Cerebrovascular radiological features of COVID-19 positive patients

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Abstract. – OBJECTIVE: To investigate acute cerebrovascular diseases (stroke and intracranial hemorrhage) by cranial radiologic examinations of patients infected with coronavirus disease 2019 (COVID-19) and with neurological signs.

PATIENTS AND METHODS: Between March 2020 and May 2021, patients who were admitted to the Emergency Department and had a positive reverse transcription-polymerase chain reaction (RT-PCR) test and underwent Multidetector Computed Tomography (MDCT) and/or Magnetic Resonance Images (MRI), and/or diffusion MRI due to neurological findings were included in the study.

RESULTS: The study reviewed a total of 925 patients, including 404 (43.67%) female and 521 (56.32%) male patients. The distribution of imaging methods was as follows: 805 (71%) patients had cranial MDCT, 71 (6.35%) patients had MRI, and 241 (21.57%) patients had diffusion MRI. Of the total 925 patients, 128 (13.8%) patients were detected with cerebrovascular diseases, 92 (9.9%) patients were detected with ischemic or hemorrhagic stroke, 37 (4%) patients were detected with intraparenchymal hemorrhage, 10 (1.1%) patients were detected with subarachnoid hemorrhage, and four (0.43%) patients were detected with subdural hemorrhage. There was no statistically significant difference in the incidence of subdural, subarachnoid, parenchymal hemorrhage, and stroke in terms of gender. While there was a significant difference in stroke according to age, there was no statistically significant difference in subdural, subarachnoid, and parenchymal hemorrhagic. Three (0.32%) patients were diagnosed with acute disseminated encephalomyelitis (ADEM)'s-like demyelinating lesions.

CONCLUSIONS: Cerebrovascular diseases, which may cause severe disability and even threaten the patient's life, should be kept in mind, especially in COVID-19 patients who present with neurological symptoms.

Key Words:
COVID-19, SARS-CoV-2, COVID-19 neurologic outcomes, Intracranial hemorrhage, Cerebrovascular diseases, Subdural hemorrhage, Subarachnoid hemorrhage, Parenchymal hemorrhage, Stroke.

Introduction

The new type of coronavirus pandemic, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been seriously affecting human health since December 2019. At the beginning of the pandemic, neurological complications were considered to be relatively rare. However, the evidence suggesting neurological involvement in patients with coronavirus disease 2019 (COVID-19) is increasing every day[1].

It has been reported that a large number of patients show neurological symptoms ranging from acute cerebrovascular diseases, encephalitis, and inflammatory demyelination, especially isolated sensor neural deficits such as anosmia and dysgeusia[2]. It is difficult to establish causality with current data. There are three possible mechanisms known to date. The first is neurotropism, that is, an affinity for angiotensin-enzyme (ACE2) receptors in the central nervous system (CNS). The second is autoimmunity and the third is cytokine storm and hypercoagulable state[1].

To the best of our knowledge, there are a few studies[1,3,4] investigating cerebrovascular diseases in COVID-19 patients. Most of the studies are in the form of case reports or case series.

Our aim in this study is to reveal the incidence of cerebrovascular diseases such as subdural hemorrhage (SDH), subarachnoid hemorrhage (SAH), intraparenchymal hemorrhage (IPH), and ischemic or hemorrhagic stroke in patients with positive COVID-19 including reverse transcrip-

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tion-polymerase chain reaction (RT-PCR) test and neurological symptoms.

Patients and Methods

This study was designed as a retrospective, single-center, open-label, non-randomized clinical study. We did not perform any experiments on human participants.

The data were collected through the hospital information system. The age, gender, real-time RT-PCR test results, and radiologic examination [multidetector computed tomography (MDCT) and/or magnetic resonance images (MRI)] of patients were examined from the hospital information system and picture archiving and communicating system (PACS).

Patients admitted to the Emergency Outpatient Clinic of the Malatya Turgut Ozal University Faculty of Medicine between March 2020 and May 2021 were included in the study. Patients who were found to be positive for COVID-19 according to the real-time RT-PCR test of throat swab samples and had a cranial MDCT and/or MRI and/or diffusion MRI due to neurological findings were included in the study. The radiological findings were evaluated by four radiologists with 23, 20, 18, and 25 years of experience, respectively.

Patients with insufficient diagnostic quality (2 patients) and/or unclear margins (1 patient) and/or radiological findings defined as atypical for cerebrovascular disease (4 patients) in the cranial radiological examination were excluded from the study.

Pijls et al[5] reviewed 59 studies. In this meta-analysis involving 36,470 patients, they found that patients aged 70 years and older were at higher risk for COVID-19 infection. They have reported that patients aged 70 and over are the more at-risk group for COVID-19. So, in our study, while evaluating adult patients according to age group, we evaluated them in two groups 70 years and older and under 70 years old.

CT

Cranial CT was performed on the following scanner models. Philips Ingenuity CT, 2014, 128 slices, serial no: 600021 (Philips Healthcare, the Netherlands). Philips MX, 2014, 16 slices, serial no: EP16E140004 (Philips Healthcare, the Netherlands). These CT scanners were used only for COVID-19 patients during the pandemic period. All patients' CT examinations were non-contrast examinations.

MRI

Cranial MRI was performed on the following scanner models. Magnetom Amira, 2019, serial number 174075 (Siemens Healthineers, Germany).

Visual Assessments

The radiological findings were evaluated by four radiologists. All imaging aspects were reviewed by at least one board-certified radiologist. When available, previous cranial radiological features were also assessed. Disagreements regarding findings were resolved by consensus immediately after all individual ratings had been performed.

Statistical Analysis

The numerical figures obtained from the measurements were expressed as mean±standard deviation, and the data obtained by counting were expressed as frequency (%). The Student's *t*-test was used to analyze the significance of the age and gender groups. The prevalence of the above was evaluated using the Fischer exact test. The results were evaluated within a 95% confidence limit, assuming $p < 0.05$ as the significance level.

Results

Patient's Demographics

The study reviewed a total of 925 patients, including 404 (43.67%) female and 521 (56.32%) male patients. The mean age of patients was 63.19±18.40 (range, 18-102) years. Of these patients, the mean age of female patients was 63.15±19.42 (range, 18-102) years. The mean age of male patients was 63.23±17.58 years, ranging from 18 years to 99 years.

The distribution of cerebrovascular diseases by age and gender is presented in Tables I and II. Of the total 925 patients, 128 (13.8%) patients were detected with cerebrovascular diseases, including 89 (7.9%) female and 57 (5.1%) male patients. Of the total 925 patients, 374 (40.43%) patients were 70 and over 70 years old, and 551 (59.56%) pa-

Table I. Distribution of cerebrovascular diseases according to age.

Cerebrovascular diseases	Age	Yes n	Yes %	None n	None %	p
Ischemic or hemorrhagic stroke	<70	42	4.5	509	55.0	0.005*
	≥70	50	5.4	324	35.0	
	Total	92	9.9	833	70.0	
Intraparenchymal hemorrhage	<70	21	2.3	530	57.3	0.735
	≥70	16	1.7	358	38.7	
	Total	37	4.0	888	96.0	
Subarachnoid hemorrhage	<70	5	0.5	546	59.0	0.536
	≥70	5	0.5	369	39.9	
	Total	10	1.1	915	98.9	
Subdural hemorrhage	<70	1	0.1	550	59.5	0.309
	≥70	3	0.3	371	40.1	
	Total	4	0.4	921	99.6	
Total	<70	62	6.7	489	52.8	0.007*
	≥70	66	7.1	308	33.3	
	Total	128	13.8	797	86.2	

Abbreviations: n = number; % = rate; p = statistical significance value of chi-square (χ^2) test; *$p < 0.05$: There is a statistically significant difference between groups.

tients were under 70 years old. There was no statistically significant difference in the incidence of cerebrovascular diseases in terms of gender (p = 0.502). There was a statistically significant difference in the incidence of cerebrovascular diseases in terms of age (p = 0.007).

Of the total 925 patients, 92 (9.9%) patients were diagnosed with ischemic or hemorrhagic stroke, including 50 (5.4%) female and 42 (4.5%) male patients. The mean age of patients with stroke was 71.21±13.47 (range 32 to 95) years. There was no statistically significant difference in the incidence of ischemic or hemorrhagic stroke in terms of gender (p = 0.740). There was a statistically significant difference in the incidence of ischemic or hemorrhagic stroke in terms of age (p = 0.005). The incidence of intracranial hemorrhage (ICH) was 5.51% (n = 51). When the distribution of ICH was examined, it was determined that 10 (19.6%) patients had SAH, 4 (7.84%) patients had SDH, and 37 (72.5%) patients had IPH.

Of the total 925 patients, 37(4%) patients were detected with IPH, including 26 (2.8%) female

Table II. Distribution of cerebrovascular diseases according to gender.

Cerebrovascular diseases	Sex	Yes n	Yes %	None n	None %	p
Ischemic or hemorrhagic stroke	Female	50	5.4	471	50.9	0.740
	Male	42	4.5	362	39.1	
	Total	92	9.9	833	90.1	
Intraparenchymal hemorrhage	Female	26	2.8	495	53.5	0.920
	Male	11	1.2	393	42.5	
	Total	37	4.0	888	96.0	
Subarachnoid hemorrhage	Female	7	0.8	514	55.6	0.527
	Male	3	0.3	401	43.3	
	Total	10	1.1	915	98.9	
Subdural hemorrhage	Female	2	0.2	519	56.1	1.000
	Male	2	0.2	402	43.5	
	Total	4	0.4	921	99.6	
Total	Female	76	8.2	445	48.1	0.502
	Male	52	5.6	352	38.1	
	Total	128	13.8	797	86.2	

Abbreviations: n = number; % = rate; p = statistical significance value of chi-square (χ^2) test.

Figure 1. The patient, who was diagnosed with COVID-19 14 days ago, refused treatment and received no medication, came to the emergency service with diffuse pons bleeding. Axial CT imaging shows a hyperdense appearance consistent with acute hemorrhage that completely covers the pons region.

and 11 (1.2%) male patients with a mean age of 68.13±14.79 (range, 28-92) years (Figure 1). There was no statistically significant difference in the incidence of IPH in terms of age (p = 0.735) and gender (p = 0.920).

Of the total 925 patients, four (0.4%) patients were detected with SDH, including two (0.2%) female and two (0.2%) male patients with a mean age of 77.25±6.29 (range, 68-82) years (Figure 2). There was no statistically significant difference in the incidence of SDH in terms of age (p = 0.309) and gender (p = 1.000.).

Of the total 925 patients, 10 (1.1%) patients were detected with SAH, including seven (0.8%) female and three (0.3%) male patients with a mean age of 68.70±13.98 (range, 43-90) years (Figure 3). There was no statistically significant difference in the incidence of SAH in terms of age (p = 0.536) and gender (p = 0.527).

The distribution of radiological imaging and cerebrovascular diseases is represented in Table III. The distribution of the radiological imaging method evaluated retrospectively in our study is as follows. 925 patients underwent 1,117 radiological imaging methods. Of the total 1,117 radiological examinations, 805 (72.06%) were cranial CT, 71 (6.35%) MRI, 241 (21.57%) diffusion MRI. It was determined that 14 patients underwent MRI and diffusion MRI, 116 patients CT and diffusion MRI, four patients CT and MRI, 29 patients CT, MRI and diffusion MRI, 656 patients only CT, 24 patients only MRI, and 82 patients only diffusion MRI.

Cranial CT examination revealed 94 (10.2%) cerebrovascular diseases, four (0.4%) SDH, 52 (5.6%) stroke (Figure 4A-F), 30 (3.2%) IPH, eight (0.9%) SAH. Cranial MRI examination revealed 15 cerebrovascular diseases, zero SDH, 10 (1.1%) stroke, four (0.4%) IPH, one (0.1%) SAH. Diffusion MRI examination revealed 54 cerebrovascular diseases, none SDH, 45 (4.9%) stroke, eight (0.8%) IPH, one (0.1%) SAH.

Of the total 925 patients, three (0.3%) patients were diagnosed with acute disseminated encephalomyelitis (ADEM)'s-like demyelinating lesions (Figure 5A-C). The mean age of the patients was 37.66±17.89 (range, 18 to 53) years. All of these patients were under 70 years of age (p = 0.277). All of them were male (p = 0.261).

Discussion

The main clinical manifestation of human coronaviruses is the respiratory system. The cause of

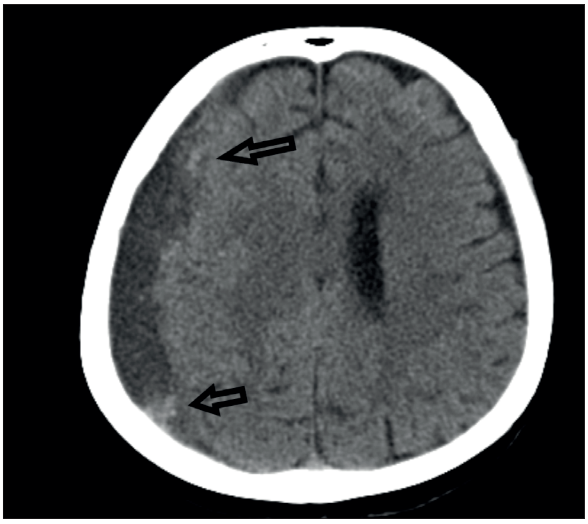

Figure 2. Axial CT image: Diffuse hyperdense acute subdural hematoma (arrows) and hypodense chronic subdural hematoma sites are observed in the right fronto-tempero-parietal region.

Figure 3. Axial CT imaging: Hyperdense intracranial hematoma of the right centrum semiovale (arrowhead). In addition, hyperdense subarachnoid hemorrhage extending to the subcortical area is observed in the central sulcus region (arrow).

death is usually acute respiratory failure. In addition, extra respiratory symptoms such as neurological findings have been reported recently[6]. Moa et al[7] reported that of the 214 patients with a confirmed COVID-19 diagnosis in the laboratory, 78 (36.4%) had characteristic neurological signs of SARS-CoV-2 infection. A publication confirming these findings was made in Spain. Romero-Sanchez et al[8] reported that neurologic manifestations are common (57.4%) in hospitalized patients with COVID-19.

These neurological findings are evaluated in three groups CNS manifestations (disorders of consciousness, dizziness, cerebrovascular disease, headache, seizure, and acute ataxia), peripheral nervous system manifestations (anosmia/dysgeusia, cranial neuropathies, nerve pain, and vision impairment), and musculoskeletal system manifestations[7]. In our study, we examined life-threatening cerebrovascular diseases from these neurological manifestations.

Recent studies suggest some possible mechanisms explaining how COVID-19 causes neurological involvement, but the evidence of causality or effect is weak[6]. The reasons suggested as the cause of neurological involvement are as follows. It is neurotropism, that is, an affinity for ACE2 receptors in the CNS. Autoimmunity, cytokine storm, and hypercoagulation are other possible causes[1,6].

Romero-Sanchez et al[8] have hypothesized that cerebrovascular manifestations of SARS-CoV-2 infection may arise as a result of a combination of endothelial damage and hypercoagulability. COVID-19 associated coagulopathy is characterized by initial elevations in fibrinogen and d-dimer. It leads to both vascular thrombosis and parenchymal hemorrhage[9]. In our opinion, this may be the most likely mechanism of occurrence of cerebrovascular diseases in patients with COVID-19. Of course, risk factors should not be ignored.

Gogia et al[1] reported a COVID-19 positive case with ICH. They stated that the possible reason could be hypertension, the anticoagulant treatment used, and the underlying coagulopathy due to COVID-19. They suggested that a combination of COVID-19 related underlying coagulopathy, concomitant diseases such as hypertension, and triple therapy (aspirin, enoxaparin, and clopido-

Table III. Distribution of radiological imaging methods and cerebrovascular diseases.

Radiological imaging method	n	%	Cerebrovascular Diseases	n	%
CT	805	72.06	Stroke	52	5.6
			Intraparenchymal hemorrhage	30	3.2
			Subarachnoid hemorrhage	8	0.9
			Subdural hemorrhage	4	0.4
MRI	71	6.35	Stroke	10	1.1
			Intraparenchymal hemorrhage	4	0.4
			Subarachnoid hemorrhage	1	0.1
			Subdural hemorrhage	-	-
Diffusion MRI	241	21.57	Stroke	45	4.9
			Intraparenchymal hemorrhage	8	0.8
			Subarachnoid hemorrhage	1	0.1
			Subdural hemorrhage	-	-

Abbreviations: n = number of patients; % = rate.

grel) may have contributed to life-threatening ICH in their patient[1]. Al-Olama et al[3] described a case of COVID-19-associated meningoencephalitis complicated with ICH and SDH. Madi et al[10] described a COVID-19 positive patient who presented with ICH following severe ITP (Idiopathic thrombocytopenic purpura). Pan et al[2] reviewed sixty-one studies published between 2019 and 2020 comprising 711 patients. They found that the main neuro-radiological findings for patients with mild classification were white matter abnormalities, ischemic infarction, and cranial nerve abnormalities, while the main findings in patients with severe classification were ischemic infarction, ICH, and white matter abnormalities in this systematic review. Pan et al[2] found that ICH was found in 13 (31.0%) patients and ischemic infarct 13 (33.3%) patients when they evaluated neuro-radiological findings in severe COVID-19 infection (42 patients). Pan et al[2] emphasized that the high prevalence of white matter abnormalities, ischemic infarction, and hemorrhage detected in brain imaging of COVID-19 patients support the above-mentioned disease mechanisms. For patients aged 80 and over, the incidence of ICH rate has been reported as 6.8%[11].

The incidence of ICH (SDH, SAH, and IPH) varies according to the groups in which the study was performed. For example, incidences differ in hospitalized patients with COVID-19 positive, patients with ICH, or patients with neurological symptoms who are positive for COVID-19 as in our study. The rate of ICH in these subgroups has been reported to be between 0.1% and 31%. In our study, the incidence of ICH was 5.02%, at a rate similar to these studies.

Crean et al[4] reported a COVID-19 positive patient with SAH; they suggested that severe COVID-19 disease could be linked to ICH from cytokine storms or coagulation abnormalities. A study was done to evaluate the risk of developing SAH in patients with COVID-19. Qureshi AI et al[12] did not find an increased risk of SAH in COVID-19 positive patients compared to COVID-19 negative patients (0.1% *vs.* 0.2%). However, Qureshi Al et al[12] found that there was a significantly increased risk of morbidity and in-hospital mortality in COVID-19 positive patients with SAH compared to those without COVID-19 (31.4% *vs.* 12.2%)[12]. In our study, 10 (0.9%) patients were detected with SAH.

There are case reports and case series on IPH, but we could not find a clinical study. Chalil et al[13] reported a 48-year-old COVID-19 positive female patient with bilateral parietal and occipital IPH. Charrave et al[14] reported an unusual case of corpus callosum hematoma in a COVID-19 patient. The incidence of IPH was 3.8% (42) in our study. This ratio, which we found in our study, was quite remarkable.

Doyle et al[15] reviewed a total of 51 patients who received extracorporeal membrane oxygenation due to COVID-19. They found that only one (1.96%) of 51 patients had SDH. Of the total 925 patients, four (0.4%) patients were detected with SDH. This rate is similar to recent studies. There is a need for large-series studies.

Mahammedi et al[16] reviewed a total of 135 consecutive hospitalized patients with COVID-19 with acute neurological symptoms. They found that 38 (28%) of their patients had acute ischemic infarction, 14 (10%) ICH, and 22 (36%) white matter disease. Ischemic and/or hemorrhagic stroke was detected in 107 (9.6%) patients in our study at a similar rate to that study.

Katz et al[17] investigated the rate of hemorrhagic conversion after ischemic stroke in 10,596 hospitalized COVID-19 patients in 11 New York Hospitals, retrospectively. Katz et al[17] reported that 86 (0.81%) had an ischemic stroke and that eight of those patients had evidence of simultaneous hemorrhage (0.08%). This low incidence may depend on the selected population. There is a need for large-series studies.

ADEM's-like demyelinating lesion is a demyelinating inflammatory disorder of the CNS. It is a rare disease. However, some studies reported an increased incidence of ADEM's-like demyelinating lesion after COVID-19 epidemics. Recently, numerous case series/reports have described cases of ADEM's-like demyelinating lesion linked to COVID-19 infection. Wang et al[18] showed that the clinical picture of COVID-19-associated, ADEM's-like demyelinating lesion can be associated with SARS-CoV-2 infection, based on the systematic review of 48 cases. Interestingly, six (0.5%) patients were diagnosed with ADEM's-like demyelinating lesion in our study. ADEM's-like demyelinating lesion is a very rare disease. It is suggested that the incidence is increased in patients with COVID-19. ADEM's-like demyelinating lesion detected in our study is 0.5%, which is quite a high rate. It should be noted that young patients with COVID-19 disease and neurological symptoms may have ADEM's-like demyelinating lesion.

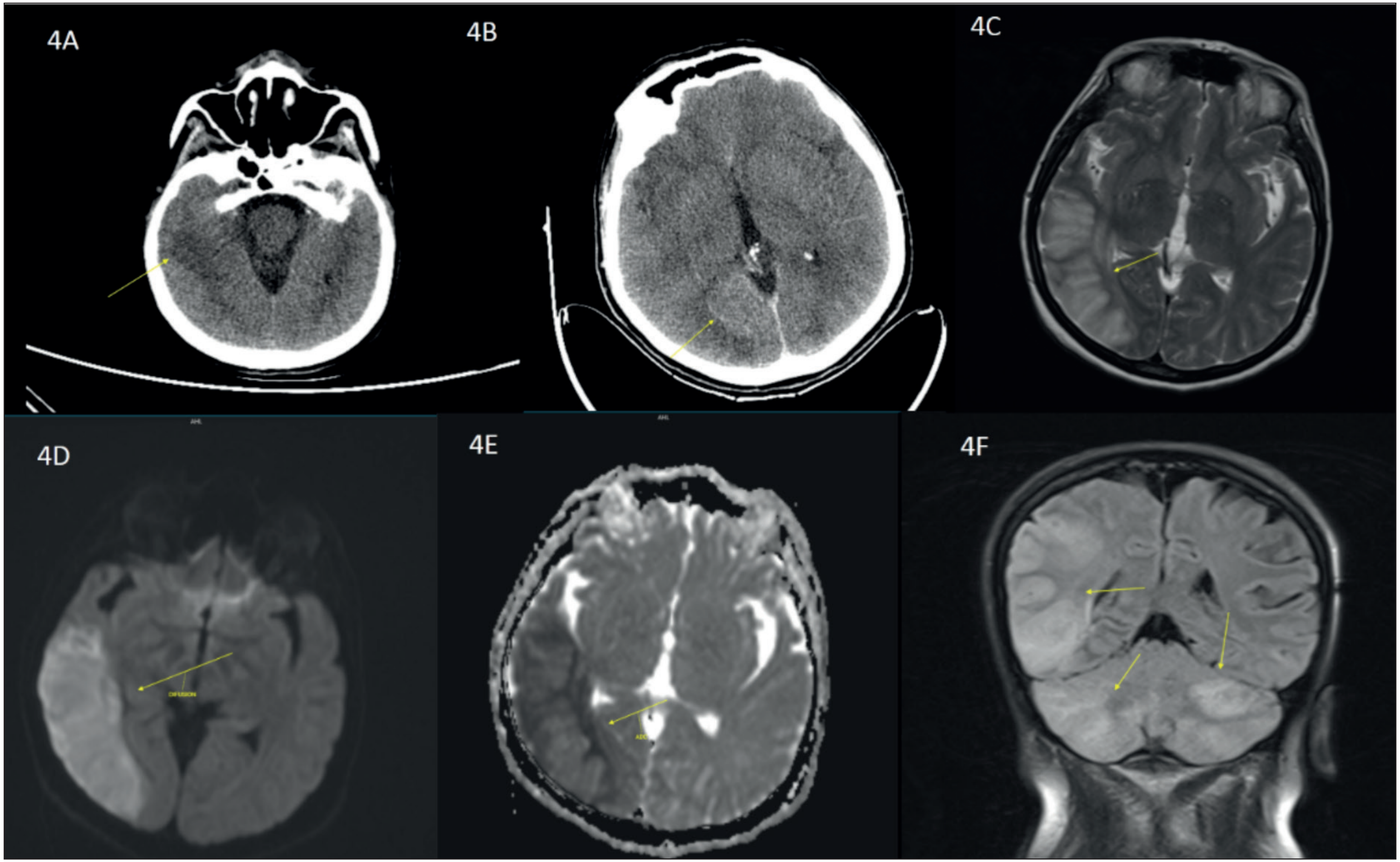

Figure 4. ***A***, Axial CT imaging: In the right temporal region, an acute infarction site is observed, which is more hypodense than in the parenchyma. **B**, Axial CT imaging: In the right occipito-parietal region, the infarct site is monitored, which is monitored with more hyperdense than in the parenchyma. **C**, Axial T2W imaging: Diffuse t2 hyperintensity is observed in the region corresponding to the infarction site on CT in the right temporo-occipital region. **D**, Axial DWI MRI imaging: Hyperintensity secondary to diffusion restriction is observed in the right temporo-occipital region. **E**, Axial ADC MRI imaging: Hypointensity secondary to diffusion restriction is observed in the right temporo-occipital region. **F**, Coronal T2W imaging: In the same patient, t2 hyperintensity is observed on the right in accordance with the common diffuse infarction site, which includes the temporo-parieto-occipital region and the bilateral cerebellar hemisphere.

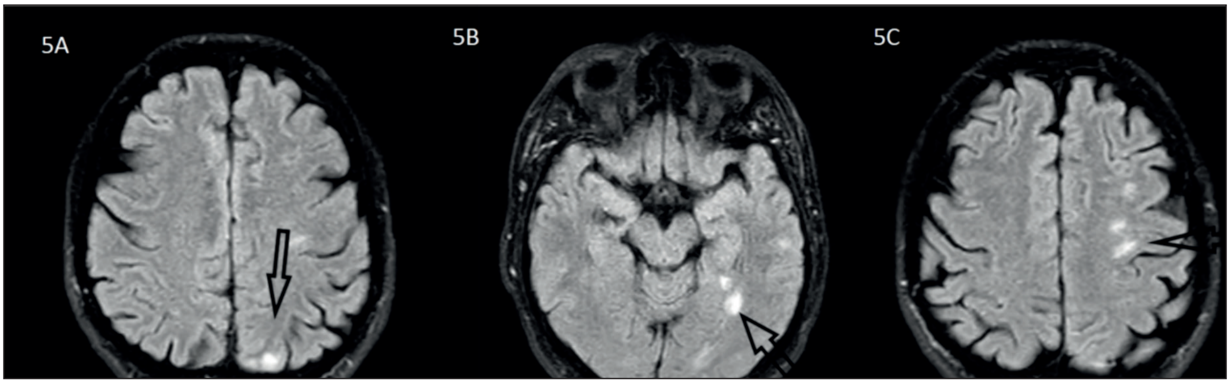

Figure 5. *A*, Axial T2/FLAIR brain MRI imaging: Several ADEM's-like demyelinating lesions are observed in the localization (region) of the left mesencephalon (arrow). ***B***, Axial T2/FLAIR brain MRI imaging: In the posterior parietal region, several ADEM's-like demyelinating lesions with a subcortical location are observed (arrow). ***C***, Axial T2/FLAIR brain MRI imaging: Several ADEM's-like demyelinating lesions with a high convexity of the left fronto-parietal subcortical location are observed (arrow).

Study Limitations

We should also consider some limitations. This work is not performing a full neurologic evaluation of every patient and a complete diagnostic workup. The main reason for this is that our study is a retrospective, cross-sectional study. The data were obtained retrospectively, so selection bias may arise, and some important information could be missing. Since this study is a single-center study, the data does not necessarily reflect the incidence of cerebrovascular diseases of patients with COVID-19 in the community and any findings must be considered with that in mind. Moreover, our work is a descriptive and retrospective series, and as such we could not determine without any doubt whether the cerebrovascular disease of the patients was caused by the COVID-19 infection or by other factors such as cross-immunity, inflammatory reaction, or side effects of the treatments (such as anticoagulant, antiaggregant treatments). Risk factors (hypertension, smoking, obesity, diet, inactivity, drug use, etc.) that may cause cerebrovascular diseases could not be evaluated.

Conclusions

Cerebrovascular diseases, which may cause severe disability and even threaten the patient's life, should be kept in mind, especially in COVID-19 patients who present with neurological symptoms. It should be kept in mind that advanced age, comorbidities, and used anticoagulant drugs increase the risk of cerebrovascular disease. We think that more studies should be done on this subject.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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Availability of Data

The data and materials generated/analyzed in the present study are available from the corresponding author upon request.

Informed Consent

Due to the retrospective nature of the study, informed consent of the patients was not required.

Ethical Approval

This study was approved by the Institutional Ethics Committee of Malatya Turgut Ozal University (document date and number: 03.08.2021, 2021-45).

Author' Contribution

Conceptualization: BP, Data curation: BP, MA, MS, ND, Formal analysis: BP, Funding acquisition: BP, MA, MS, ND Investigation: BP, MA, MS, ND, Methodology: BP, Project administration: BP, MA, MS, ND Resources: BP, MA, MS, ND, Software: BP, MA, MS, Supervision: BP, MA, MS, ND Validation: BP, MA, Visualization: BP, MA, MS, ND Writing-original draft: BP, Dag Writing-review & editing: BP, MA, MS, ND.

Consent to Participate

Since it is a retrospective study, the patient consent form was not obtained from subjects involved in the study.

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