Clinical Spectrum of Neurological Complaints in COVID-19: Experiences from a COVID-19 Referral Hospital in Indonesia

Rocksy Fransisca V. Situmeang[1], Astra Dea Simanungkalit[1] , Anyeliria Sutanto[1], Aristo Pangestu[2]

[1] Neurology department, Siloam Hospital Lippo Village, Tangerang, Banten, Indonesia
[2]Faculty of Medicine, University of Pelita Harapan, Tangerang, Indonesia

Citation : Rocksy Fransisca V. Situmeang, Astra Dea Simanungkalita, Anyeliria Sutanto, Aristo Pangestu. Clinical Spectrum of Neurological Complaints in COVID-19:
Experiences from a COVID-19 Referral Hospital in Indonesia
Medicinus. 2021 February; 9(1): 14-26
Keywords : COVID-19; neurological complaint; neurological complication;
Neurological manifestation; SARS-CoV-2
***Correspondance** : Rocksy Fransisca V. Situmeang, Sp.S
Neurology Department
Siloam Hospital Lippo Village
Siloam Street No.6 Lippo Karawaci
Tangerang, Banten, 15811, Indonesia
+62 812-9092-821
E-mail : rocksy.fvs@gmail.com
Online First : September 2021

Abstract

Background : The main feature of COVID-19 is symptoms of respiratory system disorder, however there has been an increase in reports of neurological symptoms that appear in COVID-19 patients. Several previous studies have linked SARS-CoV-2 with nervous system damage. Research studying neurological complaints in confirmed COVID-19 patients in Indonesia is still lacking

Aim: To identify neurological, laboratory and imaging findings in COVID-19 patients with neurological symptoms.

Methods: This study was a cross-sectional observational study conducted at Siloam Hospitals Mampang, a COVID-19 referral hospital in South Jakarta. We analyzed medical records of confirmed COVID-19 patients during the period of April - July 2020. The data collected included demographic data, comorbidities, neurological manifestations, laboratory examinations, and neuroimaging.

Results: There were 22 confirmed COVID-19 patients with neurological complaints referred to a neurologist. The mean age of patients was 60.4 (SD 15.8) years. The most common neurological complaints were altered mental status (50%), hemiparesis (27.3%), and tremor (22.7%). More than half of the patients (81.8%) had a comorbid condition or past history related to neurological symptoms. Laboratory examination results showed increased NLR (neutrophil-lymphocyte ratio) (50%), anemia (45.5%), and leukocytosis (40.1%). The most common neuroimaging feature was infarct (50%) in Brain CT scan.

Conclusion: The neurological complaints in COVID-19 patients are mostly associated with exacerbation of pre-existing comorbidities as a result of the severe inflammatory process triggered by COVID-19. Further research is needed to establish the mechanism of nervous system dysfunction in COVID-19

Background

Since first reported in Wuhan at the end of 2019, the SARS-CoV-2 virus, which caused the viral pneumonia outbreak known as COVID-19, has spread to more than 215 countries.[1] As of July 2020, there has been approximately 18 million confirmed cases with a fatality of 700 thousand cases.[2] SARS-CoV-2 is an enveloped, non-segmented, single-strand RNA virus with a diameter of 65-125 μm, and preferentially infects cells of the respiratory tract.[3,4] Symptoms of COVID-19 vary between individuals, ranging from mild to life-threatening conditions such as respiratory failure, septic shock, and multiorgan failure.[5] Based on a previous study conducted by Chen et al, the most common symptoms complained among COVID-19 patients include fever, cough, fatigue, dyspnea, sore throat, headache, and conjunctivitis.[6] Severe manifestations were predominantly found in the elderly and patients with pre-existing comorbid conditions, such as hypertension and diabetes.[6,7]

Although the primary manifestations of COVID-19 involve the respiratory system, there has been increasing reports of neurological symptoms in COVID-19 patients.[8] Nervous system involvement may be caused by direct invasion of the central nervous system (CNS) by the virus, immune-mediated inflammation, or as complications due to the systemic effects of COVID-19.[8,9] A systematic review conducted by Nepal et al revealed that the most frequently encountered neurological symptoms include disorders of smell (59%), taste (56%), myalgia (25%), and headaches (20%). Research that studies neurological manifestations in confirmed COVID-19 cases in Indonesia is very lacking. Therefore, we conduct this study in order to identify clinical, laboratory, and imaging findings on COVID-19 patients with neurological complaints.

Methods

Study design and population

This study was a cross-sectional observational study conducted at Siloam Hospitals Mampang, a COVID-19 referral hospital in South Jakarta. The patients included in this study were confirmed COVID-19 patients with complaints of neurological symptoms, and were referred to a neurologist during that period. We analyzed medical records belonging to COVID-19 patients confirmed by real-time reverse transcriptase polymerase-chain-reaction (rt-PCR), collected via nasopharyngeal swab, during the period of April - July 2020.

Data collection

The data obtained were secondary data from medical records. Demographic data collected include age, gender, presence of pre-existing comorbidities, and past medical history. The neurological symptoms described were complaints that necessitated a referral to neurology, or the chief complaint that resulted in patient admission. Examination of vital signs were obtained from the emergency department, or the last examination done at the isolation ward. Neurological evaluation and examination was conducted by a neurologist. Laboratory test results included complete blood count and other significant results. Imaging examinations were performed according to the anatomical sites of the neurological complaint. Neurological diagnosis was made by a neurologist according to clinical, laboratory, and radiological findings.

Results

During April - July 2020, there were 22 confirmed COVID-19 patients with neurological complaints. Of the 22 patients, 13 (59.1%) were female and 9 (40.9%) were male. The mean age of the patients was 60.4 (SD 15.8) years old. Demographic data, clinical, laboratory and imaging findings detailed in Table 1. Characteristics of pre-existing comorbidities, past history, neurological manifestations and diagnoses were presented in Table 2. More than half of the patients

(81.8%) had comorbid conditions or past medical history associated with neurological symptoms. The most complained neurological symptom was altered mental status (50%), followed by hemiparesis (27.3%), and tremors (22.7%). Ischemic stroke was found in 6 cases (27.3%). Laboratory examination results (Table 3) showed an increased NLR ratio (50%), anemia (45.5%), and leukocytosis (40.1%). Out of the 10 patients who underwent brain imaging examination (Table 3), 6 (50%) of them showed an ischemic / infarct

Table 1. Summary of demographic data and clinical features

No	Age (years)	Gender	Comorbidities/ Past History	Neurologic manifestations	Vital signs	Laboratory results	Imaging results	Diagnosis
I	63	Male	DM, HT, history of ischemic stroke 1 month ago	Loss of consciousness and right hemiparesis since 2 days ago	GCS: E4M6V5 BP: 120/70, HR: 105, RR: 20 (on ventilator), T: 37.2	Hb: 9.2, WBC: 12.4, thrombocyte 170, BG 204, K: 3.3, albumin: 3	Infarct	Ischemic stroke + DKA
II	46	Female	History of colorectal carcinoma	Delirium, recurrent general seizure (3 times,duration 5 minutes each, duration of alertness between seizure was 15 minutes) since 1 day ago	GCS: E4M6V5 BP: 104/60, HR: 90, RR: 18, T: 37.1, SpO2:99%	Hb: 11, WBC 23.3, segmented neutrophil:l: 88%, lymphocyte: 6%, NLR: 15, thrombocyte 448, Na: 117, K: 5.6, CRP: 5.3	NR	Metastatic brain tumor
III	98	Female	History of AF	Loss of consciousness, left hemiparesis, and myoclonic	GCS: E1M1V1 brainstem reflexes (-)	NR	Brainstem infract	Ischemic stroke + AF
IV	47	Male		Loss of appetite since 1 weeks ago, left hemiparesis since and left central facial nerve palsy since 1 days agp	GCS:E3M5V4 BP: 144/86, HR: 96, RR: 30, T: 37.8, SpO2: 94%	Hb: 12.8, WBC: 13.7, thrombocyte 658, segmented neutrophil: 86%, lymphocyte: 4%, NLR: 21.5, BG: 226	Infarct	Ischemic stroke
V	57	Male	DM, HT, History of ischemic stroke 6 months ago	Delirium and tremor since 2 days ago	GCS: E4M5V4 BP:120/80, HR:74, RR:20, T:37, SpO2: 99% E4M5V4	Hb: 12, WBC: 21, segmented neutrophil: 93%, lymphocyte: 2%, NLR: 46.5, ureum 85, creatinine: 4.5, Na: 117, K: 1.01	Old infarct	Metabolic encephalopathy +hyponatremia
VI	70	Male	History of Alzheimer's Disease with parkinsonism, bed ridden	Dyspnea since 1 week ago, accompanied by tremor and rigidity	GCS: E4M6V5 BP: 126/88, HR: 87, RR: 24, T: 37.1	Hb: 12.1, WBC: 20, ESR: 45, segmented neutrophil: 87%, lymphocyte: 4%, NLR: 21.75, LDH: 437, Na: 130	NR	Alzheimer's Disease + parkinsonism
VII	76	Female	History of lung carcinoma	Aphasia since few months ago, fever and dyspnea since 1 days ago followed by loss of consciousness	GCS: E4M4 aphasia BP: 110/70, HR: 78, RR: 22, T: 39	WBC: 5.8 , segmented neutrophil: 61%, lymphocyte: 27%, NLR: 46.5	Multiple hyperdense lesions and multiple bleeding on right frontal and left parietal lobes.	Metastatic brain tumor
VIII	64	Female	History pulmonary embolism on heparin	Left hemiparesis and left central facial nerve palsy since 1 day ago	GCS: E4M6V5 BP: 215/120, HR: 88, RR: 18, T: 36	WBC: 12.1, segmented neutrophil: 77%, lymphocyte: 19%, NLR: 4.05, INR: 0.91, BG: 313, HbA1c: 14.1, Na: 135, D-dimer: 0.62	Acute infarct on basal ganglia,right frontoparieta l lobes, subacute infarct on left thalamus	Ischemic stroke
IX	77	Female	History of craniotomy because of intracranial	Loss of consciousness since 1 day ago	GCS: E4M6 aphasia BP: 137/99, HR: 81, RR: 20, T: 37.5	Hb: 9.4, WBC: 9.7, segmented neutrophil: 68%, lymphocyte: 17%, NLR: 4, Na: 133, K: 6.2,	NR	Epilepsy

			aneurysm rupture 7 years ago			AST: 66, ALT: 77, creatinine: 1.48		
X	64	Male	HT, history of ischemic stroke 1 week ago	Recurrent tonic seizure (duration of each seizure: 5 minutes) since 1 day ago	GCS: E4M6V5 BP: 160/100, HR: 60, RR: 20, T 37.1	WBC: 11.38, segmented neutrophil: 71%, lymphocyte: 14%, NLR: 5.07, ureum: 85, creatinine 2	NR	Acute symptomatic seizure
XI	80	Female	History of femur fracture 1 year ago, history of Alzheimer's Disease	Disatria and disfonia since 3 months ago, cough and dyspnea since 1 day ago. Physical exam: left LMN hypoglossal palsy	GCS: E4M6V5 BP: 147/75, HR: 94, RR: 30, T: 37.5	WBC: 6, segmented neutrophil: 63%, lymphocyte: 18%, NLR: 3.5, aPTT: 40.5 (control:30) , PT 12.6 (control: 10.9), INR: 1.17, albumin: 3.37, Na: 135, CRP: 99.14	Head CT-Scan: chronic SDH	Chronic SDH + AD
XII	58	Female	HT, History of ischemic stroke 5 months ago,	Tremor on right extremity, left hemiparesis, and pelvic pain since 6 days ago	GCS: E4M6V5 BP: 122/78, HR: 87, RR: 22, T: 37	TSH HS: 0.41, Free T4: 16.83	Xray: old fracture column femur	Parkinsonism
XIII	45	Female	Obesity, sepsis, DM, post myocarditis, history on mechanical ventilation for 20 days	Tetraparesis since 1 month ago	GCS: E4M6Vett BP:120/94, HR: 88, RR: 20, T: 36	Hb 8.8, WBC: 17.27,segmented neutrophil: 70%, lymphocyte: 13%, NLR: 5.38, CRP: 66.5, PT: 13.4 (10.2), aPTT: 53.4 (control 33), D-dimer: 1.99	NR	Susp MG (respon on mestinon), dd hipokalemia
XIV	38	Male		Recurrent pain in both thighs and radiating to calf since 5 days ago, no history of trauma. Physical findings: tenderness on thigh	GCS: E4M6V5 BP: 120/87, HR: 88, RR: 21, T: 37	Hb 10.6, WBC 3.87, segmented neutrophil: 59%, lymphocyte: 25%, NLR: 2.36, AST: 66, ALT: 74, CRP: 35, Na: 130, K: 3.2	NR	Myalgia
XV	71	Female	HT, NSTEMI, on heparin medication	Loss of consciousness since 1 day ago, gross hematuria and petechiae	GCS: E3M5Vett BP: 171/88, HR: 93, RR: 15, T: 37.1	Hb 9.6, WBC 19.5, segmented neutrophil: 81%, lymphocyte: 6%, NLR: 13.5, PT: 10.4 (control 10.2), INR: 1.13, aPTT :40.1 (control 35.4) AST: 42, ALT: 51, ureum: 123.3, creatinine: 1.36	Infarct in brainstem	Brainstem ischemic stroke
XVI	40	Male	History of Parkinson Disease for 5 years	Dyspnea, cough, fever, and tremor since 2 weeks ago	GCS: E4M6V5 BP: 119/87, HR: 88, RR: 21,T: 37	NR	NR	Parkinsonism
XVII	55	Female	History of right lung chondrosarcoma and hyperthyroid for 1 year,	Paraparesis (unable to walk) and paresthesia since 3 weeks ago	GCS: E4M6V5 BP: 98/72 (on norepinefrin), HR: 105, RR: 24, T: 37	FT4: 65, TSHS <0.05, albumin: 2.72	PET-Scan: increased FDG uptake in right lung superior lobe and multiple lymph nodes	Polyneuropathy + paraneoplastic syndrome
XVIII	26	Female		Tremor of both hands, abdominal pain, fever, and myelena since 1 weeks ago	GCS: E4M6V5, BP: 114/87, HR: 90, RR: 28, T: 38.3	Hb: 7.4, WBC: 4.7, thrombocyte: 66, segmented neutrophil: 79%, lymphocyte: 17%, NLR: 4.68, ureum: 74, creatinine: 1.8, AST: 100, ALT: 91, PT 15.1 (control 13.8), aPTT 33(control: 30), fibrinogen: 123, D-dimer: 11.120,	Head CT-Scan: normal	Myoclonic on CKD

XIX	65	Male	DM, history of low back pain since 2 years ago	Delirium and worsened low back pain since 3 days ago	GCS: E1M5V2 BP: 119/75 (on norepinephrine), HR: 105, RR: 25, T: 36.9	NR	Head CT-Scan: normal	Metabolic encephalopathy + DKA
XX	69	Female	History of colorectal carcinoma, sepsis	Loss of consciousness and right hemiparesis	GCS: E1M3Vett, BP: 105/82, HR: 94, RR: 22, T: 36.8	NR	Head CT-Scan: acute infarct left basal ganglia	Stroke ischemic
XXI	54	Female	HT	Low back pain since 1 week ago with history of falling 2 weeks ago	GCS: E4M6V5, BP: 148/75, HR: 62, RR: 18, T: 37	NR	Xray: compression fracture L1	Compression fracture L1
XXII	66	Male		Loss of consciousness for 30 minutes 1 week ago, general weakness	GCS: E4M6V5, BP: 105/70, HR: 88, RR: 20, T: 36.9	Hb 14.2, WBC: 6, thrombocyte: 156, segmented neutrophil: 67%, lymphocyte: 26%, NLR: 2.57, ESR: 40, CRP: 60, AST: 80, ALT: 75, LDH: 909, Na: 125, K: 2.4	Brain MRI: normal	Metabolic encephalopathy + hypokalemia hyponatremia

NR: not reported, DM: diabetes mellitus, HT: hypertension, AF: atrial fibrillation, DKA: diabetic ketoacidosis, GCS: Glasgow Coma Scale, CT: computed tomography, MRI: magnetic resonance imaging, BP: blood pressure (mmHg), HR: heart rate (x/minutes), RR: respiratory rate (x/minutes), T: temperature (^{0} Celsius), Hb: hemoglobin (g/dL), WBC: white blood cell (x 10-3/mL), thrombocyte (x 10-3/mL), BG: blood glucose (mg/dL), NLR: neutrophil:a lymphocyte ratio, CRP: C-reactive protein (mg/dL), Na: natrium (mmol/L), K: kalium (mmol/L), LDH: lactate dehydrogenase (IU/L), INR: International Normalized Ratio, PT: prothrombin time (seconds), aPTT : activated partial thromboplastin time (seconds), ESR: erythrocyte sedimentation rate (mm/h), TSH: thyroid stimulating hormone (mU/L), FT4: free T4 (ng/dL), AST: aspartate transaminase (U/L), ALT: alkaline transaminase (U/L), ureum (mg/dL), creatinine (mg/dL), D-dimer: mcg/mL, fibrinogen (mg/mL), albumin (g/dL)

Table 2. Characteristic of clinical features

	Total (n)	Percentage(%)
Comorbidities/Past history		
HT	6	27.3
DM	3	13.6
Obesity	1	4.5
Ischemic Stroke	4	18.2
Malignancy	4	18.2
Colorectal	2	9.1
Lung	2	9.1
AF	1	4.5
Alzheimer's Disease	2	9.1
Parkinson Disease	1	4.5
Parkinsonism	1	4.5
Pulmonary emboli	1	4.5
Rupture aneurysm	1	4.5
Fracture femur	1	4.5
Sepsis	2	9.1
Myocarditis	1	4.5
NSTEMI	1	4.5
Neurological manifestation		
Altered mental status	11	50
Loss of consciousness	8	36.4
Delirium	3	13.6
Hemiparesis	6	27.3
Seizure	2	9.1
Tremor	5	22.7
Tetraparesis	1	4.5
Paraparesis	1	4.5
Myoclonia	1	4.5
Dysatria	1	4.5
Dysphonia	1	4.5
Pain	4	18.2
Pelvic pain	1	4.5
Low back pain	2	9.1
Thigh pain	1	4.5
Aphasia	1	4.5
Unilateral facial weakness	2	9.1
Neurological diagnosis		
Ischemic stroke	6	27.3
Metastatic brain tumor	2	9.1

Metabolic encephalopathy	3	13.6
Alzheimer's Disease	3	13.6
Myoclonic on CKD	1	4.5
Epilepsy	1	4.5
Acute symptomatic seizure	1	4.5
MG	1	4.5
Compression fracture	1	4.5
Parkinsonism	3	13.6
Chronic SDH	1	4.5
Myalgia	1	4.5
Polyneuropathy ec paraneoplastic syndrome	1	4.5

Discussion

Altered mental status

The most frequently encountered neurological complaint was altered mental status (50%), followed by hemiparesis (27.3%) and tremors (22.7%). This result is similar to the study conducted by Helms et al, in which altered mental status was found in 69% of confirmed COVID-19 patients admitted to the ICU.[10] The mechanism of altered mental status in COVID-19 is still unclear. SARS-CoV-2 has been shown to have neurotropic features that enable it to invade the CNS directly via attachment to ACE2 receptors in capillaries, or via penetration of the cribriform plate through the olfactory nerve.[11,12] However, direct invasion as the cause of COVID-19 encephalopathy is still doubtful, as several studies report that positive CSF-PCR examinations were only found in less than 10% of cases.[13] An interesting theory is the possibility of severe systemic inflammation caused by cytokine storm as the main mechanism of cerebral damage in COVID-19.[14] Several studies showed that there was a significant increase in pro-inflammatory cytokines in the CSF of COVID-19 patients with encephalopathy [15,16,17], as well as a significant improvement in response to intravenous steroids.[15,18,19] The possibility of autoimmune mechanisms can also be considered, given the relationship between COVID-19 and GBS (Guillain Barre syndrome) [20] and clinical improvement with the administration of immunotherapy (intravenous immunoglobulin 15[,18,19] and plasmapheresis[17]).

Ischemic stroke

Ischemic stroke occurs in 27.3% of patients, with the most common clinical feature of altered mental status and hemiparesis. The results of our study revealed a higher incidence of stroke than in the study conducted by Mao et al, which showed that acute cerebrovascular disease occurred only in 6% of COVID-19 cases.[21] This difference may be due to variations in the study sample, in which our sample was COVID-19 patients who complained of neurological symptoms (n = 22), while the study conducted by Mao et al included all COVID-19 patients in general (n = 214). This made our sample more likely to have more severe conditions, as evidenced by the examination of inflammatory markers that tend to be higher in our study. The

number of subjects with pre-existing comorbidities were higher in our sample compared to the study by Mao et al (81% vs 38%).[21] The underlying cause of ischemic stroke in COVID-19 is thought to be COVID-19-associated-coagulopathy (CAC), which appears in acute systemic inflammatory response, mediated by cytokines and proinflammatory agents. The CAC is characterized by an increase in blood coagulant markers (D-dimers, fibrinogen degradation products, fibrinogen), as well as peripheral inflammation markers (CRP), and mild thrombocytopenia.[22] In severe conditions of COVID-19, coagulopathy can also occur with a pattern similar to disseminated intravascular coagulation (DIC), due to excessive consumption and activation of coagulation factors, characterized by increased PT, aPTT, and D-dimer, and thrombocytopenia. [22.23]

Anemia

Anemia was present in 45.5% of cases, with a mean hemoglobin value of 10.29 (SD: 1.61). SARS-CoV-2 can cause anemia through various mechanisms. The interaction of SARS-CoV-2 with hemoglobin receptor molecules such as ACE2, CD147, and CD26 will induce a reaction between spike protein and

membrane receptors, triggering viral endocytosis.[24] Further hemolysis occurs through damage to the heme on 1-beta-chain of hemoglobin.[25] By activating CD147 and CD26, SARS-CoV-2 can attack erythroblasts in bone marrow, causing progressive anemia.[24] Free circulating heme caused by hemolysis may damage endothelial, resulting in diffuse endocellitis.[24,26] Previous studies also reported several case reports of autoimmune hemolytic anemia associated with COVID-19, so that the possibility of an autoimmune process should also be considered.[27,28] In this study we were unable to further explore the causes and pathomechanisms of anemia due to limited laboratorium facilities.

Increased NLR Ratio

Out of 22 cases, an increased NLR ratio was found in 11 cases (50%). Increased NLR ratio was associated with severe COVID-19 and a poor prognostic factor. The study conducted by Yan et al showed that the NLR ratio tended to be higher in the non survival group (median: 49.06, interquartile range (IQR): 25.71-69.70) compared to the survival group (median: 4.11, interquartile range (IQR): 2.44-8.12, p <0.01). The study also stated that an NLR more than 11.74 had a significant correlation with hospital mortality (odds ratio = 44,351; 95% confidence interval = 4,627-425,088).[30] The mechanism of increased NLR ratio in COVID-19 is still unclear. The increase in neutrophils occurs due to a hyperinflammatory process in COVID-19, evidenced by an increase of classic neutrophil chemoattractant (CXCL1, CXCL2, CXCL3, CXCL5, CXCL20, and interleukin-8) in cells infected with SARS-CoV-2.[31,32] Lymphopenia can occur due to bone marrow suppression, immune - mediated-destruction, as well as sequestration due to activation of the ACE2 receptor by SARS-CoV2.[33,34] The mean NLR ratio in our study was quite high (16.99, SD: 15.23), but we could not compare the outcome in our sample with that previous study due to lack of data and most of the patients were still in treatment.

Electrolyte imbalance

Electrolyte imbalance was present in 7 cases (31.8%), with the most common abnormality being hyponatremia (6 cases, 28.6%), followed by hypokalemia (4 cases, 18.2%), and hyperkalemia (2 cases, 9.1%). A study conducted by Lippi et al showed that sodium and potassium levels were found to be lower significantly in severe COVID-19.[35] The mechanism of hyponatremia in COVID-19 is still unclear. Previous studies linked syndrome of inappropriate antidiuretic hormone secretion (SIADH) as a cause of hyponatremia in COVID-19 pneumoniae.[36] A study by Berni et al showed that levels of interleukin-6, a pro-inflammatory cytokine core in the COVID-19 cytokine storm, was inversely

related with sodium.[37] This suggests that the systemic inflammatory system may also play a role in the development of hyponatremia. Hypokalemia is thought to occur due to activation of the ACE2 receptor, resulting in decreased ACE2 expression, which in turn triggers an upregulation in angiotensin II, leading to increased excretion of potassium by the kidneys. [37,38] Hypokalemia can also be caused by gastrointestinal loss, such as vomiting and diarrhea, which are common in COVID-19.[37,39]

Correlation of pre-existing comorbidities with neurologic complaint on COVID-19

More than half (81.8%) of the study sample in this study had pre-existing

comorbidities or past history associated with the neurological complaint. These results indicate that it is likely that COVID-19 does not cause direct nervous system damage, but induces dysfunction through the exacerbation of pre-existing neurological disorders, presumably via the hyperinflammation mechanisms. SARS-CoV-2 can cause a widespread inflammatory cascade condition through activation of the ACE2 receptor, leading to severe acute systemic inflammation mediated by interleukin (IL)-6, which increases the number and response of proinflammatory cytokines such as IL-17, IL-21, and IL- 22.[40,41] The cytokine storm causes widespread endothelial dysfunction, including damage to the blood-brain-barrier.[14] SARS-CoV-2 infection, accompanied by comorbidities, tended to be more severe than without comorbidities ($p < 0.03$)[21]. A study conducted by Sarfo et al showed an increase in the recurrent stroke rate during January 2020 - June 2020 compared to the previous year (19.0% vs 10.9%, $p = 0.0026$).[42] Neuroimaging studies conducted by Lu et al showed the possibility of microstructural and functional damage in global gray matter volume (GMV), GMVs in the left Rolandic operculum, right cingulate, bilateral hippocampi, left Heschl's gyrus. Global MD of WM in COVID-19 were correlated with memory loss [43], so there may be decline in cognitive function, especially in patients with pre-existing dementia.

Limitation

The limitation of our study is that we cannot perform more specific laboratory tests, so we could not further investigate the causes of abnormal laboratory results. Furthermore, neuroimaging and some laboratory tests were not performed in all patients, so we could not compare and describe the data.

Conclusion

We have found that neurological complaints in COVID-19 patients are mostly associated with exacerbation of pre-existing comorbidities as a result of the severe inflammatory process triggered by COVID-19. Further research is needed to establish the mechanism of nervous system dysfunction in COVID-19.

References

1. Pinna P, Grewal P, Hall JP, Tavarez T, Dafer RM, Garg R. Neurological manifestations and COVID-19: Experiences from a tertiary care center at the Frontline. Journal of Neurological Scineces 2020 415;116969 https://doi.org/10.1016/j.jns.2020.116969

2. World Health Organization Coronavirus Disease (COVID-19), Situation Report- 117, Accessed May 16, 2020 https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200516-covid-19-sitrep-117.pdf?sfvrsn=8f562cc_2.

3. Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes Metab Syndr. 2020; 14(4): 407-412. https://doi.org/10.1016/j.dsx.2020.04.020

4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

5. Pascarella G, Strumia A, Piliego C, Bruno F, Del Buono R, Costa F, *et al*. COVID-19 diagnosis and management: a comprehensive review. *J Intern Med* 2020; 288: 192– 206. https://doi.org/10.1111/joim.13091

6. Chen N, Zhou M, Dong X *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study.*The Lancet* 2020; 395: 507-13. https://doi.org/10.1016/S0140-6736(20)30211-7

7. Yang J, Zheng Y, Gou X *et al.* Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. International journal of infectious diseases. *IJID* 2020; 94: 91-5.

8. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, *et al*. Neurological associations of COVID-19. Lancet Neurol 2020; DOI : 10.1016/S1474-4422(20)30221-0

9. Nepal G, Rehrig JH, Shrestha GS, Shing YW, Yadav JK, Ojha R, *et al.* Neurological manifestations of COVID-19: a systematic review. *Crit Care* 24, 421 (2020). https://doi.org/10.1186/s13054-020-03121-z

10. Helms J, Kremer S, Merdji, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med 2020; 382:2268-2270. https://doi.org/10.1056/NEJMc2008597

11. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanism. ACS Chem Neurosci 2020; 11(7):995-998. https://doi.org/10.1021/acschemneuro.0c00122

12. Abboud H, Abboud FZ, Kharbouch H, Arkha Y, El Abbadi N, El Ouahabi A. COVID-19 and SARS-CoV-2 infection: pathophysiology and clinical effects on nervous system. World Neurosurg 2020; 140:49-53. https://doi.org/10.1016/j.wneu.2020.05.193

13. Mondal R, Ganguly U, Deb S, Shome G, Pramanik S, Bandyopadhyay D, *et al.* Meningoencephalitis associated with COVID-19: A systematic review. https://doi.org/10.1101/2020.06.25.20140145

14. Majid F, Ali M, Somayeh M, Cyrus R. Neurobiology of COVID-19. Journal of Alzheimer's Disease 2020; 76:3-19. https://doi.org/10.3233/JAD-200581

15. Pilotto A, Odolini S, Masciocchi S, Comelli A, Volonghi I, Gazzina S, et al. Steroid-Responsive Encephalitis in Coronavirus Disease 2019. Annals of Neurology 2020; https://doi.org/10.1002/ana.25783

16. Panariello A, Bassetti R, Radice A, Rossotti R, Puoti M, Corradin M, et al. Anti-NMDA receptor encephalitis in a psychiatric Covid-19 patient: A case report. Brain, Behaviour, and Immunity 2020; 87:179-181. https://doi.org/10.1016/j.bbi.2020.05.054

17. Dogan L, Kaya D, Sarikaya T, Zengin R, Dincer A, Ozkan I, et al. Plasmapheresis treatment in COVID-19–related autoimmunemeningoencephalitis: Case series. Brain, Behavior, and Immunity 2020; 87: 155-158. https://doi.org/10.1016/j.bbi.2020.05.022

18. Dellamare L, Gollion CM, Grouteau G, Rousset D, Jimena G, Roustan J. COVID-18-associated acute necrotizing encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. J Neurol Neurosurg Psychiatry 2020 . https://doi.org/10.1136/jnnp-2020-323678

19. Zambreanu L, Lightbody S, Bhandari M, Hoskote C, Kandil H, Houlihan CF, et al. A case of limbic encephalitis associated with asymptomatic COVID-19 infection. J Neurol Neurosurg Psychiatry 2020; https://doi.org/10.1136/jnnp-2020-323839

20. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: A case report. J Clin Neurosci 2020; 76:233-235. https://doi.org/10.1016/j.jocn.2020.04.062

21. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurology 2020; 77(6):683-690. https://doi.org/10.1001/jamaneurol.2020.1127

22. Divani AA, Andalib S, Di Napoli M, Seletska A, Mayer SA, Torbey M, et al. Coronavirus Disease 2019 and stroke: clinical manifestation and pathophysiological insight. Journal of Stroke and Cerebrovascular Disease 2020; 29(8): 104941. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104941

23. Levi M, Toh H, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol.* 2009; 145: 24-33 https://doi.org/10.1111/j.1365-2141.2009.07600.x

24. Cavezzi A, Troiani E, Corrao S. COVID-19: hemoglobin, iron, and hypoxia beyond inflammation A narrative review. Clin Pract 2020; 10(2): 1271. https://doi.org/10.4081/cp.2020.1271

25. Wenzhong L, Hualan L. COVID-19: Attacks the 1-beta chain of hemoglobin and captures the porphyrin to inhibit human heme metabolism. ChemRxiv 2020. Preprint. 10.26434/chemrxiv.11938173.v8.

26. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endothelitis in COVID-19. Lancet2020;395: 1417-8.

27. Lazarian G, Quinquenel A, Bellal M, Siavellis J, Jacquy C, Re D, *et al.* Autoimmune haemolytic anaemia associated with COVID-19 infection. British Journal of Haematology 2020; 290 (1): 29-31. https://doi.org/10.1111/bjh.16794

28. Hindilerden F, Yonal-Hindilerden I, Akar E, Yesilbag Z, Kart-Yasar K. Severe Autoimmune Hemolytic Anemia in COVID-19 İnfection, Safely Treated with Steroids. Mediterr J Hematol Infect Dis. 2020;12(1):e2020053. https://doi.org/10.4084/mjhid.2020.053

29. Kubo S, Hosomi N, Hara N, Neshige S, Himeno T, Takeshima S, *et al.* Ischemic stroke mortality is more strongly associated with anemia on admission than with underweight status. Journal of Stroke and Cerebrovascular Disease 2017; 26(6): 1369-1374. https://doi.org/10.1016/j.jstrokecerebrovasdis.2017.02.016

30. Yan, X, Li, F, Wang, X, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross-sectional study. J Med Virol. 2020; 1– 9. https://doi.org/10.1002/jmv.26061

31. Didangelos A. 2020. COVID-19 hyperinflammation: what about neutrophils? mSphere 5:e00367-20. https://doi.org/10.1128/ mSphere.00367-20.

32. Gralinski LE, Sheahan TP, Morrison TE, Menachery VD, Jensen K, Leist SR, Whitmore A, Heise MT, Baric RS. 2018. Complement activation contrib- utes to severe acute respiratory syndrome coronavirus pathogenesis. mBio 9:e01753-18. https://doi.org/10.1128/mBio.01753-18

33. Huang I, Pranata R. Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis. Journal of Intensive care 2020; 8(36):1-10. https://doi.org/10.1186/s40560-020-00453-4

34. Li T, Qiu Z, Zhang L, Han Y, He W, Liu Z, et al. Significant changes of peripheral T lymphocyte subsets in patients with severe acute respiratory syndrome. J Infect Dis. 2004;189:648–51. https://doi.org/10.1086/381535

35. Lippi, G., South, A. M., & Henry, B. M. (2020). Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). *Annals of Clinical Biochemistry*, *57*(3), 262–265. https://doi.org/10.1177/0004563220922255

36. Habib MB, Sardar S, Sajid J. Acute symptomatic hyponatremia in setting of SIADH as an isolated presentation of COVID-19. *IDCases*. 2020;21:e00859. https://doi.org/10.1016/j.idcr.2020.e00859

37. Berni A, Malandrino D, Parenti G, Maggi M, Poggesi L, Peri A. Hyponatremia, IL-6, and SARS-CoV-2 (COVID-19) infection: may all fit together?. J Endocrinol Invest. 2020;43(8):1137-1139. https://doi.org/10.1007/s40618-020-01301-w

38. Chen, D, Li, X, Song, Q, et al. Hypokalemia and clinical implications in patients with coronavirus disease 2019 (COVID-19). medRxiv. Epub ahead of print 29 February 2020. https://doi.org/10.1101/2020.02.27.20028530

39. Pan, L, Mu, M, Yang, P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. Am J Gastroenterol. 2020; 115: 766–773. https://doi.org/10.14309/ajg.0000000000000620

40. Song P, Li W, Xie J, Hou Y, You C. Cytokine storm induced by SARS-CoV-2. Clin Chim Acta 2020; 509:280-287. DOI: j.cca.2020.06.017

41. Wu D, Yang XO. TH17 responses in cytokine storm of COVID-19: An emerging target of JAK2 inhibitor. Journal of Microbiology, Immunology, and Infection 2020; 53(3):368-370. https://doi.org/10.1016/j.jmii.2020.03.005

42. Sarfo FS, Mensah NO, Opoku FA, Adusei-Mensah N, Ampofo M, Ovbiagele B. COVID-19 and stroke: Experience in a Ghanaian healthcare system [published online ahead of print, 2020 Jul 16]. *J Neurol Sci*. 2020; 416:117044. https://doi.org/10.1016/j.jns.2020.117044

43. Lu Y, Li X, Geng D, Mei N, Wu P, Huang C, et al. Cerebral micro-structural changes in COVID-19 patients-An-MRI-based 3-month follow up study. E Clincical Medicine 2020; 100484. https://doi.org/10.1016/j.eclinm.2020.100484