



Covid-19 and Cardioembolic Stroke

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Objectives

- ▶ To review **neurologic complications of covid-19**
- ▶ To review **epidemiology of stroke associated with covid-19**
- ▶ To review **pathophysiology of stroke associated with covid-19**
- ▶ To review **covid-vaccines associated stroke**

Introduction

- ▶ Neurologic complications in patients with COVID-19 are common
- ▶ In more than **80 percent** of hospitalized patients (more common in critically ill patients)
- ▶ **Myalgias, headache, encephalopathy, and dizziness** are **most common** (one-third of patients)
- ▶ **Dysgeusia or anosmia** are **less common**
- ▶ **Stroke, GBS, ADEM, and seizures** are **uncommon**
- ▶ Some patients have **persisting** symptoms such as **cognitive dysfunction, headache, and numbness**

Epidemiology

Epidemiology

- ▶ Stroke appears to be **relatively infrequent** in the setting of COVID-19
- ▶ The incidence of **ischemic stroke** in moderate to severe covid-19: **0.1% to 6.9%** (average incidence of **2%**); Patients with severe COVID-19 had a **fivefold** increase of the risk of stroke
- ▶ The incidence of **intracranial hemorrhage**: **0.2 to 0.9 %**
- ▶ The incidence of **CVT**: **0.08 %**

Epidemiology

- ▶ Stroke occurs **1 to 3 weeks after onset of COVID-19** symptoms (the median delay of stroke from COVID-19 symptoms onset is **8.8 (6.3–11.6)** days) , although stroke may be the initial presentation leading to hospitalization in a minority of reported patients
- ▶ The mean **age** of patients with COVID-19 and stroke appears similar to those without COVID-19 (the median age of **68 compared** with **71**)
- ▶ Some reports observed that ischemic stroke occurred in young patients with COVID-19, including children, these appear to represent a **minority** of cases

Epidemiology

- ▶ **Male** predominance (controversial)
- ▶ Most of the COVID-19 patients who develop acute ischemic stroke have **preexisting cardiovascular risk factors** (e. g. hypertension, hyperlipidemia, atrial fibrillation, and diabetes mellitus); previous stroke is relatively rare
- ▶ Even if COVID-19 is a predisposing factor, the risk was mainly seen in those who were **already at risk** for acute ischemic stroke due to other cardiovascular risk factors

Epidemiology

- ▶ More common subtypes include are **cryptogenic** or **cardioembolic** (embolic stroke of undetermined significance (**ESUS**))
- ▶ The surprisingly high proportion of COVID-19 patients presenting with cryptogenic strokes may be attributed to:
 - ❑ limited resources and time to complete a thorough investigation
 - ❑ high pressure on healthcare system
 - ❑ social distancing recommendations

Pathophysiology

Pathophysiology

Possible pathophysiological mechanism of stroke in patients with COVID-19:

1. Hyperinflammation and Thrombophilia
2. The alternative RAS pathway
3. Cardioembolism

Hyperinflammation & Thrombophilia

- ▶ SARS-CoV-2 is a cytopathic virus that causes injury and death of affected cells
- ▶ Viral and alveolar cell fragments, recognized as pathogen by the local macrophages
- ▶ Macrophage activation leads to a local pulse of proinflammatory acute-response cytokines (TNF and IL-1 β) and chemotactic cytokines, facilitating a sustained increase of IL-6 and the cytokine release syndrome; Serum level of IL-6 may predict the risk of ischemic stroke
- ▶ During the hyperinflammatory state, the overproduction of proinflammatory acute-response proteins and adhesion molecules, together with the circulating activated leukocytes, may result in the augmentation of the local inflammatory process in the ischemic brain (possible explanation of the increased ischemic stroke severity in patients with COVID-19)

Hyperinflammation & Thrombophilia

- ▶ SARS-CoV-2 has the ability to enter and facilitate local inflammation and **endotheliitis**, which could possibly explain the presence of **impaired microcirculatory function**
- ▶ During this hyperinflammatory state, locally activated platelets induce the release of neutrophil extracellular traps (NETs) covered with tissue factor, which in turn **activates the extrinsic coagulation cascade** leading to thrombin formation

Hyperinflammation & Thrombophilia

- ▶ This cross-talk between **innate immunity, platelets, and endothelial cells** in the maladaptive host immune system leads to excessive activation of microvascular **thrombosis** and **hypercoagulability**
- ▶ This is reflected in the extremely elevated D-dimer levels
- ▶ Furthermore, several studies reported the presence of antiphospholipid antibodies in COVID-19 patients . Nevertheless, it remains unknown whether these antibodies play a role in thrombogenesis in COVID-19 patients

The alternative RAS pathway

- ▶ The RAS is the primary peptide hormone system in charge of blood pressure and volume regulation in circulation
- ▶ The **classical RAS pathway** involves renin, which stimulates the production of angiotensin I from angiotensinogen
- ▶ ACE transforms angiotensin I and generates the biologically potent peptide, angiotensin II
- ▶ Apart from ACE, ACE2 plays a pivotal role for the **alternative RAS pathway**
- ▶ The alternative RAS system provides **endogenous neuroprotection** especially in the acute ischemic stroke phase with its **vasodilation, anti-inflammatory, and antioxidant effects**

The alternative RAS pathway

- ▶ SARS-CoV-2 selectively binds with the S glycoprotein to ACE2, leading to:
 - ❑ downregulation of the ACE2 expression in the affected cells
 - ❑ higher formation of Ang II by ACE
- ▶ As a result, SARS-CoV-2–related **inhibition of neuroprotective effects of ACE2** may result in severe stroke

Cardioembolism

- ▶ Cardiac injury is one of the **leading causes of death** in COVID-19 after respiratory dysfunction
- ▶ Elevated markers of cardiac injury such as **troponin I** (**17%** among hospitalized COVID-19 patients) and **CK-MB** reported in COVID-19 patients have been shown to correlate with disease severity
- ▶ It manifests with acute **myocarditis, pericarditis, arrhythmia, shock, cardiac failure** and **MI**
- ▶ Myocardial injury in patients with COVID-19 can be either attributed to **nonspecific myocarditis, myocardial infarction, direct SARS-CoV-2 injury, or indirect injury through stress and inflammatory response**
- ▶ In the setting of hyperinflammation and thrombophilia in COVID-19 patients, **stasis and thrombus formation in the dysfunctional LV** is an important possible cause of cardioembolism

Cardioembolism

- ▶ Systemic inflammation and myocardial dysfunction in the setting of increased cardiac output may lead to **malignant ventricular arrhythmias** or **atrial fibrillation (AF)**, which in turn can be a potential cause of cardioembolism.
- ▶ Sepsis and hyperinflammatory response may predispose in **AF**, which was prevalent in 19% to 21% of hospitalized COVID-19 patients
- ▶ AF may significantly increase the risk of ischemic stroke or cardiovascular death in these patients

Outcome

Outcome

- ▶ Patients with COVID-19 and acute ischemic stroke reported **increased stroke severity** (NIHSS: **10** among vs. **6**), predicting a higher risk of poor disease outcome
- ▶ AIS due to **large vessel occlusion** is more common in COVID-19 cases
- ▶ **Simultaneous involvement of different vascular territories** in AIS is frequent
- ▶ There is some evidence that the **response to mechanical thrombectomy** may be more **limited**

Outcome

- ▶ There is increased **length of hospital stay** in covid-related stroke (mean **17.4 days** vs **8 days**)
- ▶ More patients **require ICU care** in the setting of covid (**58.7** vs **44.7%**)
- ▶ **51%** of patients with COVID-19 and acute ischemic stroke had **severe disability** at discharge (modified Rankin Scale score **4** vs. **2**),
- ▶ **Increased mortality** (**twofold** in compared to non-covid stroke and **threefold** in compared to covid without stroke)
- ▶ Patients with COVID-19 and acute ischemic stroke have a much higher occurrence of **multisystem involvement** including acute kidney injury, hepatic failure, and respiratory failure.

Stroke after COVID Vaccines

Stroke after COVID Vaccines

- ▶ Studies reported the occurrence of stroke after administration of COVID-19 vaccination
- ▶ All forms of stroke including ischemic (mostly MCA territory), ICH, and CVST have been encountered
- ▶ Most of the evidence pertaining to stroke following COVID-19 vaccination are case reports, therefore, the incidence of stroke after COVID-19 vaccination is not precisely known.
- ▶ Most patients who suffered from stroke after COVID-19 vaccination were **women, under 60 years** of age, and after the ChAdOx1 nCoV-19 **(AstraZeneca)** vaccine and **within 1 to 21 days** after vaccination

Stroke after COVID Vaccines

- ▶ Thrombosis is usually seen in the context of VITT (**Vaccine-induced immune thrombotic thrombocytopenia**)
- ▶ These have been characterized by thrombocytopenia, similar to that seen in heparin-induced thrombocytopenia but in the absence of heparin and with antibodies to platelet factor 4.
- ▶ The diagnosis of VITT-associated stroke should be made with high suspicion because of its rapid and diverse clinical manifestations.

Recommendations

Recommendations

▶ COVID-19 screening in AIS patient:

- ❑ During the pandemic, testing all patients with suspected stroke for COVID-19 at the time of admission is recommended
- ❑ Many patients presenting with stroke may test positive even when systemic signs of infection are absent; so, this approach helps in early recognition and appropriate isolation measures
- ❑ In addition, the presence of acute COVID-19 in a patient with stroke has implications for the underlying mechanism causing stroke, the long-term risk of recurrence, and potentially for the choice of optimal therapy both in the short and long term.

Recommendations

▶ Etiologic testing in AIS patient:

- ❑ Given the frequent association of stroke in COVID-19 with typical vascular risk factors, the initial diagnostic approach should otherwise be similar to the approach generally used for all patients with suspected stroke.
- ❑ Diagnostic testing to identify underlying stroke mechanism should include brain and neurovascular imaging and cardiac evaluation, with treatment appropriate to the identified mechanism
- ❑ Routine testing recommended for all patients hospitalized with COVID-19 includes a **complete blood count (CBC), platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer.**

Recommendations

► Vaccination:

- ❑ During the period of COVID-19 vaccination, a **high index of suspicion** is required to identify thrombotic episodes
- ❑ Stroke should be considered when a patient develops any persistent or unusual neurological symptoms, especially constant headaches, within 4 weeks of COVID-19 vaccination
- ❑ However, it is important to remember that these **side effects are and much less common** than both cerebral venous thrombosis and ischemic stroke associated with COVID-19 infection itself
- ❑ Since the advantages of COVID-19 vaccination outweigh the risk of stroke or any other neurological, the public should be reassured **that the vaccination program is still the best way to combat COVID-19**

Recommendations

Population	Recommendation
Asymptomatic patient with positive covid PCR	No prophylaxis
Outpatient setting	Individual risk assessment for AIS
Inpatient setting	Prophylactic LMWH (if not contraindicated)
Discharged patient	Prophylactic anticoagulation for 45 days (if not contraindicated)



Thank You