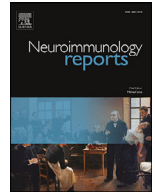




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## Covid-19 vaccine (covishield) heralding Moyamoya angiopathy<sup>☆,☆☆,☆☆</sup>

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### ABSTRACT

**Introduction:** Thrombotic complications leading to cerebrovascular events occurring in conjunction with Covid-19 vaccination though rare, is well-documented. Moyamoya Angiopathy is a progressive intracranial vasculopathy leading to recurrent strokes.

**Case presentation:** We present two index cases of young patient presenting with stroke and TIA following Covid-19 vaccination (COVISHIELD) leading to unmasking of Moyamoya Angiopathy.

**Conclusion:** Arterial stroke following Covid-19 vaccination is documented, but uncommon. However, in the background of a vasculopathy, it may not be so rare. Moyamoya Angiopathy has been closely studied in the model of inflammatory pathophysiology in genetically predisposed patients leading to progressive vaso-occlusive disease. Few reports of Covid-19 infection potentiating Moyamoya Angiopathy symptoms are also documented. Thus, as an extrapolation of the inflammatory etiopathogenesis of Moyamoya Angiopathy, Covid-19 vaccination can similarly affect the Moyamoya symptomatology. These two index cases open new lines of enquiry regarding the interplay of Covid-19 vaccination and neurological destabilization in patients with underlying vasculopathy of inflammatory pathophysiology.

### Introduction

Vaccination against SARS-CoV-2 has been an important breakthrough to manage the COVID-19 pandemic (Alammar, 2021). However, as our experiences with the vaccine side effects continue to grow, several cerebrovascular events in close temporal association to vaccination are being reported.

Cerebral venous sinus thrombosis (CVT) has been the more frequently reported cerebrovascular side effect compared to arterial stroke (Garg and Paliwal, 2021; Dutta et al., 2021). Moyamoya angiopathy (MMA) is a chronic progressive occlusive intracranial vasculopathy characterized by steno-occlusive lesions of terminal internal carotid artery (ICA) or proximal anterior cerebral artery (ACA) and/or middle cerebral artery (MCA) with formation of abnormal vascular network at the base of the brain, classically appearing as a “puff of smoke”. Inflammatory state has been postulated to initiate and enhance progression of changes of MMA influencing the cytokine pathways (Das et al., 2019, 2020, 2021a,b,2021c, 2022a,2022b). We herein report two index case of young patient presenting with acute ischemic stroke and TIA finally diagnosed to be MMA, with neurological symptoms precipitated in close temporal association to COVISHIELD vaccination.

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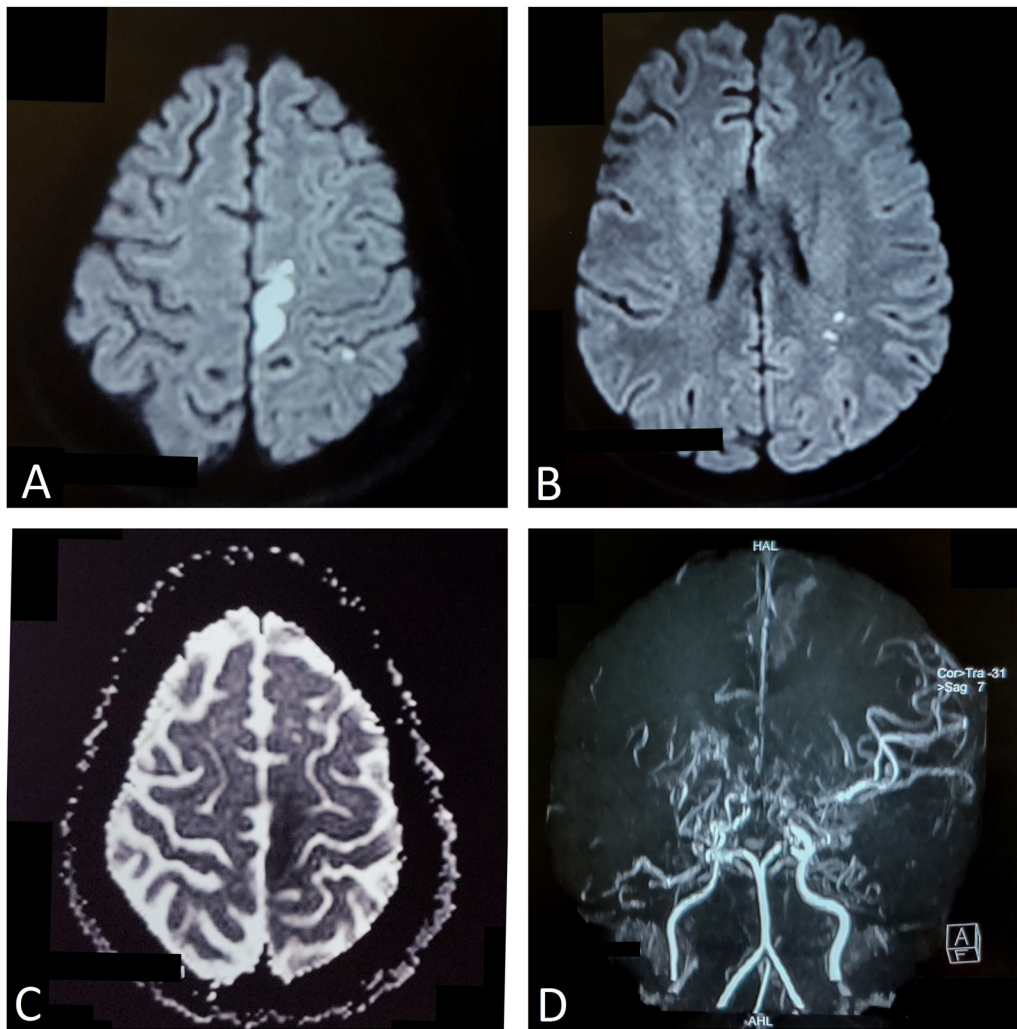
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### Case report

**Case 1:** A 25-year-old female, without any previous neurological complaints, presented to us with acute onset right hemiparesis, 3 days following vaccination with the second dose of COVISHIELD. There was no other neurodeficits. Magnetic resonance imaging (MRI) Brain revealed acute DWI restriction in high left parietal region with corresponding changes in ADC. Magnetic resonance angiography (MRA) revealed bilateral terminal ICA, and proximal MCA and ACA narrowing with collateral formation suggestive of Moyamoya angiopathy (Fig. 1).

**Case 2:** A 28-year-old male, without any previous neurological complaints, presented to us with recurrent episodes of transient left upper limb monoparesis with slurring of speech lasting for 1–2 min with self-resolution. This started 15 days following vaccination with the first dose of COVISHIELD. There was no other neurodeficits on history or physical examination. MRI Brain didn't reveal any acute DWI restriction. Magnetic resonance angiography (MRA) revealed bilateral terminal ICA with collateral formation suggestive of Moyamoya angiopathy (Fig. 2).

Both the cases were extensively evaluated for secondary causes. Complete blood count including platelet count, erythrocyte sedimentation rate (ESR), serum electrolytes, blood sugar, lipid profile were normal. High sensitivity C-reactive protein (hsCRP), coagulation profile, anti-nuclear antibody (ANA), vasculitis profile, thyroid profile, viral markers, screening for hyper-coagulable state (serum homocysteine, protein-C, protein-S, anti-thrombin III, factor V mutation, anti-



**Fig. 1.** LEGEND: MRI Brain Diffusion weighted imaging sequence shows acute restrictions in the left parietal region(A,B); with corresponding hypodensity in ADC sequence(C); MR Angiography shows bilateral terminal ICA, proximal MCA and ACA stenosis with formation of compensatory collaterals suggestive of Moyamoya Angiopathy(D).

phospholipid antibodies profile), hemoglobin electrophoresis, serum lactate, and serum angiotensin converting enzyme (ACE) levels were unyielding. Basic cardiothoracic work-up (chest X-ray, electrocardiogram, and echocardiography) and Carotid Doppler didn't reveal any potential source for thrombo-embolism. Anti-platelet factor-4 (PF4) antibodies were negative. Both the patient were managed conservatively and counseled for revascularization surgery.

## Discussion

Covid-19 infection has been seen to be a risk factor for stroke. It was reported in an estimated 1.4% Covid-19 infected patients. The major mechanisms implicated were hypercoagulability, vasculitis and cardiomyopathy. In comparison to Covid-19 infection itself, the cerebrovascular adverse effects seen with vaccination against Covid-19 is much less. Among the several reported cases of vaccine associated cerebrovascular events, CVT appears to occur more frequently than arterial stroke (Garg and Paliwal, 2021; Dutta et al., 2021; Das et al., 2021c; Markus, 2021).

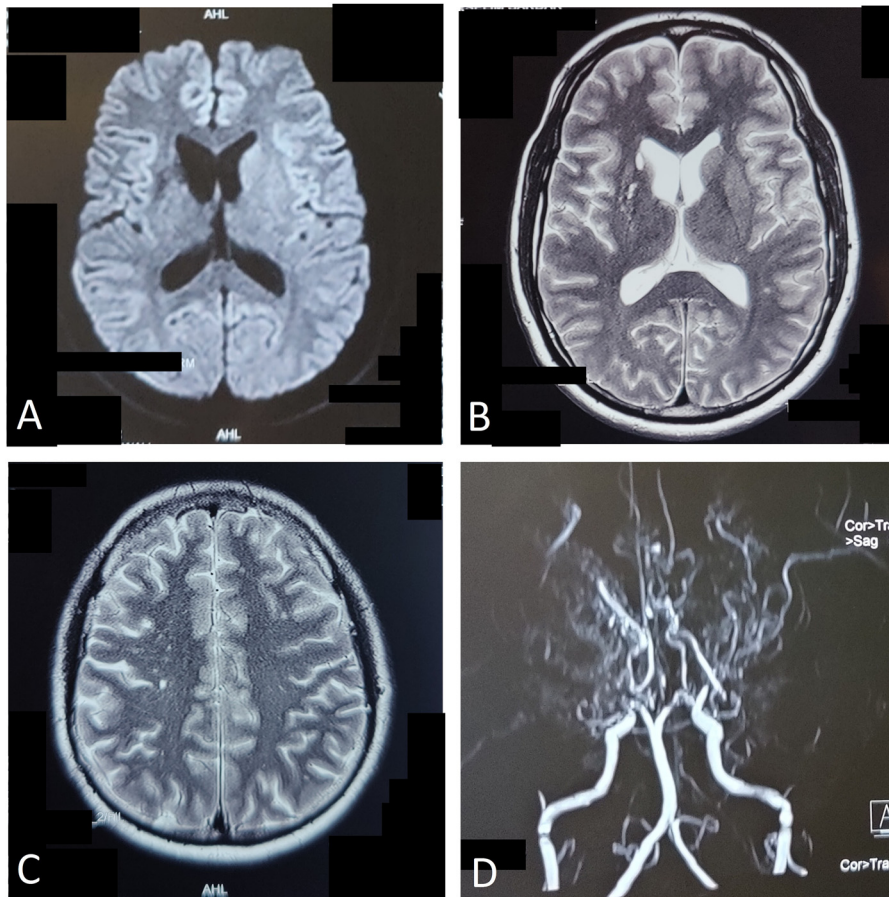
The pathophysiological mechanism underlying these events has been termed vaccine-induced immune thrombotic thrombocytopenia (VITT), generally clinically manifests within 5 to 30 days after administration of adenovirus vector-based vaccines. It mimics heparin-induced throm-

bocytopenia (HIT) with a positive platelet-activating antibody to PF4 (anti-PF4)/heparin complexes, thrombocytopenia and a predisposition to forming thrombi. Microscopic findings showed vascular thrombotic occlusions occurring in the vessels of multiple body organs along with marked inflammatory infiltration (Garg and Paliwal, 2021; Dutta et al., 2021; Markus, 2021; Blauenfeldt et al., 2021; Malik et al., 2021). However, our patient didn't have any evidence of thrombocytopenia or reactivity to anti-PF4 autoantibodies.

Stroke following varicella and influenza vaccination has been described and it was contemplated that similar to their natural infections, these vaccines can lead to intracranial angiopathy leading to narrowing and occlusion of the vessels and resultant ischemic stroke (Alammar, 2021). A similar possible mechanism may also be involved in the COVISHIELD vaccines, besides causing hypercoagulable state leading to thromboembolisms.

Moyamoya Angiopathy is considered to be an immune reactive Vasculitis resulting from vascular immune injury and inflammation response via (I) anti-inflammatory mediators (IL-4, IL-10, IL-13, IFN- $\alpha$  and TGF- $\beta$ ) leading to acceleration or acute aggravation of MMA by affecting vascular reactivity and auto-regulation, (II) pro-inflammatory mediators (IFN- $\beta$ , IFN- $\gamma$ , TNF- $\alpha$ , IL-1, IL-6) influencing initiation and often fulminant progression of MMA by activating RNF dependent signal transducing pathway. Thus, any acute systemic inflammatory response





**Fig. 2.** LEGEND: MRI Brain Diffusion weighted imaging sequence shows no acute restriction(A); T2 weighted sequence showing scattered hyperintensities in right Globus Pallidus and Caudate(B) and right Centrum Semi-ovale(C); MR angiography showing bilateral terminal ICA, proximal MCA and ACA stenosis with formation of compensatory collaterals suggestive of Moyamoya Angiopathy(D).

might lead to hyperplasia of intimal vascular smooth muscle cells and neovascularization by proliferation of endothelial cells, leading to angiogenesis causing luminal narrowing and collateral formation in genetically predisposed patients. Das et al. observed worsening of neurological symptoms among 64.3% MMA patients with Covid-19 infection in their study (Das et al., 2021c; Ghosh et al., 2020; Mikami et al., 2019; Bersano et al., 2016). We propose that vaccine related aberrant inflammatory pathway activation can possibly influence these down-signaling pathways leading to aggravation of Moyamoya symptoms similarly.

These two cases of MMA in whom symptoms were precipitated following COVISHIELD vaccination, opens up a new line of enquiry regarding its safety among patients with pre-existing intracranial vasculopathy. The presence of an association may not necessarily imply causality. However, in the light of a possible unifying inflammatory pathophysiological basis between Moyamoya Angiopathy and Covid-19 vaccination, caution must be exercised till future robust observations are available.

#### Disclosure

Dr Shambaditya Das, (Prof) Dr Biman Kanti Ray, (Prof) Dr Alak Pandit, Dr Ajitava Dutta, Dr Saumen Bhat, Dr Dwaipayan Bhattacharyya, Dr Arka Prava Chakraborty, Dr Raju Agrawal, Dr Souvik Dubey have no disclosures to make.

#### Authorship agreement

I, Dr Souvik Dubey take full responsibility for the data, the analyses and interpretation, and the conduct of the research. I have full access to all the data and have the right to publish any and all data, separate and apart from the guidance of any sponsor.

#### Data availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for the purposes of replicating procedures and results.

#### Declaration Competing of interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

#### Informed consent for participation in research study

The patient's legally authorized representative consented (written) to use of the information elaborated in the manuscript.

#### Ethical approval information

Approval was obtained from the institutional ethics committee of Institute of Post-graduate Medical Education & Research, Kolkata, India. (Ethics committee name- IPGME&R Research oversight committee; Reference number- ECR/35/Inst/WB/2013/RR-16; Dated- 27.03.2017.) The procedures used in this study adhere to the tenets of the Declaration of Helsinki. A written informed consent was obtained from all individual participants included in the study.

#### Author contributions

Shambaditya Das: Conceptualization-Equal, Data curation-Lead, Formal analysis-Equal, Investigation-Equal, Methodology-Equal,

Resources-Equal, Supervision-Equal, Visualization-Equal, Writing-original draft-Lead, Writing-review & editing-Equal. Biman Kanti Ray: Conceptualization-Equal, Project administration-Equal, Supervision-Equal, Visualization-Equal, Writing-review & editing-Equal. Alak Pandit: Conceptualization-Equal, Project administration-Equal, Supervision-Equal, Visualization-Equal, Writing-review & editing-Equal. Ajitava Dutta: Data curation-Equal, Formal analysis-Equal, Investigation-Equal, Resources-Equal, Supervision-Equal, Writing-review & editing-Equal. Saumen Bhat: Data curation-Equal, Formal analysis-Equal, Investigation-Equal, Writing-review & editing-Equal. Dwaipayan Bhattacharyya: Data curation-Equal, Formal analysis-Equal, Investigation-Equal, Writing-review & editing-Equal. Subhadeep Gupta: Data curation-Equal, Formal analysis-Equal, Investigation-Equal, Writing-review & editing-Equal. Arka Prava Chakraborty: Data curation-Equal, Formal analysis-Equal, Investigation-Equal, Writing-review & editing-Equal. Raju Agrawal: Data curation-Equal, Formal analysis-Equal, Investigation-Equal, Writing-review & editing-Equal. Souvik Dubey: Conceptualization-Equal, Formal analysis-Equal, Methodology-Equal, Project administration-Equal, Supervision-Equal, Visualization-Equal, Writing-review & editing-Lead.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.nerep.2022.100100](https://doi.org/10.1016/j.nerep.2022.100100).

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