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General Medicine

NEUROLOGICAL INVOLVEMENT IN COVID AN OBSERVATIONAL STUDY

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ABSTRACT The rapid spread of the coronavirus disease 2019 (COVID-19) pandemic has shaken hospitals worldwide. Some authors suggest that neurologic involvement could further complicate the disease. This study is a observational study in 103 patients diagnosed with COVID-19 who underwent neuroimaging . Analyzed variables were neurologic symptoms and acute imaging findings. The most frequent symptoms that motivated neuroimaging examinations were mild nonfocal neurologic symptoms, stroke, focal neurologic symptoms, postsedation encephalopathy, and seizures. No cases of encephalitis or direct central nervous system involvement were detected. Thirteen patients presented with acute ischemic events, and 7, with hemorrhagic events; however, most reported multiple vascular risk factors. Despite the large cohort of patients with COVID-19, we found a large number of symptomatic patients with negative neuroimaging findings, and no conclusions can be drawn concerning concrete associations between neuroimaging and COVID-19.

KEYWORDS :

INTRODUCTION:

The coronavirus disease 2019 (COVID-19) pandemic caused by the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) started in Wuhan, China, in December 2019 and spread rapidly. The clinical hallmark of the disease is viral pneumonia with fever and dry cough. Patients can suddenly progress to acute respiratory distress syndrome and, in severe cases, to death due to respiratory or multiorgan failure. Early publications were centered on these most salient and emergent aspects of the disease, mainly respiratory, but later articles suggested different sorts of neurologic complications.**1**-**5** Proposed mechanisms for neurologic implications include the following:Direct central nervous system spread, based on the known neurotropism of previous SARS-COV strains, which could access the CNS via olfactory pathways or the bloodstream, causing meningitis and encephalitis.**4**-**6** The involvement of the respiratory center in the brain stem may hypothetically justify the well-documented rapid respiratory deterioration with marked hypoxia despite a lack of symptomatic dyspnea.**2**-**7**Indirect neurologic involvement due to an excessive systemic proinflammatory response, which may cause widespread dysregulation of homeostasis with coagulopathy and may also increase the risk of acute cerebrovascular diseases.**8**,**9** Parainfectious autoimmune-based neurologic complications such as acute disseminated encephalomyelitis and Guillain-Barré syndromes, which are recognized complications of microbial infections.**10**-**12** Several studies have described neurologic symptoms in patients with COVID-19. These symptoms mainly include dizziness, headache, ataxia, and confusion.**5**-**7**-**13** One case report suggested viral meningoencephalitis and ventriculitis with reverse transcription polymerase chain reaction (RT-PCR) positive for SARS-CoV-2 in the CSF of a young patient with consciousness disturbance and seizures.**6** Anosmia and dysgeusia, which are highly prevalent in early infection,**14** have been proposed in support of the hypothesis of CNS spread via the olfactory tract.**3** Cerebrovascular events in patients with COVID-19 have also been documented; Klok et al**15** described 3 cases of acute ischemic stroke in a cohort of 184 patients (1.6%) in the intensive care unit, while another preprint article described acute cerebrovascular accidents (ischemic and hemorrhagic) in 13 patients of 221 (5.9%).**16** To the best of our knowledge, neuroimaging of the disease has not itself been evaluated to date.

MATERIALS AND METHODS:

In this observational study we collected data from patients admitted to our tertiary care center between March 1 and April 18, 2020, with RT-PCR positive for SARS-CoV-2 in whom brain neuroimaging was performed. Eligibility criteria were the following: a positive record of RT-PCR for SARS-CoV-2; neuroimaging performed, including either head CT or MR imaging; and 16years of age or older. Exclusion criteria were the following: neuroimaging performed >5 days before diagnosis (based on a median incubation period of 5.1days**17**), or low-quality imaging on visual assessment.Regarding the protocol of our center, the RT-PCR for SARS-CoV-2 testing was performed if the patient presented with severe respiratory symptoms (respiratory rate of >30 breaths per minute, blood oxygen saturation of <95%, with oxygen administered at 35%) or pulmonary infiltrates on x-ray suspicious for viral pneumonia..The minimum required imaging protocol consisted of head CT with or without contrast from the cranial base to the apex or MR imaging, including T1WI, T2WI, T2*WI, DWI, and FLAIR. Available CTA was also reviewed but not included as an eligibility criterion. Variables reviewed included basic demographic and clinical characteristics, symptoms motivating neuroimaging, and acute neuroimaging findings.

RESULTS:

During the hospitalization period, 112 patients underwent head neuroimaging (17 head MR imaging, 111 head CT, and 27 CTA). Of these patients, 9 were excluded (1 with MR imaging + CT; 2 with CT + CTA; 6 with CT), 8 of them because imaging was performed >5 days before SARS-CoV-2 diagnosis and 1 because of low-quality imaging. Accordingly, the final number of participants was 103 .The most common reason for neuroimaging was a nonspecific state of headache, mild alteration of consciousness, transitory dysarthria, or gait abnormality, in 40 patients (4 CT + MRI, 2 CT + CTA, and 34 CT scans). Neuroimaging showed no acute findings in 36 patients. Two patients had distal small-vessel acute infarctions (1 cerebellar, 2 left prefrontal), a single patient had a left parietal lobar acute hematoma, and another had a basilar tip aneurysm.The second most common reason for neuroimaging was an activated code stroke or transient ischemic attack in 25 patients (7 CT + CTA + MRI, 1 CT + MRI, 11 CT + CTA, and 6 CT scans). We found 6 acute parenchymal hematomas: 3 deep basal ganglia and 3 lobar. Large-vessel occlusion was observed in 8 patients. Included were 3 patients categorized as having small-vessel occlusion, 2 acute lacunar infarctions, and 1 patient with multiple, multi-territory small distal acute parenchymal infarctions. Finally, 8 patients had no acute neuroimaging findings.Eleven patients underwent neuroimaging for focal neural symptoms that did not fulfill criteria for code stroke (2 CT + CTA + MRI, 1 CT + MRI, 1 MRI, 1 CT + CTA, and 6 CT scans). Two patients with known malignancy had an increase in the size of previously known brain metastases: One of them presented with visual field disturbance; the other, with mild acral paresis. Another patient with abducens nerve palsy had a large aneurysm at the origin of the right posterior-inferior cerebellar artery. The other 8 patients had no acute neuroimaging findings: One of them presented with diplopia, and the other 7, with mild acral paresis.Seventeen patients underwent CT for trauma involving the craniofacial region. Sixteen had no relevant acute intracranial findings. One had a focal left-parietal parenchymal hemorrhagic concussion.Five patients underwent CT (1 of them also with CTA) because of a Glasgow Coma Scale score below 7. Four of them were patients with delayed recovery of consciousness after prolonged sedation in the intensive care unit. One was a patient with severe respiratory failure. None had any acute findings on CT or CTA.Three patients had CT performed due to seizures. None of them had acute

findings. Two of them were known to have had epileptogenic lesions: One had chronic calcified neurocysticercosis lesions, and the other had extensive areas of encephalomalacia due to a prior cerebrovascular accident. For the 1 patient with no history of seizures or epileptogenic lesions, neuroimaging findings were normal, and seizures were considered to be related to carbapenem neurotoxicity, which was administered due to concurrent extended-spectrum β-lactamase *Klebsiella pneumoniae* infection. Two isolated miscellaneous cases included a case of COVID-19 initial presentation with Guillain-Barré syndrome and normal neuroimaging (CT) findings, and a case of *Staphylococcus aureus* endocarditis with mycotic aneurysms on CTA. The above cases include 20 cases of nontraumatic cerebrovascular accidents, with 3 not presenting as code stroke. Details of cardiovascular risk factors in these patients are provided in . Most notably, 75% of all patients with a cerebrovascular accident had at least 1 vascular risk factor, and 61% had at least 2, without considering age. However, in the case of the 7 patients with parenchymal hematomas, 3 had no vascular risk factors and were younger than 70years of age. Moreover, of the 4 patients with lobar hematomas, none had imaging characteristics or clinical history of cerebral amyloid angiopathy or any other predisposing factor.

DISCUSSION:

A causal relationship with COVID-19 infection may be reasonably ruled out in some patients, such as the ones with neuroimaging performed because of traumatic brain injury or the case of bacterial endocarditis. Cases with vague symptoms such as a mild transitory altered level of consciousness or mild nonspecific focal neurologic symptoms had mostly normal neuroimaging results or alternative diagnoses independent of COVID-19, such as brain metastases and unruptured aneurysms. Furthermore, 4 patients with encephalopathy after prolonged sedation had normal neuroimaging findings. A nonspecific delay in conscious-level recovery is not uncommon in patients with deep and prolonged sedation, which many patients with COVID-19 require. Neuro-imaging is performed in these patients to rule out other occult complications, which, in these cases, were indeed ruled out. The remaining patients, in our opinion, warranting consideration as possibly related to COVID-19 included 13 patients with acute ischemic lesions, 7 patients with acute hemorrhagic lesions (4 lobar and 3 deep basal ganglia), 3 patients with seizures, and 1 patient with Guillain-Barré syndrome and normal neuroimaging findings.There was a high prevalence of vascular risk factors among acute ischemic cerebrovascular events. Nevertheless, in the case of acute hemorrhagic lesions, several cases had no previous risk factors.

The neurologic symptoms in patients with COVID-19 described in several articles are nonspecific, and inconclusive for any underlying organic neurologic damage. These symptoms in-cluded dizziness, headache, ataxia, and confusion, which are frequent transient symptoms of diverse scenarios such as infections, prolonged hospitalization periods, and posttreatment or postprocedural states, among others.**5**'**13** A case report suggested viral meningoencephalitis and ventriculitis in a patient with RT-PCR positive determination on CSF and negative on the nasopharyngeal swab for SARS-CoV-2. This patient presented with nonspecific neurologic symptoms such as consciousness disturbance and seizures, and imaging findings were not specific.**6** Regarding anosmia and dysgeusia, a pre-peer review study suggested that non-neural support cells but not sensory neural cells express the angiotensin-converting enzyme 2 receptor, which is targeted by the virus.

This finding would support the hypothesis that anosmia and dysgeusia are merely a peripheral phenomenon.**18** As for acute cerebrovascular events in COVID-19, some considerations prevent establishing causality based on published studies.**15**'**16** Prior common patient underlying conditions/risk factors that may cause cerebrovascular events seem overlooked; and risk-stratified control datasets are not used to robustly confirm a higher incidence of cerebrovascular events or the real increase of risk in patients with COVID-19. Finally, parainfectious processes are thought to be triggered by an immune response, and about two-thirds of patients have a recent history of viral or bacterial respiratory or gastrointestinal tract infection,**19** so it seems perfectly plausible that SARS-COV-2 may also trigger these kinds of diseases, as is suggested in the literature.**10**'**12**

There are several important limitations to this study, mainly due to the rapid expansion of the disease and the critical situation of many patients, which requires a reorganization of hospital resources centered on providing the best possible assistance.

CONCLUSION:

We have analyzed the patients with COVID-19 published to the date and focused on those with neurologic symptoms requiring neuroimaging. We have not found specific neuroimaging presentations of the virus, and a large number of symptomatic patients appear to have negative neuroimaging findings. The well-demonstrated virus-associated coagulopathy may logically increase the risk of cerebrovascular events (in our experience possibly more hemorrhagic), but further studies with risk-stratified control cohorts are required to determine the real impact. Finally, autoimmune parainfectious entities seem plausible, as they are in the context of other infectious processes.

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