lower limits of normal and B cells usually recover fast, but the risk of viral infections is increased.

The most potent immunotherapies are the monoclonal antibodies (mAbs) alemtuzumab, ocrelizumab and natalizumab. Alemtuzumab causes long-lasting, extensive depletion of $CD4^+$ and $CD8^+$ T cells that

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Box 1 | **Neurological disorders and COVID-19**

Neurological symptoms reported in COVID-19 patients

- Dizziness
- Headache
- Obtundation
- Hypogeusia
- Ageusia
- Hyposmia
- Anosmia
- Myalgia

Neurological disorders reported to occur with COVID-19

- Stroke (ischaemic, haemorrhagic, secondary to coagulopathy)
- Sinus venous thrombosis
- Cerebral haemorrhage
- Encephalopathy
- Altered mental status
- Meningitis
- Encephalitis
- Febrile seizures
- Acute haemorrhagic necrotizing encephalopathy
- Acute disseminated encephalomyelitis
- Myelitis
- Myasthenia gravis
- Miller–Fisher syndrome
- Guillain–Barré syndrome
- Polyneuritis cranialis

Neurological patients at risk in the context of COVID-19

- Alzheimer disease
- Parkinson disease
- Motor neuron disease
- CNS disorders with reduced mobility or immobility
- Neuromuscular disorders with reduced mobility and compromised respiratory function
- Autoimmune conditions
  - Multiple sclerosis
  - Neuromyelitis optica spectrum disorders
  - Myasthenia gravis
  - Guillain–Barré syndrome
  - Chronic dysimmune neuropathies

compromises responses to viruses, so alemtuzumab has been associated with an increased risk of infections.

Ocrelizumab depletes all B cells except stem cells and the antibody-manufacturing plasmablasts and plasma cells. Depletion is maintained for 6–12 months. Viral infections have been associated with ocrelizumab treatment and, over time, hypogammaglobulinaemia raises the risk of infection. If a patient receiving ocrelizumab contracts COVID-19, delay of subsequent ocrelizumab infusions might be appropriate.

Of the mAbs, natalizumab might pose the fewest problems in the management of MS in the era of SARS-CoV-2. This antibody reversibly blocks migration of lymphocytes into the brain and gastrointestinal tract. Besides rare cases of progressive multifocal leukoencephalopathy, natalizumab is not associated with an increased risk of infections. Extended interval dosing might allow immunosurveilling T cells to access the CNS.

Dosing intervals and monitoring requirements for immunotherapies must also be considered in the management of patients with MS in the COVID-19 era. For example, cladribine tablets can be taken at home and demanding monitoring is not necessary. By contrast, the frequent administration and extended monitoring, required with some mAbs, could increase the risk of exposure to SARS-CoV-2 in medical centres.

The B cell-depleting antibodies rituximab and inebilizumab can control NMOSD activity[9] and necessitate the same considerations as ocrelizumab in the context of COVID-19. The complement-blocking mAb eculizumab, which is approved for treatment of NMOSD, has not been associated with an increased risk of viral infections. Satralizumab and tocilizumab — both of benefit in NMOSD — target the IL-6 receptor and so are of particular interest in the context of COVID-19. IL-6 is prominent in the cytokine storm that underlies acute respiratory distress syndrome (and potentially nervous system damage) in COVID-19[7], so these antibodies might be of therapeutic use in COVID-19.

Standard treatment for chronic inflammatory demyelinating polyneuropathy includes short pulses of intravenous steroids or long-term oral steroids, repeat high-dose intravenous immunoglobulin (IVIg) and plasma exchange. Long-term corticosteroid use carries a risk of infection, so is not advisable in patients with COVID-19. Immunoglobulins are of no concern in this regard and could provide protection. Home delivery of IVIg or subcutaneous administration rather than centre-based infusion[10] could reduce the risk of exposure to SARS-CoV-2.

One point to consider in future is how disease-modifying therapies affect responses to vaccination. Given that vaccination against SARS-CoV-2 is considered the ultimate measure to contain the pandemic, the properties that allow a vaccination to be effective while receiving immunotherapy will be important.

In conclusion, the reported neurological manifestations of COVID-19 are multiple, but neither their true incidence nor their causative links have been established. However, COVID-19 affects the management of patients with neurological diseases in many ways. The risks and benefits of immunoactive treatments in neuroimmunological disorders and adjustments to these treatments must be assessed. In addition, new ways of remote monitoring and health care delivery are needed.

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Competing interests

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