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ORIGINAL PAPER

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Neurological complications encountered in imaging studies in association with COVID-19 – a single center analysis

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ABSTRACT

Introduction and aim. COVID-19 is a viral infectious disease, which was first reported in patients with unusual pneumonia in December 2019. However, as the pandemic progressed, extrapulmonary manifestations including various neurologic complications have been started to be increasingly reported. In this retrospective study, we tried to search the neurological complications seen in our patients with positive rRT-PCR test for COVID-19 and examine the underlying associated risk factors.

Material and methods. We have retrospectively analyzed the neuroimaging studies performed in our patients with positive rRT-PCR test for COVID-19 between April, 2020 and August, 2021. Both computed tomography (CT) scans and magnetic resonance imagings (MRI) of brain, head & neck region and the spine were retrospectively evaluated for the presence of any complications in patients with positive rRT-PCR test for COVID-19.

Results. There were 147 patients having neuroradiological imaging studies performed for various neurological symptoms. Among these patients we detected 10 acute neurologicalcomplications.The most common was acute ischemic stroke in 5 patients and intracranial hemorrhage in 3 patients, two of which were intraventricular hemorrhage. The other complications included a preasumed cytotoxic lesion of corpus callosum in a 18 year old girl and lumbar spondylodiscitis complicated with psoas abcess in a 47 year-old man.

Conclusion. In COVID-19 patients severe neurological complications can occur even as a presenting manifestation. Early cytotoxic endothelial injury can be the underlying cause in these patients and should be further studied in larger series in terms of what the susceptibility factors in these patients.

Keywords. COVID-19, direct viral toxicity, endotheliitis

Introduction

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) associated coronavirus disease 2019 (COVID-19) is a viral infectious disease, which was first reported in patients with unusual pneumonia in December 2019 at Wuhan, China.[1] It was recognized as a pandemic by the World Health Organization (WHO) on 11 March 2020.[2] The main mode of transmission is human-to-human spread via respiratory droplets presenting primarily with pulmonary manifestations. However, as the pandemic progressed, extrapulmonary complications started to be frequently reported. Neurological manifestations, ranging from headache, myalgia, hyposmia/anosmia, hypogeusia/ageusia to severe complications such as impaired consciousness, stroke, encephalitis and encephalopathies have been also reported particularly in severelly ill patients from the disease.[3-6] In a case series of 214 patients, neurologi-

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cal complications have been observed in 36.4% of the overall cases and the more severe complications were reported in patients with more severe infection. In this case series 5.7% (5 patients) of the neurological complications were acute cerebrovascular diseases (4 patients with ischemic stroke and 1 patient with cerebral hemorrhage).[4] Acute cerebrovascular diseases most of which are acute ischemic stroke were reported up to 6% of hospitalized patients with severe inflammatory state.[7] The hyperinflammatory state and associated edothelial damage has been suggested as an endogenous pathway in the pathophysiology. However, although less frequent, some neurological complications have been reported in young COVID-19 patients without severe disease, even as an presenting manifestation leading to the diagnosis of COVID-19.

Aim

In this retrospective study, we tried to search the neurological complications seen in our patients with positive rRT-PCR test for COVID-19 and examine the underlying associated risk factors.

Material and methods

We have retrospectively analyzed the neuroimaging studies performed in our patients with positive rRT-PCR test for COVID-19 between April, 2020 and August, 2021. Ethics approval has been obtained from Altınbas University School of Medicne Bahcelievler Medical Park Hospital Ethics Committee. Both computed tomography (CT) scans and magnetic resonance imagings (MRI) of brain, head & neck region and the spine were retrospectively evaluated for the presence of any complications in patients with positive rRT-PCR test for COVID-19. The CT images were obtained using 64 channel MDCT scanners (Philips Medical Systems, Brilliance 64, the Netherlands). MR imaging was performed with the Siemens 3T MAGNETOM Skyra MRI scanner. The pulse sequences were coronal FLAIR (TE/TR =125/10000 msec; TI=2800 msec), axial T2 (TE/TR=80/3000 msec), axial T1 (10/2000 msec), diffusion-weighted imaging (DWI) (TE/TR=120/3500 msec) with apparent diffusion coefficient (ADC) maps.

Results

There were 147 patients having neuroradiological imaging studies performed for various neurological symptoms including headache, anosmia, vertigo, impaired consciousness, transient ischemic attacks, acute neurological deficits and peripheral neuropathic symptoms in patients with positive rRT-PCR test for COVID-19. Among these patients we detected 10 acute neurologicalcomplications. The most common was acute ischemic stroke (AIS) (5 patient with M/F; 3/2, mean age; 75) (Fig. 1, 2) followed by intracranial hemorrhage (ICH) (Fig. 3, 4) (3 patients with F/M: 2/1, mean age; 73); all of these 8 cases were older age patients (older than 60 years). All of them had at least one traditional cardiovascular risk factors including hypertention (HT), type 2 diabetes (T2DM), obesity and/or smoking.

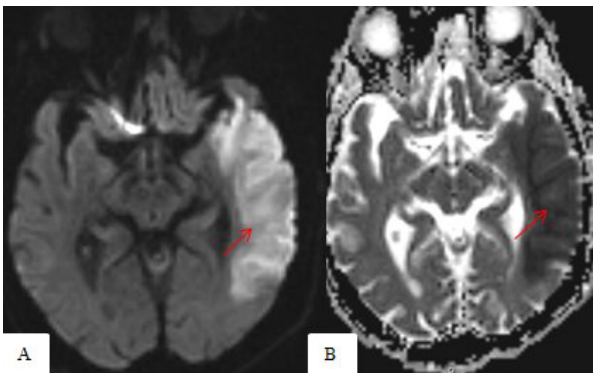

Fig. 1. A 72-year-old male patient with T2DM, HT, obesity and smoking history presented with COVID-19 pneumonia and followed in ICU. A) DWI and B) ADC mapping of the brain show restricted diffusion at the left MCA territory characterized with hyperintensity on DWI (A, arrow) and corresponding low signal intensity on ADC mapping (B, arrow) compatible with AIS

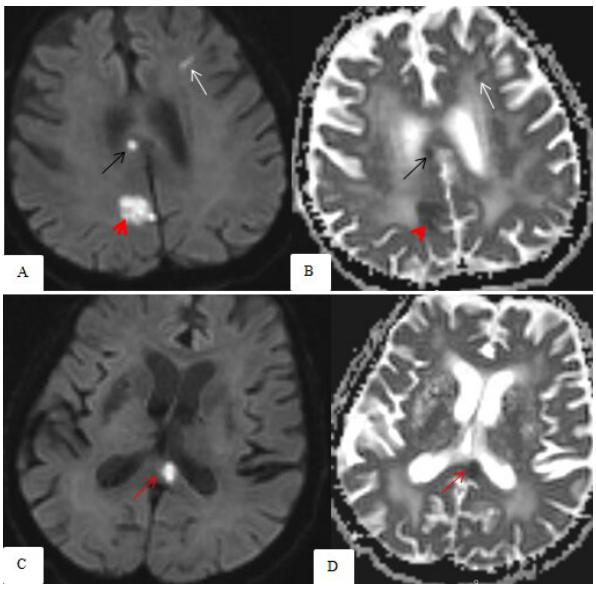

Fig. 2. A 92-year-old female patient with with hypertention who presented with COVID-19 pneumonia and followed in ICU. A) DWI and B) ADC mapping of the brain show multifocal restricted diffusion at the left anterior corona radiata (A,B white arrow), at the right parasagittal frontal (A,B ablack arrow) and parietal lobes (A,B red arrow head), at the splenium of corpus callosum (C,D red arrow)

In all of the ICH patients and 3 of the AIS patients the cerebrovascular events occured in intensive care unit (ICU) when they were under management for severe COVID-19 pneumonia. The other two patients

with AIS had also COVID-19 pneumonia but were being followed in hospital setting, not in ICU. All of these patients were under anticoagulation treatment, except one patient with AIS of left MCA territory, due to his previous history of ICH and one patient with intraventricular hemorrhage (IVH) due to uncontrolled HT during the ICU course (Table 1).

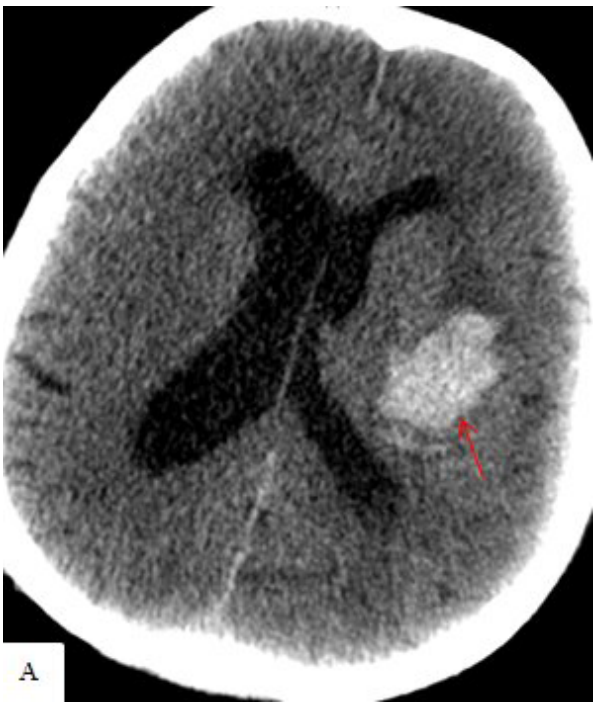

Fig. 3. A 60-year-old male patient presented with COVID-19 pneumonia and followed in ICU with anticoagulation treatment. Parenchymal window axial CT image shows acute left thalamic cerebral hematoma (arrow)

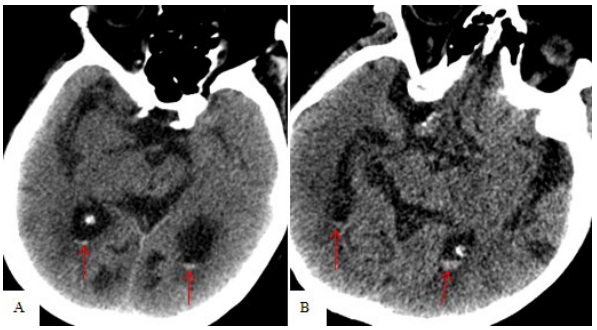

Fig. 4. A 78-year-old female patient under anticoagulation (A) and a 81 year old female patient without prophylactic anticoagulatiob presented with COVID-19 pneumonia and followed in ICU. Axial CT images show small amoutns of IVH (A,B, red arrows) without obvious parenchymal hemorrhage

The other complications included a preasumed cytotoxic lesion of corpus callosum (CLCC) in a 18 year old girl (Fig. 5).

In this young patient with positive rRT-PCR test for COVID-19 presenting with presyncope, a focal restricted diffusion in the splenium of the corpus callosum was present on MRI and CLCC was considered in this previously healthy patient despite the lack of follow-up MRI to show its reversibility.There was no other white matter lesion to suggest demyelinating processes.The last complication was lumbar spondylodiscitis (LSD) complicated with psoas abcess in a 47 year-old man with no relevant medical history except long lasting smoking (Fig. 6).

These two complications occured at the absence of any pulmonary disease and were the presentations of the patients that lead to the diagnosis of COVID-19 (Table 2).

Table 1. Demographic features of the patients

	Age	Sex	Medical history	Presentation with COVID-19 pneumonia	ICU	Location	Anticoagulation
AIS	92	Female	HT	Yes	Yes	Bifrontal, right parietooccipital sulcus, splenium of the corpus callosum	yes
	67	Female	HT, smoking	Yes	No	Right hemipontine	Yes
	75	Male	Obesty,T2DM, HT, smoking	Yes	Yes	Left MCA territory	No (previous ICH)
	72	Male	Smoking	Yes	Yes	Left MCA territory	Yes
	69	Male	HT, T2DM, smoking	Yes	No	right frontal and left parietal	Yes
ICH	81	Female	HT	Yes	Yes	IVH	No (uncontrolled HT)
	78	Female	Obesity, T2DM, HT	Yes	Yes	IVH	Yes
	60	Male	HT, smoking	Yes	Yes	Left thalamic	Yes

AIS; acute ischemic stroke, ICH; intracranial hemorrhage, HT; hypertention, T2DM; type 2 diabetes mellitus, ICU; intensive care unit, MCA; middle cerebral artery, IVH; intraventricular hemorrhage

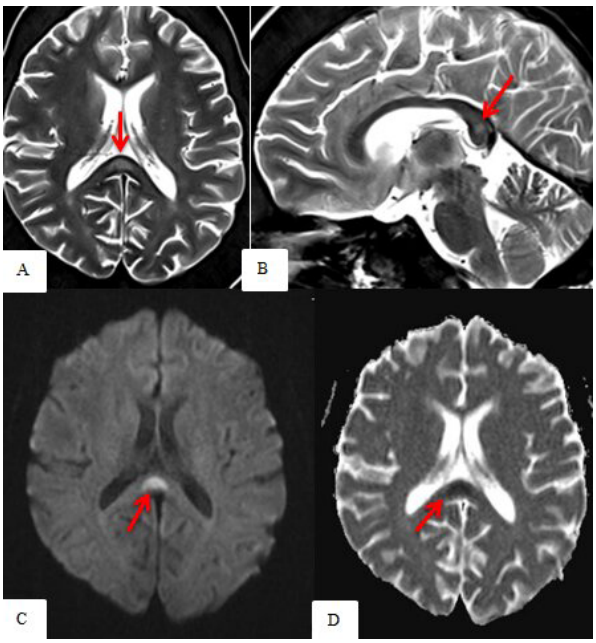

Fig. 5. MRI showing CLCC; A) axial T2w and B) sagittal T2w images showing hyperintense lesion at the splenium of the corpus callosum (A,B; red arrows). C) DWI and D) ADC map show restricted diffusion of the lesion (C,D; red arrows)

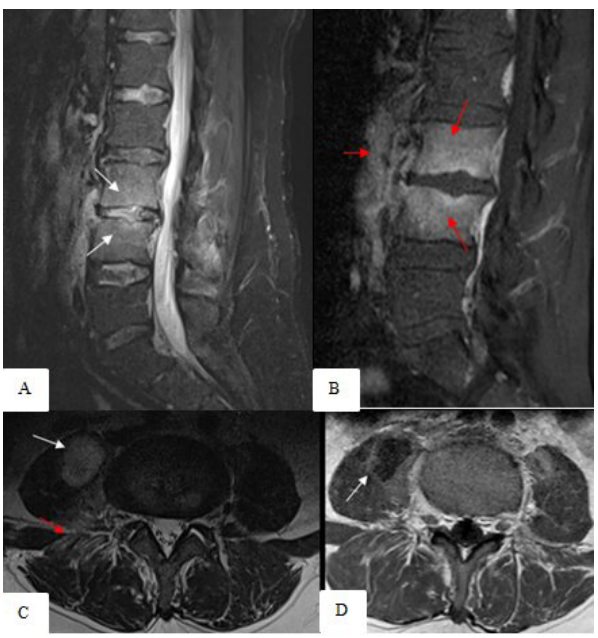

Fig. 6. Lumbar MRI demonstrating abnormally increased signal intensity involving L3-L4 vertebral bodies on sagittal STIR image (A, white arrows) and the contrast enhancement in both the involved vertebral bodies and also in the inflammatory prevertebral soft tissue on sagittal postcontrast T1w image (B, red arrows). Abnormal signal intensity involving the right prevertebral soft tissue (C, red arrow) and the encapsulated hyperintens collection in the right psoas muscle (C, white arrow) are demonstrated on axial T2w image. The enhancing wall with central necrotic cavity on axial poscontrast T1w images (D, white arrow) is shown

Table 2. The complications other than acute cerebrovascular diseases

	Age	Sex	Medical history	COVID-19 pneumonia	Presenting symptom
CLCC	18	Female	None	No	Presyncope
LSD	47	Male	Smoking	No	Severe back pain

CLCC: cytotoxic lesion of corpus callosum, LSD; lumbar spondylodiscitis

Discussion

The mechanisms underlying the neurological complications caused by SARS-CoV-2 have become a research of interest due to various neurological symptoms that have been reported increasingly as the pandemic progresses. Moreover, many of the neurological complications are probably underreported due to the lack of further diagnostic evaluations. In COVID-19, an inflammatory state with increased level of cytokines, including IL-6, is generated and suggested as an endogenous pathway in the pathophysiology of most of the complications including cerebreovascular diseases in severe cases. The hyperinflammatory state has been shown to be associated with subsequent coagulopathy characterized with increased level of procoagulant mediators, which can present with thrombotic events like venous thrombosis, pulmonary thromboembolism, acute myocardial infarction and acute ischemic stroke, resulting in prophylactic anticoagulation in the management of COVID-19 patients, if the coagulation parameters are suitable.[8] In a study conducted in 16 critically ill patients, it was found that in correlation with increased level of IL-6; the fibrinogen, platelet and D-dimer levels were also increased.[9] In this endogenous pathway the hyperinflammatory state is also suggested as a cause of endothelial damage. Early in the pandemic, the endothelial damage was shown in the form of lymphocytic endotheliitis in the lungs of deceased COVID-19 patients. An angiocentric inflammation with pulmonary vessel enlargement having extensive endothelial injury, as opposed to the normally expected lung's vasoconstriction response to pneumonia was well demonstrated.[10,11] Although histopathologic evaluation of CNS is scarce, this endotheliopathy has been also demonstrated in various other organs including heart, kidney, liver and small intestine of three COVID-19 patients in a postmortem examination.[12] Endothelial damage in the microcirculation can cause ischemia as a result of subsequent vasoconstriction and also serves as an additional predisposing factor for prothrombotic events with dysregulation of antithrombotic functions of the endothelium. Moreover, although less frequently reported and most often considered as a result of thereupathic anticoagulation in COVID-19 patients, hemorrhagic manifestations have

been also supposed to be associated with the endothelial damage as a possible cause of rupture of arterial wall.[13] Cezar-Junior et al. demonstrated four cases of subarachnoid hemorrhage (SAH) in patients with COVID-19 and suggested to some extent the exacerbated systemic inflammatory process as a cause.[14] As our knowledge, IVH which is much more common as a secondary complication of intraparenchymal hemorrhage or SAH, has been very rarely reported as a primary in association with COVID-19.[15] Two of our ICH cases were presented with primary IVH, one of which was not under anticoagulation due to uncontrolled HT. Older patients with already damaged endothelium due to one or more traditional cardiovascular co-morbidities are expected to be more prone to these complications, as seen our patients. On the other hand, Harris CL. et al. reported a fatal case of IVH with associated hydrocephalus without obvious parenchymal source of bleeding in a 32 year-old young man who was not on any anticoagulation or antiplatelet medication and had no significant comorbidities.[16] We did not see AIS and ICH in patients without preexisting cardiovascular risk factors at the absence of moderate to severe COVID-19. Likewise, in a study including 219 hospitalized patients with COVID-19 in Wuhan, Chine acute stroke were found more likely in older patients presenting with severe pulmonary infection, having cardiovascular risk factors, as in our patients.[17] In addition, a few studies demonstrated AIS cases at the absence of severe pulmonary/systemic disease and cardiovascular comorbidities.[18,19] An example is a case series by Oxley et al. reporting five cases of large vessel stroke in COVID-19 patients younger than 50 with no previous medical history. [20] In these cases a direct toxic endothelial injury rather than the endogenous pathway of exacerbated systemic hyperinflammatory state seen in severe disease, can be considered. The most proposed mechanism underlying this direct neurotropism of COVID-19 is the expression of angiotensin-converting enzyme 2 (ACE-2) receptors in the endothelium which are used by SARS-CoV-2 for viral entry to the host cells via their large spike glycoproteins present in all Coronaviruses as a family. ACE-2 receptors are widely expreseed in the type 2 alveolar cells, epithelial cells of the gastrointestinal tract, and also in the endothelial cells.[21-23] SARS-CoV-2 would theoretically use ACE2 receptors expressed in cerebrovascular endothelial cells and cause direct virus induced toxicity. Our two atypical cases of CNS complications occured as a presenting manifestation of COVID-19 also suggest the direct viral toxicty as the underlying pathophysiology of early neurological presentations. A few reported cases of CLCC and posterior reversible encephalopathy syndrome in association with COVID-19 and also our preassumed case of CLCC suggest a direct cytotoxic endothelial injury in the cerebral vasculature resulting in damage to vascular autoregulation and cerebral perfusion.[24-28] Furthermore, in our last patient presenting with LSD, there was no previous history of spinal instrumentation or any trauma. Laboratory results excluded tuberculosis and brucellosis. Abdominopelvic imaging excluded the other possible causes of psoas abcess originating from gastrointestinal diseases like appendicitis, diverticulitis or perforation and urinary diseases. We thought that these pyogenic complications could have been associated with hematogenous dissemination from asymptomatic colonization sites via SARS-CoV-2 induced endotheliitis.[29] In this patient, the longlasting smoking history could have served as a contributing factor for the occurance of early endothelial damage. Another support from our experience is that, we encountered and reported in our previous studies that the pulmonary vasoplegia is present not only in severe systemic disease associated with cytokine storm but also in very limited early pneumonia, meaning that vasoplegia can present early in the disease and could have been also present in the systemic vasculature including the cerebral vessels and can responsible for early extrapulmonary and neurological complications.[30]

Conclusion

In COVID-19 patients despite the paucity of data, severe neurological complications can occur and clinicians should have a high clinical suspicion particularly in patients with severe disease. Moreover, it should be kept in mind that neurological complications can also occur even as a presenting manifestation in the absence of any pulmonary disease. Early cytotoxic endothelial injury can be the underlying cause in these patients and should be further studied in larger series in terms of what the susceptibility factors in these patients, like receptor polymorphism. Our study also shows that, in addition to AIS which has been more frequently reported till now, ICH cases and interestingly primary IVH can be included in severe neurological manifestations seen in patients with COVID-19. In addition, as a viral infectious disease SARS-CoV-2 can be also associated with pyogenic complications from asymptomatic bacterial colonization sites possibly via hematogenous dissemination due to viral induced endotheliitis.

Declarations

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Author contributions

Conceptualization, B.E.; Methodology, B.E.; Formal Analysis, B.E. and H.Ö.; Investigation, B;E; and A.Ö.A.; Writing – Original Draft Preparation, B.E.; Writing – Review & Editing, B.E and H.Ö.; Supervision, B.E. and HÖ.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

The data sets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethics approval

Ethics approval has been obtained from Altınbas University School of Medicne Bahcelievler Medical Park Hospital Ethics Committee.

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