

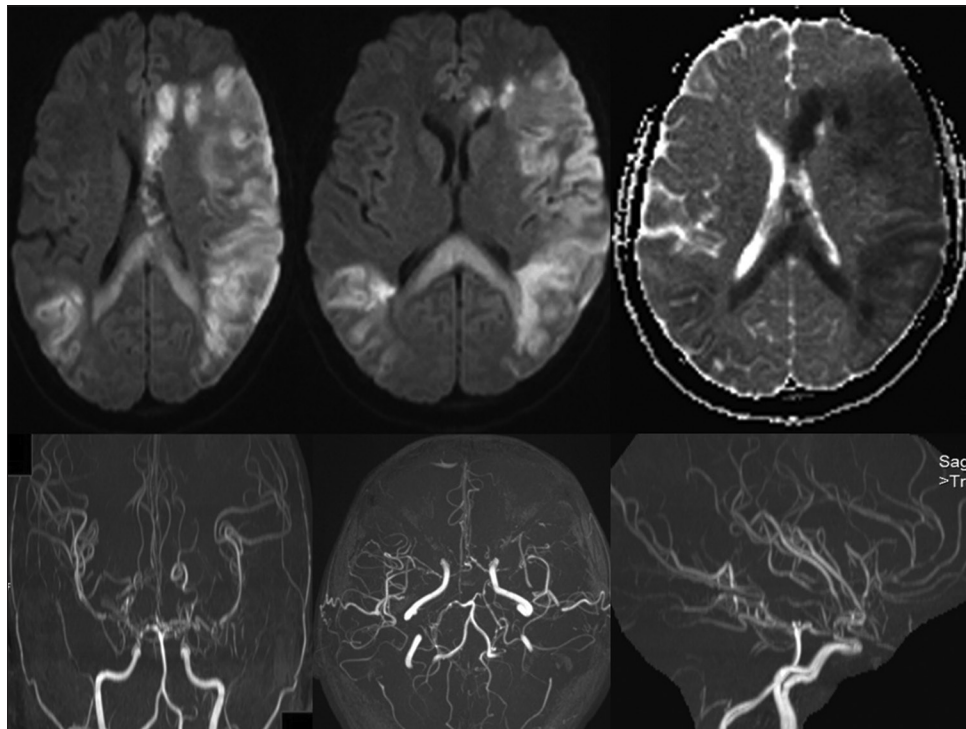
## A Case of Moyamoya Syndrome with Isolated Protein S Deficiency Unmasked by Pregnancy

Sir,

Reporting the case of a 23-year-old primigravida with normal preconception and antenatal period, at 35 weeks of gestation with two episodes of transient ischaemic attacks (TIA) (3-5 mins) of left-sided hemiparesis along with left homonymous hemianopia followed by throbbing, excruciating, holocranial headache a week later. Headache persisted and patient was admitted for institutional care where she went into labour the next day and baby was delivered vaginally. Baby cried at birth and had a weight of 2.3 kg. Shortly after delivery patient developed some behavioural abnormality like undue smiling, vacant look, incoherent speech and improper response to verbal commands, which was initially thought as postpartum psychosis. On the 4<sup>th</sup> day of delivery, patient developed sudden onset right-sided weakness along with unconsciousness. There was no other significant history. Patient was referred to tertiary care neurology center for further evaluation. On examination, patient had a blood pressure of 160/80 mmHg, was akinetic mute, right hemiparesis with an extensor right plantar. Differentials at this point were cerebral venous sinus thrombosis, reversible cerebral vasoconstriction syndrome,

recurrent thromboembolic stroke, and posterior reversible encephalopathy syndrome.

Routine blood investigations were normal. Magnetic Resonance Imaging (MRI) of brain showed multiple lesions in the territory of left middle cerebral artery (MCA), anterior cerebral artery (ACA), right MCA as well as watershed area of the left MCA-ACA region [Figure 1], which were hypointense on T1 and hyperintense on T2 and T2 fluid attenuated inversion recovery (FLAIR) sequences showing restriction in Diffusion Weighted Imaging (DWI), suggestive of acute infarcts. Similar involvement was seen in the splenium of corpus callosum (“Boomerang sign”) also suggesting infarction. T2 FLAIR also revealed leptomeningeal collaterals (“Ivy Sign”). MR angiography Brain by time of flight sequences (TOF) showed narrowing of bilateral distal internal carotid arteries (ICA) along with bilateral proximal MCA (Left>Right) with collaterals which was consistent with Moyamoya angiopathy (MMA) [Figure 1]. MR Venography (TOF sequences) brain, MR Angiogram of neck neck (TOF sequences) and arch of aorta were normal. After 24 hr electrocardiogram recording, Echocardiography, ultrasound



**Figure 1:** Diffusion weighted Imaging shows acute infarcts in left frontoparietal cortex and underlying subcortex, left perisylvian, right posterior parietal cortex and the splenium of corpus callosum, along with watershed infarct in the left MCA ACA territory. ADC map shows hypointensities corresponding to the DWI restriction. MR Angiography shows narrowing of bilateral distal ICA along with bilateral proximal MCA (L>R) along with collaterals. Both PCAs are also narrowed

abdomen with Doppler of renal and lower limb vessels were normal. Search for other causes of stroke was made including prothrombin time (PT), activated partial thromboplastin time (APTT), antineutrophil cytoplasmic antibody (ANCA) panel, antinuclear antibodies ANA (by Hep2 method), anti Ro, La, angiotensin converting enzyme (ACE), high performance liquid chromatography (HPLC), VDRL, Thyroid Profile, antiphospholipid antibodies, HIV, homocysteine, protein C and S, AT III, factor V Leiden mutation. Protein S came as <9% (55-123%). Others were negative. A repeat test after 3 months showed protein S was persistently low (<8%). Repeat MRI (TOF sequences) angiogram failed to show any reversal.

Course was complicated by retained bits of placenta, aspiration pneumonia and septicemia which were treated accordingly. She was started on low molecular weight heparin at therapeutic doses. Patient now in the 4<sup>th</sup> month of illness, recovering slowly with residual hemiparesis, global aphasia and a modified Rankin scale (mRS) 5 functional status. No further vascular event has occurred.

This case has an enigmatic presentation and a lot of associated peculiarities. Firstly, the age at presentation falls outside the usual bimodal distribution found in MMA. The mean delay in having onset of first neurological symptom to the final diagnosis in Eastern India is about  $14.7 \pm 41.7$  months.<sup>[1]</sup> However our patient, previously asymptomatic had a stormy course over 1-2 weeks. Moreover, ischemic stroke as a presentation in MMA is less common than intracranial hemorrhage in Asian adults.<sup>[2]</sup>

Severe headache with stroke can be found in many conditions in this age group like cerebral venous sinus thrombosis (CVT), reversible cerebral vasoconstriction syndrome (RCVS), subarachnoid hemorrhage with vasospasm, primary CNS angitis, intracranial arterial dissection or vascular complication of an infective etiology. CVT was ruled out as the infarcts followed arterial territory in the backdrop of a normal venogram.

There was no evidence of vasculitis or hemorrhage or signs of intracranial infection. RCVS was the next best differential but the lack of demonstrable reversibility on repeat imaging and a classical angiogram specific to the sites of MMA pointed more towards our diagnosis. Moreover, most patients of RCVS have a benign course with headache as a sole complaint without any neurodeficit. Deficits if any, are usually mild to moderate (i.e., mRS 0-2) and tend to improve within days to weeks.<sup>[3]</sup> On the other hand, thunderclap headache in MMA is associated with microaneurysm rupture leading to subarachnoid hemorrhage, intraparenchymal hemorrhage with or without intraventricular hemorrhage. Chronic headache can also occur due to dilated dural venous channels taking supply from collaterals. Presence of a fulminant and downhill clinical course pointed more towards a vasculopathy rather than a benign one.

Acute Transient Psychotic Disorders may occur in the postpartum period within 4 weeks of delivery. Commonly

in the absence of a paretic or non-paretic neurodeficit an underlying organic cause can be overlooked.<sup>[4]</sup> Retrospectively speaking, the patient's behavioral abnormality can be hypothesized as being a Wernicke's aphasia due to lesion in the posterior perisylvian area or a disconnection syndrome due to the splenic infarct. Subsequent infarct in the left orbitofrontal region explains the patient being akinetic mute due to disruption of the circuit responsible for motivation and behavior regulation.

Radiologically, in MMA brain atrophy is present in upto 63% of the patients and has a direct relation with the diagnostic latency.<sup>[1]</sup> Our patient did not have brain atrophy. DWI showed restriction in the splenium of corpus callosum along with hypointensity in ADC (Apparent Diffusion Coefficient) map, suggestive of infarction, ("Boomerang Sign") [Figure 1]<sup>[5]</sup> in addition to the described infarcts. Causes of bilateral corpus callosal infarcts are mainly embolic, anatomical variations around circle of Willis and hypoperfusion.<sup>[6]</sup> Callosal infarcts are rare owing to the rich blood supply from three vascular territories and their presence may indicate hemodynamic compromise, which is common in MMA.<sup>[7]</sup> Simultaneous involvement of both the anterior and posterior circulation along with bihemispheric large vessel occlusion and watershed infarcts made the suspicion of a vasculopathy with probable underlying systemic pathology much stronger.

Search for secondary causes revealed severe protein S deficiency. Other causes as mentioned above were ruled out. MMA can be commonly associated with neurofibromatosis type 1, Sickle Cell Disease, Down's syndrome, systemic lupus erythematosus, Antiphospholipid antibody syndrome. Other prothrombotic states like Thalassemia are also implicated.<sup>[8]</sup> Transient deficiency ruled out by repeat testing at 3 months. Protein S deficiency with Moyamoya syndrome (MMS) is rare and ischemic events occur mainly in the pediatric population.<sup>[9]</sup> Previously, a case of acute intraventricular hemorrhage with MMS and protein S deficiency was described.<sup>[10]</sup>

To conclude, MMA can have a stormy presentation heralded by recurrent TIA. Pregnancy can unmask an underlying vascular compromise. Not all post partum psychoses can be attributed to inorganic causes. Protein S deficiency can cause MMS and ischaemic events in adults.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

There are no conflicts of interest.

**Arka P. Chakraborty, Souvik Dubey, Peyalee Sarkar, Shambaditya Das,  
Biman K Ray, Alak Pandit**

Department of Neurology, Bangur Institute of Neurosciences, Kolkata,  
West Bengal, India

**Address for correspondence:** Prof. Alak Pandit,  
2<sup>nd</sup> Floor, New Building, Bangur Institute of Neurosciences, 52/1A, Shambhunath  
Pandit Street, Bhowanipore, Kolkata, West Bengal, India.  
E-mail: dralakpandit@gmail.com

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