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Original article

CLINICAL AND LABORATORY CHARACTERISTICS OF PATIENTS WITH ACUTE ISCHEMIC STROKE AND COVID-19: CASE SERIES AND LITERATURE REVIEW

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Abstract

Introduction: COVID-19 is closely linked to coagulopathy and consequently thromboembolism, thus increasing the probability for development of ischemic strokes.

Aim: The purpose of our study was to evaluate the clinical, laboratory and neuroimaging characteristics as well as outcome in patients with COVID-19 who developed acute ischemic stroke (AIS), hospitalized at the COVID Center at the University Clinic for Neurology in Skopje, N. Macedonia during the period of November 2020 - March 2021.

Material and methods: We conducted a retrospective analysis of ten patients with acute ischemic stroke, out of 566 COVID-19 patients hospitalized at the COVID Center at the University Clinic for Neurology in Skopje, N. Macedonia. during the period of November 2020 - March 2021. Demographic characteristics, level of consciousness, stroke type, region and volume, presence of hemorrhagic transformation and mass effect, comorbidities, level of D-dimer and inflammatory markers, presence of pneumonia and outcome of the patients were analyzed.

Results: Majority of patients developed ischemic strokes secondary to large-vessel occlusion in the anterior circulation and only one patient had posterior circulation stroke. Three patients developed massive stroke with hemorrhagic transformation and mass effect. Seven patients developed COVID-19 associated pneumonia.

Conclusion: Acute ischemic stroke in patients with COVID-19 is more likely to occur in elderly patients with cardiovascular comorbidities. Aging, comorbidities, impaired level of consciousness and increased level of D-dimer and CRP on admission along with COVID-19 pneumonia contribute to the fatal outcome.

Keywords: acute ischemic stroke, COVID-19 infection, COVID-19 pneumonia, clinical and laboratory characteristics

Introduction

The disease of coronavirus-2019 (COVID-19), which first emerged in December 2019, in Wuhan, China, has rapidly expanded and become a global pandemic with 5,570,163 deaths worldwide, as declared by the World Health Organization on January 21st, 2022[1]. It is a highly contagious infectious disease caused by the novel beta-coronavirus SARS-CoV-2. While at the onset of the disease the respiratory tract tropism of the virus was already known, due to the mainly respiratory symptoms it manifested, in further reports it became clear that

COVID-19 is a multiple organ infection and therefore affects several systems, including the nervous system[2]. Numerous studies concerning SARS-CoV-2 neurotropism and how it manages to penetrate the central nervous system (CNS) have been published. Postmortem studies of patients who died of COVID-19 have proven its presence in the nervous system, mostly in the capillary endothelium and the frontal cortex, but also in the brainstem[3]. Moreover, antibodies against SARS-CoV-2 proteins have been identified in the cerebrospinal fluid (CSF) of patients with encephalopathy. Autopsy reports have established that the brain tissue of patients with COVID-19 tends to appear hyperemic, edematous and with degenerated neurons[4]. Neurological involvement in patients with COVID-19 have been observed in 36% of cases, with the cerebrovascular diseases being the most prevalent complications in severe cases[5].

Aim

The purpose of our study was to evaluate the clinical, laboratory and neuroimaging characteristics as well as outcome of patients with COVID-19 who developed acute ischemic stroke (AIS), hospitalized at the COVID Center at the University Clinic for Neurology in Skopje, N. Macedonia during the period of November 2020 - March 2021.

Material and methods

We conducted a retrospective analysis of ten patients with stroke and COVID-19 infection, out of a total of 566 patients hospitalized at the center during the second wave of the pandemic. Diagnosis of acute ischemic stroke was confirmed by computed tomography (CT) of the brain and neurological examination. Presence of pneumonia was confirmed by CT of the chest and physical examination. We analyzed demographic characteristics (age, gender), level of consciousness, stroke type, region and volume, presence of hemorrhagic transformation and mass effect, presence of comorbidities (hypertension, cardiomyopathy, atrial fibrillation, diabetes mellitus, chronic obstructive pulmonary disease, previous stroke), level of D-dimer and inflammatory markers (C reactive protein (CRP), lactate dehydrogenase (LDH), white blood cells (WBC)), presence of pneumonia and outcome in the patients. Stroke volume for each patient was calculated in cm^3 according to the ABC/2 formula (length x width x number of CT slices x CT slice thickness / 2). Slice thickness was 3.6 mm. We used descriptive statistical analysis.

Results

We have analyzed 4 females and 6 males with COVID-19 and AIS. Their demographic, laboratory and clinical characteristics are summarized in Table 1. The mean age of patients was 68 years (range 54 - 82 years). On admission, 5 patients were alert, 3 were somnolent and 2 were soporous. Nine patients developed AIS secondary to large-vessel occlusion in the anterior circulation, namely in the vascular territory of middle cerebral artery (MCA). Only one patient had a posterior circulation stroke (in the vascular territory of posterior cerebral artery-PCA) (Figure 1). Three patients developed massive MCA ischemic stroke with hemorrhagic transformation and mass effect. Mean stroke volume was 122 cm^3 (range 2-336 cm^3). All patients had confirmed COVID-19 infection (SARS-CoV-2 RT-PCR positive), whereas seven of them developed COVID-19 associated pneumonia. We obtained laboratory analysis from 9 patients; 1 patient had lethal outcome soon after the admission and data were not available. All 9 patients had increased level of D-dimer above 500 ml/L, with mean value of 3256 mg/L (range 724-10000 mg/L) (Figure 2). Increased values of CRP were registered in 8 patients, mean value of 59.7 mg/dL (range 6.9-186.6 mg/dL) (Figure 3). Increased values of WBC were seen in 4 patients, mean value of 13.8 (range 11.26-16.1 10^9/L).

Table 1. Demographic, laboratory and clinical characteristics of 10 patients with AIS and COVID-19

A	G	LOC	PNA	SL	SV cm³	HT	ME	HTA	DM	HLP	AF	CMP	COPD	RS	D-d <500 ml/l	CRP mg/dl	WBC 10^9/L	LDH U/L	OTD
52	M	Alert	Yes	R MCA	336	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	979	119.2	9.08	345	Alive
54	M	Somnolent	No	R MCA	205	No	No	Yes	No	Yes	No	No	No	No	724	6.9	13.23	200	Alive
66	F	Alert	Yes	L MCA	12	No	No	Yes	Yes	Yes	No	No	No	Yes	1314	14.6	8.6	163	Alive
66	M	Alert	Yes	R MCA	132	Yes	Yes	Yes	No	No	No	No	Yes	No	1175	17.6	14.8	189	Alive
68	M	Alert	Yes	L MCA	20	No	No	Yes	No	No	No	No	No	No	4118	33.1 5	16.1	499	Alive
70	F	Alert	No	L PCA	11	No	No	Yes	No	Yes	No	No	No	No	814	4.9	9.17	333	Alive
71	F	Somnolent	No	R MCA	2	No	No	Yes	Yes	No	No	Yes	No	No	1972	37.4	5.12	227	Fatal
75	M	Somnolent	Yes	R MCA	37	No	No	Yes	No	No	No	No	No	No	8212	62.9	11.26	537	Fatal
77	M	Soporous	Yes	R MCA	263	Yes	Yes	Yes	No	No	Yes	Yes	No	No	/	/	/	/	Fatal
82	F	Soporous	Yes	R MCA	203	No	No	Yes	Yes	No	Yes	Yes	No	No	10000	186.6	7.63	290	Fatal

A-Age, G-Gender, LOC -Level of consciousness on admission, PNA – Pneumonia, SL- Stroke location, SV-Stroke volume, HT- Hemorrhagic transformation, ME - Mass effect, HTA- Hypertension, DM- Diabetes mellitus, HLP- Hyperlipidemia, AF- Atrial fibrillation, CMP- Chronic cardiomyopathy, COPD- Chronic obstructive pulmonary disease, RS- Recurrent stroke, D-d- D-dimers, CRP- C reactive protein, WBC- White blood cells, LDH- Lactate dehydrogenase, OTD-Outcome at discharge

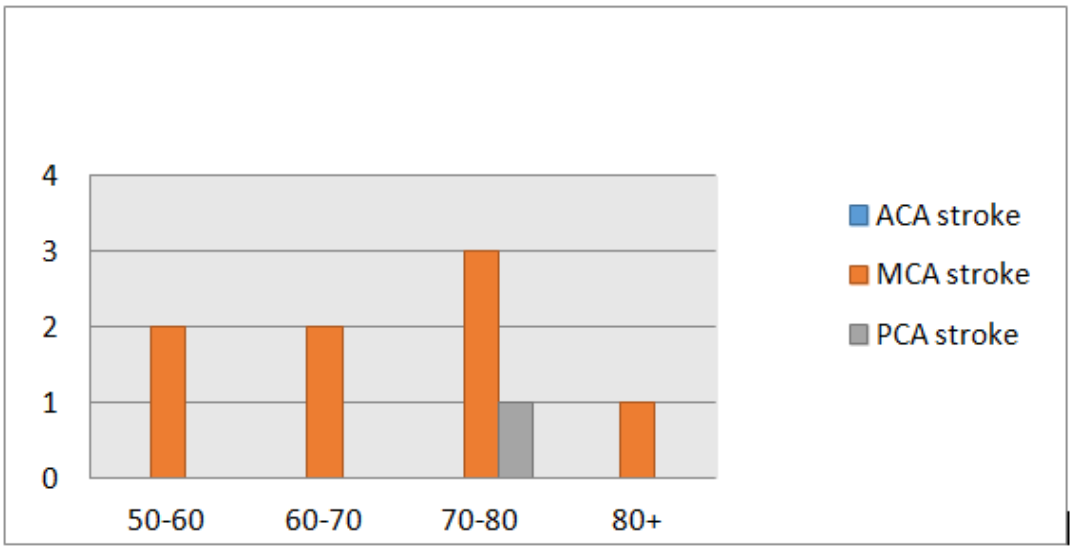

Fig. 1. Distribution of AIS by vascular territory in different age groups in patients with AIS and COVID-19 (x- number of patients, y-years)

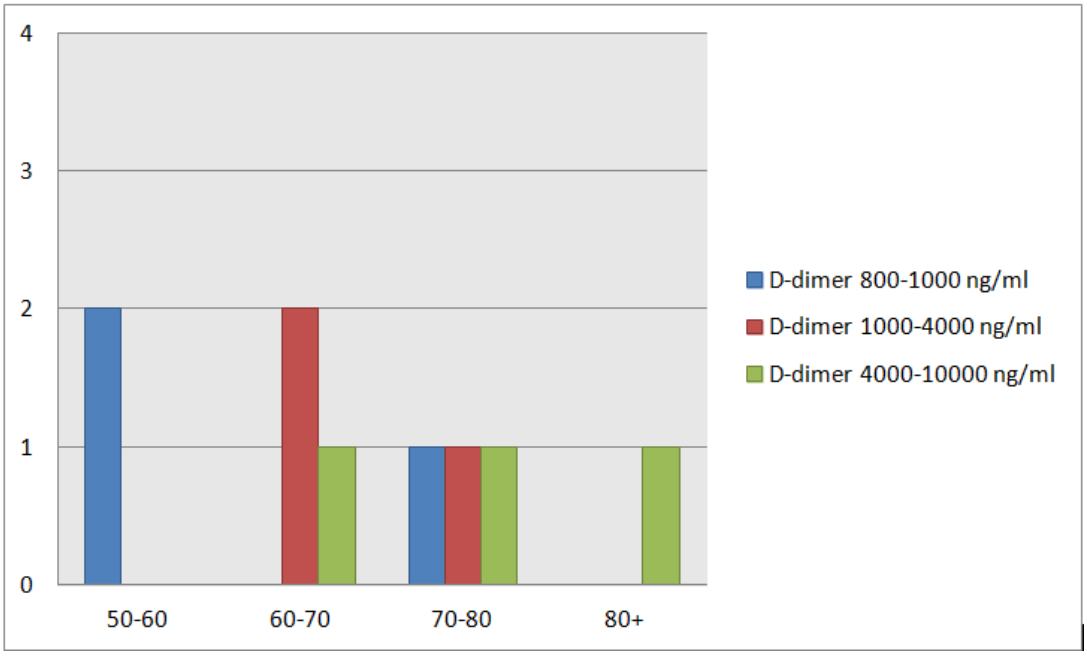

Fig. 2. Distribution of D-dimer levels in different age groups in patients with AIS and COVID-19 (x- number of patients, y- years)

Increased LDH levels were seen in 5 patients, mean value of 400 U/L (range 290-537 U/L). Hypertension was the most frequent risk factor, present in all 10 patients (100%). Diabetes mellitus and hyperlipidemia were registered in 4 patients (40%), chronic cardiomyopathy in 3 patients (30%), atrial fibrillation in 2 (20%), COPD and previous stroke in one patient (10%) (Figure 4). Six patients (60%) were discharged in a stable condition and 4 (40%) had lethal outcome. Due to the extraordinary conditions on account of the pandemic, further diagnostic testing for determining stroke etiology was unable to be performed.

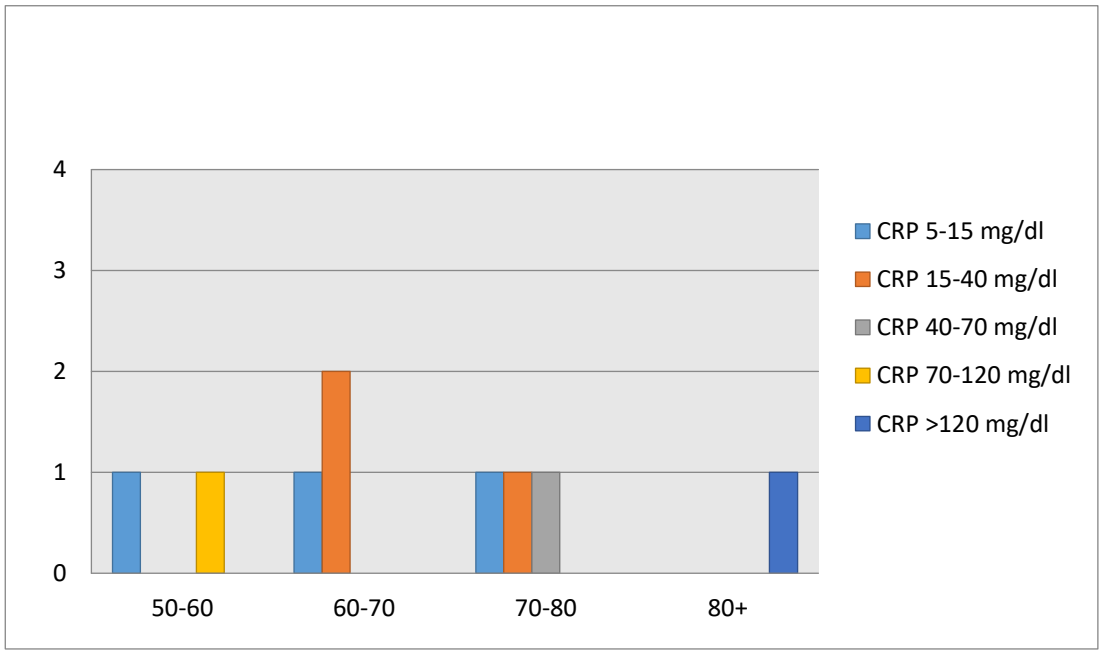

Fig. 3. Distribution of CRP levels in different age groups in patients with AIS and COVID-19 (x-number of patients, y-years)

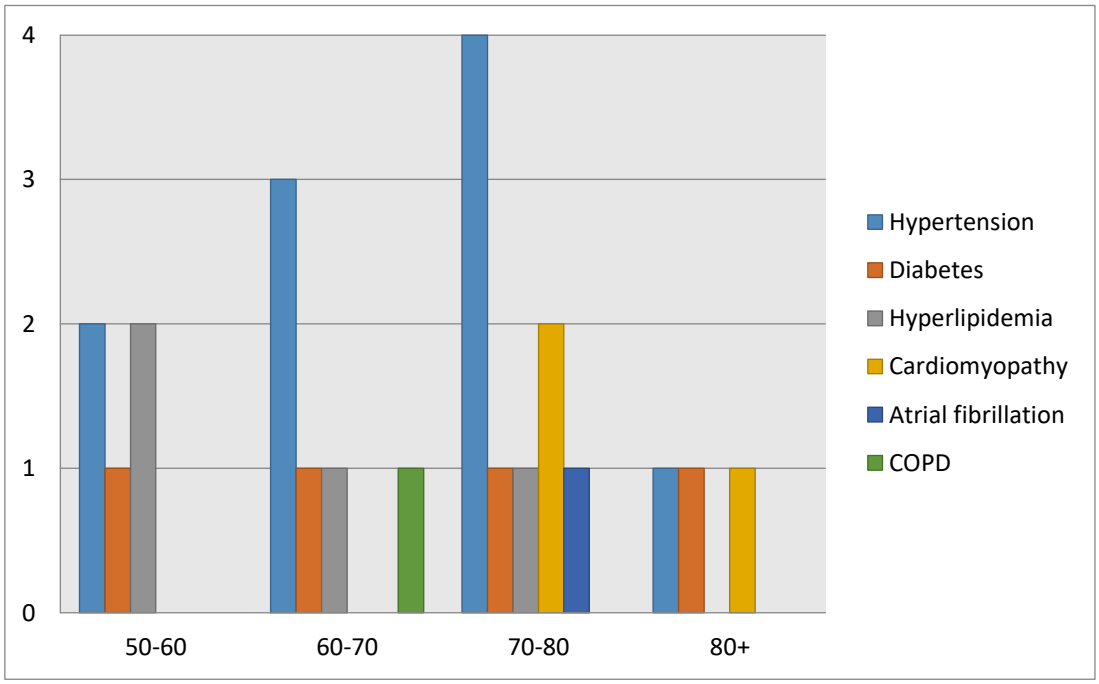

Fig. 4. Distribution of comorbidities in different age groups in patients with acute ischemic stroke and COVID-19 (x-number of patients, y-years)

Below we present three cases of AIS and COVID-19, i.e., the oldest and the youngest patients with anterior circulation AIS, and the only case of AIS in the posterior circulation.

Case series

Patient 1 - A 52-year-old male patient, positive for SARS-COV-2, with bilateral bronchopneumonia was referred to our Clinic from another facility where he had been treated for COVID-19 (Figure 5). On admission the patient presented with left-sided weakness, left-

sided central facial palsy and deviation of the head and eyes to the right. Brain CT scan demonstrated massive AIS in the vascular territory of the right MCA, with a volume of 336 cm^3 (Figure 6). The patient had hypertension, diabetes type 2, and coronary stent placement surgery seven years ago. Routine blood test results showed increased levels of erythrocyte sedimentation rate (ESR) (40), blood glucose (8.3 mmol/L), LDH (345 U/L), D-dimer (979 ng/ml) and CRP (119.2 mg/dl). Other parameters were in normal range. During the hospital stay, a considerable decrease in WBC count, CRP, LDH and D-dimer levels was observed. On the control CT scan, hemorrhagic transformation of the AIS and mass effect was registered. The patient was treated with subcutaneous low-molecular weight heparin (LMWH), anti-edematous, antithrombotic, corticosteroid and other symptomatic therapy. However, a recurrent increase in the D-dimer levels was detected right before discharge, due to which the patient was prescribed oral anticoagulant therapy (Rivaroxaban) for a period of one month. The patient was discharged in a significantly improved physical and neurological condition, with stabilized pulmonary symptomatology and improved neurological deficit.

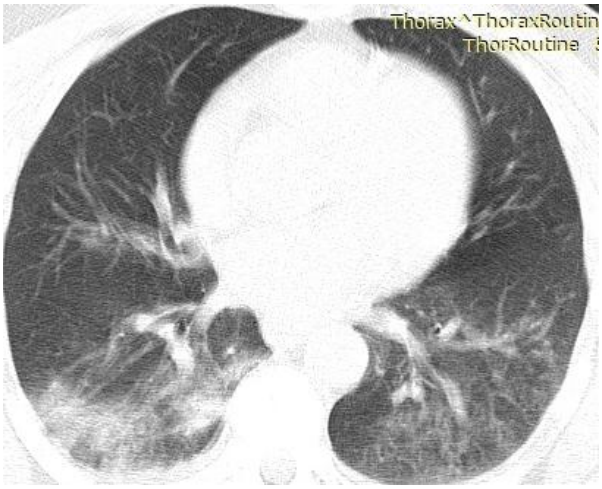

Fig. 5. Bilateral bronchopneumonia in a 52 years old COVID-19 male patient with massive MCA stroke

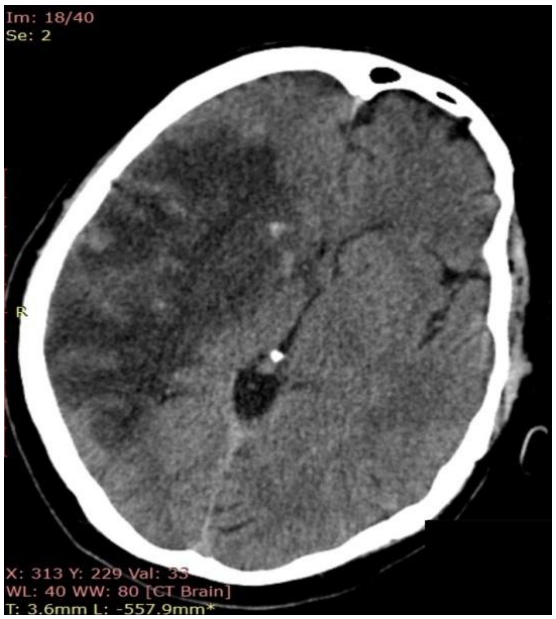

Fig. 6. Massive MCA stroke with haemorrhagic transformation and mass effect in a 52 years old COVID-19 male patient

Patient 2 **-** A 82-year-old female patient, positive for SARS-CoV-2, with COVID-19 pneumonia, was transferred to our Clinic from another facility (Figure 7). On admission the patient presented with impaired level of consciousness (soporous), with left-sided hemiparesis, with positive Babinski sign and deviation of the head and eyes to the right. First CT scan on admission was normal and the second CT scan conducted the next day showed MCA AIS with a volume of 203 cm^3 (Figure 8). Regarding comorbidities, the patient suffered from hypertension, cardiomyopathy and diabetes, while the ECG performed on the day of admission revealed previously undiagnosed atrial fibrillation. On auscultation, a diminished vesicular breathing along with bilateral crackles was detected. Her blood pressure was 170/100 mmHg, heart rate was 100 beats/min, and arterial oxygen saturation was 90% on room air. Routine blood test results showed increased levels of ESR (78), blood glucose (17,7 mmol/L), LDH (>290 U/L), D-dimer (>10000 ng/ml) and CRP (186.6 mg/dl). Other parameters were in normal range. The patient was treated with subcutaneous LMWH, antiedematous, antihypertensive, antithrombotic and other symptomatic therapy. During the hospital stay, the patient's condition deteriorated and despite all measures, two days later the patient died from cardiorespiratory failure.

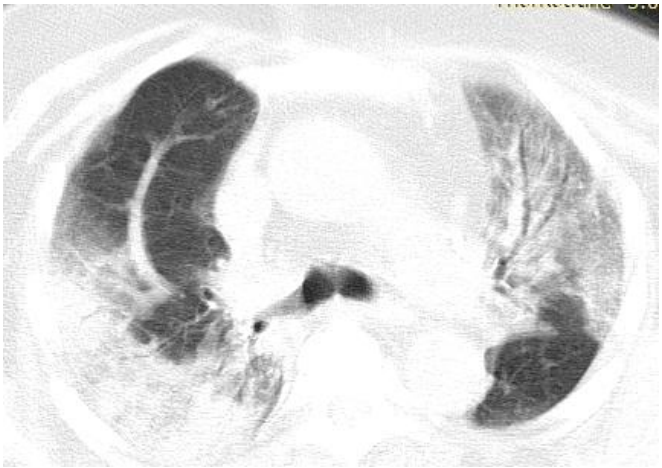

Fig. 7. Bilateral massive bronchopneumonia in a 82 years old COVID-19 female patient with massive MCA stroke

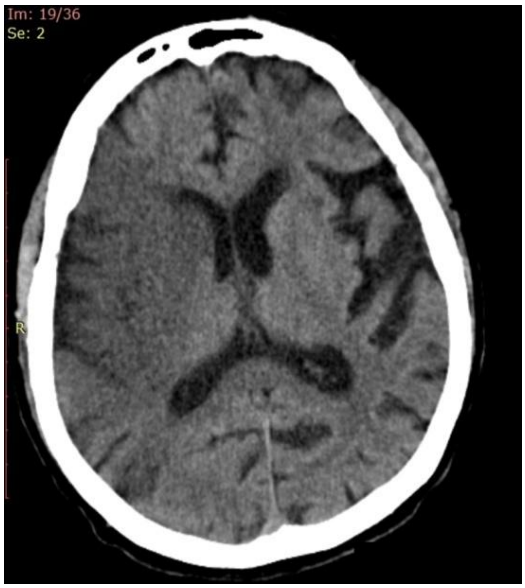

Fig. 8. Massive MCA AIS in a 82 years old COVID-19 female patient

Patient 3 **-** A 70-year-old female patient, positive for SARS-CoV-2, with a history of resistant hypertension was admitted due to symptoms of neurological deficit lasting for one week, presented with right-sided hemiparesis and sensory-motor dysphasia. The CT scan revealed AIS in the vascular territory of the left PCA (temporobasal, paramedial region), with a volume of 11 cm^3 (Figure 9). Routine blood test results showed increased levels of LDH (333 U/L) and D-dimer (814 ng/ml). Other parameters were in normal range. During the hospital stay, a normalization of the D-dimer levels was observed. The patient was treated with subcutaneous LMWH, antithrombotic, antihypertensive, antilipemic and other symptomatic therapy. Quadruple antihypertensive treatment was started and the patient was discharged home with stabilized hypertension and improved physical and neurological condition.

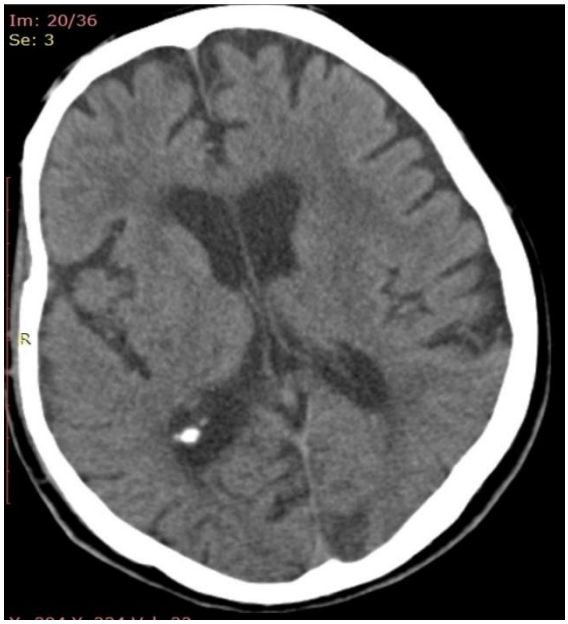

Fig. 9. PCA stroke in a 70 years old female patient with COVID-19 patient

Discussion

Out of 556 patients with confirmed SARS-CoV-2, 10 (1.7%) developed AIS following COVID-19 infection.

All of these patients were elderly and had concomitant comorbidities, with the cardiovascular ones being the most common.

Proposed Pathophysiology

Viral neurotropism **-** It is thought that similar to other beta-coronaviruses, SARS-CoV-2 can infect the brain by entering the cerebral microcirculation, by attaching to and acting on the angiotensin converting enzyme-2 (ACE-2) receptors[6] expressed on the cell membranes of both neuronal and glial cells, in the motor cortex and in the brainstem [7]. Once the spike (S) protein of SARS-CoV-2 is bound to ACE-2, it undergoes a proteolytic cleavage of its two subunits S1 and S2 mediated by the transmembrane serine protease 2 (TMPRSS2), promoting the virus's entry into the cell[8]. The effect of ACE-2 receptors on SARS-CoV-2 was also demonstrated by *in vivo* studies in mice, which showed that mice which expressed smaller amounts of ACE-2 presented milder symptoms because of the drastic reduction in the virus replication[9]. So far, three possible pathways through which SARS-Co-2 manages to infect the brain have been identified: via the distribution of the virus through the general circulation by means of infected monocytes, through infection of the olfactory epithelial cells

and transport via the olfactory nerves, and by the axial retrograde transport from the digestive and the respiratory tract (rich in ACE-2 receptors) to the brain via the vagal nerve[10].

Cytokine storm - Our body generates inflammation in response to SARS-CoV-2, creating the so-called cytokine storm, during which interleukin 6 (IL-6) and other factors play an essential role by leading to the activation of matrix metalloproteinases, enzymes capable of compromising the BBB and enabling the virus's penetration into the CNS [11,12]. IL-6 stimulates the synthesis of fibrinogen in the liver, the synthesis of platelets through megakaryocytes, as well as the secretion of tissue factor (TF) by monocytes, thus promoting the coagulation cascade and leading to a hypercoagulable state[13].

Coagulopathy - Increased D-dimer, fibrinogen, factor VIII, and Von Willebrand factor indicate a close association between SARS-CoV-2 and coagulopathies[14]. It has been estimated that over 95% of patients with COVID-19 have increased D-dimer levels. COVID-19 induces hypercoagulable state by increasing the levels of procoagulants such as factor VIII, and reducing the natural anticoagulants such as antithrombin[15]. Hypercoagulable state together with inflammation leads to thrombus formation, promotes thromboembolic events and increases the risk of cardiovascular diseases (CVD)[14].

Similarly, a study involving 27,676 patients from 54 health centers found that ischemic stroke in the presence of COVID-19 is infrequent and affects only patients with other comorbidities, mainly cardiovascular [16]. On the other hand, a study conducted by Li *et al.* on 11 patients from a single center with COVID-19, showed that 9 of the 11 patients with COVID-19 developed ischemic strokes, one of them developed intracranial hemorrhage, and one had cerebral venous sinus thrombosis, thus making ischemic stroke the most common CVD among patients with COVID-19[17]. In correlation with these studies, the number of our patients who developed stroke was relatively small compared to the total number of patients with COVID-19 admitted during that period.

Furthermore, all of them had associated cardiovascular comorbidities. The most commonly registered was hypertension, present in all patients, followed by diabetes, which affected four patients; another three patients had hyperlipidemia, three had chronic cardiomyopathy, one had atrial fibrillation and another one had COPD. Similarly, in a study conducted by Mao *et al.* involving a total of 214 patients, 37% of the observed patients developed neurological complications, whereas 5.7% of them manifested strokes. Consistent with our study, all patients were elderly with cardiovascular comorbidities, and had increased D-dimer levels on admission[18]. Because of the disrupted health care service during the pandemic, further diagnostic investigations for determining stroke etiology could not be completed. The increased D-dimer and other inflammatory marker levels on admission, point towards a possible association of stroke with the hypercoagulable state caused by COVID-19[19]. Ghannam *et al*. reported that 48.8% of neurological disorders in patients with COVID-19 are cerebrovascular, with the ischemic stroke being present in 87.5% of the cases[14]. Likewise, a cohort retrospective study suggests that the incidence of stroke development in hospitalized patients with COVID-19 is 7-8 higher than in those hospitalized with influenza, which proves the impact of the hypercoagulable state in the occurrence of ischemic stroke[20]. The 2020 New York study by Yaghi *et al.* showed that COVID-19-associated strokes are more severe and most likely to be embolic, thus increasing the rate of embolic and cryptogenic strokes. In contrast to ours, this study found that patients who developed stroke in the presence of COVID-19 were younger compared to those without [21].

In terms of stroke localization and stroke volume, with the exception of one patient who developed PCA stroke, all of the patients manifested MCA strokes with varying volumes. Three of the patients had massive strokes accompanied with hemorrhagic transformation and

mass effect. We calculated the volume of each stroke according to the ABC/2 formula and concluded that the largest stroke had a volume of 336 cm^3, while the smallest one measured 2 cm^3.We noticed that stroke volume is not in direct proportion with mortality, i.e. only one patient who developed massive stroke, with hemorrhagic transformation ended fatally. In contrast, age was seen to have a direct negative impact regarding the patient's final outcome, due to which four of the patients who ended up fatally were elderly, respectively above 70 years old. This is explained by the fact that older patients in addition to a more common rate of comorbidities such as hypertension, atherosclerosis and atrial fibrillation have also a longer proinflammatory response as the result of the deficient cellular and humoral immunity, thus leading to a poor outcome[22].

It is worth mentioning that COVID-19 involves the heart muscle too, both directly by the virus's affinity on the ACE-2 receptors and indirectly through the inflammatory response during the cytokine storm. Hypoxemia also increases the heart's rate in a compensatory manner and causes secondary stress on it, thus increasing the risk of cardiomyopathy[23]. In this regard, three of our deceased patients suffered from chronic cardiomyopathy. On the other hand, half of the patients, or five out of ten, presented as being alert on admission and the other half displayed altered level of consciousness, with three of them being somnolent and the remaining two soporous. Except for one patient who showed somnolence on admission, all of the patients with impaired level of consciousness on admission ended up fatally.

In a systematic study of all publications made in relation to stroke patients and COVID-19 from 1 November 2019 to 8 July 2020, 899 stroke patients from 30 studies were analyzed[24]. The analysis showed that although stroke is a rare complication of COVID-19, it often results in significant morbidity and mortality. Stroke in COVID-19 is associated with older age, with comorbidities and severe disease.

Conclusion

Our study indicates that AIS in patients with COVID-19 is more likely to occur in elderly patients with cardiovascular comorbidities. Aging, comorbidities, impaired level of consciousness as well as increased levels of D-dimer and CRP on admission along with COVID-19 pneumonia contribute to patient fatal outcome.

Conflict of interest statement. None declared.

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