Neurology in the time of COVID-19

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Epidemics and pandemics in human history are not the exception but the rule. Bill Gates was prophetic in 2015 'if anything kills ten million people in the next few decades, it is likely to be an infectious virus rather than a war. Not missiles, microbes'.

The Black Death (1347), the Great Plague of London (1665) and the Spanish Flu outbreak which killed 50 million people occurred in 1918. In 1997, the H5N1 bird flu epidemic occurred and was followed, in 2002, by the coronavirus outbreaks of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. These were followed by the re-emerging pathogen epidemic; Ebola virus, unexpectedly, exploded in West Africa in 2013. While the world was celebrating the success of victory over Ebola, in 2015, the Zika epidemic reared its head. Significant neurological complications only featured in the Zika outbreak: congenital microcephaly, Guillain-Barre syndrome, myelitis and meningoencephalitis.[1]

CORONAVIRUSES

The most well-studied coronavirus is the betacoronavirus, mouse hepatitis virus, that has provided model systems for the study of encephalitis and multiple sclerosis. In humans, coronaviruses usually cause common cold symptoms. However, the emergence of two zoonotic betacoronaviruses, SARS-CoV and MERS-CoV, revealed their full pathogenic potential.[2]

In December 2019, Zhu *et al*[3] described patients with pneumonia epidemiologically linked to a seafood and wet animal market in Wuhan, China. A novel coronavirus, SARS-CoV-2, was identified. WHO labelled the disease as COVID-2019. Further genomic analysis reveals that SARS-CoV-2 is similar to the betacoronavirus detected in bats but is a distinctly separate clade from SARS-CoV and MERS-CoV.

A metallopeptidase, angiotensin-converting enzyme 2 (ACE2), has been identified as the functional cellular receptor for the SARS coronavirus.[4] This protein is expressed on alveolar epithelial cells, intestinal enterocytes and arterial and venous endothelial cells. In the brain, positive staining was only found on vascular cells but not on neurons or microglia.[5] Homology modelling suggests that SARS-CoV-2 might also use ACE2 as a cell receptor although with some amino acid variation.[6] This could be a potential mechanism for dissemination of the virus into the brain by the circulation. Some have speculated that dissemination into the CNS (central nervous system) could also occur via the olfactory nerve across the cribiform plate.[7] In support of this hypothesis are clinical reports of anosmia as a frequent occurrence in COVID-2019.

The clinical characteristics of COVID-19 are similar to those of SARS-CoV and MERS-CoV: the most common symptoms are fever and cough. There are, however, some clinical differences: diarrhoea seems less common and chest X-ray abnormalities may be less frequent. Lymphopaenia seems to be a feature of all three syndromes.[8 9]

NEUROLOGICAL COMPLICATIONS

Using SARS and MERS as exemplars, a review of the literature shows no clear signal to implicate these coronaviruses as a direct cause of neurological complications. The cases described included critical care neuromyopathy, rhabdomyolysis, Guillain-Barre syndrome and cases of ischaemic stroke ascribed to hypercoagulability, sepsis and possible vasculitis.[10 11]

There is, however, pathological evidence of coronavirus in the brain. Immunohistochemical and in situ hybridisation techniques on autopsy material from SARS patients identified SARS-CoV in the cerebrum, although at much lower levels compared with lung.[12]

A recent retrospective series of 214 patients from Wuhan described the neurological manifestations of patients with COVID-19. Seventy-eight (36.4%) had neurological.complications. Symptoms included headache and disturbed consciousness. Six patients had strokes—ischaemic and haemorragic. The authors postulate this could be related to elevated d-dimer levels. 'Muscle injury' defined by elevated creatine kinase levels occurred in 23 patients.[13] In a review of neurological complications, Liu *et al*[14] describe a case of COVID-19 encephalitis.

ROLE OF THE NEUROLOGIST

What will be required is what neurologists always do: foremost, a careful assessment of the clinical features. This means more neurologists working at the frontline. The clinical data will need to be complemented by imaging, neurophysiology and cerebrospinal fluid examination. This may require dedicated equipment and personnel.

It will be necessary to try and differentiate any direct effects of the virus against the effects of systemic illness on the nervous system. This includes complications due to hypoxia, sepsis, secondary hypercoagulable states and disseminated intravascular coagulation. Other variables that will need consideration are drug toxicities and inherent morbidities due to prolonged stay on intensive care such as critical care neuromyopathy. As always, postmortem studies will be crucial in giving us answers.

What could be the effects of the coronavirus itself ? By extrapolating the experience of other viral infections one could expect: meningoencephalitis, cerebellitis, myelitis, ADEM(acute disseminated encephalomyelitis), myositis, rhabdomyolysis and neuropathy including a postinfectious Guillain-Barre syndrome. Individual case reporting will be a valuable portal for dissemination of information. In view of the documented lymphopaenia, it would be prudent to be alert to the infective complications encountered in immunosuppression. This may be compounded by the frequent use of high dose corticosteroids to treat the pneumonitis and ARDS (acute respiratory distress syndrome). A case of tuberculous meningitis in a patient with COVID-19 highlights the importance of avoiding a blinkered approach.[14]

PATIENTS WITH NEUROLOGICAL DISORDERS

The other current area of concern for neurologists is the vulnerability of patients with neurological diseases to COVID-19. This applies especially to patients on disease-modifying treatments and immunosuppression.

Many neurological patients are at increased risk beyond that of being older and male, with diabetes, heart disease or COPD (chronic obstructive pulmonary disease).[15] There are no clear data on outcomes of patients with pre-existing neurological diseases or their

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treatment, and in particular, the effects of immunosuppression.

Patients with respiratory insufficiency from neuromuscular weakness or musculoskeletal limitations such as kyphoscoliosis are likely to be at higher risk in severe COVID-19 infection. Patients with <60% predicted FVC (forced vital capacity) are unlikely to wean from ventilation and patients with <40% FVC are likely to be on NIPPV (noninvasive positive-pressure ventilation) already. Patients with lung, renal or liver comorbidity (eg, vasculitis) are at higher risk. Patients with metabolic diseases may deteriorate acutely under stressful conditions.

The mechanisms and pathology of the acute deterioration in respiratory reserve are poorly understood. However, a cytokine storm and activation of type II pneumocytes seem to play key roles.[16] The cytokine profile in patients severely affected with COVID-19 is similar to that observed in secondary haemophagocytic lymphohistiocytosis syndrome.[17 18] This observation may have treatment implications with interleukin (IL)-1 (anakinra) and IL-6 (tocilizumab) blockade.[19] High dose steroids have clearly been identified as a comorbid risk factor for poor outcome. Broad-spectrum high potency immunosuppressants such as cyclophosphamide, alemtuzumab and the anti-CD20 monoclonals are very likely to be high risk for infection and poor antiviral response (table 1). This level of immunosuppression has been identified as a risk factor in seasonal influenza, although this was in patients with other comorbidities such as underlying cancer.[20] The more commonly used oral immunosuppressants have to be assumed to be a risk but in some series no additional risk is identified.[21] Since the effect of immunosuppressants are so long lasting and the risk of disease relapse on stopping results in additional compromise, patients need to follow the standard advice for social distancing and self-isolation for those deemed as high risk.

In summary, during these extraordinary times, neurologists will need to be involved in the frontline and be vigilant for the neurological complications of COVID-19. Patients with neurological disorders, especially those on immunomodulatory therapies, will require close monitoring.

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Table 1 Recommended management of immunosuppressants

	Patients initiating treatment	Patients already on treatment
DMTs/treatments with low risk of infections		
Beta interferon Glatiramer acetate Dimethyl fumarate* Teriflunomide† IVIg/ SCIg PLEX	General health advice. Initiate treatment as usual.	General health advice. Continue treatment.
DMTs/treatments with risk of infections but associated with risk of rebound disease activity		
Fingolimod‡ Natalizumab§	General health advice. Consider delaying initiation of treatment or an alternate DMT, taking into account the risks and benefits.	General health advice. Continue treatment.
DMTs/treatments with risk of infections with a long duration of action		
Ocrelizumab Rituximab Cyclophosphamide	General health advice. Consider delaying initiation of treatment or an alternative DMT, taking into account the risks and benefits. Anti-CD20 antibodies may significantly suppress adaptive humoural immunity to novel pathogens.	General health advice. If treatment is due, consider checking CD19 count along with routine FBC and immunoglobulin levels. If patient is neutropaenic, lymphopaenic and/or CD19 <1% consider delaying treatment course, taking into account the risks and benefits.
Immune-reconstitution therapies		
Cladribine Alemtuzumab HSCT	General health advice. Do not initiate treatment, consider an alternative DMT.	General health advice. Delay further courses of treatment, taking into account the risks and benefits, and reassess periodically.
Steroid-sparing agents		
Azathioprine* Methotrexate Mycophenolate	General health advice. Consider delaying initiation of treatment or an alternate DMT, taking into account the risks and benefits.	General health advice. If clinically stable, then continue treatment, taking into account the risks and benefits, and reassess periodically. NB. Risk of relapse risk and relapse treatment.

*Careful attention should be paid to lymphocyte counts, ensure >0.5×10^9.
†If initiating teriflunomide, be aware of the need for 2 weekly blood test monitoring and the risks of frequent hospital visits in an epidemic.
‡Careful attention should be paid to lymphocyte counts, ensure >0.2×10^9.
§In patients on natalizumab, consider extended interval dosing after discussion of risks and benefits to reduce hospital visits in an epidemic.
DMT, disease modifying therapy; FBC, full blood count; HSCT, haematopoietic stem cell transplantation; IVIg, intravenous immunoglobulin; NB, nota bene; PLEX, plasma exchange; SCIg, subcutaneous immunoglobulin.

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