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.

Intracranial hemorrhages in critical COVID-19 patients: report of three cases☆

Hemorragias intracraneales en pacientes críticos COVID-19: reporte de tres casos

Dear Editor:

Although the most common symptoms of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are respiratory, neurological manifestations have also been described, particularly among critical patients, including encephalopathy, seizures, and cerebrovascular disease.[1,2]

We hereby present three cases of intracranial bleeding in patients with coronavirus disease 2019 (COVID-19) who were admitted to our unit with severe pneumonia to receive treatment with mechanical ventilation and sedation. Because of the need for prolonged intubation, all patients underwent a tracheotomy. All of them tested positive for SARS-CoV-2 in a nasopharyngeal swab polymerase chain reaction (PCR) test and, based on our unit's protocol, were treated with lopinavir/ritonavir, hydroxychloroquine, azithromycin, and ceftriaxone for 5 days, dexamethasone for 10 days, and low-molecular-weight heparin (LMWH) at anticoagulant doses if their D-dimer levels were greater than 1000 ng/mL. During the examination performed on their admission to the unit, they all maintained a good level of consciousness, with a Glasgow score of 15 and no focal neurologic signs (none of them had a previous history of cognitive impairment).

The first patient was a 65-year-old man with hypertension and diabetes, in which case sedation was discontinued after 10 days of evolution due to observing respiratory improvement and, at a neurological level, a low level of consciousness, with a Glasgow score of 5. An electroencephalogram (EEG) revealed severe encephalopathy and a cranial computerized tomography (CT) scan showed a frontal, left, intraparenchymal hemorrhagic focus measuring 7 mm, associated with a perilesional edema, and another millimetric focus in the right cerebral convexity. At the time of the diagnosis of intracranial hemorrhage, the blood tests peformed reflected thrombocytopenia of 95,000/μl and D-dimer levels of 1600 ng/mL, because of which treatment with LMWH at a dose of 1 mg/kg every 12 h was started, although it was subsequently discontinued.

The second case corresponded to a 64-year-old man with a history of hypertension and diabetes. After 12 days of hospitalization, sedation was withdrawn, observing an alteration in his levels of consciousness, with a Glasgow score of 6. An EEG revealed data of moderate encephalopathy and a cranial CT scan showed multiple foci of supratentorial, intraparenchymal hemorrhage in both cerebral hemispheres. In addition, blood tests reflected thrombocytopenia of 85,000/μl and D-dimer levels of 3900 ng/mL, because of which treatment with LMWH at an intermediate dose of 0.5 mg/kg every 12 h was started. Treatment with LMWH was subsequently discontinued until further progression of his condition was evidenced, at which time the Neurosurgery Department was consulted, with surgical treatment being ruled out.

In order to complete the diagnostic study, a nuclear magnetic resonance imaging (MRI) scan was performed, identifying a fairly similar radiological pattern consisting in bilateral involvement of the white matter, predominantly in the parieto-occipital region (Fig. 1A), associated with multiple hemorrhagic lesions, subarachnoid hemorrhage, and subcortical microhemorrhages. The subsequent clinical evolution of both patients with the supportive therapy was good.

The last case corresponded to a 69-year-old man who, after discontinuing sedation on day 13 of the evolution of his disease, presented with a low level of consciousness and right hemiplegia. An EEG revealed evidence of severe encephalopathy and a cranial CT scan showed generalized hypodensity of the supratentorial white matter and a large, left, frontal hematoma causing deviation of the midline (Fig. 1B). The neurosurgeon performed an emergency craniectomy to evacuate the hematoma, observing that the hemorrhage originated in the cortical arterioles, as well as friable and dark brain tissue, because of which an intraoperative biopsy was performed, identifying signs of a thrombotic microangiopathy and an endothelial lesion without evidence of associated vasculitis nor necrotizing encephalitis.

At an analytical level, the blood tests revealed D-dimer levels of 7000 ng/mL and a normal platelet count, due to which he was

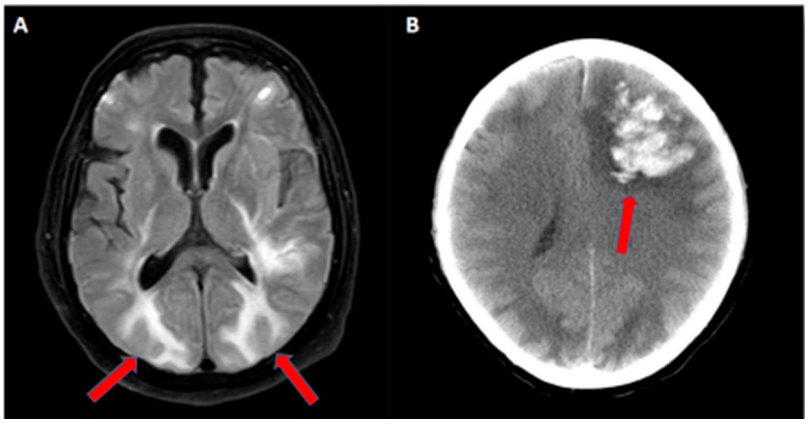

Fig. 1. (A) Axial fluid-attenuated inversion recovery (FLAIR) MRI sequence showing bilateral, subcortical, hyperintense lesions with vasogenic edema in the parieto-occipital cerebral lobes (red arrows). (B) Cranial CT showing a large, left, frontal hematoma causing midline deviation (red arrow).

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administered anticoagulation therapy with LMWH. The patient's subsequent neurological evolution was good, although he presented with sequelae in the form of right hemiparesis on discharge.

A stroke can occur during the acute phase of the infection or even days and weeks following resolution of the viral phase.

Several pathophysiological mechanisms contribute to the increased risk of stroke in COVID-19 patients. The SARS-CoV-2 can infect the endothelial cells of the central nervous system, causing an inflammatory response in the blood vessels and endothelial damage, both of which, together with the thrombocytopenia present in some critical patients and the anticoagulant therapy, can contribute to the onset of microhemorrhages or cerebral hemorrhages.[3–5]

Because it is easy to overlook stroke in critically ill patients who are sedated and relaxed, we recommend early imaging if a patient has an altered consciousness or focal neurologic signs after discontinuing sedation.

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Conflict of interest

The authors declare no conflict of interest.

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Research during the SARS-CoV-2 pandemic☆

Investigación durante la pandemia por SARS-CoV-2

Mr. Editor,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19) pandemic has had an unprecedented impact on recent medical history. Despite the advances made, the rapid spread of the virus has caused us to be faced with a total lack of scientific evidence on which to base our health care decisions. It is because of this that the scientific community has focused its attention on this disease, responding with an unparalleled number of studies to date. Thus, as of 17 July 2020, 2654 studies concerning COVID-19 were registered in clinicaltrials.gov, 1480 of which were classified as clinical trials (CTs). At a national level, the Spanish Clinical Trials Registry (REec, *Registro Español de Estudios Clínicos*) lists 101 clinical trials (10 completed, 51 recruiting, and 40 not started).

This scientific explosiveness has also involved drug research ethics committees (DRECs), whose activity has had to be adapted by means of remote meetings aimed at providing a quick response to the researcher's applications. In our DREC, we have managed to hold all ordinary meetings and to even add five extraordinary meetings (three involving the Permanent Committee). Between March and June of this year, we evaluated 75 studies (43 concerning COVID-19), which is a similar figure to the mean number of studies evaluated over the three previous years (73.3 studies). With three studies pending a final decision, 38 studies relating to COVID-19 have been approved to date (95% of those evaluated), another one has been cancelled by the sponsor, and the remaining one has been considered not evaluable due to corresponding to a purely care-related project. The median time elapsed until a final ruling was issued for these COVID-19 studies was 14 calendar days, as opposed to 21 days throughout the previous years. The characteristics of these studies, their comparison with respect to previous years, and the data of the REec are presented in Table 1. When considering the multicentric nature of the REec studies, one can see that those promoted by the industry are mostly multicentric (88.5%) in contrast to those promoted by public entities (39.7%) and by the researchers themselves (11.5%).

It is important to highlight the difficulty to evaluate studies during this stage, as the absence of evidence on which to base our health care was reflected in the absence of a scientific basis to support the practices to be evaluated, which is a particularly relevant matter in the context of clinical trials.[1] One cannot forget that the role of DRECs is not to develop research, but to ensure that this research conforms to fundamental ethical principles without allowing the context to modify these principles or their relevance.[2]

As mentioned earlier, Spain has been very prolific in terms of clinical trials. According to REec data, there are currently 26 ongoing trials using chloroquine or its derivatives, 10 using tocilizumab, 9 using corticosteroids, 7 using lopinavir-ritonavir, 6 using sarilumab, and 5 using remdesivir as investigational drugs. Without further delving into these studies or their specific designs, it is highly likely that there is a certain degree of overlap between some of them, with the consequences that this undoubtedly entails in terms of recruitment capacity and time to completion, as well as the risk that these studies might lack sufficient statistical power to reach valid conclusions. This overlap has been detected even in the studies evaluated by our committee, due to which we have unsuccessfully urged the researchers to unify their trials. It should be noted that this concern for the statistical power of studies has also emerged beyond our national setting.[3] For example, efforts have been made in Italy to combat this phenomenon by appointing a single national committee to evaluate all studies involving drugs for the treatment of COVID-19.[4] Other authors advocate for the continuous review of these studies and for the early termination of those without the intention of providing relevant information or merging with other studies of similar characteristics.[1] In other cases, these

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