

# Coagulopathy and thrombosis following COVID-19 resolution resulting in late Hyperacute ischemic stroke in moyamoya disease – A case report

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## ABSTRACT

**Background.** Moyamoya disease (MMD) patients who untreated with bypass surgery are prone to frequent and recurrent ischemic stroke or transient ischemic attack (TIA). Although, multiple traditional risk factors can account for this event, recent COVID-19 pandemic also contributed to the increased rate of stroke recurrence among this population by means of multiple pathogenesis, including thrombosis.

**Case presentation.** Herein we described an MMD patient who suffered from acute ischemic stroke lately after the resolution of COVID-19 infection with neurocognitive deficits as the prominent symptoms. Coagulopathy with the resulting thrombosis was thought to play a central role in this case.

**Conclusions.** COVID-19 infection may increase the risk of stroke recurrence among patients with MMD, particularly those who do not yet undergo surgical bypass procedure. Coagulopathy with thrombosis was thought to play a central role, even after the infection itself had subsided.

**Keywords:** COVID-19 infection, Moyamoya disease, coagulopathy, thrombosis, cognitive deficits

## List of abbreviations

ADC – Apparent diffusion coefficient

ASL – Arterial spin labeling

BMI – Body mass index

COVID-19 – Coronavirus disease 2019

DWI – Diffusion weighted imaging

ER – Emergency room

ESUS – Embolic stroke of undetermined source

FLAIR – Fluid attenuation inversion recovery

GRE – gradient echo sequences

HDL – High density lipoprotein

ICA – Internal carotid artery

MCA – Middle cerebral artery

MMD – Moyamoya disease

MRC – Medical Research Council

PCA – Posterior communicating artery

SWAN T2 – star-weighted angiography

STA – Superficial temporal artery

## BACKGROUND

Moyamoya disease (MMD) is an idiopathic progressive steno-occlusion of the end part of internal carotid arteries (ICAs) and its branches with the following development of poor and brittle collateral

blood flows. The corresponding conditions, when untreated surgically, may lead to frequent recurrence of ischemic stroke or TIA as high as 10% per year, particularly among children and young adults [1]. There are multiple traditional risk factors for stroke recurrence in MMD, including increased BMI and homo-

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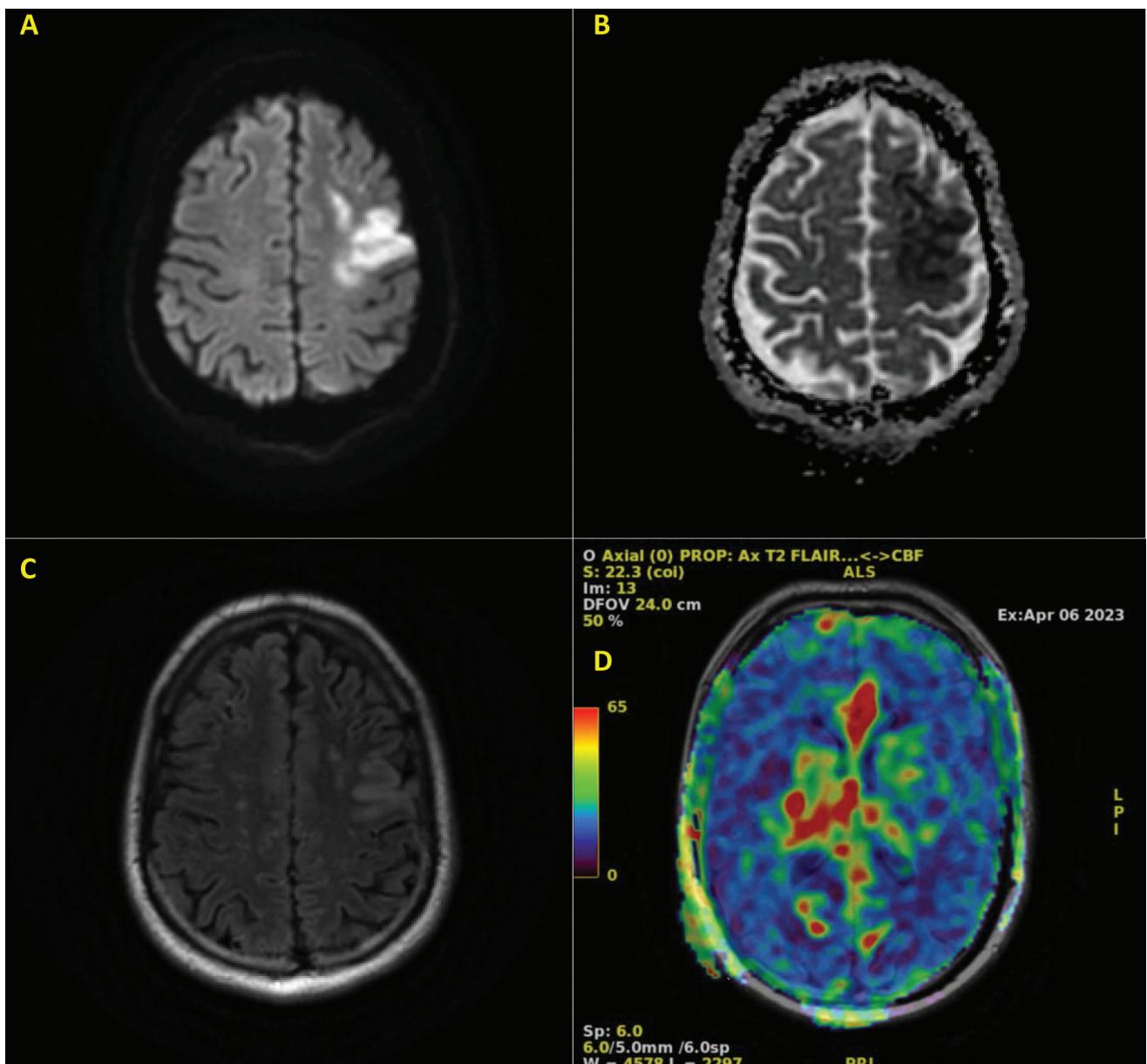
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**FIGURE 1.** Axial head MRI showing (A) DWI sequence of hyperintensity on the left cortical-subcortical frontal region with (B) concurrent hypointensity on ADC, and (C) matched hyperintense T2-FLAIR sequence, indicating late hyperacute onset of ischemic stroke. (D) arterial spin labeling (ASL) sequence of the same patient demonstrated relative hyperperfusion on the central of circle of Willis as a sign of high collaterals density with apparent hypoperfusion of the left cortical area, suggesting poor cerebral perfusion on the cortical and subcortical area

cysteine levels [2], low HDL cholesterol levels [3], presence of diabetes mellitus, PCA stenosis, and those who underwent indirect bypass surgical procedure [4]. However, the recent COVID-19 pandemic also contributed to the increased rate of new onset stroke or its recurrence among MMD patients, either directly or indirectly (e.g. COVID-19 vaccine-induced), presenting acutely during infection, or lately after the infection has subsided [5–7]. Herein we described a case of young adult Asian male patient who had an episode of acute ischemic stroke a week following resolution of COVID-19 infection, presenting with high d-dimer levels with marked disproportion of severity toward cognitive deficits than sensory-motor.

## CASE PRESENTATION

A 38-year old Asian male patient was brought to ER by his colleague because he was seen disoriented and unable to communicate or act accordingly since 8 hours ago when he was checking-out from the hotel. Last time known normal was 11.00 pm the night before (according to his colleague). Upon ER checking by doctor, patient could open his eyes spontaneously but disoriented to time and space, able to respond to simple questions with short answer (“yes” or “no”), unable to recall both short and long term memory prior to event, and showing lack of ability to follow simple instructions to varying degrees (e.g. raising hands, closing eyes). He was reported by his

colleague to have mild headache and fever in the past 2 days but did not consume any specific medications or check himself up to a healthcare facility. Prior illness history and medication were unknown and patient was a foreigner who travelled solo for business purpose and his relatives were initially unable to be contacted at the ER. However, upon checking-up his belongings, we found a bottle of clopidogrel 75 mg qd with no specific indication on its label.

On physical examination, patient was alert but disoriented to time, place, and unable to address the medical personnels. Vital signs were within normal limits, except slight increased of forehead temperature (37.4°C). Patient demonstrated mild paresis of XIIth cranial nerve accompanied with right flaccid hemiparesis (MRC grade 4+) and hemihypesthesia. A working diagnosis of acute cerebrovascular event was made and head MRI (DWI, ADC, T2-FLAIR, ASL, GRE, and SWAN) and MRA with ad hoc gadolinium was done immediately, by which it displayed abnormal restricted diffusion at cortical and subcortical left frontal lobe on DWI, hypointensity on ADC, and hyperintensity on T2 and FLAIR, with no hyperintensity on T1 sequence suggesting acute ischemic stroke with matched DWI and T2-FLAIR (Figure 1A-C). ASL sequence showed significant tissue hypoperfusion on the left frontal cortical and subcortical lobe when compared with the right (Figure 1D). Intracranial MRA exhibited occlusion of R-L MCA, R-L ACA, R-L PCA with multiple basal and cortical collateral vessels resembling puff of smoke appearance, whereas extracranial MRA exhibited no stenosis or occlusion (Figure 2A-B). Among abnormal laboratory results were leukocytosis (12,500 cells/mm<sup>3</sup>; PMN predominant) and markedly elevated d-dimer levels (2,820 ng/mL). Subsequent head MRV was obtained and neither venous thrombosis nor congestion was

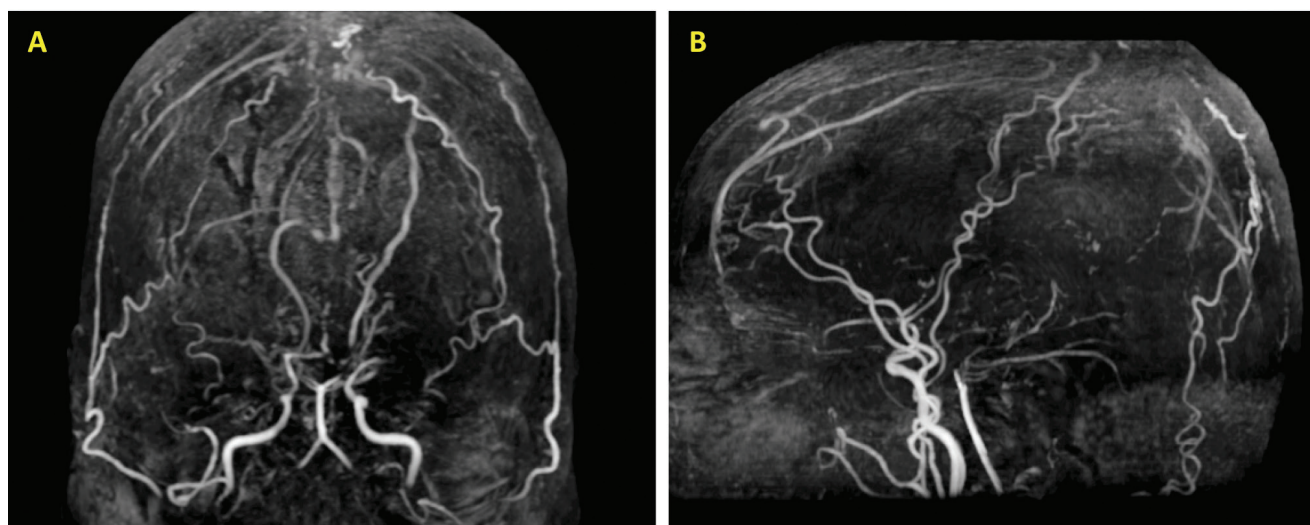
seen. CXR, EKG, and echocardiography results were all within normal limits.

Patient was diagnosed with acute ischemic stroke with MMD. This was also confirmed from his caregiver that the diagnosis of Moyamoya has been made since 2019. Patient occasionally experienced transient but self-limited loss of memory prior to and after the diagnosis were known. Of note, recently he also suffered from COVID-19 infection and had negative swab PCR test just a week before his flight.

Given the nature of matched DWI-FLAIR condition and the natural history of MMD, conservative treatments were administered and elective STA-MCA bypass surgery was planned. Further neurocognitive evaluations during inpatient follow-up revealed that patient suffered from ideomotor apraxia, anomia, aphasia, dysgraphia, dyslexia, and dyscalculia. Patient was treated and rehabilitated for a total of 13 days with notable improvements in his neurocognitive performance. At one month post stroke, patient underwent STA-MCA bypass surgery uneventfully.

## DISCUSSION

We reported a new onset of stroke in a patient with MMD with prior history of COVID-19 infection. Although currently not on an active infection, patient suffered from elevated d-dimer levels suggesting an active thromboembolic state. COVID-19 was known to be associated with increased risk of coagulopathy as reflected by elevated d-dimer levels. In fact, high d-dimer levels can persist to months even after the infection itself has subsided [7]. Increased d-dimer levels are usually associated with more severe pulmonary symptoms or reflecting increased rate of thromboembolism [8,9]. However, our patient only had mild symptoms (e.g. intermittent



**FIGURE 2.** (A) Stumble MRA of anterior-posterior view and (B) radial left sagittal view demonstrated severe steno-occlusion of bilateral proximal MCA, ACA, and PCA accompanied with basal and cortical collateral vessels resembling “puff of smoke”, indicating MMD

cough with minimal phlegm, fever, fatigue, and joint pain) during the infection period and was not currently infected by COVID-19. Regardless, elevated d-dimer levels are a predictor of both new onset of stroke and stroke recurrence [10,11]. Of note, one study reported an increased rate of embolic stroke of undetermined source (ESUS) due to increased d-dimer levels and that the risk increased linearly with d-dimer values [12]. Although the pathomechanism is most likely multifactorial, elevated d-dimer levels may also play a role for the development of significant (>50%) multiple intracranial arterial stenosis as a result of MMD. One longitudinal study followed patients with MMD who had COVID-19 infection and 64% demonstrated exacerbation or new onset of neurological symptoms [5]. The authors hypothesized hypercoagulability, vasculitis, and cardiomyopathy as potential pathogenesis of new onset of stroke in MMD. These conditions further exacerbates the already compromised cerebral vascularization in Moyamoya patients, reflecting that these patients are among the special population group prone to suffer from new stroke episode during and after COVID-19 infection.

His initial presentation of disorientation and amnesia is not uncommon among patients with Moyamoya. One study reported a patient with MMD who presented with transient amnesia and confabulation, later to be discovered on MRI that she had an acute cerebral infarction at the left subcortical and

right parieto-occipital lobe [13]. In fact, given the extensive proximal intracranial arteries stenosis and prior history of similar neurological symptoms, our patient may have already had vascular cognitive impairment or specifically, post-stroke cognitive impairment before it declined further after this episode [14]. Patient also demonstrated apraxia, anomia, aphasia, dysgraphia, dyslexia, and dyscalculia, all of which can be explained by the location of the infarct, i.e. at the left frontal cortical and subcortical lobe [15]. Furthermore, the neurocognitive impairment was disproportionate to the extent of motor and sensory deficits. We hypothesized that the collaterals formed could compensate the occlusion and help perfuse the motor area but that prolonged and recurrent ischemia may have diminished the cognitive reserve, thus making the cognitive deficits clinically overt [16].

## CONCLUSIONS

Current and previous history of COVID-19 infection may increase the risk of new episode of acute ischemic stroke among patients with MMD by means of inducing hypercoagulability and vasculitis on top of the already poor cerebral vascularization. MMD patients may also exhibit predominantly neurocognitive disorders rather than motor or sensory deficits as usually seen among patients with AIS without MMD, thus serves as a critical sign of a new onset of stroke among this special population group.

*Conflict of interest:* none declared

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