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Looking Through the Smoke: A Case Report of Unilateral Moyamoya Disease Resulting In Partial Anterior Circulation Stroke in Young Sri Lankan Female

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Abbreviations: ACA: Anterior Cerebral Artery; ADL: Activities of Daily Living; ICA: internal Carotid Artery; MCA: middle cerebral artery; MMD: moyamoya disease; MRA: Magnetic Resonance Angiography; MRC: Medical Research Council; MRI: Magnetic Resonance Imaging; mRS: modified Rankin Scale.

Abstract

Moyamoya disease is an uncommon vascular cause of young onset stroke. We present a case of a 35-year-old Sri Lankan female with recurrent transient ischaemic attacks and migrainous type headache presenting with dense Middle Cerebral Artery (MCA) territory ischaemic infarct, who on extensive workup was diagnosed to have typical cerebral angiographic evidence of intracranial cerebrovascular occlusion and "puff of smoke", which are typical of Moyamoya disease. She was commenced on low dose aspirin, high intensity statin and extensively rehabilitated with physiotherapy and occupational therapy. She had a favourable outcome with near normal functional capacity. This case is the first from the country to report on this rare condition.

Introduction

Moyamoya disease is a chronic bilateral cerebrovascular occlusive disease with female preponderance (female to male ratio around 2:1), commonly seen in East Asian paediatric and young adult populations, manifesting as ischaemic or haemorrhagic infarcts of the anterior circulation, migrainous headache, epilepsy or transient ischaemic events [1]. Whilst both genetic factors might play a role in the pathogenesis, the exact pathogenesis is not yet elucidated. Cerebral angiography is the gold standard in diagnosis. The entity called unilateral moyamoya disease or moyamoya syndrome is characterized by a later age of onset and presence of secondary causes such as irradiation. However there is a debate whether it represents a unilaterally manifesting spectrum of the same disease, as a minority tend to progress to involve bilateral cerebral vessels with time. The presented case is of a young Sri Lankan mother with migrainous headache and several transient ischaemic attack and later an ischaemic infarct of same territory, being diagnosed with unilateral Moyamoya disease on angiographic evidence. This case the first of its kind reported from Sri Lanka, and also underscores Moya Moya disease as a significant cause of stroke in young individuals. This rare cerebrovascular disorder can lead to devastating consequences, particularly when undiagnosed or misdiagnosed.

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Case Presentation

A 35-year-old, right-dominant, Sri Lankan female and mother of three young children, presented to a private hospital in Sri Lanka with one week history of persistent, left ear and temporal pain and mild fever with chills. She gave no history of anoerexia, ear discharge, ear fullness, tinnitus, vertigo, nausea, generalized headache, neck pain, photophobia and phonophobia. A consultant Otolaryngologist had seen her, and found no abnormalities in her systemic examination or otoscopic examination of the left ear. Her vital functions were normal and had no features of meningism, local ear inflammation, cardiac murmurs, skin rashes or focal neurology. Her past history was significant only for two episodes of transient ischaemic attack involving weakness of left upper limb and left side of the face, about a year ago. Although she had been investigated with brain imaging and cardiac and cardioelectrophysiological investigations, she had not been on long term secondary preventive medications. She also had a recent history of migrainous type headache for past 6 months which responded to simple analgesics like paracetamol. Otherwise, she denied any history of cardiac illness, arrhythmias, pregnancy losses, features of connective tissue disorders, hypoglycaemic episodes, hyperviscosity symptoms, amarousis fugax, blood transfusion, high risk sexual behaviour or recreational drug abuse. She also denied any family history of vascular, haematological or connective tissue disorders.

She was admitted as an in-patient for observation and prescription of parenteral analgesics and sedatives for severe ear pain. She remembered waking up the next day with a periorbital anaesthesia, had walked to her bathroom about five feet away, brushed her teeth and acutely fell down with a heaviness and numbness of the left side of the body (with the upper limb involvement more than the lower limb involvement). At that moment, she did not have any headache, preceding chest or neck pain, trauma to head or neck, no any palpitations. She also denied any visual blurring, diplopia, dysarthria or aphasia, seizures, deterioration of mentation, or change in bladder or bowel control.

At that point she had normal vital functions, but had a pyramidal type weakness of left face, left arm (MRC-medical research council power grade 0) and left leg (MRC power grade 3). As she already hospitalised she was immediately seen by a neurologist. Table 1 summarizes the investigations performed on her. Noncontrast computed tomography revealed a hypodensity of right frontal periventricular white matter keeping with an acute infarct. Diffusion weighted sequence of Magnetic Resonance Imaging (MRI) of the brain revealed large right middle cerebral artery (MCA) territory infarction, with the size and extent of the infarct possibly unsalvageable by thrombolysis. Her Magenetic Resonace Arteriogram (MRA) revealed stenosis of M1 and M2 segments of right MCA, proximal part of A1 segment of right Anterior Cerebral Artery (ACA). She was not offered any thrombolytic therapy and facilities for large vessel mechanical thrombectomy was not available. Four vessel Digital Subtraction Angiography (DSA), done on a subsequent day revealed complete occlusion of right carotid top and proximal right MCA and right ACA with filling defect of the distal branches via pial collateral through posterior cerebral artery. Abnormal revascularization in the region was suggestive of Moyamoya syndrome (Figure 1). The next few days she was kept for observation and for specialized aetiology-screening investigations and was transferred to rehabilitation hospital for further stroke care.

Table 1: Summary of investigations.

Test (unit)	Value
WBC (x 10^3 /mm^3)	6.28
Haemoglobin (g/dL)	14.1
MCV (fL)	83.4
Platelet count (x 10^3/ mm^3)	267
Blood picture	No abnormal cell lines
ESR (mm/ hour)	7
CRP (mg/dL)	12.4
eGFR (ml/kg/1.73 m^2)	116
Serum sodium (mmol/L)	143
Serum potassium (mmol/L)	4.05
Serum total calcium (mmol/L)	2.2
Serum inorganic phosphorus (mg/dL)	4.4
Serum uric acid (mg/dL)	5.5
Aspartate transaminase (U/L)	15
Alanine transaminase (U/L)	19
Serum bilirubin (mg/dL)	0.8
Alkaline phosphatase (U/L)	54
Serum albumin (g/L)	4.4
Serum globulin (g/L)	4.5
INR	0.92
APTT (sec)	35
ANA (IIF technique)	Positive titre (1:80) with fluorescence pattern cytoplasm
Lupus anticoagulant screen (ratio)	1.09 (0.8 – 1.2)
Cardiolipin – IgM antibody (MPL)	3.2 (<13)
Cardiolipin – IgG antibody	negative
Beta 2 glycoprotein – IgM antibody (SMU)	2.78 (< 20)
Beta 2 glucoprotein – IgG antibody (SMU)	0.45 (<20)
Plasma homocysteine (umol/L)	11.44
FBS (mg/dL)	80.4
HbA1c (%)	5.2
24 hour holter recording	normal
Transthoracic and trans oesophageal echocardiogram	Normal systolic and diastolic function, with no intra atrial septal abnormality in bubble contrast technique
Chest radiograph	normal
Doppler scan of neck vessels	No significant thickening of intima media complex or any atheromatous plaques in CCA, proximal internal carotid artery (ICA) or external carotid artery (ECA).
CT angiogram of neck and large vessels of thorax	Apparent short narrowing of left vertebral artery. Rest of the extracranial vessels were normal.

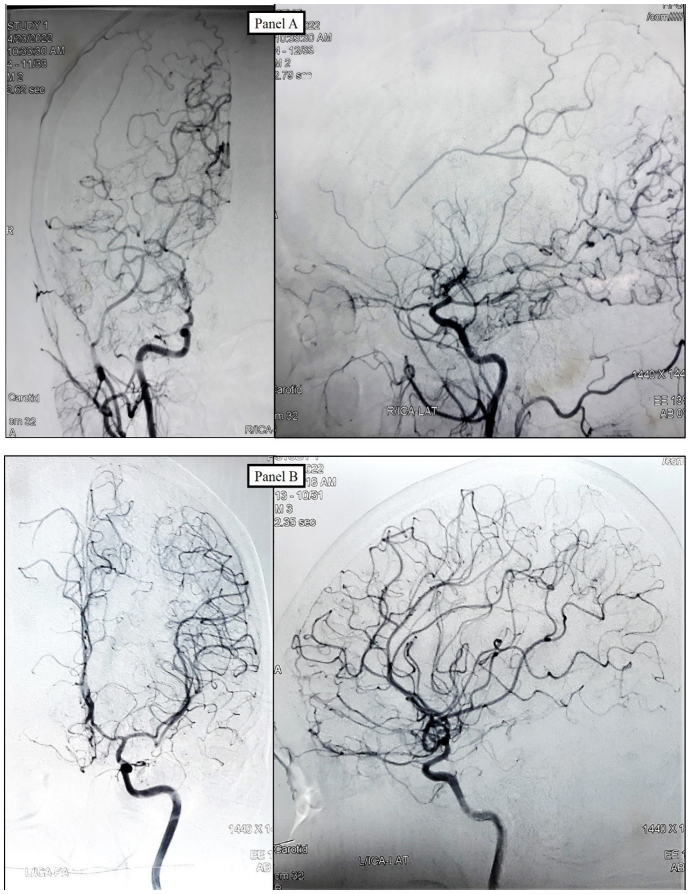

Figure 1: Panel A. coronal and sagittal DSA images of right sided intracranial vessels, showing occlusion of R/S MCA, proximal R/S ACA, and collaterals forming puff of smoke appearance.
Panel B. normal coronal and sagittal DSA images of left sided intracranial vessels, for comparison.

On admission to the rehabilitation unit, she had a dense left hemiplegia with a modified Rankin scale (mRS) of 4. She was only capable to mobilize with a wheel chair, and that too required assistance of a caregiver. She was dependent on most of the other basic Activities of Daily Lining (ADLs) as well. Her language, swallowing, bladder and bowel functions were intact. She was subjected to vigorous physiotherapy session of close to 5 hours per day for 4 days of the week. The exercises were supervised by a trained physiotherapist and involved muscle strengthening exercises, balance training and training on gradual mobilization, initially with aid of a walking aid and later to some independence. Simultaneously, she was offered in patient occupational therapy about two to four 3 hour long - session per week mainly to stimulate tactile perception of affected upper limb (e.g. using mirror therapy) and then to achieve fine and gross motor activities of the affected hand. She had been motivated throughout the session, and did not reveal any depressive symptoms. Her family including her three children come to see her on a daily basis to provide emotional and psychological support. At the end of two and a half weeks she was discharged on aspirin 150 mg nocte. And atorvastatin 40 mg nocte, with outpatient upper limb physiotherapy and occupational therapy arranged. On discharge her mRS index improved to 3, and had a disability mainly confined to the left upper limb (proximal muscle groups having MRC power grade of 3, and the distal muscle group having MRC power grade of 2). She had good static and dynamic sitting balance, good standing balance and was able to walk without assistance up to 20 feet. She however required assistance with activities like dressing or washing which require both arms.

Discussion

The occurrence of ischaemic stroke under 45 years, also referred to as “young stroke” results in significant loss to the person, family and the community [2]. Overall there is an increased male prevalence in young stroke as in the older age groups. Although there is an increased incidence of conventional risk factors such as smoking, diabetes, hypertension, obesity and dyslipidaemia due to the metabolic shift, in the absence of such, one should screen for other uncommon etiologies of genetic and acquired hyper coagulopathy, vasculopathy, and cardiac and large vessel thromboembolic phenomenon.

The other possible differential diagnosis for this reported patients include a cerebellitis or cerebral abscess from an ear infection, infection or inflammation of neck vessels, hemiplegic migraine given the background history of headache and cerebral venous sinus thrombosis. Migraine with aura may result in cerebral hypo perfusion during the aura [1]. The occurrence of similar neurological events resulting from ischemia of same vascular territory and absence of audible bruits in the neck point towards the most likely diagnosis a distally located vasculopathy of right anterior circulation. This can result from various pathogenic processes such as fibrotic stenosis, vasculitis, atherosclerosis, external occlusion or vascular spasms. Since our patient had a marginally high ANA, she was screened for presence of possible antiphospholipid antibodies. Her negative ESR and absence of angiographic abnormalities in the rest of the body, makes Takayasu arteritis unlikely.

Considering the patient's clinical presentation, lack of traditional risk factors for stroke, neurological examination findings, and the characteristic neuroimaging findings, the diagnosis of Moyamoya disease is justified. Moyamoya disease, an inherent primary disease process causing bilateral progressively evolving stenosis of the anterior intracranial blood circulation is an uncommon cause of young stroke. The condition is mainly described in East Asian population with an annual incidence of 6.03 per 100000, and carries a female preponderance [1]. The disease process may extend from the proximal parts of the intracranial Internal Carotid Artery (ICA) to involve the proximal parts of the Anterior Cerebral Artery (ACA) and Middle Cerebral Artery (MCA) territories. The involvement of posterior circulation is uncommon. Intra cranial arterial stenosis results in a compensatory response of enlargement and proliferation of many smaller lenticulostriate arteries. This gives rise to the characteristic angiographic appearance of a "Puff of Smoke”, and is translated into Japanese as "Moyamoya”. Catheter-based Digital subtraction Angiography is the current gold standard for diagnosis. The Suzuki staging system by Suzuki and Takaku is a six-stage angiographic system that aids in decisions pertaining to management (Table 2) [3]. Histological of involved arteries may show irregularities of the internal elastic lamina, narrowing of the lumen, intimal thickening, and intimal thickening, hyperplasia with vacuolar degeneration in smooth muscle cells of the tunica media [1]. Nevertheless, biopsy is not a requirement for making the diagnosis.

Table 2: Suzuki Grading system [3].

Grade	Definition
I	Narrowing of ICA apex
II	Initiation of moyamoya collaterals
III	Progressive ICA stenosis with intensification of moyamoya-associated collaterals
IV	Development of ECA collaterals
V	Intensification of ECA collaterals and reduction of moyamoya-associated vessels
VI	Total occlusion of ICA and disappearance of moyamoya-associated collaterals

Several antibodies (APP, GPS1, STRA13, CTNB1, RQR1, EDIL3), vascular angiogenic growth factors (VEGF), matrix metalloproteinase, hepatocyte growth factors, and interleukins (IL-1B), dysfunction of endothelial colony forming cells, abnormal expression of circular RNA in mitogen activated protein kinase signaling pathway are implicated in the pathogenesis of Moyamoya disease [1].

Clinical presentations include migraine-type headache and transient ischaemic events, both of which the reported patient too had. Headache may be due to irritation of the meningeal nociceptive fibers by expanding neovascularization Ischaemic stroke is commoner than haemorrhages. Epilepsy is also a recognized presentation. An international multicenter stroke database showed that 90% of MMD patients initially presented with ischemic stroke, 7.5% with a transient ischemic attack, and 2.5% with hemorrhagic stroke [4]. Hyperventilation, hypoxia, hypotension, hypocarbia, hyperthermia, and relatively increased cerebral metabolism with insufficient cerebral blood flow to meet the increased demand contribute to ischaemic events in Moyamoya disease. It is worth noting that our patient had the transient ischaemic events and stroke during deep sleep process, though this association has not been previously described. An increased cerebral metabolism for unknown reason during the sleep may have been contributory.

Unilateral Moyamoya disease, also known as Moyamoya syndrome is often secondary to another pathological process such as radiation vasculitis, sickle cell disease, neurofibromatosis type I and Trisomy 21 [1]. However, we could not find a suggestive secondary cause in our patient. Unilateral disease is generally seen among older age group and can have different distributional pattern. It is still unclear whether the unilateral disease belongs to the same clinical spectrum that includes bilateral disease, or whether is a clinical entity per se. The former is supported by a few follow-up studies, where persons with unilateral disease later develop contralateral involvement, but its incidence is very low.

Early recognition of this rare cerebrovascular disorder is crucial for appropriate management and timely intervention to prevent further stroke occurrences. In this case, the patient's treatment with antiplatelet therapy (aspirin) and statin medication (atorvastatin), coupled with rehabilitative measures, contributed to an improvement in her modified Rankin scale index and functional status, especially regarding her mobility and upper limb function. Follow-up outpatient therapy aims to maintain her functional gains and overall quality of life. With no medical therapies that have been successful in halting progression, and with no neuro-interventional endovascular surgeries that have successfully stented stenotic segment, the current treatment for MMD is largely via open surgical methods. Surgical options may be in the form of direct or indirect cerebrovascular bypass. Direct bypasses are most suitable for those presenting as an ischaemic event. Direct and combined bypasses have shown superiority in preventing future ischaemic events, in comparison to indirect bypasses [1]. Neither the direct nor the indirect bypass methods showed a statistically significant difference in the preventing future cerebral bleeds. There is no added benefit of intervening with direct bypass in those advanced disease process compared to conventional conservative ischaemic stroke management. Early intervention therefore is most likely to prevent future neurologic decline. However such interventional options are not readily available in the local setting. Interestingly, several other studies did not demonstrate any efficacy of aspirin in preventing the postoperative risk of developing ischaemic events following bypass surgery for MMD [1].

Conclusion

Moyamoya disease is a chronic, progressive disease, which without effective management options, carries a significant risk of morbidity in individuals affected by stroke. Being a contributor for young-onset stroke, it carries implications to the family and the economy as well. It is imperative to intervene early by surgical bypassing techniques to preserve function and prevent a progressive decline. However the availability of such high-end techniques is an issue in developing nations like ours. Future studies to investigate the underlying pathophysiological cause may potentiate development effective targeted medical or endovascular therapies.

Consent for publication

The consent for publication was obtained from the patient.

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