
Ischemic Stroke in a Postpartum Patient: Understanding the Epidemiology, Pathogenesis, and Outcome of Moyamoya Disease

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BACKGROUND Moyamoya disease (MMD), or spontaneous occlusion of blood vessels in the circle of Willis, is a noninflammatory, nonatheromatous vasculopathy that often presents with ischemia or hemorrhage and has a tendency to affect young women. We discuss a case of a woman 7 days postpartum with new onset strokes, suspected initially to have benign angiopathy of the central nervous system (BACNS)/postpartum angiopathy versus primary CNS vasculitis. Cerebral angiography was suspicious for MMD and the patient underwent surgical revascularization.

OBJECTIVES To review the epidemiology, presentation, diagnosis, differential diagnosis, treatment, prognosis, and postpartum maternal outcomes of MMD.

METHODS The authors reviewed the English-language literature published between 1996 and 2004 using Medline databases. Additional articles were obtained from references described in literature obtained by the primary search.

RESULTS MMD is characterized by severe bilateral stenosis of the distal internal carotid arteries and their first branches, with prominent collateralization. Autoantibodies relating to endothelial cell dysfunction have been studied as possible pathogenetic mechanisms. The gold standard for diagnosing MMD is digital subtraction contrast angiography (DSA). MMD-related findings on imaging studies may, at times, be mistaken for those of vasculitis. A surgical approach may need to be considered. Despite treatment, the overall prognosis of MMD is worse in adults compared with children.

CONCLUSION Awareness of the specific features of MMD is crucial for clinical decision-making to avoid unnecessary exposure to aggressive immunosuppressive therapy. It is important for rheumatologists to consider MMD in the differential diagnosis of suspected CNS vasculitis.

Semin Arthritis Rheum 35:250-259 © 2006 Elsevier Inc. All rights reserved.

KEYWORDS Moyamoya disease, Moyamoya syndrome, primary CNS vasculitis, benign angiopathy, postpartum, ischemic stroke

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Source of support: none.

Disclaimers: none.

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Neurologic manifestations of rheumatic disease are not uncommon and represent a challenge to the clinician; they can be seen in the setting of systemic vasculitides and connective tissue diseases such as systemic lupus erythematosus, Sjogren's syndrome, or antiphospholipid antibody syndrome (1). Less frequently, the central nervous system (CNS) may be the only area of involvement, in which case primary CNS vasculitis or benign angiitis of the CNS (BACNS) may be suspected, depending on the clinical setting (2). We describe a patient presenting with new onset stroke 7 days postpartum. A rheumatologic and neurologic work-up were undertaken, and CNS vasculitis was a consideration. Ultimately the patient was diagnosed with probable Moyamoya disease (MMD) and treated with revascularization surgery. Moyamoya disease, or spontaneous occlusion of the circle of Willis, is a noninflammatory vasculopathy predominantly affecting the intracranial vessels, first described in Japan in 1957 (3-5). Patients with MMD typically present with clinical findings related to acute cerebral ischemia or intracranial hemorrhage. Clinical and radiographic differences among BACNS, primary CNS vasculitis, and MMD may be subtle, but awareness of the specific features of MMD is crucial for clinical decision-making to avoid unnecessary exposure to aggressive immunosuppressive therapy, where a surgical approach may need to be considered.

Case Report

A 34-year-old Korean-American woman with a past medical history significant for major depression 10 years ago presented with tearfulness, social withdrawal, apathy, and mutism 5 days postpartum. The symptoms began 3 days after a

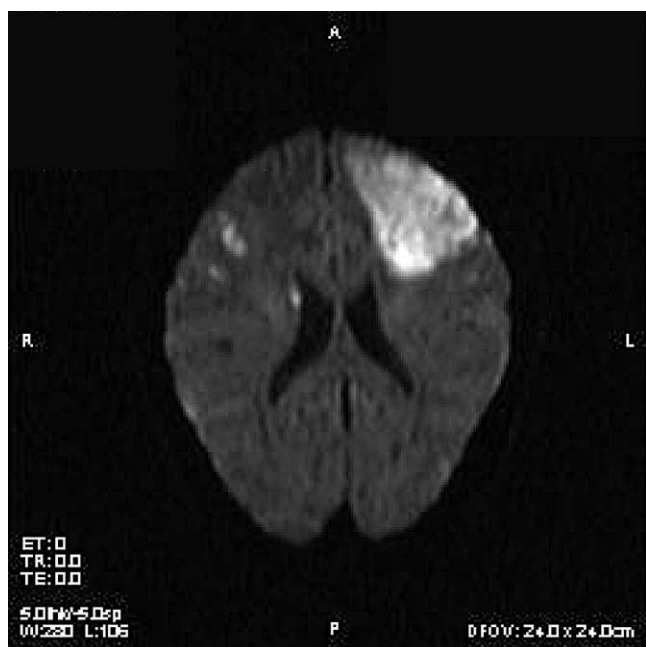


Figure 1 Axial diffusion-weighted image demonstrating acute left frontal infarction.

Abbreviations

ACA	anterior cerebral artery
BACNS	benign angiopathy of the central nervous system
bFGF	basic fibroblast growth factor
C-section	cesarean delivery
CNS	central nervous system
CRABP-I	cellular retinoic acid-binding protein-I
CSF	cerebrospinal fluid
CTA	computed tomography angiogram
DSA	digital subtraction contrast angiography
EDAMS	encephalomyoarteriosynangiosis
EDAS	encephaloduroarteriosynangiosis
EMS	encephalomyosynangiosis
EMAS	encephalomyoarteriosynangiosis
GANS	granulomatous angiitis of the CNS
IACNS	isolated angiitis of the CNS
ICA	internal carotid artery
MCA	middle cerebral artery
MMD	Moyamoya disease
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
PACNS	primary angiitis of the CNS
STA-MCA	superficial temporal artery to middle cerebral artery
TIA	transient ischemic attack
TNF- α	tumor necrosis factor-alpha.

normal spontaneous vaginal delivery of a healthy full-term female infant, notable only for an episode of hypertension to 160/80 mm Hg that responded to a single dose of labetalol 10 mg given intravenously.

The patient's family history was significant for a mother who had suffered a peripartum stroke, which was diagnosed as an "autoimmune disorder" by doctors in Korea, and was placed on chronic corticosteroids. No definitive diagnosis was ever made and the mother died of multiorgan failure 22 years later. A maternal aunt also had a history of stroke at age 30 years, unrelated to pregnancy. The patient had no history of miscarriages, previous thrombosis, renal disease, blood dyscrasias, or joint problems. She denied use of sympathomimetic agents, over-the-counter preparations, herbal medicines, or Eastern remedies. The patient was a resident of a Los Angeles suburb and denied alcohol, tobacco, or drug use, history of sexually transmitted disease, recent foreign travel, sick contacts, or chemical exposure. The review of systems was negative for fever, chills, shortness of breath, loss of consciousness, seizure activity, headache, vertigo, dizziness, vision changes, oral or genital ulcers, alopecia, facial or body rash, photosensitivity, incontinence of bowel or bladder, nausea/vomiting, or diarrhea.

The patient was initially diagnosed with postpartum depression by her obstetrician and psychiatrist. Physical examination showed expressive aphasia and a flat affect, but no motor deficits. Magnetic resonance imaging (MRI) of the pituitary done on the day after admission did not

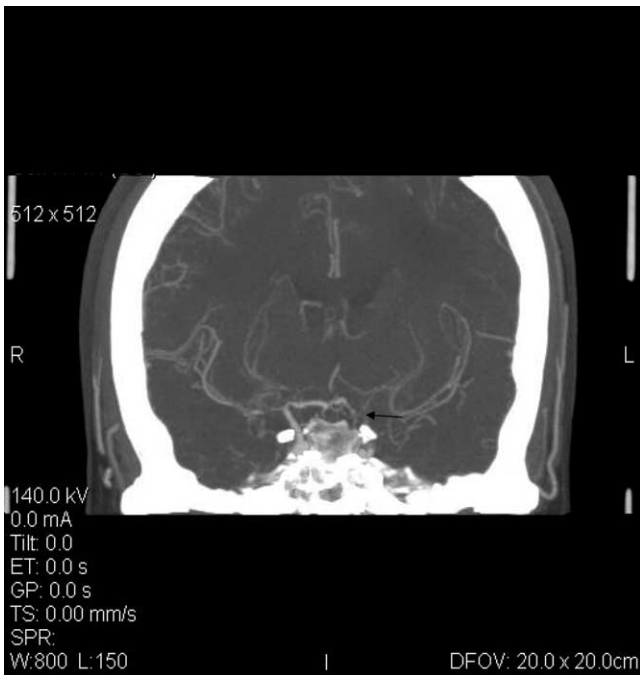


Figure 4 Coronal thick-section reconstruction of a CT angiogram demonstrates severe irregular stenoses and occlusions in the anterior and middle cerebral artery circulation as well as tight stenosis of the supraclinoid segment of the left internal carotid artery (see arrow).

arteries (Fig. 3). A CTA demonstrated tight stenosis of the left supraclinoid carotid artery as well as bilateral MCA stenoses (Fig. 4). Throughout the 2nd day after admission, the patient's neurologic status worsened, with increased dysarthria and progressive pronator drift of the left upper and lower extremities, along with worsening left-sided weakness.

A cerebral angiogram showed narrowing of the left internal carotid artery (ICA) at the cervical and supraclinoid segments (Fig. 5). There was virtual occlusion of the left ICA, but filling of the left anterior choroidal and posterior communicating arteries. Enlargement of the left superficial temporal artery with demonstration of collaterals to falcine vessels at the distal aspect also was noted. There was no evidence of aneurysmal formation or arteriovenous malformation. On the right, there was marked attenuation of the proximal right MCA with lack of opacification of hemispheric vessels. The supraclinoid was mild-to-moderately narrowed and there was narrowing of the origin of the right A1 segment. The vertebral-basilar circulation demonstrated pial collaterals that supply the MCA territories bilaterally to the level of the Sylvian fissures and bifurcations. Review of these findings with the neuroradiologist raised the suspicion of Moyamoya disease. Postpartum angiopathy was less likely as reversible vasoconstriction did not appear to be the underlying mechanism based on imaging findings and the patient's clinical course.

On hospital day 4, the patient went to the operating

room and had a right temporal craniotomy with superficial temporal artery anastomosis to an unaffected branch of the MCA. A portion of the frontal branch of the superficial artery and a small biopsy of the dura were sent for pathology review. Biopsy results of the arterial specimen showed minimal intimal hyperplasia. No granulomas, vasculitis, amyloid, fibromuscular dysplasia, or diagnostic thrombus or embolus were identified. The right frontal dura was without vascular abnormalities or inflammation.

The patient has been followed for 12 months and subsequently has undergone extensive outpatient speech, oc-

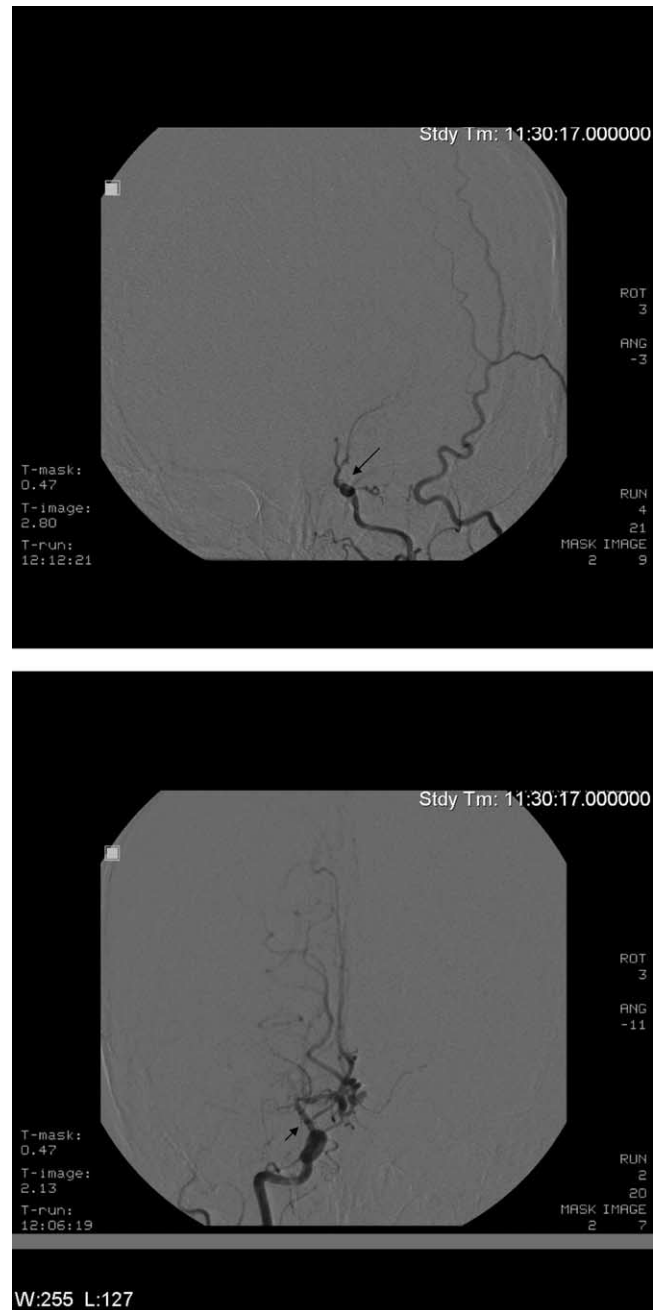


Figure 5 (a) Contrast angiogram of the left ICA shows supraclinoid occlusion (see arrow) with no antegrade filling of the MCA or ACA. (b) Contrast angiogram demonstrating severe right supraclinoid ICA stenosis (see arrow) with no filling of the MCA.

cupational, and physical therapy. She has residual cognitive, speech, and motor deficits and has not been able to return to her previous work as a neonatal intensive care unit nurse.

Methods

The literature was reviewed using Medline for articles published between 1996 and 2004 with the terms “Moyamoya disease” and “Moyamoya syndrome.” The search was limited to English-language studies and humans, with emphases on epidemiology, presentation, diagnosis, differential diagnosis, treatment, prognosis, and postpartum maternal outcomes. Additional articles were obtained from references and materials described in articles obtained in the primary search. Those articles identified from the search were reviewed by the authors and abstracted.

Results

Definition and Terminology

Loosely translated, the word “moyamoya” means “hazy” like a “puff of smoke” in Japanese and was so named because of the appearance of collateral vessels at the base of the brain (3). Although initially thought to be confined to the Japanese, in recent years it has been found among patients of all races and ethnicities (6). However, age distributions and clinical manifestations of this disease differ between Japanese and non-Japanese populations (6-8).

Presentation

The presentation of patients with MMD may include seizures, ischemic events, and hemorrhagic strokes. There is a bimodal distribution of disease presentation, with the highest peak in the first decade of life and a second smaller peak in the fourth decade (8). Clinical presentations tend to vary based on age at onset. In children, the predominant presentation is related to ischemic events from hypoperfusion, such as strokes or frequent transient ischemic attacks (TIAs), or, less frequently, seizure activity (4,5). The ischemic symptoms in children may also manifest as monoparesis or hemiparesis, sensory impairment, visual field defects, speech disturbance, or involuntary movements (9). These may be provoked by hyperventilation (such as with crying, coughing, straining, blowing out candles, or playing a wind instrument), which can decrease cerebral blood flow through an autoregulatory system triggered by the acute decrease in P_{aCO_2} (5,10). Frequently, mental retardation may be present in these children, which may be a secondary consequence of the cerebral infarcts and atrophy from underlying disease and not a primary part of the pathogenesis of MMD (11).

In adults, especially in Japanese and Korean patients, presentation usually involves sudden onset of headache or hemiparesis, with or without altered mental status. These are typically the clinical manifestations of underlying intracranial hemorrhage from rupture of the abnormal, thin-walled collateral system (“moyamoya vessels”) or aneurysms (4,12).

However, epidemiologic studies from the US and other countries outside of Japan show a much higher frequency of ischemia-related presentations without hemorrhage (6,13). Seizures also may be a presenting feature in adults.

Epidemiology

In Japan, where the prevalence is highest, a survey by the Japanese Ministry of Health and Welfare in 1995 identified 3900 patients with MMD treated in 1994, with a calculated prevalence rate of 3.16 per 100,000 and a calculated crude annual incidence rate of 0.35 per 100,000 (8). Although cases have been reported in all age groups, the age distribution in Japanese patients showed a bimodal peak, with the first peak at 10 to 14 years and a second smaller peak between 25 and 49 years (8,11). The ratio of female-to-male patients was 1.8:1 and a family history of MMD was seen in 10% of patients (8).

In the US, over 300 cases of MMD have been reported in the literature with the largest cohort ($N = 32$) from the University of Texas–Houston, where clinical expression of the disease was different from that classically described by the Japanese (6,13). In this group, the distribution was not bimodal and the mean age at diagnosis was 32 years. Ischemic events (TIA or stroke) were the most common presenting feature in both adults and children (6). Reports from Korea show that the adult population with MMD is 20% greater than in Japan with a female-to-male ratio of 1.3:1 (7,14). Korean patients have a higher incidence of hemorrhage and infarction and fewer TIAs or seizures than observed in Japanese subjects (7).

Etiology and Pathogenesis

The etiology of MMD remains unknown and a variety of genetic, environmental, bacterial, and viral causes have been postulated. Reported associations include previous head and/or neck infections and inflammation, such as tonsillitis, otitis media, or sinusitis (15). The mode of inheritance is thought to be polygenic (16). Studies of families with MMD have shown possible linkage with chromosome 3p24.2-26, 6q25, and 17q25, and more recently 8q23 (17-20). A Japanese study of 5 families revealed higher incidence of MMD in siblings over offspring of patients, and only female cases were observed among monozygotic twins (16).

Cerebrospinal fluid (CSF) studies from Hojo and coworkers of 3 patients with MMD revealed a novel CSF protein (21). A more recent study of 20 MMD patients found elevated levels of a CSF protein with similar characteristics to that detected by Hojo and coworkers. This was identified as cellular retinoic acid-binding protein-I (CRABP-I), which may be associated with intimal thickening and increased basic fibroblast growth factor (b-FGF) (22). The effects of CRABP-I are believed to be related to the decreased inhibitory effect of retinoic acid on growth factor-stimulated smooth muscle cell proliferation and migration, which may lead to intimal thickening (22).

Serum studies of 32 patients with definite MMD demonstrated a high frequency of autoantibodies to alpha-

fodrin subunits, a product of endothelial cell apoptosis-associated cleavage/breakdown (23). Autoantibodies against alpha-fodrin have also been described in Sjogren's syndrome cases with neurologic manifestations (24-26). One reported case described a patient with moyamoya-like findings who had underlying Sjogren's disease (27). The association of antibodies to alpha-fodrin with MMD may be mediated by the effect of TNF- α and other proinflammatory cytokines on endothelial cell activation, contributing to the pathogenesis of vessel occlusion in MMD (23).

Differential Diagnosis

The differential diagnosis of young patients presenting with multifocal ischemic infarctions without concomitant rheumatic disease includes hypercoagulable states, emboli, primary CNS vasculitis, and benign angiopathy of the CNS (28). It is also important to rule out infectious or lymphoproliferative disorders as well as side effects of medications, especially sympathomimetic agents (28). Hypercoagulable states that may cause cerebral ischemic events include polycythemia vera, thrombotic thrombocytopenic purpura, idiopathic thrombocytosis, hyperproteinemias, sickle cell anemia, inherited and acquired clotting abnormalities, and circulating antiphospholipid antibodies (29). Cardiogenic cerebral emboli can arise from dysrhythmias, valvular disease, intracardiac thrombi or tumors, akinetic myocardium, endocarditis, or congenital heart defects, such as a patent foramen ovale, demonstrated by echocardiography and/or electrocardiography (29).

Primary CNS vasculitis is a rare, often fatal, disorder first described in the 1950s. Several terms have been used in the literature to describe vasculitis of the CNS including granulomatous angiitis of the CNS (GANS), isolated angiitis of the CNS (IACNS), and primary angiitis of the CNS (PACNS). The gold standard for diagnosis relies on histopathology, revealing leptomeningeal and cortical vascular involvement with granulomatous angiitis with or without necrotizing vasculitis and unaffected nearby arteries and veins. Diagnosis also may be based on classic angiographic findings of alternating stenosis and ectasia in multiple vascular distributions, without significant microaneurysms (28). CSF findings have been abnormal in 80 to 90% with an aseptic meningitis picture consisting of modest pleocytosis, elevated protein, and occasionally elevated IgG synthesis rates and oligoclonal bands (28). Patients with primary CNS vasculitis tend to be middle aged (mean age 46 years), be predominantly male (69%), have a less acute presentation (mean time from symptom onset to diagnosis of about 5 months), and may show diffuse neurologic dysfunction manifested as decreased mentation or altered level of consciousness (28). These patients generally require aggressive immunosuppressive therapy with high-dose glucocorticoids and cytotoxic drugs.

In contrast, benign angiopathy of the CNS has a more benign clinical course despite high probability angiographic findings for primary CNS vasculitis (30). These patients were more likely to be female (female-to-male ratio 4.3:1), have an

acute onset of symptoms with a mean time from symptom onset to diagnosis of 25 days, and normal or mildly abnormal CSF (31). The underlying mechanism in these cases has been postulated to be reversible vasospasm or vasoconstriction; these findings have been seen in patients who are postpartum, have received sympathomimetic agents, or have hypertension (31). While angiographically indistinguishable from primary CNS vasculitis, the benign angiopathy cases have better outcomes without angiographic or clinical progression, and in some cases, angiographic resolution on follow-up studies after treatment with corticosteroid and/or calcium channel blocker therapy (31).

Diagnosis

Members of the Research Committee of Spontaneous Occlusion of the Circle of Willis of the Japanese Ministry of Health and Welfare have established guidelines for the diagnosis and treatment of MMD (12). The diagnostic criteria rely on the presence of the following: (1) stenosis or occlusion of the distal ICA (carotid fork) and/or the proximal MCA; (2) abnormal vascular network in the basal ganglia, base of the brain, or in the vicinity of stenotic lesions; and (3) bilateral involvement of findings. Detection by cerebral angiography has classically been described as the gold standard. However, comparative study of MRI with MRA to conventional angiography found MRI with MRA to be an acceptable alternative, showing occlusive lesions and basal moyamoya vessels, with the caveat of lower spatial resolution (32,33). For a definitive diagnosis, these findings should be seen in the absence of neurofibromatosis (von Recklinghausens' disease), Down syndrome, sickle cell anemia, brain neoplasm, head trauma, brain irradiation, meningitis, autoimmune disease, and arteriosclerosis, as similar vascular imaging abnormalities may occasionally be found in association with these disease processes (12). When the similar changes on neuroradiologic imaging are associated with any of the previously mentioned conditions, the process should be called moyamoya syndrome, instead of disease (5). Probable MMD is the term applied to adult patients with unilateral disease, although children with unilateral disease may progress to bilateral lesions (11).

The abnormal vascular network is composed of thin-walled collateral vessels seen at the base of the brain (Fig. 6), involving thalamoperforate, anterior and posterior choroidal, and lenticulostriate arteries and external to internal carotid anastomoses (3). These are thought to be a response to chronic ischemia from narrowing or occlusion of the internal carotid and anterior and middle cerebral arteries (3,4,34). Intracranial aneurysms also may be seen in the circle of Willis, in the collateral network, or in the posterior or anterior choroidal, posterior cerebral, or Heubner's artery (5). Digital subtraction contrast angiography (DSA), with its high level of special resolution, reveals maximal visualization of the blood vessels and provides useful information if surgical intervention is planned. However, in light of the inherent risks associated with angiography, and with advances in noninvasive imaging techniques, a good-quality MRA is an effective way

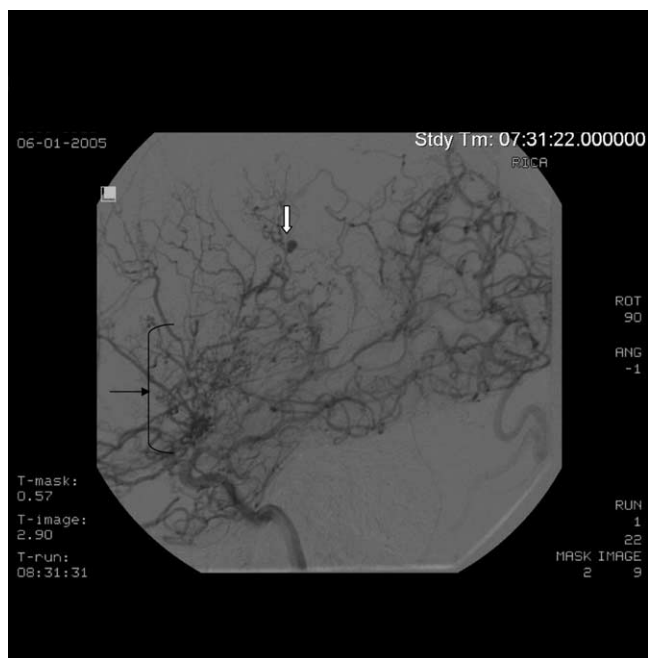


Figure 6 A cerebral angiogram from a different patient demonstrates little to no filling of the anterior and middle cerebral arteries. The prominent perforating vessels and collaterals from the posterior cerebral artery (see black arrow) represent the hazy “Moyamoya” vessels. An aneurysm (see white arrow) is also present on a distal perforating vessel.

to detect occlusions or stenoses and the presence of collaterals (5,12,33). MRI and MRA also have been useful in assessing postoperative changes in patients who undergo surgical treatment for MMD (35,36).

Histopathology

Autopsy studies of brain tissue from MMD patients often reveal evidence of prior ischemic infarction. Hemorrhage, when it occurs, is seen in the basal ganglia and periventricular or intraventricular region (37). The collateral blood vessels form an irregular network of pial anastomoses that penetrate the brain. Autopsy specimens from involved vessels show concentric fibrocellular intimal thickening and a wavy, multilayered elastic lamina and medial thinning (38,39). These changes occur without evidence of significant atherosclerosis, inflammation, or emboli (38). Although vascular involvement was generally considered to be intracranial, more recent studies in children and adults reveal similar, but less advanced changes in extracranial vessels. A study of 17 children with MMD showed intimal thickening in small branches of superficial temporal arteries in 9 patients (40). The changes were similar to those in intracranial vessels, but of a lower grade. A similar case series of superficial temporal artery specimens from 13 adult patients also displayed intimal thickening without fibrinoid necrosis or lipid deposition (41). These changes may be the result of higher levels of bFGF seen in the tissues (endothelium and smooth muscle) and CSF of MMD patients compared with patients with atherosclerotic cerebrovascular disease. Basic FGF is believed to

induce both angiogenesis and endothelial cell proliferation, resulting in stenosis and collateral formation, respectively (42,43).

Treatment

Currently, no known curative or remittive treatment exists. The initial treatment is usually supportive, based on symptoms and findings at presentation, and is aimed at maintaining cerebrovascular function. In patients presenting with ischemic symptoms, antithrombotic agents are usually employed. Antiplatelet agents are generally preferred to anticoagulants because of the known risk of intracranial hemorrhage in patients with MMD. Small series have been reported using calcium channel blockers to reverse ischemic symptoms. Anticonvulsants have a role in patients presenting with seizures. Corticosteroids have been used but are of questionable value.

Hemorrhagic cases may require ventricular drainage and hematoma removal, depending on size and location (12). In ischemic cases, treatment is aimed at increasing blood flow to areas of hypoperfusion by creating a collateral circulation (44). Surgical procedures also have been used in an attempt to slow the development of abnormal vessel formation and to decrease the risk of CNS bleeding caused by hemodynamic stress on moyamoya vessels, with mixed results (4,11,45,46). Treatment may involve early surgical revascularization with direct or indirect procedures, or a combination of both. Direct procedures are used more frequently in adults and indirect procedures in children (11,13). No randomized, controlled trials for ischemic infarction recurrence have been published that compare different revascularization procedures with each other, or to medical therapy.

Much debate exists as to which surgical procedure, if any, should be done (47). Direct procedures such as superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis or extracranial to intracranial bypass to the anterior cerebral artery or the posterior cerebral artery have been performed in many patients (48). First used in the mid-1970s, STA-MCA anastomosis is more difficult to perform in children because of the small size of these vessels (49). Indirect surgical procedures include encephaloduroarteriosynangiosis (EDAS), and less frequently, encephalomyosynangiosis (EMS), encephalomyoarteriosynangiosis (EMAS), and encephaloduroarteriomyosynangiosis (EDAMS), as well as omental or muscle (gracilis/latissimus dorsi) transplantation to the anterior or posterior cerebral artery (50). EDAS involves direct application of a segment of the STA and an adjacent strip of galea to the pial surface, while with EMS a temporal muscle flap is applied directly to the pial surface (4,44). Both of these procedures improve MCA territory perfusion. However, they do not significantly augment perfusion when the anterior or posterior cerebral arteries are involved, in which case omental or muscle transplantation may be necessary (4,50).

With EMS and EDAS, a successful postoperative outcome depends on collateral formation. This requires neovascularization from the extracranial soft tissue to the ischemic brain

over the 3- to 6-month postoperative period. A comparison of collateral development after indirect revascularization in children and adults found that the group of patients over the age of 30 years had poor collateral development (51). The investigators speculated that there might be an age-associated decline in production of certain angiogenic factors (51). A recent study noted that elevation of bFGF in MMD seems to be specific and clinically may be a useful indicator to predict the efficacy of indirect revascularization after surgery (43). In a small study, patients with poor end results of indirect revascularization procedures had significantly lower levels of bFGF in the CSF; this led the authors to speculate that good neovascularization could be predicted in patients with disturbed cerebral vascular reserve and high-level bFGF (43).

Prognosis

Despite medical and/or surgical treatment, the prognosis is generally considered worse in adults than in children, with a higher mortality attributed to more frequent hemorrhagic presentations (4). In younger patients, vessel occlusion tends to be progressive, leading to repetitive ischemic attacks and often worsening neurologic function in surgically untreated patients (52). The long-term follow-up comparing medical to surgical management of Japanese patients presenting with ischemia has shown a trend toward less future ischemic attacks after direct revascularization (11). There was also a trend toward less cognitive decline and improved quality of life after surgical intervention in pediatric patients with recurring symptoms (53). In the US, a 5-year follow-up of 35 patients demonstrated no statistically significant difference overall in ischemic infarction incidence between medical or surgical management despite different presentations (6). However, there was a difference in timing of ischemic infarction risk, with surgical patients having a higher ischemic infarction incidence in the first year postoperatively but a subsequent steady decline in risk thereafter (6). Another US study of 20 patients also found no statistically significant difference in recurrence of ischemic events or functional outcome between medical and surgical treatment (13). The divergent results may reflect differences in disease severity due to patient selection processes.

The effectiveness of revascularization procedures for decreasing future re-bleeding remains controversial. A follow-up study of 36 medically treated patients who presented with hemorrhagic disease showed re-bleeding to be an important factor in poor neurologic outcome and increased risk of death (54). This study also found that patients presenting at an older age (between 46 to 55 years old) had a higher likelihood of having a re-bleeding episode, and among those who re-bled, an increased frequency of further re-bleeding episodes (54). One small study of hemorrhagic presentation reported decreased re-bleeding and decreased hemodynamic stress on collaterals after combination STA-MCA anastomosis with EDAMS (46). In a retrospective review of 42 Japanese patients who presented with hemorrhage, one-third had at least another episode of bleeding (55). Often, the re-bleeding occurred in a different hemisphere than the first, from other

weak points in the diffuse collateral network. This was also true in the 4 patients who had undergone indirect revascularization. As revascularization procedures generally target a specific vascular distribution, they may not necessarily decrease risk of re-bleed from other areas of the brain (55). A prospective, randomized trial is reportedly underway in Japan for patients who have intracranial bleeding to study the incidence and prognosis of recurrent bleeding attacks after direct bypass treatment with risk factor modification in MMD compared with medical management alone (56).

MMD and Pregnancy—Maternal Outcomes

Pregnant women with MMD either have known histories of MMD before pregnancy, are diagnosed during pregnancy, or are diagnosed postpartum (57). Komiyama reviewed the obstetric complications in 30 cases of pregnant patients with a history of previously diagnosed MMD, of which 17 had prior ischemic disease. Twenty-five of 30 patients delivered via Cesarean delivery (C-section). Only 1 patient with a history of nonsurgically managed, ischemic MMD developed hemorrhagic complications at 30 weeks, leading to a healthy infant, but akinetic mutism in the mother (57). Twenty-three patients diagnosed with MMD during pregnancy, delivery, or postpartum were studied and most (16 of 23) presented with intracranial hemorrhage. Two patients underwent therapeutic abortion; 14 patients delivered by C-section, and 4 patients had vaginal delivery. There were 2 newborn deaths, 3 maternal deaths, and 6 mothers had poor neurologic recoveries; 2 developed akinetic mutism. Overall C-section is the preferred method of delivery, as hypertension and hyperventilation could be avoided. Vaginal delivery is not contraindicated as long as it is not prolonged. C-section is generally recommended over vaginal delivery in cases of maternal instability (such as intracranial hemorrhage), fetal distress, or maternal hypertension that is difficult to control (58). When C-section is performed, every effort should be made to keep the patient normothermic, normotensive, and normocapnic during anesthesia (59). Patients with known MMD who are of childbearing age should be educated on the increased morbidity and mortality of pregnancy and require close follow-up throughout gestation (58).

Discussion

The case presented herein represents the typical diagnostic and therapeutic dilemmas encountered in subjects where MMD is part of the differential diagnosis. The postpartum presentation of this patient complicated the picture. The findings in this patient were felt to be suspicious for MMD, but not diagnostic, due to the absence of the classic changes of extensive fine collaterals with the appearance of a “puff of smoke.” Figure 6 shows a classic example of the abnormal collateral network of “moyamoya” vessels in a different case. This condition should be suspected in young women who present with multifocal ischemic infarctions or intracranial hemorrhage. It is more frequently seen in women of Japanese and Korean descent, but has been reported in all races and

ethnicities, as well as in men. The exact etiology remains unclear, but a variety of causes have been postulated. The role of autoantibodies and growth factors related to endothelial cell dysfunction may prove to be a promising area of future investigations. The CNS events are usually of acute onset and occur without background systemic disease. The differential diagnosis includes primary CNS vasculitis, benign angiopathy of the CNS, hypercoagulable states, lymphoproliferative disorders, infection, and rheumatologic diseases presenting with CNS abnormalities. In our patient, benign angiopathy of the postpartum state secondary to vasospasm was initially suspected. The characteristic changes on cerebral angiography and biopsy led to a diagnosis of MMD. The identification of the underlying disease process is important as corticosteroids and cytotoxic therapy are of limited value in this entity and pose a significant risk for toxicities.

Surgical revascularization appears to be the procedure of choice for MMD with an ischemic presentation. Some controversies exist regarding which direct or indirect procedure gives the best collateralization and postoperative clinical improvement. Overall, despite medical and/or surgical treatment, the prognosis of MMD is worse in adults than children, especially in patients presenting with hemorrhagic disease. Further study assessing direct bypass treatment in patients with hemorrhagic presentations is underway in Japan. Pregnant women with MMD are at risk for CNS complications during delivery, especially intracranial hemorrhage. C-section under carefully controlled conditions during anesthesia is generally the recommended method of delivery.

MMD is a relatively rare occlusive disease of the CNS vasculature. It predominantly affects younger patients compared with atherosclerotic CNS disease. Ischemic events and/or hemorrhagic events may complicate the disease course with associated morbidity and mortality. Imaging studies typically show changes similar to vasculitis. Features suggestive of MMD include bilateral involvement of the distal internal carotid artery and/or the middle cerebral arteries, and the presence of an abnormal vascular collateral network at the base of the brain or in the vicinity of the stenotic lesions. It is therefore important for rheumatologists to consider MMD as part of the differential diagnosis of suspected CNS vasculitis.

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