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Neurological involvement in COVID-19: cause or coincidence? A neuroimaging perspective

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ABSTRACT

The rapid spread of the COVID-19 pandemic has shaken hospitals worldwide. Some authors suggest that neurological involvement could further complicate the disease. This descriptive study is a cross-sectional review of 103 patients diagnosed with COVID-19 who underwent neuroimaging (over a total of 2,249 COVID-19 patients in our center). Analyzed variables were neurological symptoms and acute imaging findings. The most frequent symptoms that motivated neuroimaging exams were mild non-focal neurological symptoms, code-stroke, focal neurological symptoms, post-sedation encephalopathy, and seizures. No cases of encephalitis or direct central nervous system involvement were detected. Thirteen patients presented acute ischemic events and seven hemorrhagic; however, most reported multiple vascular risk factors. Despite the large cohort of COVID-19 patients, we found a large number of symptomatic patients with negative neuroimaging, and no conclusions can be drawn concerning concrete associations between neuroimaging and COVID-19.

ABBREVIATIONS

Central nervous system (CNS); CT-angiography (CTA); Traumatic brain injury (TBI); Cerebrovascular accident (CVA)

INTRODUCTION

The COVID19 pandemic caused by the SARS-CoV-2 virus started in Wuhan, China, in December 2019 and spread rapidly. The current focus is in North America and Europe. Spain, and particularly Catalonia, where the virus wave has overwhelmed the hospitals, is one of the most hard-hit regions of Europe.

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 [1], but later papers suggest different sorts of neurological complications [2–6].

Proposed mechanisms for neurological implications include:

- Direct central nervous system (CNS) spread, based on known neurotropism of previous SARS-COV strains, which could access CNS via olfactory pathways or bloodstream, causing meningitis and encephalitis [5,7]. The involvement of the respiratory center in the brainstem may hypothetically justify the well-documented rapid respiratory deterioration with marked hypoxia despite lack of symptomatic dyspnea [3,8].
- Indirect neurological involvement due to an excessive systemic pro-inflammatory response which may cause widespread dysregulation of homeostasis with coagulopathy and may also increase the risk of acute cerebrovascular diseases [1,9].
- Para-infectious 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 neurological symptoms in COVID-19 patients. These symptoms mainly include dizziness, headache, ataxia, and confusion [6,8,13]. One case-report suggests viral meningoencephalitis and ventriculitis with positive RT-PCR on cerebrospinal fluid in a young patient with consciousness disturbance and seizures [7]. Anosmia and dysgeusia, which are highly prevalent in early infection [14], have been proposed in support of the hypothesis of CNS spread via olfactory tract [4]. Cerebrovascular events in COVID-19 patients have also been documented: Krok et al. described 3 cases of acute ischemic stroke in a cohort of 184 ICU patients (1.6%) [15], while another preprint paper described acute cerebrovascular accidents (ischemic and hemorrhagic) in 13 patients out of 221 (5.9%) [16]. Finally, some cases of para-infectious autoimmune-based neurological manifestations concurrent to active COVID-19 have been described, including hemorrhagic necrotizing encephalopathy [12] and Guillain-Barré syndrome [10,11].

To the best of our knowledge, neuroimaging of the disease has not itself been evaluated to date.

Our objective is to present a large series of COVID-19 patients with neurological symptoms requiring neuroimaging.

CASE-SERIES

METHODS

This manuscript has been revised for publication by the research ethics committee of our tertiary hospital. The data of the patients were anonymized for the purposes of this analysis. The confidential information of the patients was protected in accordance with national and European Union norms. Unspecific informed consent to participate in research projects was obtained from all patients. Waiver of a specific informed consent was provided by the ethics committee for this retrospective study.

We performed a retrospective cross-sectional review of patients admitted to our tertiary care center between March 1st to April 18th 2020 with positive RT-PCR for SARS-CoV-2 in whom brain neuroimaging was performed.

Eligibility criteria were: 1) Positive record of RT-PCR for SARS-CoV-2; 2) Performed neuroimaging including either Head CT or MRI; and 3) 16 years old or older. Exclusion criteria were: 1) Neuroimaging performed more than 5 days before diagnosis (based on median incubation period 5.1 days [17]); or 2) Low-quality imaging on visual assessment.

Regarding our center's protocol, the RT-PCR for SARS-CoV-2 testing was performed if the patient presented severe respiratory symptoms (respiratory rate > 30 breaths per minute, blood oxygen saturation < 95%, with oxygen administered at 35%); or pulmonary infiltrates in x-ray suspicious of viral pneumonia. Furthermore, PCR testing was also performed on all inpatients, on patients who fulfilled criteria for in-hospital admission, on candidates for invasive surgical or interventional procedures, and on all hospital personnel with any respiratory or suspicious symptoms. Finally, also on vulnerable populations such as immunocompromised patients.

Minimum required imaging protocol consisted of 1) head CT with/without contrast from cranial base to apex, or 2) MRI, including T1WI, T2WI, T2*WI, DWI, and FLAIR. Available CT-angiography (CTA) were also reviewed but not included as eligibility criteria.

Variables reviewed included basic demographic and clinical characteristics, symptoms motivating neuroimaging, and acute neuroimaging findings.

Reasons for neuroimaging were grouped in seven categories: 1) “mild non-focal neurological symptoms” englobing symptoms such as headache, transient mild ataxia, dysarthria or mild confusion not fulfilling code-stroke criteria; 2) “activated code stroke/transient ischemic attack”; 3) “other focal neurological symptoms”; 4) “traumatic brain injury”; 5) “post-sedation encephalopathy”; 6) seizures; and 7) miscellany.

All imaging studies were independently reviewed by two certified neuroradiologists (PNB and APE). Demographics, clinical characteristics and neuroimaging indication were extracted from patients' clinical histories and neuroimaging. Quality assessment of the images was subjectively performed by both certified neuroradiologists (PNB and APE). Disagreements were solved by consensus.

RESULTS

From March 1st to April 18th, 2020, a total of 2,249 SARS-CoV-2 RT-PCR were admitted in our center. During the hospitalization period, 112 of these patients underwent head neuroimaging (17 Head-MRI, 111 Head-CT, and 27 CTA). Of these patients, nine were excluded (one with MRI+CT; two with CT+CTA; six with CT), eight of them because imaging was performed more than five days before SARS-CoV-2 diagnosis and one because of low-quality imaging (Figure 1). Accordingly, the final number of participants was 103 (Table 1).

Reasons for neuroimaging matched with neuroimaging findings are summarized in Figure 2 and are presented below by categories. Specific results in patients with MRI-only are presented in table 2.

1. Mild non-focal neurological symptoms. The most common reason for neuroimaging was a non-specific state of headache, mild alteration of consciousness, transitory dysarthria, or gait abnormality, with 40 patients (four CT+MRI, two CT+CTA, and 34 CT). Neuroimaging showed no acute findings in 36 patients. Two patients had distal small vessel acute infarctions (one cerebellar, one left prefrontal), a single patient had a left parietal lobar acute hematoma, and another had a basilar top aneurism.

2. Stroke/TIA. The second-most common reason for neuroimaging was an activated code-stroke or transient ischemic attack in 25 patients (seven CT+CTA+MRI, one CT+MRI, 11 CT+ CTA, and six CT). Six acute parenchymal hematomas were found: 3 deep basal ganglia, 3 lobar. Large vessel occlusion was observed in eight patients.

Three cases categorized as small-vessel occlusion included two acute lacunar infarctions and one patient with multiple multi-territory small distal acute parenchymal infarctions. Finally, eight cases had no acute neuroimaging findings.

3. Focal neurological symptoms. Eleven patients underwent neuroimaging for focal neural symptoms that did not fulfill criteria for code-stroke (two CT+CTA+MRI, one CT+MRI, one MRI, one CT + CTA, and six CT). Two patients with known malignancy had an increase in the size of previously known brain metastases, one of them presented 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 eight patients had no acute neuroimaging findings, one of them presented diplopia, the other seven mild acral paresis.

4. Traumatic brain injury (TBI). Seventeen patients underwent CT for trauma involving the craniofacial region. Sixteen had no significant acute intracranial findings. One had a focal left-parietal parenchymal hemorrhagic concussion.

5. Post-sedation encephalopathy: Five patients underwent CT (one of them with CTA also) because of Glasgow Coma Scale below 7. Four of them were patients with delayed recovery of consciousness after prolonged sedation in the ICU setting. One was a patient with severe respiratory failure. None had any acute findings on CT or CTA.

6. Seizures: 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 one patient, with no history of seizures or epileptogenic lesions, neuroimaging was normal, and seizures were considered to be related to carbapenem neurotoxicity, which was administered due to concurrent extended-spectrum β-lactamase *Klebsiella pneumoniae* infection.

7. Two isolated miscellaneous cases included a case of COVID-19 debut with Guillain-Barré syndrome, with normal neuroimaging (CT), and a case of *Staphylococcus aureus* endocarditis with mycotic aneurysms on CTA.

The above cases include 20 cases of non-traumatic cerebrovascular accidents (CVA), three of them not presenting as code-stroke. Details of cardiovascular risk factors in these patients are detailed in table 3. Most notably, 75% of all CVA patients had at least 1 vascular risk factor, and 61% had at least two, without considering age. However, in the case of the seven parenchymal hematomas, 3 had no vascular risk factors and were below 70 years of age. Moreover, of the four lobar hematomas, none had imaging characteristics or clinical history of cerebral amyloid angiopathy or any other predisposing factor.

DISCUSSION

We have analyzed one of the largest series of COVID-19 patients published to the date and focused on those patients with neurological symptoms requiring neuroimaging. The patients included in our analysis presented a varied spectrum of neuroimaging indications and findings. Nevertheless, a large number of symptomatic patients appeared to have negative neuroimaging.

A causal relationship with COVID-19 infection may be reasonably ruled out in some patients, such as the cases with neuroimaging performed because of TBI or the case of bacterial endocarditis. Cases with vague symptoms such as mild transitory altered level of consciousness or mild non-specific focal neurologic symptoms presented mostly normal neuroimaging results or alternative diagnoses independent of COVID-19, such as brain metastases and unruptured aneurysms. Furthermore, four cases of encephalopathy after prolonged sedation had normal neuroimaging. A non-specific delay in conscious-level recovery is not uncommon in patients with deep and prolonged sedation, which many COVID-19 patients require. Neuroimaging 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, seven patients with acute hemorrhagic lesions (four lobar and four deep basal ganglia), three patients with seizures, and one patient with Guillain-Barré syndrome and normal neuroimaging.

It is important to emphasize that there was a high prevalence of vascular risk factors among acute ischemic cerebrovascular events. Nevertheless, in the case of acute hemorrhagic lesions, there were several cases without such previous risk factors. Moreover, as illustrative data, during the same period, the number of code-stroke protocols activated in our center dropped 30% from the previous year. Out of 97 patients with activated code-stroke in this time-period, 18 were SARS-CoV-2 positive (19%) versus 79 which tested negative. To date, no reliable data is available on the prevalence of the infection in the local population.

The neurological symptoms in COVID-19 patients described in several papers are non-specific, and inconclusive for an underlying organic neurological damage. These symptoms included dizziness, headache, ataxia, and confusion, which are frequent transient symptoms of diverse scenarios such as infections, prolonged hospitalization periods, and post-treatment or post-procedural states, amongst others [6,13]. A case-report suggested viral meningoencephalitis and ventriculitis in a patient with positive RT-PCR determination on CSF and negative on the nasopharyngeal swab. This patient presented non-specific neurological symptoms such as consciousness disturbance and seizures, and imaging findings were not specific [7].Regarding anosmia and dysgeusia, a pre-peer-review study suggests that non-neural support cells but not sensory neural cells express the ACE2-receptor that is targeted by the virus. This 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 seems 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 COVID-19 patients. 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 disease, 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 of the patients, which requires a reorganization of hospital resources centered on providing the best possible assistance. Firstly, despite the relatively large sample of COVID-19 patients (2,249), only 103 who underwent neuroimaging could be included in this study. This could be partially explained by reasons such as: severely ill patients may not display neurological symptoms or may not be able to undergo imaging; or the concern for transporting infected patients and contaminating radiology equipment that may prompt a higher threshold for imaging indication. Secondly, not all presumably infected patients were tested, so the number of COVID-19 patients may be underestimated. Thirdly, full clinical and follow-up information was of limited availability, and complete neurologic examination was not always performed by an experienced neurologist, meaning that our results do not represent all the clinical neurological syndromes affecting these patients. Nevertheless, despite these limitations, we believe this local review is relevant mainly because COVID-19 is a global phenomenon, and many other centers probably experience the same hindrances that hinder robust data analysis.

CONCLUSION

We have analyzed one of the largest series of COVID-19 patients published to the date and focused on those with neurological 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. 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 para-infectious entities seems plausible, as they are in the context of other infectious processes.

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	All patients	**Inpatients**	**Emergency Ward**
n	103	64	39
Sex			
- male n (%)	63 (61 %)	37 (58 %)	26 (67 %)
- female n (%)	40 (39 %)	27 (42 %)	13 (33 %)
Age years	74 (50.2 - 90)	71.5 (48 - 90)	75 (30.3 - 89)
Imaging technique			
- CT	102 (99 %)	63 (98 %)	39 (100 %)
- CTA	25 (24 %)	14 (22 %)	11 (28 %)
- MRI	16 (16 %)	13 (20 %)	3 (8 %)

Table1. Demographic and imaging technique characteristics. Categorical variables [*n (%)].* Age *[median (p5-p95)].*

Reason for MRI	n	Findings of MRI	
Code stroke	8	Acute ischemic (small vessel)	3
		Acute ischemic (large vessel)	2
		Parenchymal hemorrhage	3
Other focal neurological symptoms	4	Metastasis	2
		Aneurysm	1
		Normal	1
Mild non-focal neurological symptoms	4	Acute ischemic	1
		Parenchymal hemorrhage	1
		Normal	2

Table2. Patients undergoing MRI.

	All code stroke & CVA	Ischemic	Hematoma	Normal
n	28	13	7	8
Sex				
- male	16 (57 %)	7 (54 %)	6 (86 %)	3 (38 %)
- Female	12 (43 %)	6 (46 %)	1 (14 %)	5 (63 %)
Age years [median (range)]	71 (45-89)	74 (45-89)	68 (49-78)	73.5 (67-77)
Vascular risk factor				
- Hypertension	20 (71 %)	9 (69 %)	4 (57 %)	7 (88 %)
- Hypercholesterolemia	14 (50 %)	7 (54 %)	2 (29 %)	5 (63 %)
- Diabetes mellitus	9 (32 %)	3 (23 %)	2 (29 %)	4 (50 %)
- Smoker	2 (7 %)	0 (-)	1 (14 %)	1 (13 %)
- Atrial fibrillation	2 (7 %)	2 (15 %)	0 (-)	0 (-)
At least 1 CV risk factor	21 (75 %)	10 (77 %)	4 (57 %)	7 (89 %)
At least 2 CV risk factors	17 (61 %)	7 (54 %)	3 (43 %)	7 (89 %)

Table3. Demographic and vascular risk factors in cerebrovascular accident and all code-stroke patients. Abbreviations: Cardio-vascular (CV); Cardio-vascular Accident (CVA).

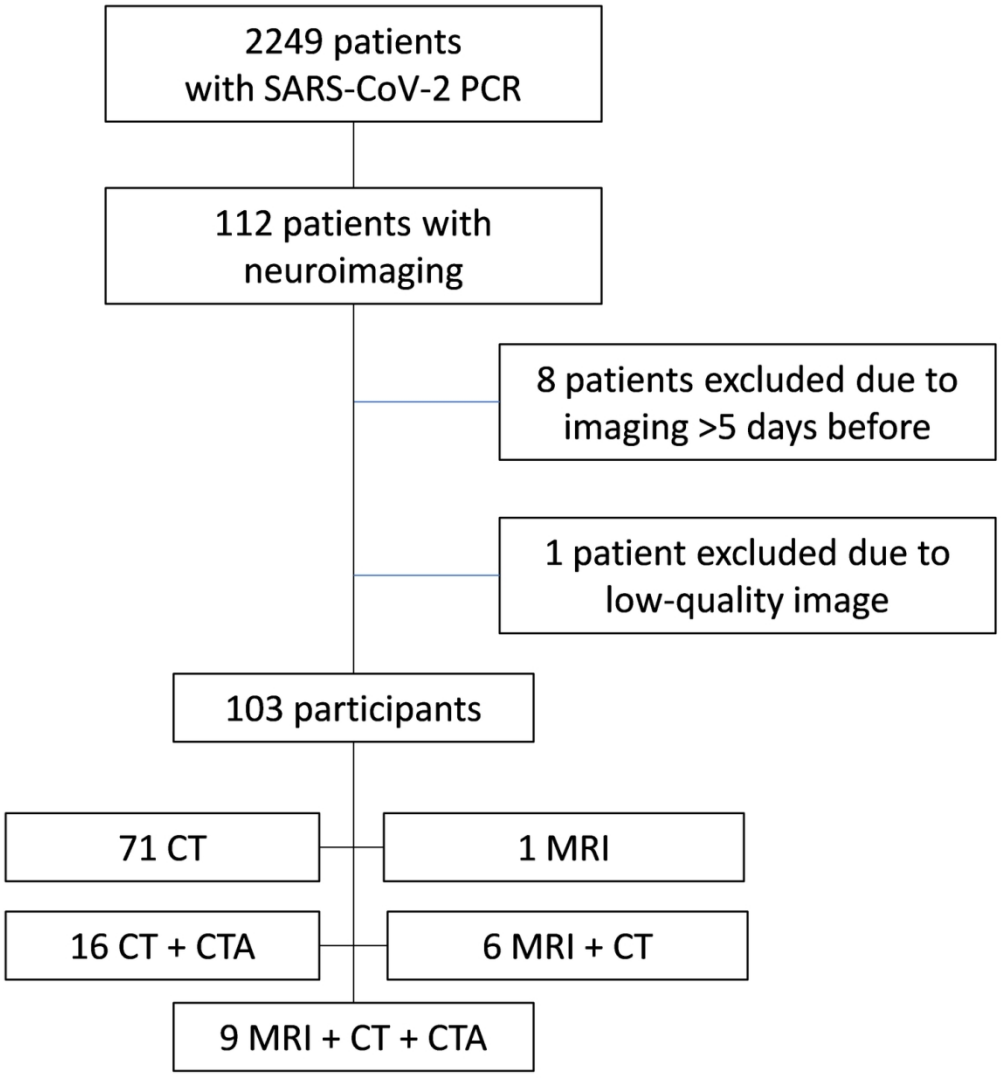

Figure1. Recruitment flowchart.

125x135mm (300 x 300 DPI)

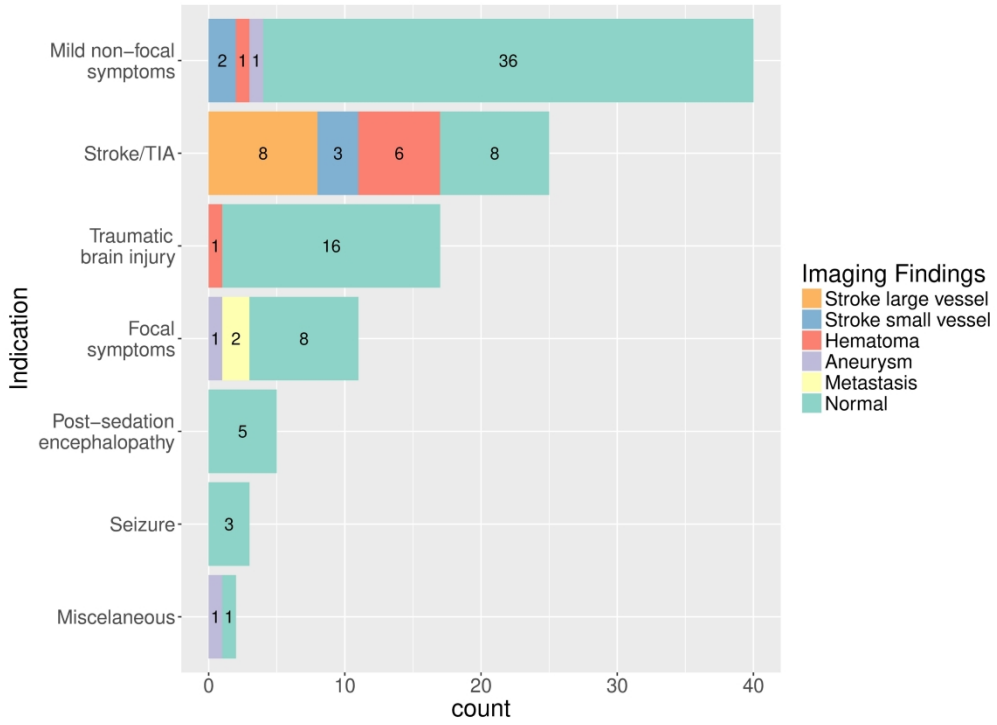

Figure2. Summary of results, including all neuroimaging patients (MRI/CT). Reason for neuroimaging on the y-axis. Neuroimaging findings color-coded in legend. Notes: Mild non-focal neural symptoms refers to any mild state of altered consciousness, mild transient dysarthria, mild transient gait abnormality, or headache; lacunar or small distal cortical infarctions not susceptible to thrombectomy were considered "small-vessel."

290x210mm (300 x 300 DPI)