COVID-19 with ischemic stroke manifestations

Maria Belladonna Rahmawati1*, Yovita Andhitara2, Rahmi Ardhini3, Aditya Kurnianto2, Amelia Carissa Pertiwi3, Rony Parlindungan Sinaga3, Adinda Larastiti3

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 Weight 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.

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 Weight 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).8 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  | Age  | Sex | Stroke Risk Factors | Location | Time from COVID-19 manifestations to stroke symptom onset (days) | Primary Neurological Symptoms | Cerebral Imaging | COVID-19 Characteristics | Laboratory parameter on initial presentation | Outcome |
|----------|------|-----|---------------------|----------|---------------------------------------------------------------|-------------------------------|-------------------|-------------------------|-----------------------------------------------|----------|
| 1        | 65   | M   | No                  | Anterior | 14                                                           | Right side weakness, aphasia  | Large infarction in left frontal and parietal lobe (MCA territory) | Cough, Hypoxic respiratory failure | WBC (10E3/mcl) 6.34 | ICU admission Yes |
| 2        | 69   | M   | Yes                 | Anterior and posterior | 3    | Unconsciousness, left side weakness, dysarthria     | Unconsciousness, left side weakness, dysthria | Large infarct in right MCA territory, left pontine infarction | Encephalopathy, Hypoxic respiratory failure | Platelet count (10E3/mcl) 216 | ICU LOS 5 days |
| 3        | 80   | F   | No                  | Anterior  | 3    | Right-side weakness, chorea, dysarthria | Right-side weakness, chorea, dysarthria | Multiple, bilateral MCA territory infarction | Cough Mild hypoxia | CRP (mg/L) 11.8 | |
| 4        | 81   | M   | Yes                 | Anterior  | 7    | Unconsciousness, right side weakness      | Unconsciousness, right side weakness | Multiple, bilateral MCA territory infarction | Fever | D-dimer (ng/mL) 35400 | |
| 5        | 51   | M   | No                  | Anterior  | 3    | Left side weakness, headache            | Left side weakness, headache | Large right MCA territory infarction | Cough | INR 0.86 | |
| 6        | 51   | F   | Yes                 | Anterior  | 8    | Seizure, unconsciousness, right side weakness | Seizure, unconsciousness, right side weakness | Large left MCA territory infarction | Fever, Cough Mild hypoxia | LDL (mg/dL) NA | |

**Clinical Risk Factors**
- History of previous stroke
- Diabetes
- Hypertension
- Hyperlipidemia
- Atrial Fibrillation / Flutter
- DVT/PE

**Clinical Feature**
- Cough
- Hypoxic respiratory failure
- Encephalopathy
- Hypoxic respiratory failure
- Fever
- Cough
- Mild hypoxia

**COVID-19 Therapy**
- Meropenem
- Azithromycin
- Hydroxychloroquine
- Oseltamivir
- Moxifloxacin
- Lopinavir-Ritonavir

**ACE/ARB use**
- No

**Thrombolysis**
- No

**Anticoagulant**
- Fondaparinux

**Antiplatelet**
- ASA
- Clopidogrel

**Laboratory parameter on initial presentation**
- WBC (10E3/mcl) 6.34
- Platelet count (10E3/mcl) 216
- CRP (mg/L) 11.8
- D-dimer (ng/mL) 35400
- INR 0.86
- LDL (mg/dL) NA
- Triglyceride (mg/dL) NA
- HbA1C 11.2

**Outcome**
- ICU admission Yes
- ICU LOS 5 days

**Laboratory parameter on initial presentation**
- CRP (mg/L) 11.8
- D-dimer (ng/mL) 35400
- INR 0.86
- LDL (mg/dL) NA
- Triglyceride (mg/dL) NA
- HbA1C 11.2

**Outcome**
- ICU admission Yes
- ICU LOS 5 days
CASE REPORT

Registry (22.7% large vessel and 7.6% lacunar). 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. 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.

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.

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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.

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AUTHOR CONTRIBUTION

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

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|                         | 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
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