Evaluation of Intracranial Vascular and Non-Vascular Pathologies in Patients Hospitalized Due to COVID-19 Infection

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Abstract

Introduction: Although SARS-CoV-2 is a respiratory virus and presents with respiratory system infection, different clinical presentations may appear by affecting other organs and systems. Along with vascular diseases in COVID-19 disease, other conditions involving CNS such as meningocephalitis, cerebral edema and lesions on corpus callosum. The possible underlying mechanism may be direct invasion of CNS by the virus; however, it is hypothesized that immune-mediated inflammatory response or cerebral edema may appear without direct viral invasion. Brain MRI and CT have an extremely important place in the diagnosis when CNS involvement is clinically suspected in people infected with COVID-19. The aim of the present study was to review vascular and non-vascular pathologies appeared during COVID-19 infection and contribute to the literature for early diagnosis.

Material and Method: The study was monocentric, retrospectively designed between March 2020 and May 2021 in a tertiary healthcare facility. Among the patients who underwent neurological evaluation, patients with anomaly in brain MRI and CT were included in the study.

Findings: Among 5,430 patients who have been admitted due to COVID-19 between the dates mentioned above, 51 patients including 27 (52.9%) females and 24 (47.1%) males presented abnormal findings in cerebral radiological tests. Vascular abnormality was detected in 45 patients whereas 6 patients presented non-vascular abnormality. General demographic data was presented in Table 1; concomitant diseases of the patients were presented in Table 2.

Discussion: In line with the literature, this study which reviewed abnormalities of CNS involvement reflected on brain MRI and CT among neurological complications due to COVID-19 infection revealed that vascular abnormalities occur more common and vascular events constitute the majority of ischemic cerebrovascular events. Presence of concomitant diseases including advanced age and hypertension was detected as risk factors for development of vascular abnormality. It was documented that corpus callosum splenium lesion, cerebral edema, parenchymal lesions with temporary contrast enhancement have been detected among non-vascular brain anomalies which are less common and treated differently and these are at earlier ages when compared to patients with vascular anomalies with fewer co-morbidities and shorter duration of infection. Uncertainty on CNS complications of SARS-CoV2 still persists. Therefore, acute neurological symptoms with new onset should be considered during COVID-19 infection, and it is concluded that diagnosis should be supported radiologically in clinically suspected cases. It should be kept in mind that other pathologies that may require combined therapies may also exist beyond ischemic and hemorrhagic stroke. Therefore, larger cases series are needed for diagnosis and treatment.

Keywords: COVID-19, neurological manifestations, brain imaging, vascular pathologies, non-vascular pathologies.

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INTRODUCTION

World Health Organization (WHO) 2020 has announced pandemic for the disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) as Coronavirus disease 2019 (COVID-19) [1]. Although SARS-CoV-2 is a respiratory virus and presents with respiratory system infection, different clinical presentations may appear by affecting other organs and systems [2]. SARS-CoV-2 binds to Angiotensin-Converting Enzyme 2 (ACE2) through a superficial glycoprotein called spike which commonly exists in the brain as well as type 2 alveolar cells, and enters into the host cell [3]. Beyond ACE-2, the virus causes infectious injury, hypoxic injury or immune response, and may cause damage on the Central Nervous System (CNS) [4].

A retrospective study on 214 patients diagnosed with COVID-19 detected that neurological findings appeared in 78 /36.3%) patients, and 53 (24.8%) of these patients developed CNS involvement [5]. The most common CNS findings detected in this study include dizziness (36, 16.8%), headache (28, 13.1%), and acute cerebrovascular disease (5, 5.7%) on 5 patients including 4 patients with ischemic disease and 1 with hemorrhagic disease during severe COVID-19 disease. The prevalence of acute cerebrovascular disease was reported to vary between 2% and 17% in COVID-19 infection in another studies [6]. It was detected that majority of the patients who had stroke had multiple co-morbidities including advance age and hypertension, diabetes mellitus, and previous history of stroke. In addition to elder patients, case reports of stroke due to COVID-19 infection before the age of 50 have also been documented, and it has been stated that these patients are mostly in the early return of viral infection [7]. It is considered that stroke may have occurred as a result of coagulopathy and vascular endothelial dysfunction due to COVID-19 infection [8].

Along with vascular diseases in COVID-19 disease, other conditions involving CNS such as meningocephalitis, cerebral edema and lesions on corpus callosum [9,10]. The possible underlying mechanism is suggested as direct invasion of CNS by the virus [9]. However, it is hypothesized that immune-mediated inflammatory response or cerebral edema may appear without direct viral invasion.

Brain magnetic resonance imaging (MRI) and computed tomography (CT) have an extremely important place in the diagnosis when CNS involvement is clinically suspected in people infected with COVID-19. This involvement may be vascular as well as non-vascular lesion due to parenchymal injury. The treatments for these conditions which may occur due to different pathophysiology. The aim of the present study was to review vascular and non-vascular pathologies appeared during COVID-19 infection and contribute to the literature for early diagnosis.

Material and Method

The study was monocentric, retrospectively designed between March 2020 and May 2021 in a tertiary healthcare facility (Health Sciences University, Trabzon Kanuni Training and Research Hospital). The study was performed in accordance with the principles of Helsinki Declaration. The study was started after approval of hospital management and Local Ethical Committee for Non-Pharmaceutical Clinical Researches (Number: 2021/79). Both written and verbal informed consent was acquired from all participants.

Inclusion criteria; among the patients with a diagnosis of COVID-19 who underwent neurological evaluation while being followed up in the hospital, anomaly was detected in brain MRI and CT. The diagnosis of COVID-19 disease was made with presence of clinical findings (i.e. fever, weakness, cough) as well as positive SARS-Cov-2 Reverse Transcriptase (RT-PCR) test, or a negative SARS-CoV2 RT-PCR test and typical radiological findings on thorax CT for the disease. The medical record of patients hospitalized for COVID-19 were scanned. Exclusion criteria of the study were determined as suspected patients for COVID-19 diagnosis, patients with incomplete file data, non-hospitalized patients, not having a neurological examination, and those whose CT and MRI images were unavailable.

Demographic data of the patients, such as age, sex, outcome (alive or dead), concominant diseases, number of COVID-19 clinical days. In addition to neurological diseases such as Parkinson's disease, epilepsy, cerebrovascular disease; hypertension, diabetes, atrial fibrillation, coronary artery disease and renal failure were recorded as concominant diseases.

Imaging

Computed tomography (CT)

Brain CT and Thorax CT examinations were obtained on the GE Revolution EVO 128 slice (Made in USA) device. Axial, coronal and sagittal slices with a slice thickness of 5 mm were created in brain CT in the scan protocol. Slices of 3 mm on the axial plane and slices of 5 mm on the coronal plane were obtained in thorax CT. Slices were obtained as contrast-free. All evaluations were performed on slices obtained by standardized protocols.

Magnetic Resonance Imaging (MRI)

In the MRI exam, T1W, T2A and FLAIR axial sections and sagittal T2W, coronal T2A sections are obtained, followed by contrast-enhanced T1W axial and coronal sections. Slice thicknesses were 5 mm. In diffusion-weighted images, the b value is taken as 0. 500 and 1000.

Statistical analysis

The statistical analysis was performed through SPSS for Windows (version 22.0). Descriptive analyses were presented by mean ± standard deviation, minimum and maximum. The Kolmogorov-Smirnov test was used to reveal whether the data were normally distributed. Parametric tests were used to analyze normally distributed data, and non-parametric tests were used to analyze non-normally distributed data. Student t test was used for quantitatively comparing two independent groups. Non-normally distributed continuous variables were compared using the Mann-Whitney U test. Chi square test was used to compare qualitative data. Any p-value level below <0.05 was considered as statistically significant.

RESULTS

Among 5,430 patients who have been admitted due to COVID-19 between the dates mentioned above, 51 patients including 27 (52.9%) females and 24 (47.1%) males presented abnormal findings in cerebral radiological tests. The rate of abnormal findings by brain MRI and/or CT in hospitalized COVID-19 patients was 0.93%, and the mean age of these patients was 72.4 ± 14.7 years; clinical duration of COVID-19 disease by Modified Charslson Comorbidity index (MCCI) was 5.4 ± 2.7, 6.9 ± 6.5 days. Nineteen (37.3%) of 51 patients enrolled have dies whereas 32 (62.7%) patients survived.

The patients were divided into two subgroups as vascular and non-vascular; general demographic characteristics of the patients are presented in Table 1. It was found that the patients with abnormal vascular findings were older than the patients with non-vascular abnormalities; however, there was not any significant difference when the COVID-19 clinical day, the outcome of the disease (alive/dead), and the MCCI score were compared. Concomitant diseases were summarized in Table 2, and number of patients without any concomitant disease was 6. Hypertension was found significantly higher in the group with abnormal vascular findings, and no significant difference was found between the two groups for other diseases.

Number of patients with vascular abnormality was 45 whereas number of patients with non-vascular abnormality was 6. Coexistence of vascular and non-vascular anomaly was not found in the same patient. Among patients with abnormal vascular findings; 35 were classified as ischemic cerebrovascular event (0.64%) and 10 as hemorrhagic cerebrovascular event (0.18%) (5 subarachnoid hemorrhage, 4 parenchymal hemorrhage and 1 subdural hematoma).

Table 1. Demographic characteristics of patients

	Patient with abnormal vascular findings	Patients with abnormal non-vascular findings	p
Age	75.0 ±13.2	53.5 ± 11.6	0.001*
Gender F/M	22/23	2/4	0.67 †
Live/Alive	28/17	4/2	0.60
MCCI	5.8 ± 2.5	2.8 ± 3.1	0.03*
COVID-19 clinical presentation day	6.6 ± 5.4	9.3 ± 13.0	0.87

*Mann-Whitney U test, Chi-Square test

Table 2. Concomitant diseases

Diseases	All patients n, (%)	Patients with abnormal vascular findings n, (%)	Patients with abnormal non-vascular findings n, (%)	p
Hypertension	40 (78.4)	38/7	2/4	0.01
Diabetes	20 (39.2)	19/26	1/5	0.38
Coronary artery disease-cardiac failure	24 (47.1)	23/22	1/5	0.19
Atrial fibrillation	13 (25.5)	12/33	1/5	0.51
Dementia	12 (23.5)	12/33	0/6	0.31
Previous cerebrovascular disease	12 (23.5)	12/33	1/5	0.51
Renal failure	8 (15.7)	5/38	1/5	0.66
Hyperlipidemia	8 (15.7)	8/37	0/6	0.57
Chronic lung diseases	6 (11.8)	6/39	0/6	0.45
Epilepsy	2 (3.9)	2/43	1/5	0.31
Parkinson's disease	1 (2)	1/44	0/6	0.88

Fisher's exact test

The p value was obtained by comparing the presence or absence of the specified additional disease in patients with abnormal vascular and non-vascular findings.

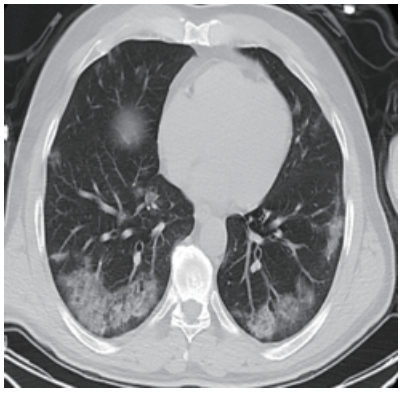

Image 1. Significant bilateral frosted glass image on lower zones of computed tomography of thorax on case 1

Four of the 6 (0.07%) patients with non-vascular abnormalities are described in detail as a case report, and one of the remaining 2 patients did not have any additional disease and died after being diagnosed with brain damage due to hypoxia after sudden cardiac arrest. The other case was the patient who was diagnosed with lung cancer before COVID-19 infection and whose lesions were found to be compatible with metastasis.

Cases with abnormal non-vascular findings;

Case 1; a 58-year-old male patient with no known disease was admitted to the hospital with a change in consciousness. Significant frosted-glass images, especially in the lower zones were found to be compatible with COVID-19 in the thorax CT performed at admission.

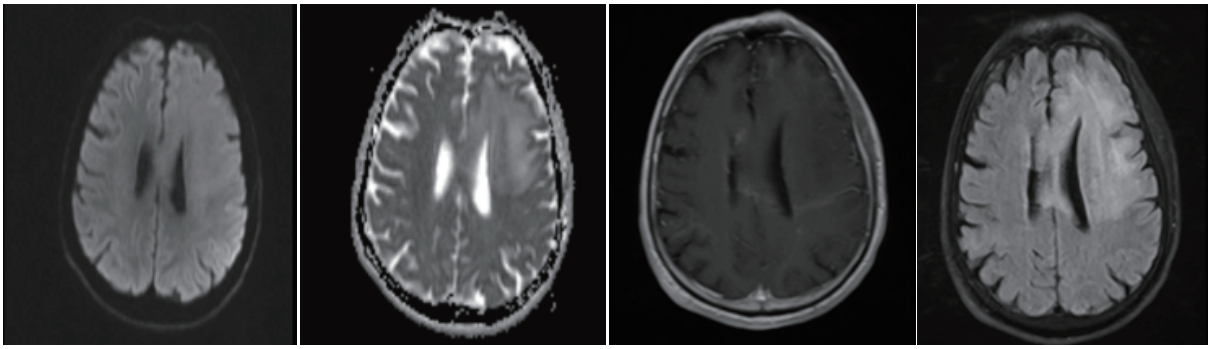

Image 2. First brain MRI images of case 1, more prominent on the left in diffusion, hyperintense in bilateral diffusion, isohyperintense in ADC, hyperintense lesion on the left in FLAIR section without significant contrast uptake

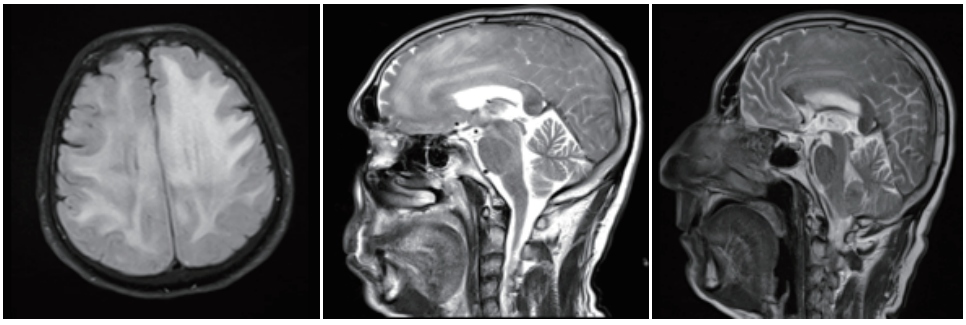

Image 3. The lesion diffusing from the corpus callosum to the opposite hemispher with a significant increase in the control brain MRI images taken after the clinical worsening of case one when compared to the initial brain MRI images

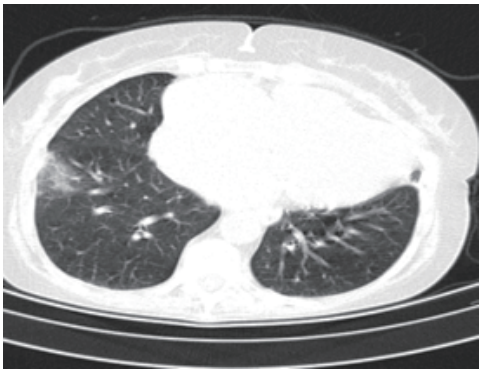

Image 4. Frosted glass image of Case 2 in Thorax CT

The patient's first brain MRI revealed findings of cerebral edema, which was detected as an isointense image in diffuse hyperintense ADC. Lesions consistent with edema extending from the corpus callosum to the right cerebellar hemisphere which were more prominent on the left frontal and hypointense images on the right temporal area, and hyperintense images on T2-weighted slices presented peripheral contrast enhancement in brain MRI. The patient, who was given antiedema treatment, had an epileptic seizure once and died on the twenty-fifth day of his hospitalization.

Case 2; a 65-year old female patient. The patient with a history of dilated cardiomyopathy, atrial fibrillation, a previous cerebrovascular accident (recovered without sequelae), chronic renal failure (in the hemodialysis program 3 times a week) was diagnosed with COVID-19 by positive SARS-CoV2 PCR test. When the COVID-19 PCR studied on the 35th day of clinical onset was positive, there was a complaint of weakness in the right arm that lasted for approximately one hour and resolved spontaneously. MRI diffusion of the brain and contrast-enhanced MRI showed more prominent bilateral punctate contrast-enhancing lesions on the right, which were considered to be demyelinating. A slight increase in the choline peak was noted in MR Spectroscopy. ANA ++ and AntiDsDNA were found higher (220.56; normal range 0-100 IU/mL). When contrast brain MRI and cervical MRI were repeated one month after the clinical presentation of the patient who was discharged with a normal neurological

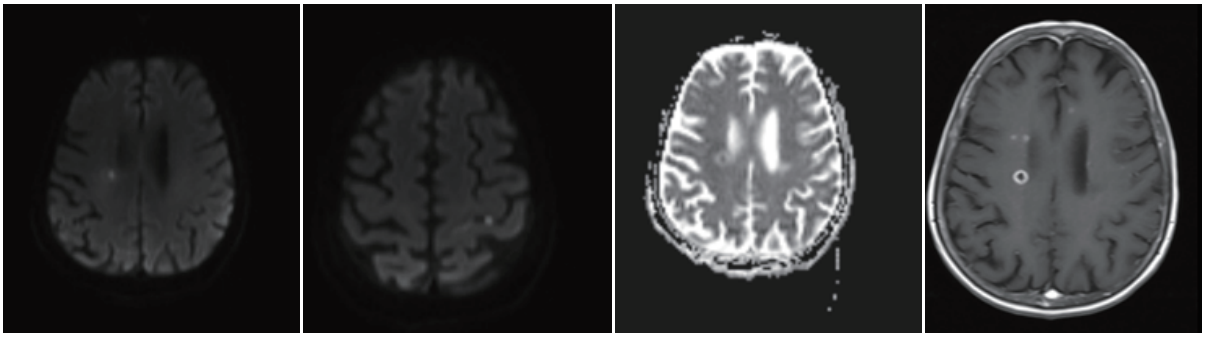

Image 5. Contrast MRI and MRI diffusion images of the brain of Case 2

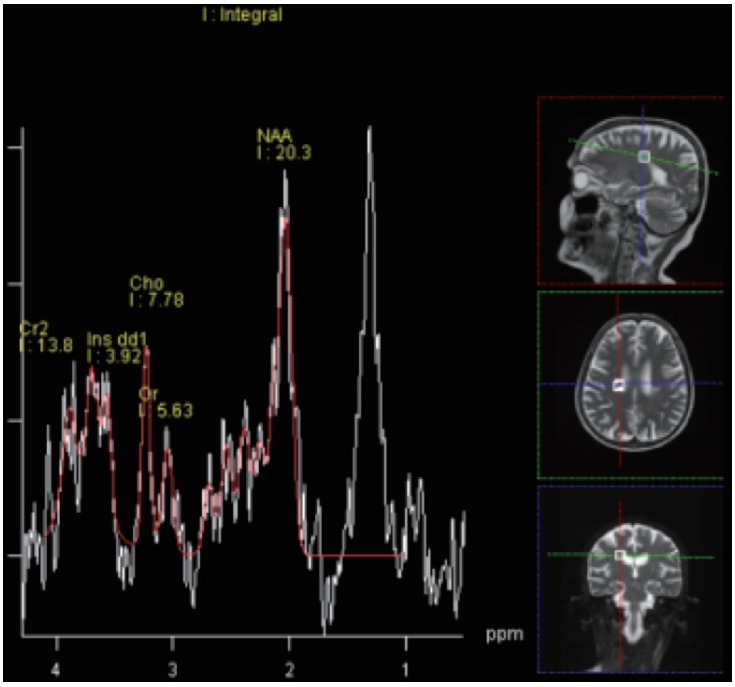

Image 6. MRI spectroscopy of Case 2

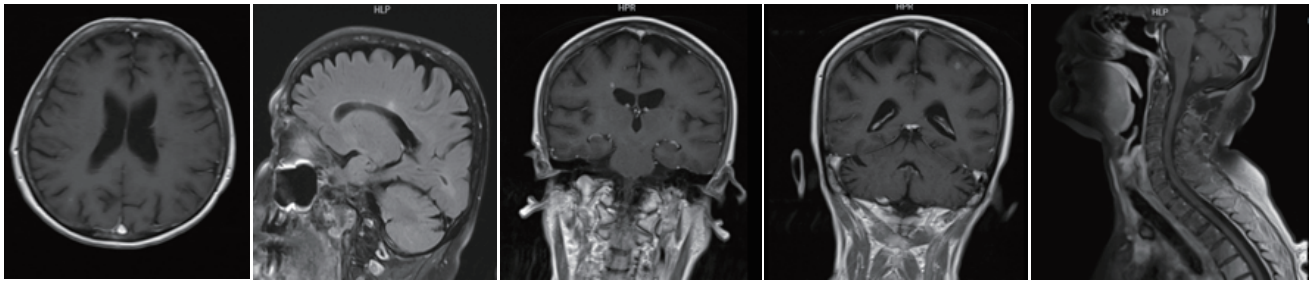

Image 7. In the control contrast brain and cervical MRI taken 1 year later in Case 2, a lesion with contrast uptake on the right disappeared whereas two punctual contrast uptake continue

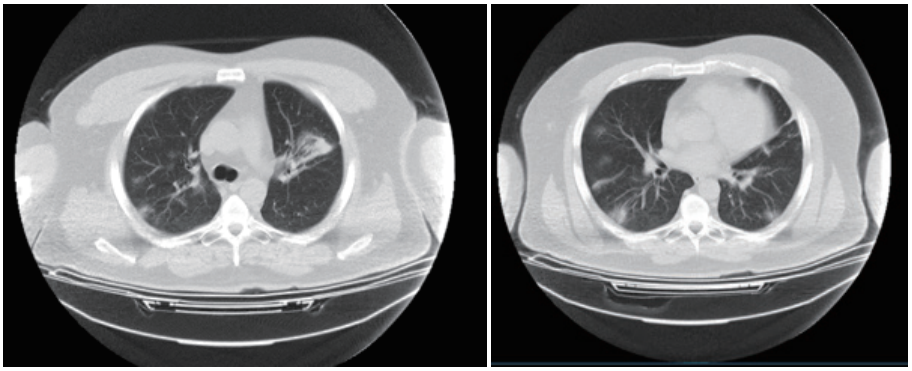

Image 8. First and second thoracic CT images of case 3 taken after clinical worsening. The first thorax CT was evaluated within normal limits, and the second thorax CT showed a frosted glass image in the bilateral posterior regions

examination, a lesion with significant contrast uptake was detected on the right side; however, one lesion with punctual contrast uptake persisted on both right and left hemispheres. Therefore, it was found to support the temporary demyelinating character of the lesions. The patient was diagnosed with systemic lupus erythematosus (SLE) induced COVID-19 disease.

Case 3; a 38-year-old male patient without any previously known disease referred to the emergency department with complaints of short-term loss of consciousness and urinary incontinence after 3 days following diagnosis of COVID-19 after positive SARS-CoV2 RT-PCR test result which was performed because of fatigue and fever. Neurological exam was within normal limits. Hyperintense lesion in corpus callosum splenium and hypointense ADC was observed in the first diffusion MRI of the brain. It was thought that this lesion might be a temporary corpus callosum lesion triggered by an epileptic

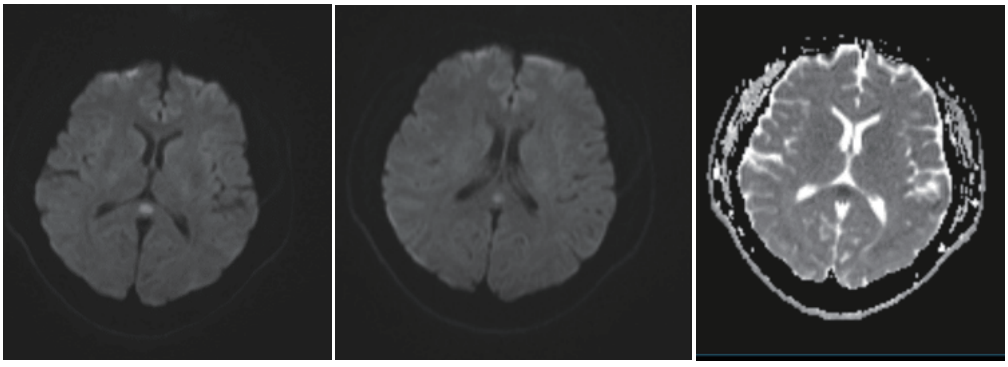

Image 9. A hyperintense lesion in the splenium part of the corpus callosum in the MRI diffusion is observed in the ADC in case 3

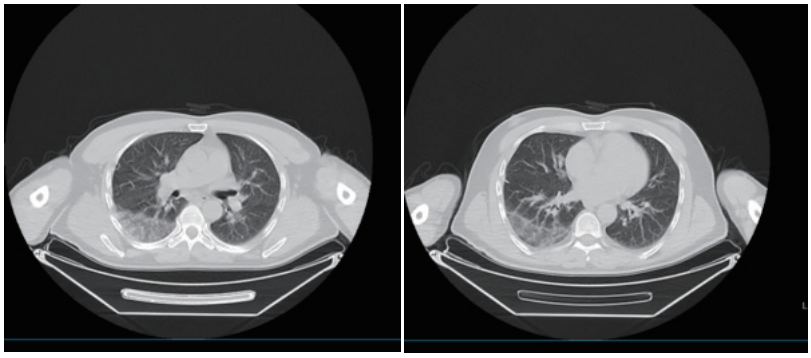

Image 10. Significant bilateral frosted-glass image on the thorax CT in Case 4

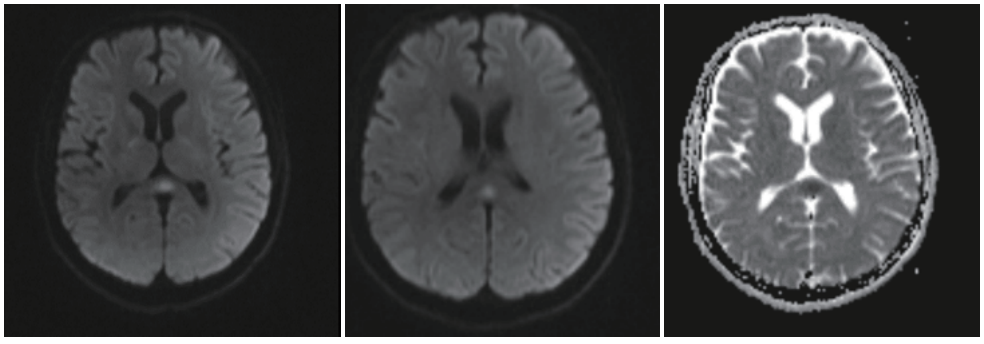

Image 11. A lesion presenting diffusion restriction in the corpus callosum by mr diffusion in case 4

seizure. Although control brain MRI was planned, follow-up MRI could not be performed because the patient did not accept.

Case 4: a 57-year-old male patient who was previously diagnosed with hypertension and diabetes was diagnosed with COVID-19 after he referred with the complaint of high fever. Prominent bilateral frosted-glass images were observed on the right in the thorax CT. The brain MRI which was taken due to dizziness complaint of the patient revealed a hyperintense lesion and a hypointense lesion in the ADC in the corpus callosum on diffusion. This lesion, which was thought to be transient, was interpreted as a temporary source of cerebral event that resolved clinically. however, a final decision could not be made because control MRI could not be performed.

DISCUSSION

In line with the literature, this study which reviewed abnormalities of CNS involvement reflected on brain MRI and CT among neurological complications due to COVID-19 infection revealed that vascular abnormalities occur more common and vascular events constitute the majority of ischemic cerebrovascular events. Presence of concomitant diseases including advanced age and hypertension was detected as risk factors for development of vascular abnormality. Non-vascular brain anomalies which are seen less frequently and treated differently have been documented as complications that may be observed at earlier ages with fewer co-morbidities and a earlier infection period.

The risk of thromboembolic complications including cerebrovascular diseases is increased in the acute phase of COVID-19 infection [(11)]. Acute inflammation caused by COVID-19 may cause hypercoagulation by increasing proinflammatory cytokine levels and serum inflammatory factors such as C-Reactive protein (CRP) and interleukin [(12)]. The incidence of ischemic stroke in hospitalized COVID-19 patients was generally found around 1% to 3% whereas the frequency of ischemic stroke in our study was found 0.64% [(13)]. Lower prevalence of cardiovascular risk factors than the literature data may be due to the different prevalence of cardiovascular risk factors in some ethnic groups and races [(14)]. However, since stroke triggering factors are still not fully revealed in COVID-19 infection, the reason for detection of different prevalence is not exactly known.

The frequency of hemorrhagic cerebrovascular events is still limited in patients with COVID-19 the prevalence in the literature is between 0.5% and 0.9% [(15)]. Similar to the literature, this rate was found 0.18% in this study. Although mechanisms underlying hemorrhagic cerebrovascular events have not been fully elucidated, it is considered that ACE-2 on the endothelial surface and arterial smooth muscle cells may bind to the virus, causing damage to the cerebral arteries or causing hemorrhage due to disruption in the blood-brain barrier by causing vasoconstriction and immunological activation via ACE-2 [(16)].

There were two patients with diffusion restriction in the splenium of the corpus callosum (DRCC) which was found as a non-vascular cerebral abnormality. The DRCC occurring during COVID-19 infection has been reported in the literature [(17)]. Although it is thought that the lesions may be more transient, inability to perform control brain MRI and brain MRI diffusion in the cases of our study caused not clarification of this issue. The clinical presentation of two patients whom this abnormality was detected presenting with epileptic seizures suggests that there may be temporary corpus callosum lesions that may be observed after the seizure. It is assumed that these lesions which occur after the seizure may be due to the rapid entry of inflammatory cells and macromolecules into the cell or cytotoxic edema [(18)].

Diffuse cerebral edema was detected in one patient, and it has been suggested in the literature that cerebral edema may occur due to vascular damage, cell death and increased vascular permeability in patients with severe COVID-19 due to cytokine storm, hyperinflammation and multiorgan injury [(19)]. The other case with non-vascular abnormality was an elder patient with secondary immune deficiency. The patient who presented with bilateral transient enhancement lesions on brain MRI was diagnosed with SLE as a result of differential diagnosis. No advanced age SLE patient diagnosed with COVID-19 was found in the literature. SLE is an autoimmune disease that may affect many systems such as CNS; and it may cause lesions in many organs including kidneys and lungs as a result of increased apoptosis due to cytokines released during COVID-19 [(20)].

Uncertainty on CNS complications of SARS-CoV2 still persists. Therefore, acute neurological symptoms with new onset should be considered during COVID-19 infection, and it is concluded that diagnosis should be supported radiologically in clinically suspected cases. It should be kept in mind that other pathologies that may require combined therapies may also exist beyond ischemic and hemorrhagic stroke. Therefore, there is a need for larger case series on diagnosis and treatment.

LIMITATIONS

The data analyzed are limited to those found in patient files due to the retrospective nature of our study. Therefore, there has been a lack of information about the course of the cases that require follow-up, especially with control MRI examination. In addition, only the patients who were hospitalized due to COVID-19 infection, who underwent neurological evaluation and who underwent cranial imaging were included. This caused exclusion of asymptomatic patients from the study due to pathology on cranial imaging.

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