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NEUROLOGICAL MANIFESTATIONS OF HOSPITALIZED PATIENTS WITH COVID-19: A CASE SERIES STUDY

M. H. Zamanian[1], A. Janbakhsh[1], F. Mansouri[1], B. Sayad[1], M. Afsharian[1], S. Vaziri[1], B. Mahdavian[1], Z. M. Afshar[1], R. Miladi[1], M. Shirvani[1], M. Noori[2], M. Salimi[3], A. Babazadeh[4], S. Ebrahimpour[4]

[1]Infectious Diseases Research Center, Kermanshah University of Medical Sciences – Kermanshah, Iran
[2]Clinical Research Development Center, Imam Reza Hospital, Kermanshah University of Medical Sciences – Kermanshah, Iran
[3]Department of Internal Medicine, Kermanshah University of Medical Sciences – Kermanshah, Iran
[4]Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences – Babol, I.R. Iran

Abstract. *There are some reports about the neurological manifestations and complications of COVID-19. We present neurological manifestations in 6 hospitalized patients with COVID-19. The patients presented with common symptoms of COVID-19 along with common findings from high-resolution computed tomography (HRCT) scan such as ground-glass opacities (GGOs). Though, RT-PCR testing of SARS-CoV-2 was negative for all 6 cases. In the current report, acute cerebrovascular diseases affected older patients, while dementia, seizure and encephalopathy affected younger ones. Three of the 6 patients had proven strokes based on their neuroimaging. Four of the 6 patients had high d-dimer levels. Two of the cases experienced convulsion. The third patient presented with typical symptoms and signs of neuroleptic malignant syndrome. The sixth case was interesting for transient dementia. Unfortunately, four out of six patients died. The recent case series report the association between neurological involvements and COVID-19 infection. Clinicians should be alert of the neurologic symptoms in the setting of COVID-19, which might even be the first presentations of this infection.*

Key words: *COVID-19, neurologic manifestations, complication, case series*

Corresponding author: *Zeinab Mohseni Afshar, Clinical Research Development Center, Imam Reza Hospital, Kermanshah University of Medical Sciences, Kermanshah, Iran, tel: +989111156511, e-mail: baboldr2019@gmail.com*

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INTRODUCTION

Corona virus disease 2019 (COVID-19) or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, which is an emerging mysterious viral disease, primarily involves the respiratory and cardiovascular systems [1-3]. However, its neurological involvement is reported somehow commonly in recent literature [4]. Neurologic manifestations can occur any time in the course of infection either preceding the respiratory symptoms or being the only manifestation of COVID-19 infection. Therefore, greater awareness of the potential neurologic complications of this condition is warranted in order to early diagnose the disease and promptly start treatment. Here, we present six COVID-19 patients with simultaneous neurological manifestations and complications (Table1).

Table 1. The demographic and clinical characteristics of the presented COVID-19 patients with neurological complications

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, Gender	75 years old, female	83 years old, female	33 years old, male	62 years old, female	24 years old, female	54 years old, male
Presenting symptoms	seizure	hemiparesis	fever, confusioz, rigidity, sweating, palpitation	lowered consciousness, fever	seizure	Transient amnesia
Oxygen saturation (%)	83	87	83	91	84	92
Neurological complication	Ischemic stroke	Ischemic stroke	NMS	Hemorrhagic stroke	Convulsion	dementia
Risk factors	hypertension , congestive heart failure	hyperlipidemia	negative	heart failure, hypertension and atrial fibrillation	negative	No
Ventilated	yes	no	yes	yes	yes	no
Outcome	Death	Discharged with partial recovery	Death	Death	Death	Discharged with partial recovery
Chest CT Findings	Typical findings for COVID-19 + bilateral pleural effusion	Typical findings for COVID-19	Typical findings for COVID-19	Typical findings for COVID-19 + pneumopericardium	Typical findings for COVID-19	Typical findings for COVID-19
Brain MRI Findings	Left thalamic and lenticulostriate lacunar infarct	Right temporoparietal lobe and caudate nucleus infarct	Normal	IVH and SAH	Normal	Normal
NIHSS	19	17	unknown	21	unknown	unknown
D-dimer (0-500 ugFEU/L) 803	1530	849	960	2400	3672	794
C-reactive protein (0-5 mg/L)	44	8	38	81	48	7
Neutrophil/Lymphocyte (K/uL)	18.4/1.1	5.7/1.3	14.3/1.7	7.9/1.2	16.8/0.8	5.9/1.3
RT-PCR test result	unknown	negative	unknown	unknown	negative	unknown

CASE 1

A 75-year-old woman presented to the emergency department (ED) with a new-onset seizure followed by a postictal phase. Her past medical history included hypertension and congestive heart failure. She was admitted to the intensive care unit (ICU), due to her hypoxemia, relative hypotension and laboratory tests indicative of sepsis, and then underwent volume replacement, central venous line (CVL) insertion and sepsis workup including brain magnetic resonance imaging (MRI) and high-resolution computed tomography (HRCT) scans. A lung CT scan revealed a mild bilateral pleural effusion, an increased pulmonary artery diameter, thickened septal lines and an air-space nodule at the basilar segment of the right lung (Figure1). Brain MRI showed a left thalamic and lenticulostriate lacunar infarct. Considering the patient's presentations, imaging findings and COVID-19 epidemic, ischemic stroke in the setting of SARS-CoV-2 infection was suspected; therefore, hydroxychloroquine (200 mg BID per os) and KALETRA (lopinavir/ritonavir) 400 mg BID and ceftriaxone 1 gram BID intravenously were started for her. After seven days of stay in the hospital, she died of respiratory failure.

CASE 2

A 83-year-old woman with no prior medical history except hyperlipidemia, was admitted to the hospital due her left-sided weakness, paresthesia and inappropriate behaviors for 1 day. At present, she had

no fever. Neurological examination showed left limb weakness along with a grade 4 limb muscle strength. Moreover, hemiagnosia and loss of proprioception were evident. Laboratory studies showed lymphopenia, abnormal coagulation tests, elevated d-dimers and hypoxemia. Brain MRI demonstrated right temporoparietal lobe and caudate nucleus infarct. HRCT of the chest revealed bilateral pulmonary parenchymal ground-glass opacities (GGOs). Real-time polymerase chain reaction (RT-PCR) of nasopharyngeal swab sample was negative for SARS-CoV-2 nucleic acid; however, due to her low arterial oxygen saturations and lung imaging consistent with COVID-19, hydroxychloroquine (200 mg BID) and KALETRA (lopinavir/ritonavir) 400 mg BID and naproxen 250 mg BID accompanied by conservative care started for her until she was discharged.

CASE 3

A 33-year-old smoker male with a history of hyperthyroidism, was admitted to ED of the Neurology clinic with a 1-week complaint of sudden weakness along with difficulty talking and walking. Physical examination revealed a high fever, confusion, muscle rigidity, diaphoresis, and tachycardia. Despite no drug history, according to his presentation, neuroleptic malignant syndrome was suspected and he underwent medical treatment for this condition. Four days after admission, he developed dyspnea and nonproductive cough, with a respiratory rate of 30 and oxygen saturation of 83% on room air. HRCT of the chest was performed in which bilateral pulmonary GGOs were evident. He was immediately intubated and ICU admitted. Highly suspicious for COVID-19, he was started on medication hydroxychloroquine (200 mg BID) and KALETRA (lopinavir/ritonavir) 400 mg BID and ceftriaxone 1 gr BID agents along with supportive care. After a nine-day-duration hospitalization, he passed away because of a cardiopulmonary arrest.

CASE 4

A 62-year-old female with a past medical history of heart failure, hypertension and atrial fibrillation presented to the ED with lowered consciousness and fever. Her daughter said that her mother suffered from a 3-day history of cough. Vital signs on presentation included fever of 38.3° C, heart rate (HR) of 64 beats per minute (bpm), respiratory rate (RR) of 18 breaths per minute, and hypoxemia with O_2 saturation (SpO_2) of 91%. On examination, bilateral extensor planter response was detected. Her laboratory tests were indicative of a lymphopenia and increased d-dimer. Her brain MRI revealed intraventricular and subarachnoid hemorrhage and her HRCT of the chest showed pneumopericardium, atelectasis at dependent areas of both lungs, patchy GGOs accompanied by consolidations at the periphery of the left lower lung, compatible with COVID-19 (Fig. 2). A few hours after admission, she developed apnea, so that she was intubated and underwent cardiopulmonary resuscitation. Unfortunately, she did not survive. Nasopharyngeal swab specimen RT-PCR result which was taken before her death turned to be positive after her passing away.

Fig. 1. lung CT scan revealed a mild bilateral pleural effusion, an increased pulmonary artery diameter, thickened septal lines and an air-space nodule at the basilar segment of the right lung

Fig. 2. HRCT of the chest showed pneumopericardium, atelectasis at dependent areas of both lungs, patchy GGOs accompanied by consolidations at the periphery of the left lower lung

CASE 5

A 24-year-old woman at 37 weeks of pregnancy was admitted to the hospital with labor pain, with no accompanying symptoms. Her past medical history was

negligible. She underwent a normal vaginal delivery (NVD) without any complication. A few hours post-partum, she developed mental status changes, fever, respiratory distress, and one episode of generalized tonic-clonic seizure. Her vital signs were as follows: respiratory rate (RR) of 60/min, heart rate (HR) of 160/min, body temperature (BT) of 38.5 °C, and SpO_2 of 84% in room air. She was immediately intubated for airway protection and transferred to the ICU. Her laboratory data were suggestive of lymphopenia, thrombocytopenia, increased inflammatory markers, mildly elevated liver enzymes, and impaired coagulation tests along with d-dimer increments. Brain magnetic resonance imaging was normal, but HRCT scan of her lungs revealed bilateral peripheral GGOs characteristic for COVID-19. She was managed as a septic shock patient; however, before complete evaluations, she died of cardiopulmonary arrest.

CASE 6

A 54 year-old-male with no past medical history was brought to the ED for a chief complaint of altered mental status, disorientation and transient amnesia. His family said that his father suffered from dyspnea, for which he was hospitalized, but was discharged with personal consent. Vital signs in the ED were significant for temperature of 37.9° C, HR of 86 beats/min, BP of 130/75 mm Hg, RR of 24 breaths/min and SpO_2 of 92% in ambient air. His neurological examination was no significant except for a disorientation, which was explained by his hypoxemia. Brain imaging did not reveal any abnormalities; however, lung HRCT demonstrated bilateral patchy GGOs. Laboratory data on admission demonstrated lymphopenia, a mild elevation in liver enzymes, along with normal inflammatory markers and increased d-dimer level. Considering these characteristic HRCT findings in the COVID-19 outbreak, he was tested for COVID-19 infection by RT-PCR and the result was reported to be positive. He was started on lopinavir-ritonavir, hydroxychloroquine and azithromycin. Five days later, he was discharged with partial improvement.

DISCUSSION

COVID-19 infection due to SARS-CoV-2, an emerging disease originated from Wuhan city in central China has imposed several challenges in all fields of medicine. The prominent features of this challenging viral infection belong to respiratory and cardiovascular systems; however, neurological manifestations are becoming increasingly observed. Most coronaviruses have been neurotropic, hence neuroinvasiveness of SARS-CoV-2 would not be unexpected [5]. Mechanisms by which SARS-CoV-2 affects the neurologic system include hypoxic brain damage and immune mediated injury. The most prevalent neurologic symptoms ever reported are headache, lightheadedness, neuralgia and delirium, while the most common complications include encephalopathy, cerebrovascular accidents, changes of consciousness and skeletal muscular damage [6]. Actually, neurological presentations and sequels of COVID-19 should be categorized into central and peripheral nervous system involvement. Among CNS manifestations, we could mention encephalopathies including acute hemorrhagic necrotizing encephalopathy (ANE), acute myelitis, cerebrovascular accidents, encephalitis, headaches and dizziness [6]. PNS involvement can be manifested as anosmia and sensory dysfunction [7]. It must be mentioned that all of the patients in recent case series were managed in our COVID-19 dedicated hospital, Golestan at Kermanshah, Iran, with HRCT findings compatible with COVID-19 pneumonia in all of them. The occurrence of neurological complications in the setting of COVID-19 infection point at a causal relationship between these manifestations and the infectious disease; however, RT-PCR testing of SARS-CoV-2 was not positive for all 6 cases. The explanation would be the low sensitivity of our RT-PCR kits and lack of experience of the personnel in taking samples. All of our patients received treatment in agreement with the standard of care for COVID-19 along with antimicrobial agents if necessary.

In most studies, patients with neurological complications were older than patients without such complications [8]. However, in our case series acute cerebrovascular diseases affected older patients, while dementia, seizure and signs of encephalopathy affected younger ages.

According to various studies, neurological involvement increases morbidity and mortality in the setting of COVID-19 [8], as in our study in which, four out of six patients died; moreover, we do not have data on the long-term outcomes and mortality of the two patients who survived and were discharged from our hospital.

Cerebrovascular accidents are divided into two main groups of ischemic and hemorrhagic etiology. Usually, these conditions occur in the elderly; however, recently, it has been reported that the new coronavirus appears to cause sudden strokes even in otherwise healthy adults of younger ages [9]. As predicted, older individuals are more prone to ischemic strokes, such as observed in our cases. However, hemorrhagic stroke most commonly affects hypertensive patients, although the patient from our case series, who developed an intraventricular and subarachnoid hemor-

rhage, was relatively hypotensive, which could not be explained and might be a unique feature of COVID-19.

Cerebrovascular accident (CVA) usually presents with focal neurological signs but here, we observed patients with imaging-proven cerebrovascular engagement, who were brought to us with the only symptom of lowered consciousness and no focal signs [4]. The explanation could be the presence of encephalopathy, which might mask other symptoms; therefore, the value of neuroimaging in these conditions is non-negligible.

Headaches and dizziness are nonspecific presentations of any COVID-19 patient [10]. It is important to note that, the presence of these symptoms does not represent neurological complications, while they can happen in any viral infection and are not helpful for the diagnosis or prognosis of COVID-19 infection. Electrolyte imbalances, body's elevated temperature, hemodynamic instability, and even interferon release due to the virus invasion to the airway are some of the explanations of headache and dizziness that occur during COVID-19 infection.

Mechanisms by which, COVID-19 predisposes to cerebrovascular accidents are various, ranging from excessive inflammation and hypoxia to immobilization and diffuse intravascular coagulation [11]. Three of the 6 patients presented here, had proven strokes based on their neuroimaging. The National Institutes of Health Stroke Scale (NIHSS) score for all of them were calculated to be above 16, which is indicative of moderate to severe stroke. Four of the 6 patients had high d-dimer levels, which could be obvious predictors of their cerebral circulation infarction and unfavorable prognosis.

Cases 1 and 5 experienced convulsion which has not been uncommon among COVID-19 patients all over the world. The underlying mechanisms by which seizures could happen in such patients include certain antimicrobials administered in the course of the infection, cerebral hypoxemia, acute renal failure, and acid-base or electrolyte disturbances, among which, hypoxemia would be the most probable underlying reason for these patients [12].

The third COVID-19 case with typical symptoms and signs of neuroleptic malignant syndrome was somehow the first such case we saw in our hospital. Up to date, there have been no other reports of such complication and no explanations yet.

The last case of these series was interesting for transient dementia which could not be explained with any mechanisms such as front temporal degeneration or electrolytes impairment, since his neuroimaging was intact and laboratory tests did not reveal a corresponding reason. One of the limitations of our study was that we did not perform cerebrospinal fluid (CSF) examinations, which might be quite helpful in interpreting the patients' conditions.

CONCLUSION

Neurologists and infectionists should be aware of the fact that COVID-19 patients can present with cerebrovascular accidents and a variety of signs and symptoms of neurological involvement. The most significant benefit of this awareness would be cautions taken by healthcare personnel in order to avoid transmission or acquiring the infection from individuals with apparently unrelated COVID-19 symptoms. At the next step, early COVID-19 diagnosis and treatment might prevent disease progression to neurological complications. However, more research is needed to identify the neurological implications of COVID-19 disease.

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