

COVID-19 with ischemic stroke manifestations



Maria Belladonna Rahmawati^{1*}, Yovita Andhitara², Rahmi Ardhini²,
Aditya Kurnianto², Amelia Carissa Pertiwi³, Rony Parlindungan Sinaga³, Adinda Larastiti³

¹Department of Neurology, Faculty of Medicine, Universitas Diponegoro-Diponegoro National Hospital, Semarang, Indonesia.

²Department of Neurology, Faculty of Medicine, Universitas Diponegoro-Dr. Kariadi Hospital, Semarang, Indonesia.

³Resident in Neurology, Faculty of Medicine, Universitas Diponegoro-Dr. Kariadi Hospital, Semarang, Indonesia.

*Corresponding author:

Maria Belladonna Rahmawati;
Department of Neurology, Faculty of Medicine, Universitas Diponegoro-Diponegoro National Hospital, Semarang, Indonesia;
mariabelladonna@fk.undip.ac.id

Received: 2021-01-23

Accepted: 2021-04-20

Published: 2021-04-30

ABSTRACT

Background: Continuous pandemic caused by coronavirus disease (COVID-19) have been associated with high morbidity and mortality. COVID-19 has been linked to a hypercoagulable state that causes cerebrovascular complications. The most common cerebrovascular complication is ischemic stroke.

Case Presentations: We report six cases of ischemic stroke with COVID-19, age 51-81 years old, consists of four males and two females. The main risk factors are hypertension and diabetes mellitus. Brain CT scan showed large vessel ischemic stroke in four patients. The patients were treated with Low Molecular Weighted Heparin followed by dual antiplatelet (aspirin and clopidogrel). The outcome was good recovery with minimal sequelae in four patients and death in two patients.

Conclusion: Most of the stroke type in COVID-19 is large vessel disease, with main risk factors of hypertension and diabetes mellitus. Treatment with low molecular weight heparin (LMWH) followed by dual antiplatelet showed promising clinical improvement.

Keywords: COVID-19, Ischemic Stroke, heparin, dual antiplatelet.

Cite This Article: Rahmawati, M.B., Andhitara, Y., Ardhini, R., Kurnianto, A., Pertiwi, A.C., Sinaga, R.P., Larasati, A. 2021. COVID-19 with ischemic stroke manifestations. *Bali Medical Journal* 10(1): 412-415. DOI: 10.15562/bmj.v10i1.2209

INTRODUCTION

COVID-19 pandemic began in December 2019 in Wuhan, China and now has already surpassed 44 million cases in the world on October 2020.¹ Virus entry through ACE-receptors in respiratory systems, but can spread to other organs including nervous system.² COVID-19 has been linked to a hypercoagulable state that causes cerebrovascular complications. The most common cerebrovascular complication is ischemic stroke.³

Incidence of stroke has been reported in 5.7% of patients with severe COVID-19 infections and 0.8% of patients with non-severe infections.^{4,5} In this case series from some academic hospitals in Semarang, Indonesia, we report clinical and radiographic characteristics of six acute ischemic stroke (AIS) patients with COVID-19 infection.

CASE PRESENTATIONS

We report six ischemic stroke cases with COVID-19, age 51-81 years old, consisting of four males and two females. All

patients had hypertension. Four patients had diabetes mellitus. Two patients had previous history of ischemic stroke. Brain CT scan showed large vessel ischemic stroke in four patients (Figure 1). The patients were treated with Low Molecular Weighted Heparin followed by dual antiplatelet (aspirin and clopidogrel). The outcome was good recovery with minimal sequelae in four patients, and death in two patients. Baseline characteristics, clinical and investigational characteristics of these patients are described in Table 1.

DISCUSSION

Baseline demographic characteristics of our patients showed men are more frequent than women. The age range was 51-81 years old. This gender and tendency are linear to current CASCADE study in Iran (male-to-female ratio: 1.16, mean age: 67.75 ± 14.3 years).⁶ The most prevalent risk factor of stroke were mostly hypertension (100%), diabetes mellitus (66.6%), hyperlipidemia (50%), and history of previous stroke (33.3%). This is similar to the Global

COVID-19 Stroke Registry, which most prevalent risk factors were hypertension (68.4%), obesity (37.4%), and diabetes mellitus. The previous stroke was reported in 11.5% patients.⁷ Atherosclerosis in the blood vessels was still the main underlying pathology.

The onset of neurological symptoms ranged from 3-14 days from the onset of COVID-19 symptoms. This is similar to the Global COVID-19 registry (median delay between the initiation of COVID-19 symptoms and stroke onset was 7 days).⁷ None of the patients has received thrombolysis because of delayed detection of neurological symptoms. This delay might be due to unawareness or fear of seeking medical help because of "stay at home" campaign at the beginning of the pandemic. The main stroke symptoms were motor and aphasia. One patient had seizure, and one had chorea. The severity of stroke symptoms was severe (mRS 4-5).

Imaging characteristic is mainly caused by large vessel disease (MCA territory) in four patients, which is linear to the Global COVID-19 Stroke

Table 1. Clinical and radiographical characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	65	69	80	81	51	51
Sex	M	M	F	M	M	F
Stroke Risk Factors						
History of previous stroke	No	Yes	Yes	No	No	No
Diabetes	Yes	Yes	No	Yes	No	Yes
Hypertension	Yes	Yes	Yes	Yes	Yes	Yes
Hyperlipidemia	Yes	Yes	Yes	No	No	No
Atrial Fibrillation / Flutter	No	No	No	No	No	No
DVT/PE	No	No	No	No	No	No
Location						
Anterior versus Posterior	anterior	Anterior and posterior	Anterior	Anterior	Anterior	Anterior
Side	left	bilateral	bilateral	bilateral	right	left
Time from COVID-19 manifestations to stroke symptom onset (days)	14	3	3	7	3	8
Primary Neurological Symptoms	Right side weakness, aphasia	Unconsciousness, left side weakness, dysarthria	Right-side weakness, chorea, dysarthria	Unconsciousness, right side weakness	Left side weakness, headache	Seizure, unconsciousness, right side weakness
Cerebral Imaging	Large infarction in left frontal and parietal lobe (MCA territory)	Large infarct in right MCA territory, left pontine infarction	Multiple, bilateral MCA territory infarction	Multiple, bilateral MCA territory infarction	Large right MCA territory infarction	Large left MCA territory infarction
COVID-19 Characteristics						
Clinical Feature	Cough, Hypoxic respiratory failure	Encephalopathy, Hypoxic respiratory failure	Cough Mild hypoxia	Fever	Cough	Fever, cough, Mild hypoxia
COVID-19 Therapy	Meropenem Azithromycin Hydroxychloroquine Oseltamivir	Meropenem Azithromycin Hydroxychloroquine Oseltamivir	Meropenem Azithromycin Hydroxychloroquine Oseltamivir	Azithromycin Oseltamivir	Azithromycin Hydroxychloroquine Oseltamivir	Moxifloxacin Lopinavir- Ritonavir
ACE/ARB use	No	No	No	No	Yes (Candesartan)	No
Thrombolysis	No	No	No	No	No	No
Anticoagulant	Fondaparinux	No	Fondaparinux	No	Fondaparinux	Enoxaparin
Antiplatelet	ASA Clopidogrel	ASA Clopidogrel	ASA Clopidogrel	ASA	ASA Clopidogrel	ASA
Laboratory parameter on initial presentation						
WBC (10E3/ mcL)	6.34	15.5	8.5	6.7	9.3	5.7
Platelet count (10E3/mcL)	216	200	281	137	205	228
CRP (mg/L)	11.8	12	Negative	NA	NA	37,9
D-dimer (ng/ mL)	35400	3833	4311.7	NA	NA	1160
INR	0.86	NA	NA	NA	NA	0.94
LDL (mg/dL)	NA	NA	108.6	75	NA	102
Triglyceride (mg/dL)	NA	NA	32.3	85	NA	69
HbA1C	11.2	NA	NA	6.4	NA	8/6
Outcome :						
ICU admission	Yes	Yes	No	No	No	No
ICU LOS	5 days	3	0	0	0	0

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
mRS on admission	4	5	5	5	4	5
mRS at discharge	1	6	1	3	2	6

*Abbreviation: DVT/PE–Deep venous thrombosis/Pulmonary Embolism; ACE/ARB–Angiotensin-Converting Enzyme/Angiotensin Receptor Blocker; ASA: Acetyl Salicyl Acid; WBC–White blood count; CRP: C-reactive protein, INR- International Normalized Ratio, LDL- Low-density Lipoprotein; mRS–Modified Rankin Scale; ICU–Intensive Care Unit; NA = Not available, LOS–length of stay, MCA-middle cerebral artery

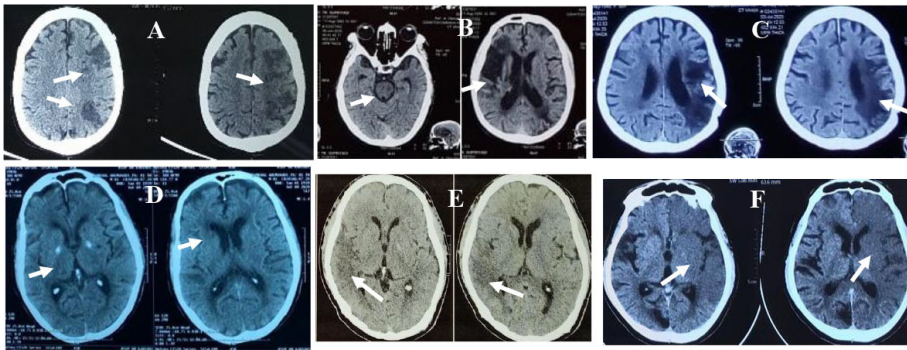


Figure 1. Brain CT scan of the patients. **A:** large infarction in left frontal and parietal lobe. **B:** infarction in right frontoparietal lobe, right posterior horn of internal capsule, left parietal lobe, and left paramedian pontine. **C:** large infarction in temporoparietal lobe, bilateral corona radiata. **D:** infarction in right caudate nucleus and thalamus, old infarction in left caudate nucleus, thalamus, lentiform nucleus and right external capsule. **E:** large infarction in right temporoparietooccipital lobe. **F:** large infarction in left frontotemporoparietal lobe (MCA territory).

Registry (22.7% large vessel and 7.6% lacunar).⁷ Initial laboratory examination didn't show specific tendency to viral infection, except thrombocytopenia in one patient. D-dimer was mostly high, proving the hypercoagulable state as the culprit. According to Spence et al.⁸ a number of mechanisms are involved in stroke in COVID-19, including a hypercoagulable state, disseminated intravascular coagulation (DIC), necrotizing encephalopathy, vasculitis, and cardiomyopathy.

COVID-19 symptoms were mostly fever, cough, and dyspnea. Severe hypoxia occurred in three patients, which two needed ICU admission. This hypoxia might trigger seizure in one of our patients and unconsciousness in three patients. Treatment for ischemic stroke mainly consisted of anticoagulant (Low molecular weighted heparin) fondaparinux or enoxaparin, and maintenance with oral antiplatelet (mostly combination of ASA and Clopidogrel). Nevertheless, owing to the prothrombotic state and

higher mortality in stroke patients with COVID-19 infection, recommendations have been made for the use of prophylactic or therapeutic anticoagulation.⁹

The severity of stroke symptoms was severe (mRS 4-5). Our study's outcomes were good recovery in four patients with minimal sequelae and death in two patients (because of the respiratory problems). An ischemic stroke patient with COVID-19 has more severe disability and higher mortality rate.

CONCLUSION

Most of the stroke type in COVID-19 is large vessel disease, with main risk factors of hypertension and diabetes mellitus. The detection of neurological deficits was late, maybe because of unawareness or afraid to go seek medical help due to pandemic. Because most of the patients came past the golden period, treatment with LMWH followed by dual antiplatelet might be promising.

FUNDING

This report doesn't receive any specific grant from government or any private sectors.

CONFLICT OF INTEREST

All author declares there is no conflict of interest regarding publication of this report.

ETHICAL CONSIDERATION

All patients or family had received signed written informed consent regarding publication of their medical data in journal article.

ACKNOWLEDGEMENT

Thank you to director of dr. Kariadi Hospital, Diponegoro National Hospital, and Telogorejo Hospital Semarang for the permission to use their patients' data for this study.

AUTHOR CONTRIBUTION

All author had contributed equally on writing the original draft and had agree for the final version of the manuscript for publication.

REFERENCES

1. World Health Organization (WHO). Novel Coronavirus (2019-nCoV) situation reports [Internet]. Geneve: WHO; (Cited October 29, 2020). Available from: <https://www.worldometers.info/coronavirus/>
2. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, Hou C, Wang H, Liu J, Yang D, Xu Y, Cao Z, Gao Z. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24(1):422. doi: 10.1186/s13054-020-03120-0.
3. Reddy ST, Garg T, Shah C, Nascimento FA, Imran R, Kan P, Bowry R, Gonzales N, Barreto A, Kumar A, Volpi J, Misra V, Chiu D, Gadhia R, Savitz SI. Cerebrovascular Disease in Patients with COVID-19: A

- Review of the Literature and Case Series. *Case Rep Neurol.* 2020;12(2):199-209. doi: [10.1159/000508958](https://doi.org/10.1159/000508958).
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, Miao X, Li Y, Hu B. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):683-690. doi: [10.1001/jamaneurol.2020.1127](https://doi.org/10.1001/jamaneurol.2020.1127).
 5. Jillella DV, Janocko NJ, Nahab F, Benameur K, Greene JG, Wright WL, Obideen M, Rangaraju S. Ischemic stroke in COVID-19: An urgent need for early identification and management. *PLoS One.* 2020;15(9):e0239443. doi: [10.1371/journal.pone.0239443](https://doi.org/10.1371/journal.pone.0239443).
 6. Ghoreishi A, Arsang-Jang S, Sabaa-Ayoun Z, Yassi N, Sylaja PN, Akbari Y, et al. Stroke Care Trends During COVID-19 Pandemic in Zanjan Province, Iran. From the CASCADE Initiative: Statistical Analysis Plan and Preliminary Results. *J Stroke Cerebrovasc Dis.* 2020;29(12):105321. doi: [10.1016/j.jstrokecerebrovasdis.2020.105321](https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105321).
 7. Ntaios G, Michel P, Georgiopoulos G, Guo Y, Li W, Xiong J, et al. Characteristics and Outcomes in Patients With COVID-19 and Acute Ischemic Stroke: The Global COVID-19 Stroke Registry. *Stroke.* 2020;51(9):e254-e258. doi: [10.1161/STROKEAHA.120.031208](https://doi.org/10.1161/STROKEAHA.120.031208).
 8. Spence JD, de Freitas GR, Pettigrew LC, Ay H, Liebeskind DS, Kase CS, Del Brutto OH, Hankey GJ, Venketasubramanian N. Mechanisms of Stroke in COVID-19. *Cerebrovasc Dis.* 2020;49(4):451-458. doi: [10.1159/000509581](https://doi.org/10.1159/000509581).
 9. Tan YK, Goh C, Leow AST, Tambyah PA, Ang A, Yap ES, Tu TM, Sharma VK, Yeo LLL, Chan BPL, Tan BYQ. COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature. *J Thromb Thrombolysis.* 2020;50(3):587-595. doi: [10.1007/s11239-020-02228-y](https://doi.org/10.1007/s11239-020-02228-y).



This work is licensed under a Creative Commons Attribution