Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Disimmune encephalopathy with onconeuronal antibodies in SARS-CoV-2 infected patients☆

Encefalopatía disinmune con anticuerpos onconeuronales en pacientes infectados por SARS-CoV-2

To the Editor:

The development of encephalopathy in the context of SARS-CoV-2 infection, even in the absence of respiratory symptoms,[1] has been associated with a broad spectrum from mild confusion to coma. We report the cases of 2 patients with altered mental status in the context of COVID-19.

Clinical cases

Patient 1

45-year-old male with fever and dyspnoea secondary to bilateral SARS-CoV-2 pneumonia, with progressive worsening, showing bilateral pulmonary thromboembolism, requiring ventilatory support in the intensive care unit (ICU). Since admission, the patient showed altered level of alertness, alternating psychomotor agitation with low level of consciousness. Cranial magnetic resonance imaging (MRI) with contrast and cerebrospinal fluid (CSF) analysis were performed, without alterations, including oligoclonal bands (OCB). The electroencephalogram (EEG) shows overall desynchronization. A 5-day cycle with immunoglobulins was started, without improvement. Ten days later, 500 mg of methylprednisolone were administered for 5 days. A second CSF analysis shows a high spinal fluid protein concentration (61 mg/dl) and SARS-CoV-2 PCR negative. Onconeural tests by indirect immunofluorescence (primate and rat neuronal tissue) and immunoblot against 12 purified neurological specific antigens (IgG) are requested, with positive anti-recoverin and anti-titin in blood. Days after the end of corticosteroids, the patient began progressive improvement until complete normalisation of mental status with normal EEG tracing at discharge.

Patient 2

33-year-old male admitted to the ICU due to decreased level of consciousness. Normal head CT and CSF with mild pleocytosis (11 /μl) and OCB and herpes PCR negative. Twenty-four hours later, he developed fever and a chest X-ray showed bilateral interstitial pneumonia, with a positive SARS-CoV-2 PCR. Treatment with hydroxychloroquine, lopinavir/ritonavir, and tocilizumab was started. EEG shows bifrontal slow-wave activity. Normal cranial MRI and negative CSF SARS-CoV-2 PCR. Onconeural tests were requested, and blood tests are positive for anti-Yo. Six days later, sedation was removed, and he was extubated. Favourable neurological progression on discharge, with no evidence of cognitive dysfunction or seizures.

Discussion

The development of encephalopathy in patients with COVID-19 is associated with severity, age, and comorbidities, due to hypoxic-metabolic-toxic or inflammatory/dysimmune aetiology, with usually normal neuroimaging and CSF.[1]

Cases of brain MRI have been described with leptomeningeal enhancement, isolated hyperintense lesions in subcortical white matter, corpus callosum, periventricular, mesial temporal lobe and hippocampus or multifocal type acute disseminated or necrotizing hemorrhagic encephalitis, as well as reversible posterior leukoencephalopathy and endotheliitis with gadolinium uptake in the frontobasal intracranial arteries.[2]

A positive SARS-CoV-2 serology or PCR in CSF is rare, although it may show pleocytosis and a high spinal fluid protein concentration.[1] Viral RNA is found in one third of brain tissue samples, although with fewer copies than in lung or pharynx. ECA2, the cellular entry receptor for SARS-CoV-2, is expressed in neurons, astrocytes, and oligodendrocytes, although at lower levels than in the lungs. Elevation of the pro-inflammatory monocyte chemoattractant protein-1 in CSF has been demonstrated, suggesting a neuroinflammatory rather than neuroinvasive mechanism. Other biomarkers of brain damage such as glial fibrillary acidic protein, in early stages, and neurofilaments in later stages, also show high levels in blood, in relation to astrocyte activation/injury.[3]

In the EEG, slowing of background activity, periodic triphasic discharges and frontal prevalence epileptiform discharges have been documented, with seizures developing in 50% of cases.

Autoimmune encephalitis is mediated by antibodies against receptors or neuronal surface proteins, triggered by a tumour or viral infection, although mostly of unknown cause. 10-20% of patients with herpetic encephalitis suffer a relapse, showing anti-NMDAR antibodies producing inflammation of the central nervous system. The mechanism is unknown; it could be due to molecular mimicry, a hypothesis that could be raised in the development of autoantibodies after SARS-CoV-2 infection, as occurs in our patients. These entities require treatment with methylprednisolone, immunoglobulins, plasmapheresis ± rituximab, or cyclophosphamide. Tocilizumab or anakinra (anti-IL-6 and IL1 therapies, related to severity in SARS-CoV-2 infection), are also postulated as emerging therapies.[4]

Cases with a favourable response to intravenous steroids at high doses and plasma replacement procedures have been published, recommending oral steroid treatment at high doses later in case of symptom persistence.[5]

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References

1. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020;382:2268–70, http://dx.doi.org/10.1056/NEJMc2008597.
2. Garg RK, Paliwal VK, Gupta A. Encephalopathy in patients with COVID-19: A review. J Med Virol. 2021;93:206–22, http://dx.doi.org/10.1002/jmv.26207.
3. Kanberg N, Ashton NJ, Andersson LM, Yilmaz A, Lindh M, Nilsson S, et al. Neurochemical evidence of astrocytic and neuronal injury commonly found in COVID-19. Neurology. 2020;95:e1754–9, http://dx.doi.org/10.1212/WNL.0000000000010111.
4. Guasp M, Arino H, Dalmau J. Autoimmune encephalitis. Rev Neurol. 2018;66 Suppl 2:S1–6. PMID: 29876905.
5. Pugin D, Vargas MI, Thieffry C, Schibler M, Grosgurin O, Pugin J, Lalive PH. COVID-19-related encephalopathy responsive to high-dose glucocorticoids. Neurology. 2020;95:543–6, http://dx.doi.org/10.1212/WNL.0000000000010354.

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