ADULT MOYAMOYA DISEASE AND SYNDROME: CURRENT PERSPECTIVES AND FUTURE DIRECTIONS: A SCIENTIFIC STATEMENT FROM THE AMERICAN HEART ASSOCIATION/AMERICAN STROKE ASSOCIATION

Slide set prepared by Naim Khoury MD

a member of the Stroke Council
Professional Education Committee

THE AMERICAN ACADEMY OF NEUROLOGY AFFIRMS THE VALUE OF THIS STATEMENT AS AN EDUCATIONAL TOOL FOR NEUROLOGISTS

American Heart Association

WRITING GROUP MEMBERS:
NESTOR R. GONZALEZ, MD, MS, FAHA, CHAIR
SEPIDEH AMIN-HANJANI, MD, FAHA, VICE CHAIR
OH YOUNG BANG, MD, FAHA
CHRISTOPHER COFFEY, PHD, FAHA
ROSE DU, MD, PHD
JORN FIERSTRA, MD, PHD
JUSTIN F. FRASER, MD, FAHA
SATOSHI KURODA, MD, FAHA
GRETCHEN E. TIETJEN, MD
SHADI YAGHI, MD, FAHA

ON BEHALF OF THE AMERICAN HEART ASSOCIATION NEUROVASCULAR INTERVENTION SCIENCE OF THE STROKE COUNCIL; COUNCIL ON CARDIOVASCULAR AND STROKE NURSING; COUNCIL ON CLINICAL CARDIOLOGY

INTRODUCTION

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- Adult moyamoya disease and syndrome are uncommon conditions with substantial morbidity and mortality and numerous ambiguities in their identification and therapy.

- Persistent barriers associated with the variable regional/racial forms of the disease, terminology used, diagnostic criteria, and treatment approaches have limited the ability to conduct rigorous studies to advance our understanding of the condition and develop improved forms of treatment.

- Objectives of this Scientific Statement
  - Provide:
    - a recognition of the heterogeneity of the disease
    - an updated, unified language for the disease phenotype differences
    - a review of therapeutic approaches and their rationale
    - suggested methodology for future research strategies

DEFINITIONS

DEFINITIONS

MOYAMOYA DISEASE (MMD)

- MMD is a cerebrovascular steno-occlusive condition characterized by progressive stenosis of the terminal portion of the internal carotid artery and the formation of an abnormal network of dilated, fragile perforators at the base of the brain

- The most recent definitions revision presented important new accords regarding the locations and magnitude of involvement necessary for the definition of MMD:
  - limitations of the previous definition that required bilateral involvement of the ICA are now removed
  - Proximal middle cerebral artery (MCA) or anterior cerebral artery (ACA) involvement suffices
  - Unilateral disease is acceptable to make the diagnosis (given the increasing evidence of progression to bilateral involvement in unilateral MMD)

✓ Therefore, MMD is now defined as "the steno-occlusive involvement of the arteries centered on the terminal portion of the intracranial carotid artery (ICA) in the absence of other etiologies that can produce arterial stenosis/occlusion"

MOYAMOYA SYNDROME (MMS)

- When a patient meets the diagnostic criteria for MMD but has other comorbidities that are associated with the vasculopathy, the condition is designated moyamoya syndrome (MMS)
- Japanese Guidelines exclude atherosclerosis, hyperthyroidism, and head trauma, but no universal agreement exists. They also do not include sickle cell disease, which has a very low incidence among East-Asian populations (whereas the association between sickle cell disease and MMS has been long recognized in Western countries with larger populations of African descent)

Autoimmune disease (SLE, antiphospholipid syndrome, polyarteritis nodosa, Sjögren syndrome, etc.).
Meningitis.
Brain tumors (ie meningioma, hemangioblastoma, craniopharyngioma, glioma).
Down's syndrome.
Neurofibromatosis type 1.
Head irradiation.
Sickle cell disease.

This statement will use the term moyamoya vasculopathy when ng non-specifically to either MMD or MMS.

EPIDEMIOLOGY

EPIDEMIOLOGY

JAPAN

- Much of the epidemiological data on MMD come from Asia
  - Incidence of 0.35-0.94 per 100,000 person-years
  - Prevalence rate of 3.16 per 100,000 population
  - Women-to-men ratio up to 1.9:1 and 11-12% have a family history of MMD
  - Bimodal age distribution (with peaks around age 10 and 40)
    - peak age of onset in men 10 to 14 years
    - peak age of onset in women 20 to 24 years

UNITED STATES

- Data available in a study from the National Inpatient Sample between 2002 and 2008
  - Incidence of 0.57 per 100 000 persons/years
  - Mean age of diagnosis was 32 years
  - Women-to-men ratio 2.6:1
  - Race distribution
    - 49% White
    - 24% Black
    - 11% Asian
  - Ethnic distribution: 11% Hispanic
  - Prevalence and incidence highest among those with Asian origin
  - Recent significant increase in incidence in patients of low-income, urban living, females, ages 18-44 and Asian/Pacific Islanders, thus pointing to socioeconomic disparities leading to increase in MMD diagnosis

GENETICS

GENETICS

SUSCEPTIBILITY GENES (WESTERN VS ASIAN POPULATIONS)

- Up to 12% of patients with MMD have a positive family history
- The Ring Finger Protein 213 (RNF213) is a susceptibility gene for MMD (RNF213 plays a role in cerebrovascular angiogenesis and remodeling)
  - p.R4810K is a major founder variant for East Asians, especially in Japanese and Korean
  - non-R4810K variants increase the risk of MMD in non-East Asian and certain Chinese populations
- Mutations in the genes ACTA2 and GUCY1A3 have also been implicated in the development of MMD

MODES OF INHERITANCE AND PENETRATION

- The mode of inheritance of MMD is unknown
- Data suggest that it is most likely autosomal dominant with incomplete penetrance
  - in heterozygotes of the RNF213 R4810K variant penetrance is as low as one per 150 (0.67%)
  - in homozygotes, penetrance is over 78%
- Pedigree analysis of highly aggregated Japanese families with MMD showed that
  - transmission is predominantly maternal
  - affected mothers produce more often female offspring
    - ➢ suggesting that the female predominance of the disease is an epigenetic modification such as genomic imprinting
- From a population-based aggregation study in Korea, familial incidence and risk of MMD in first-degree relatives was ranked from highest to lowest in:
  - affected twin
  - sibling
  - mother
  - father
- Familial occurrence in White individuals is rare

GENETICS

GENETIC SCREENING JUSTIFICATION AND POPULATIONS AT RISK

- Genetic testing in affected individuals may help shed light on the pathogenesis of the vasculopathy
  - may be helpful in differentiation of MMD from other causes of intracranial steno-occlusive diseases (such as arterial dissection or atherosclerosis) in East Asians
  - role remains uncertain in non-Asian populations where the incidence of MMD is low

- Due to the incomplete penetrance of the disease even in those who test positive for one of the identified genes, genetic testing may have no benefit in the general population and only limited benefit for unaffected members in familial cases with MMD

- Patients with moyamoya vasculopathy and concerns for a systemic disease should undergo genetic testing e.g.
  - GUCY1A3 for patients with achalasia
  - chromosomal analysis for features of Down syndrome
  - PTPN11 and CBL screening for Noonan syndrome-like symptoms
  - NF-1 gene testing for manifestations of neurofibromatosis type I

EFFECTS OF NON-GENETIC FACTORS

- Non-genetic factors are associated with MMD and MMS:
  - Cranial radiation for brain tumors
    - rates of moyamoya vasculopathy: 2 - 4.3%.
    - incidence up to 60%, in patients with NF-1 undergoing radiation for optic nerve gliomas
  - Autoimmune conditions
  - Infection (leptospirosis and HIV)

➢ *Recent studies have indicated that RNF213 functions as an antimicrobial protein with important purposes in the immune system. Together, these findings point out a potential association of immune-related responses as second hits to trigger moyamoya vasculopathy and open new avenues for future investigation.*

DIAGNOSIS AND EVALUATION

DIAGNOSIS AND EVALUATION

CLINICAL PRESENTATION

1. Ischemic and hemorrhagic events
   - Ischemia typically in anterior circulation (borderzone areas most commonly)
     - etiologies include hypoperfusion, thromboembolism, and combined mechanisms
   - Hemorrhage typically intracranial (ICH) or intraventricular (IVH) patterns
     - related to pseudoaneurysms of the moyamoya collaterals
     - Circle of Willis aneurysm formation and rupture presenting as subarachnoid hemorrhage (SAH)
2. Other neurological manifestations
   - Neurocognitive impairments (even in patients without a history of stroke
   - Headaches
     - most often migraine-like features, but symptoms may resemble other headache sub-types
3. Symptoms of associated diseases, in the case of MMS
   - Congenital and autoimmune syndromes (patients may present with complications from those underlying diseases)

Type of Event	Clinical Manifestations and Features
Neurologic Ischemic Events	Transient Ischemic Attacks and Strokes.
	Usually in carotid branches and watershed; can be both hypoperfusive and thromboembolic.
	Triggers due to hemodynamic demand - fever, dehydration, physical activity, hyperventilation.
Neurologic Hemorrhagic Events	Usually intracerebral and/or intraventricular (some subarachnoid).
	Due to rupture of deep neovascularization collaterals and pseudoaneurysms.
	Occasional associated aneurysms.
Other Neurologic Symptoms	Headaches: 1. Migraine (most common); 2. Tension-type; 3. Hemiplegic Migraine; 4. Cluster.
	Neurocognitive Impairment likely from chronic cerebral hypoperfusion.
	Secondary movement disorders.
Symptoms from Associated Conditions	
	Lupus Erythematosus.
	Rheumatoid Arthritis.
	Sickle Cell Disease.
	Neurofibromatosis 1.
	Down Syndrome.

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*MMD is an exclusion diagnosis and any of the possible etiologies of MMS should be excluded to confirm the diagnosis as MMD.

DIAGNOSIS AND EVALUATION

IMAGING OF MOYAMOYA VASCULOPATHY

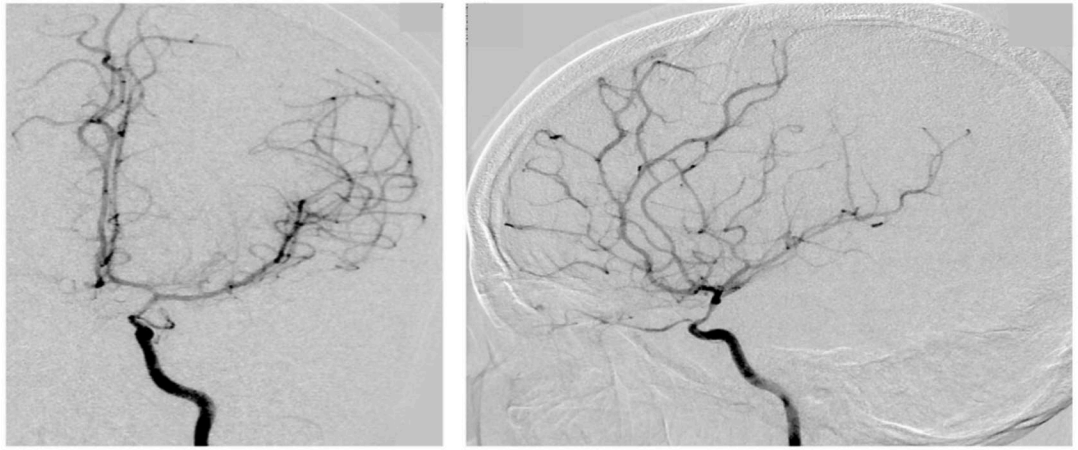
- Digital subtraction angiography (DSA) is considered the gold standard for the diagnosis of moyamoya vasculopathy
  - Suzuki's classification for DSA used to characterize the stage of the disease
    1. formation of moyamoya collateral vessels from both the intracranial and extracranial circulation
    2. progression of occlusive changes in the ICA terminus vessels progress and then decreases as the occlusive changes become pronounced and the cerebral circulation relies mainly on extracranial collaterals
- Current recommendations also include using MRI and MRA in certain cases

IMAGING DIAGNOSTIC CRITERIA (BASED ON FUJIMURA, 2022)

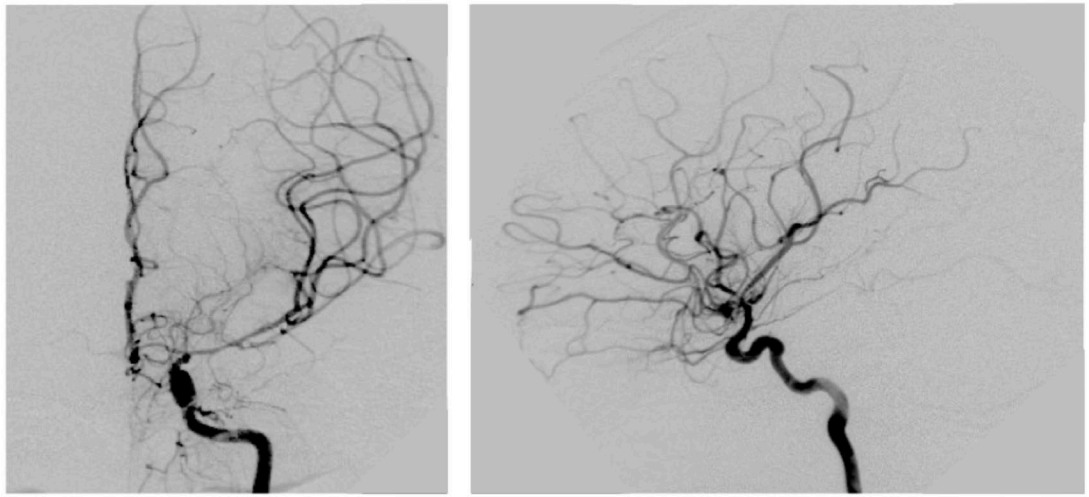
Digital Subtraction Angiography (DSA)	Magnetic Resonance Imaging/Angiography (MRI/MRA)†
Required findings	**Required findings**
1. Stenosis or occlusion in the arteries centered on the terminal portion of the intracranial internal carotid artery. **2. Moyamoya vessels (abnormal vascular networks) in the vicinity of the occlusive or stenotic lesions in the arterial phase.** **Unilateral and bilateral involvement satisfy the diagnostic criteria.**	1. Stenosis/occlusion of the terminal portion of intracranial internal carotid artery. 2. Decreased outer diameter of the terminal portion of internal carotid artery and the horizontal portion of middle cerebral artery bilaterally on heavy T2-weighted MRI. 3. Abnormal vascular networks in the basal ganglia and/or periventricular white matter on MRA. *At least 2 visible flow voids unilateral or bilateral at the basal ganglia and/or periventricular white matter are needed to be judged as representing abnormal vascular networks.
† MRI and MRA (time-of-flight; TOF) using a scanner with a static magnetic field strength of 1.5 Tesla (T) or higher.	

SUZUKI DIGITAL SUBTRACTION ANGIOGRAPHY STAGES

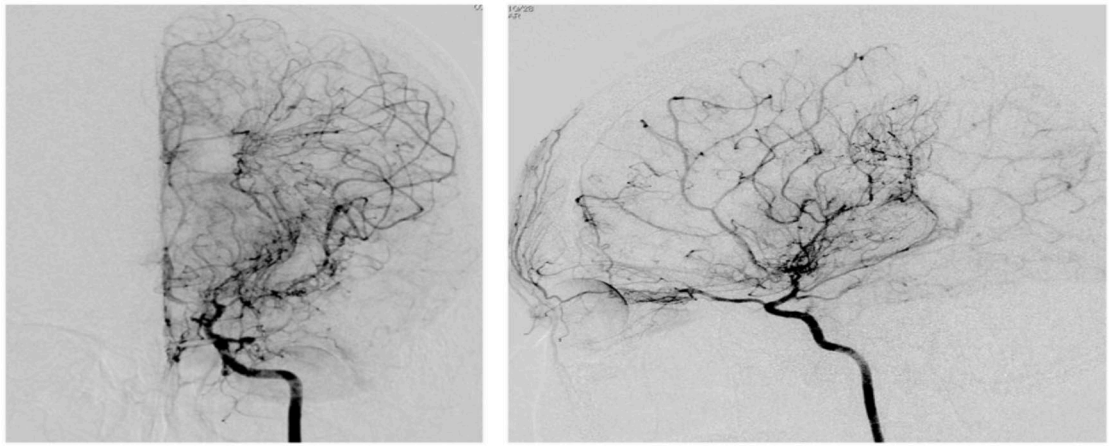
A. Stage I Narrowing of the carotid fork.



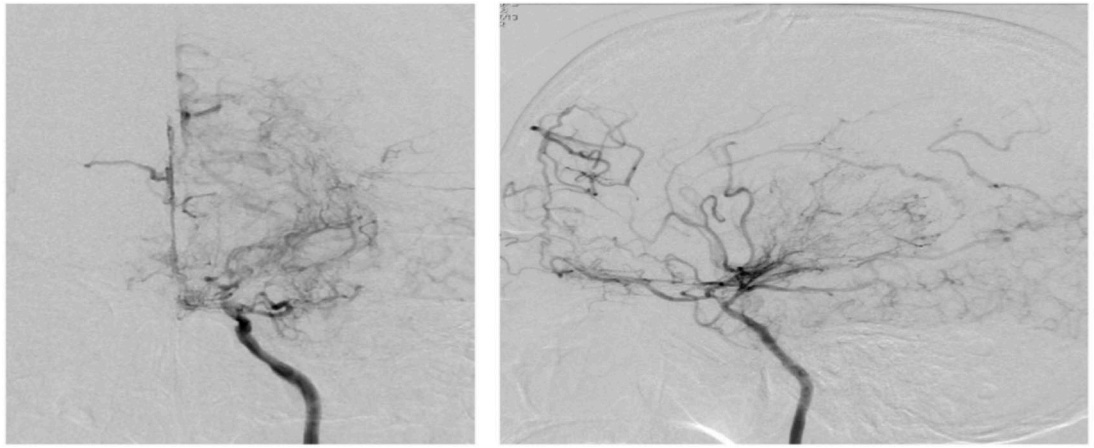
B. Stage II Initiation of the moyamoya (dilated major cerebral artery and a slight moyamoya vessel network).



C. Stage III Intensification of the moyamoya (disappearance of the middle and anterior cerebral arteries, and thick and distinct moyamoya vessels).

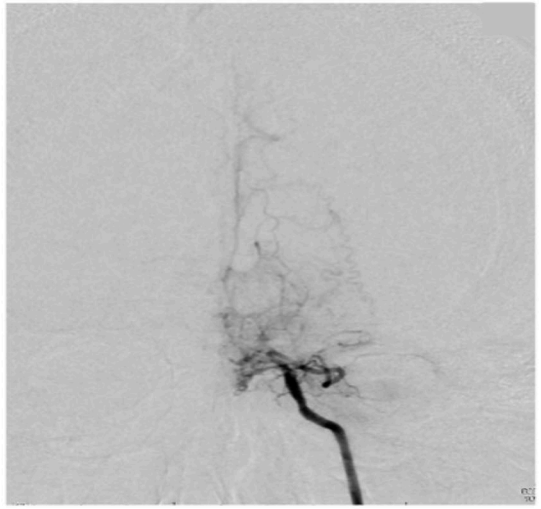


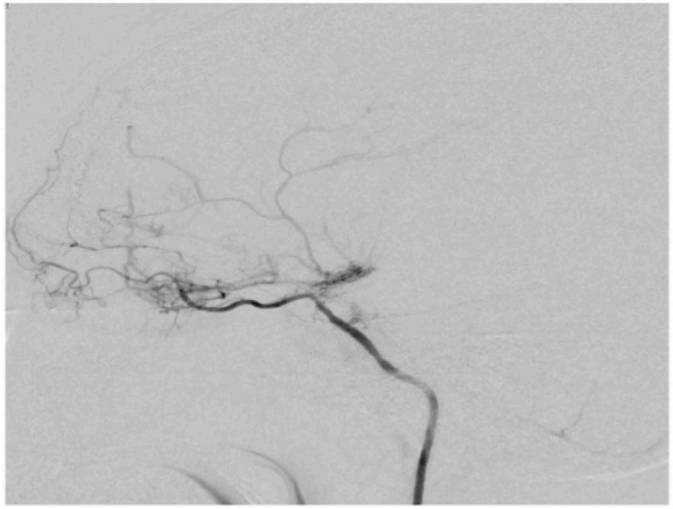
D. Stage IV Minimization of the moyamoya (disappearance of the posterior cerebral artery and narrowing of individual moyamoya vessels).



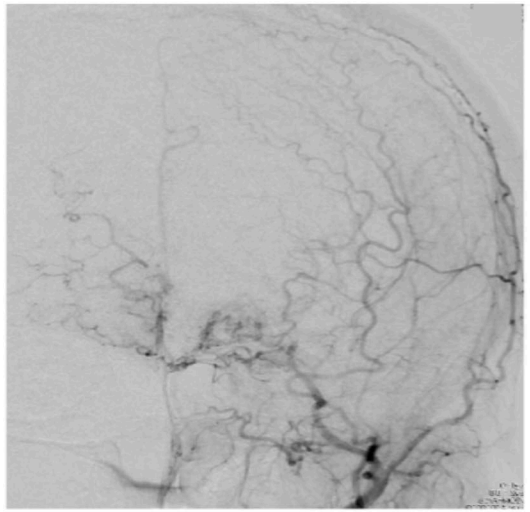
SUZUKI DIGITAL SUBTRACTION ANGIOGRAPHY STAGES

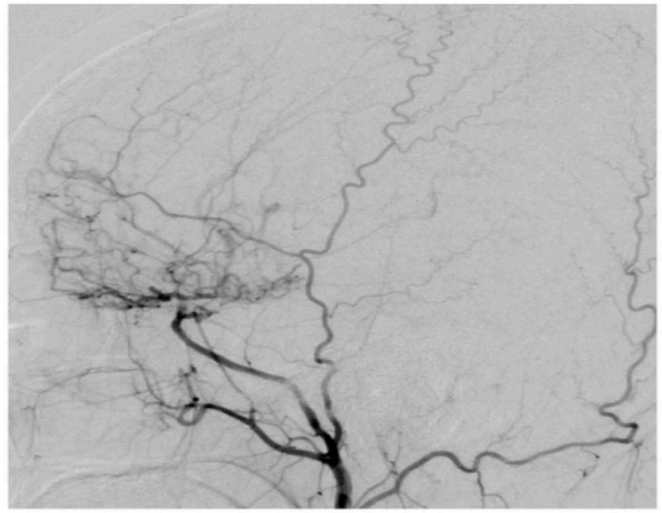
E. Stage V Reduction of the moyamoya (disappearance of all the main cerebral arteries arising from the internal carotid artery system, further minimization of the moyamoya vessels, and an increase in the collateral pathways from the external carotid artery system).





F. Stage VI Disappearance of the moyamoya (disappearance of the moyamoya vessels, with cerebral blood flow derived only from the external carotid artery and the vertebrobasilar artery systems).





DIAGNOSIS AND EVALUATION

IMAGING OF MOYAMOYA VASCULOPATHY

- MRI can help assess brain tissue injury (ie, hemorrhage, ischemia) and leptomeningeal collateral recruitment (Ivy sign)

- Some MRI sequences help refine the diagnosis
  - Three-dimensional constructive interference in steady state (3D-CISS) allows the evaluation of the outer diameter of the involved arteries, which is reduced in MMD but not in atherosclerosis
    - ➢Finding more pronounced in advanced disease when affecting vessels beyond the carotid fork (MCA and PCA)

IMAGING OF MOYAMOYA VASCULOPATHY

- Advanced PET imaging techniques measure oxygen extraction fraction (OEF), which can predict stroke in carotid occlusion patients, are not specific in MMD or MMS

- Arterial Spin Labeling (ASL) and blood oxygenation-level dependent (BOLD)-MRI can assess the extent of autoregulation exhaustion but cannot predict outcomes

NATURAL HISOTRY

NATURAL HISTORY

- Data is limited due to retrospective series
- In symptomatic patients in the United States
  - conservative (non-surgical) management is associated with 5-year risk of recurrent ischemic events
    - 65% in patients with unilateral disease
    - 82% in those with bilateral involvement
- Recurrent hemorrhage in Japanese populations: occurring in 30-60% of patients
- Korean cohort hemodynamically stable symptomatic MMD patients demonstrated
  - 5 and 10-yr stroke risks of 15% and 40% in the hemorrhagic subgroup
  - 17 and 33% in the ischemic subgroup.
- Progression of disease seen in 20% of both symptomatic and asymptomatic adult patients
  - unilateral to bilateral
  - affecting both anterior and posterior circulation
  - associated with ischemic or hemorrhagic symptoms in more than 50% of patients with progression
- Posterior circulation involvement:
  - more severe clinical manifestations at presentation
  - greater association with posterior hemorrhage
    - predictor of rebleeding
- Limited data annual risks:
  - cerebrovascular events in asymptomatic patients: about 5%
  - disease progression: about 20% over 6 years

➢ data supports the need for serial follow-up, although optimal management remains uncertain and under investigation

MEDICAL TREATMENT

MEDICAL TREATMENT

OVERVIEW OF TREATMENT

- Treatment in MMD is directed toward reducing coexisting risks of ischemic and hemorrhagic stroke
- Only one randomized clinical trial of MMD intervention has been conducted (for patients with hemorrhagic presentation)
- No RCT to guide preventive therapy for the ischemic subtype
- Despite evidence of thromboembolism, antithrombotic use is controversial due to
  - concerns for increased risk for hemorrhage
  - lack of efficacy for prevention of hypoperfusion-related ischemic events
- Survey data, albeit limited, suggest antiplatelet drugs are more frequently prescribed in Western countries than in Asia, where the hemorrhagic subtype of MMD is more common

ANTIPLATELET REGIMENS IN ISCHEMIC MMD

- In non-randomized ischemic MMD studies of antiplatelet use (compared to no antiplatelet use or to surgical revascularization)
  - mixed results regarding benefit
  - no consistent signal of an increased risk of hemorrhage
- Perioperative use of aspirin (versus no aspirin) with surgical revascularization
  - increased rate of bypass patency without elevation of bleeding risk
  - improved functional outcome
  - no benefit in prevention of recurrent ischemia demonstrated
- Addition of intravenous heparin for perioperative management increases the risk of hemorrhage without improving bypass patency
- Cilostazol (commonly prescribed for MMD):
  - Has vasodilating effects and reduced bleeding risk
  - Prospective cohort of non-surgical patients with MMD on cilostazol vs. clopidogrel
    - global recurrence of ischemic events at 5 years: 6%
    - improvement in cerebral blood flow and enhanced cognition with cilostazol compared to clopidogrel
  - A retrospective Korean cohort showed that antiplatelet therapy in MMD reduced the risk of death by 23%
    - compared to other antiplatelet regimens, survival benefit was greatest with cilostazol

SUMMARY OF ANTITHROMBOTIC AND THROMBOLYTIC USE IN ISCHEMIC MOYAMOYA DISEASE

Oral Antiplatelets	**Guidelines recommendations**				
	-AHS/ASA 2021 Secondary Prevention Guideline Recommendation: In patients with moyamoya disease and a history of ischemic stroke or TIA, the use of antiplatelet therapy, typically aspirin monotherapy, for the prevention of ischemic stroke or TIA may be reasonable (Class of Recommendation: 2b [weak], Benefit ≥ Risk; Level of evidence: C-LD [Limited Data]).[43] -2021 Japanese Guidelines for Management of Moyamoya Disease: Oral administration of antiplatelet agents may be considered as a medical treatment for ischemic MMD (Recommendation Grade: C, Level of Evidence: low).[4]				
Oral Antiplatelets + vasodilator, Cilostazol	Guidelines recommendations				
	-No specific recommendation for cilostazol use in ischemic MMD from AHS/ASA or Japanese Guidelines.[4,43]				
	Selected studies				
	Study	Study type	MMD population	Outcome measures	Results
	Seo et al, 2021. [59]	Retrospective, population-based, cohort study, comparing cilostazol vs other APD vs no APD.	Korean Health Insurance data on newly diagnosed MMD over 14 yr w 14 yr FU.	-Survival.	-Reduced mortality with: Cilostazol > other APD > no APD.
	-Chiba et al, 2018.[104] -Ando et al, 2019. [60] -Kitakami et al, 2022. [61]	Prospective observational studies comparing cilostazol vs clopidogrel.	Nonsurgical, symptomatic ischemic MMD w/o misery perfusion on PET.	-CBF on PET. -Cognition. -Recurrence of ischemic events.	-Improvement in CBF at 2 yr: cilostazol > clopidogrel.[104] -Improvement in cognition at 2 yr: cilostazol > clopidogrel.[60] -Overall APD (cilostazol or clopidogrel) led to low recurrence of ischemic events at 5 yrs.[61]
Intravenous Thrombolysis with rt-PA	Guidelines recommendations				
	-2021 Japanese Guidelines for Management of MMD: Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) may be considered under careful evaluation of the risk of hemorrhagic complication in the hyperacute phase of cerebral ischemia in MMD (Recommendation Grade: C, Level of Evidence: low).[4]				

Abbreviations: AHA/ASA: American Heart Association/American Stroke Association; APD: antiplatelet drug; CBF: cerebral blood flow; FU: follow up; MMD: moyamoya disease; PET: positron emission tomography; vs: versus; w: with; w/o: without; yr: years.

MEDICAL TREATMENT

MANAGEMENT OF ADDITIONAL VASCULAR RISK FACTORS

- Diabetes: an independent predictor of recurrent ischemic stroke in all patients
- Hypertension and dyslipidemia: are risk factors for cerebrovascular events in patients with initial asymptomatic MMD
- Increased body mass index and homocysteine: associated with a higher risk of MMD
- Prospective non-randomized study: atorvastatin use after surgical revascularization was shown to improve collateral circulation on post-operative DSA

MANAGEMENT OF MOYAMOYA HEADACHE

- Headache in moyamoya vasculopathy:
  - features of migraine (> 50% with aura)
  - or tension-type headache
- Uncertain pathophysiological mechanisms and optimal treatment
  - AVOID:
    - CGRP-targeted therapies
    - vasoconstriction (triptans, ergots)
    - medications that lower blood pressure (beta-blockers, calcium channel blockers)
- Postoperative improvement of headache is common following revascularization surgery
- Postsurgical worsening or new onset of headache also reported

SURGICAL TREATMENT

SURGICAL TREATMENT

SURGICAL INTERVENTIONS: THREE CATEGORIES

- Revascularization procedures can broadly be categorized as
  1. direct: creation of a direct extracranial-intracranial anastomosis, typically between the superficial temporal artery (STA) and middle cerebral artery (MCA)
  2. indirect: apposition of extracranial tissues including the STA, galea, temporalis muscle, and inverted dura, onto the brain surface to form a synangiosis
  3. combined

SURGICAL INTERVENTIONS COMPARED:

- Heterogeneity exists within these general categories
- Variety of surgical nuances and techniques have been described
- Direct bypass: immediate revascularization
  - technically demanding
  - greater periprocedural complications (e.g. cerebral hyperperfusion syndrome (CHS)
- Indirect bypass: relies on angiogenic proliferation and arteriogenic maturation over days or weeks

SURGICAL TREATMENT

SURGICAL INTERVENTIONS: DATA

- No RCTs have addressed revascularization surgery for ischemic stroke prevention in moyamoya

- The Japan Adult Moyamoya (JAM) trial (RCT)
  - surgical revascularization (bilateral direct bypass) vs medical therapy for hemorrhagic moyamoya
  - demonstrated reduction in rebleeding with surgery
    - ✓ 2.7%/year vs 7.6%/year; P=0.04

  - Prespecified subgroup analysis:
    - posterior hemorrhages (from PCA choroidal arteries) are at higher risk of rebleeding
      - obtained greater benefit with the surgical intervention

- Meta-analyses of retrospective and prospective single and multicenter case series:
  - support the benefit of surgical revascularization for symptomatic moyamoya
    - Benefit more evident in the hemorrhagic subgroup

SURGICAL INTERVENTIONS: AHA 2021 RECOMMENDATION FOR ISCHEMIC MOYAMOYA PREVENTION

➢ Surgical revascularization (both direct or indirect) can be beneficial for the prevention of ischemic stroke or TIA in moyamoya
  - Class 2a, LOE C-LD

(Ref: 2021 Guideline for the Prevention of Stroke in Patients with Stroke or TIA Kleindorfer et al))

- Optimal revascularization strategy debated; however, JAM and non-randomized data metanalyses suggest benefit from direct bypass over indirect
  - all available studies have major limitations
  - Rescue therapies have neen conducted (e.g. multiple burr holes and omental flaps conducted) when:
    - STA is hypoplastic or unavailable
    - prior bypass failed
    - ischemic territory is in the ACA or PCA territory (where bypasses are more technically challenging)

➢ For hemorrhagic patients, direct bypass is considered an appropriate intervention

SURGICAL TREATMENT

ANESTHETIC AND PERIOPERATIVE MANAGEMENT

- Most published studies have similar guidelines for anesthesia
  - ➢ Pre-admission for the administration of IV fluids overnight
  - ➢ Arterial line should be placed prior to induction of anesthesia
  - ➢ Systolic blood pressure (SBP) goal should be set at or above the preoperative baseline SBP at which the patient is asymptomatic
  - ➢ SBP greater than 180 mmHg should be avoided
  - ➢ Hypocapnia induced by hyperventilation can lead to vasoconstriction and ischemia
    - ➢ normocapnia with end-tidal carbon dioxide between 35 and 45 mm Hg should be maintained
  - ➢ Patients should be kept euvolemic to mildly hypervolemic intraoperatively to avoid hypotension and decreased cerebral perfusion pressure
    - ➢ for the same reasons, mannitol should be avoided

SURGICAL INTERVENTIONS: PERIOPERATIVE MANAGEMENT

- Ischemic events, seizures, and CHS are potential complications
- A review of 27 studies with 2225 patients showed
  - Cerebral Hyperperfusion Syndrome (CHS) incidence
    - 16.5% (range 11.3-22.3%)
    - 3.8% in pediatric and 19.9% in adults
    - similar incidence for direct vs combined procedure
  - ➢ Most common symptoms of CHS:
    - ➢ transient neurologic deficits (70.2%, range 56.3-82.7%)
    - ➢ hemorrhage (15.0%, range 5.5-26.9%)
    - ➢ seizure (5.3%, range 0.6-12.9%)
- Predictive factors for CHS:
  - older age
  - more severe pre-operative hemodynamic impairment
  - dominant hemisphere surgery
  - intraoperative factors (eg longer temporary occlusion time)
- ➢ CHS may be mitigated with strict blood pressure control typically with SBP<130, minocycline or edaravone

SURGICAL TREATMENT

ROLE OF ENDOVASCULAR MANAGEMENT

- Endovascular treatment of ischemic moyamoya with stent or angioplasty alone:
  - low rate of success (25%)
  - high complication rates (including devastating hemorrhage in 7%)
  - no evidence of improvement in natural history

➢ The underlying arterial shrinkage in MMD may be a consideration in the failure of endovascular strategies.

ROLE OF ENDOVASCULAR MANAGEMENT

- For hemorrhage associated with identifiable pseudoaneurysms of moyamoya collateral vessels
  - ➢ Endovascular management for aneurysm obliteration, typically through distal parent vessel occlusion
  - ➢ Open surgery for aneurysm obliteration has a high complication rate of 21-70%
  - ➢ Conservative treatment is associated with rebleeding in 40%.
    - revascularization surgery to promote thrombosis/regression indirectly by reducing hemodynamic stress on the collaterals also safe option
- Thrombolysis/mechanical thrombectomy in the setting of MMD-associated acute stroke:
  - systematic review of 10 case reports showed
    - successful reperfusion in 2 of 4 patients undergoing thrombectomy
    - improvement in 5 of 9 patients with reported functional outcomes

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

BARRIERS IN CURRENT KNOWLEDGE: RESEARCH NEEDS

- Need to develop unified diagnostic criteria
- Discover and validate definite markers
- Determine the precise pathophysiological processes involved
- Generate conclusive evidence to provide guidelines for treatment

BARRIERS IN CURRENT KNOWLEDGE: RESEARCH LIMITATIONS AND OBSTACLES

- Limited models for basic and translational research
- Absence of universally accepted terminology and diagnostic criteria
- Limited sample sizes
- Incognizant introduction of selection bias in the existing therapeutic comparative studies
  - by assigning patients to treatment groups based on the quality of the vessels to serve as donors or clinical baseline condition
    - this approach is often confused or misinterpreted as "real-world evidence (RWE)."
    - not all forms of analysis of real-world data (RWD) generate RWE.
- Scarcity of patient-oriented outcome measurements
- Lack of surrogate markers validation for clinical relevance
- Assumption of times of revascularization based on the designated time of follow-up but not on continuous or systematic early imaging evaluations

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

ROADMAP FOR FUTURE RESEARCH

- Moyamoya disease and syndrome should be considered rare diseases, allowing
  - Development of high-quality, sustainable, dynamic registries
  - Development of a unified language
  - Focus on Patient-Centered Outcome Measurements
  - Validation of appropriate surrogate markers of clinical significance
- Increase awareness in funding agencies

METHODOLOGICAL INNOVATIONS FOR FUTURE RESEARCH

- Improvements in the methodology of future studies in moyamoya should consider the application of innovative methods such as
  - dynamic global registries using RWD
  - registry-based randomized clinical trials
  - the use of innovative designs
- RWD refers to data related to patients' health obtained from routine clinical care
  - useful to generate hypotheses, assess feasibility, inform prior probability for Bayesian statistical models, and identify prognostic indicators
- The generation of RWE (conclusions regarding the potential benefits of an intervention derived from the analysis of RWD) requires
  - Minimization of bias and improved generalizability
  - Models of this methodology are in use for medical and pharmacological studies, including the U.S. FDA Sentinel System and the UK Clinical Practice Research Datalink (CPRD)

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

METHODOLOGICAL INNOVATIONS FOR FUTURE RESEARCH

- Clinical trial integration methods facilitate the collection of outcome and adverse events data using RWD.
  - This design requires little diagnostic variability in outcomes
  - Serves moyamoya well since stroke or standardized functional and cognitive evaluations are not affected by blinding
  - Requires the establishment of high-quality observational registries, which allow
    - studying the natural history of the condition
    - generating new hypotheses
    - identifying safety and signals of efficacy in different approaches
    - ➢ *Then a registry-based randomized clinical trial can build on the high-quality registry by leveraging clinical information already collected*

METHODOLOGICAL INNOVATIONS FOR FUTURE RESEARCH

- Until sufficient registries exist, RCTs in moyamoya must
  - maximize the data collected from relevant participants
  - in the most efficient manner possible
  - ➢ use of innovative designs involving
    - ➢ adaptive randomization, selection and ranking methods
    - ➢ sample size re-estimation
    - ➢ probabilistic Bayesian analyses

➢ The upfront costs of implementing such collaborations between clinicians and statisticians would have long-term benefits