pediatric stroke

MOYAMOYA ARTERIOPATHY IN CHILDREN: CLINICAL CHARACTERISTICS AND APPROACH TO CLINICAL EVALUATION

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INTRODUCTION

Moyamoya arteriopathy (MMA) is a well-recognized cause of stroke in children, that is present worldwide but more prevalent in Japan[1]. It is a progressive disease, characterized by recurrent hemi-sensorimotor ischemic symptoms and neurovascular imaging findings of stenosis and/or occlusion of intracranial arteries associated with compensatory collaterals at the brain base, that appear as a hazy puff of smoke, hence the name "moyamoya" in Japanese. Affected individuals can be asymptomatic or have symptoms related to affected regions. The recent literature has highlighted the heterogeneity of clinical phenotypes associated with MMA depending on the underlying cause, complexifying the clinical evaluation of these patients. This article aims to review the current diagnostic criteria, the epidemiological and clinical features and the outcome of childhood MMA while highlighting knowledge gaps regarding these aspects. The medical and surgical management, neuroimaging characteristics, pathophysiology, and genetic aspects of MMA are discussed in greater detail in other articles within this issue.

DIAGNOSIS AND CLASSIFICATION OF MOYAMOYA ARTERIOPATHY

Moyamoya Definitions

The earliest description of moyamoya arteriopathy emerged in the Japanese literature in the 1950's and was primarily based on neurovascular imaging findings that described a hemangiomatous malformation, stenosis or occlusion of the bilateral intracranial internal carotid arteries at the base of brain[2-4]. In 1969, Suzuki and Takaku defined moyamoya disease (MMD) as an independent disease entity and added more radiologic description by adding associated visualization of "abnormal net like vessels" or collateral vessels[5]. Since then, the Japanese Ministry of Health Research Committee on Moyamoya Disease has developed and disseminated more refined definitions to guide MMD recognition and accurate diagnosis[6].

Currently, the Japanese Ministry of Health defines MMD as a disease of unknown etiology, characterized by "either unilateral or bilateral stenosis or occlusion in the arteries centered on the terminal portion of the intracranial internal carotid artery", along with presence of "moyamoya vessels or abnormal vascular networks in the vicinity" and lack of other associated conditions/cause that can be associated with similar radiologic presentation [6].

Based on the above description, moyamoya is categorized into two distinct well-defined types:

1. Moyamoya disease (MMD): An independent disease entity that has no obvious cause identified.
2. Moyamoya syndrome (MMS): Not an independent disease entity, seen in association with other comorbid medical conditions, that may be genetic, non-genetic, syndromic, or non-syndromic.

Although not formally defined as such by the Japanese Ministry of Health Research Committee on Moyamoya, the term *moyamoya arteriopathy*, which is widely used in the literature, typically refers to the vascular phenomenon seen in moyamoya, regardless of its underlying cause. No standardized alternative terminology has been established.

Diagnostic Criteria for Moyamoya Disease

The Japanese Ministry of Health Research Committee first established the MMD diagnostic criteria in 1978 [6]. Since then, they have revised the criteria four times (1985, 1995, 2009, 2015) to guide early and accurate diagnosis of MMD and to encompass ongoing observations from clinical and research studies[7, 8]. The diagnostic criteria have been published in both Japanese and English literature, including the latest 2015 diagnostic criteria published in the English literature in 2021[6] (7). The revision was aimed to capture many features: lack of an identified etiology, inclusion of more specific description of location, severity and nature of intracranial arterial abnormalities; exclusion of terminology definite and probable cases; and provision of a list for MMD-like presentations seen with co-morbid medical conditions. However, a few controversies and limitations to the proposed criteria have been recognized that require clinical consideration and discussion.

Previously, cases were categorized as definite MMD (required bilateral involvement of the intracranial carotid arteries), or as probable MMD (cases with unilateral or unclear involvement of the intracranial carotid arteries). In the revised 2021 criteria (Figure 2) [6] , this was modified to include: 1) proximal segments of middle and/or anterior cerebral artery, instead of distal internal carotid artery involvement alone; 2) unilateral vascular involvement, instead of bilateral vascular involvement alone, as bilateral disease may not be present at onset; 3) separate criteria for cerebral angiography (CA) and magnetic resonance imaging (MRI) and angiography (MRA), as CA is typically not done at presentation (figure 1). In the revised classification, unilateral moyamoya is designated as probable moyamoya disease, while bilateral involvement fulfills the criteria for definite moyamoya disease.

The diagnostic criteria focus primarily on anterior circulation changes, particularly the internal carotid, anterior cerebral, and middle cerebral arteries, as these are typically involved early in the disease. Disease progression is commonly described using the Suzuki staging system[5] (see neuroimaging chapter), which outlines six angiographic stages based on the severity of arterial stenosis and the pattern of collateral vessel formation. Although not formally part of the diagnostic criteria, Suzuki staging is clinically useful for understanding disease severity and evolution. Posterior circulation involvement—especially affecting the posterior cerebral arteries—is not included in the staging system or diagnostic criteria, but it is increasingly recognized in pediatric moyamoya and tends to appear in later Suzuki stages, where it is generally considered a marker of advanced disease.

In the 2021 diagnostic criteria, moyamoya presentations in association with comorbid conditions are considered exclusionary of MMD diagnosis and instead designated as moyamoya syndrome (MMS) or quasi-moyamoya disease. The criteria also provide a list of conditions that

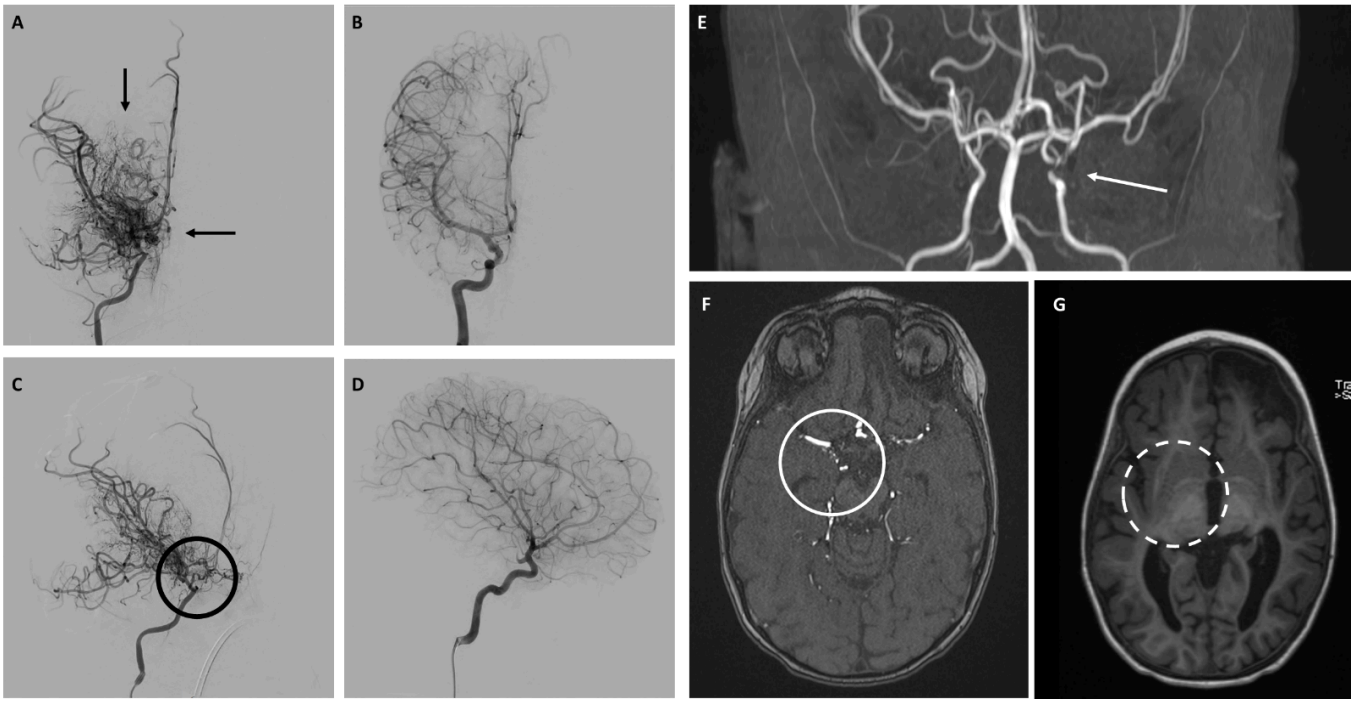


Figure 1. This figure highlights the diagnostic findings of moyamoya on conventional angiography (panel A, B, C, D) and brain MRI (E, F, G). Moyamoya is defined on angiography as bilateral stenosis or occlusion of the terminal internal carotid artery (ICA) and/or proximal anterior and/or middle cerebral arteries, along with the presence of an abnormal vascular network at the base of the brain. Lateral view shows distal ICA occlusion in a 2-year-old patient (black circle; panel A) compared to a healthy subject (C). Front view shows exuberant basal collaterals in the same patient (arrows; panel B) compared to a healthy subject (D). Moyamoya is defined on MRI as bilateral stenosis or occlusion of the distal ICA or proximal ACA/MCA on MRA, in conjunction with basal collaterals visualized on MRA or flow voids in the basal ganglia on MRI. Coronal angio-MRI view shows stenosis of the distal left ICA (white arrow; panel E), as well as collaterals (full circle white; panel F) and flow voids on T1 MRI (dashed white circle; panel G). For more information regarding neuroimaging features of moyamoya, please see the article on the subject in this issue.

qualify for MMS (autoimmune diseases, Trisomy 21, neurofibromatosis 1, history of meningitis, brain tumors, cranial radiation therapy)[6]. Unfortunately, this list does not capture all published associations and excludes conditions that are common and recognized to be associated with MMD presentation in other parts of the world. Examples include sickle cell disease, other syndromes (Alagille, Turner, Noonan and PHACES), other neurocutaneous disorders (such as hypomelanosis of Ito), congenital heart disease, coarctation of aorta, renal artery stenosis, etc. [1, 9, 10]. Additionally, no accommodations have been made to allow for the inclusion of rare and newly recognized associations.

EPIDEMIOLOGY

Moyamoya arteriopathy is identified in approximately 6–10% of children with arterial ischemic stroke (AIS) or transient ischemic attack (TIA)[1, 11, 12], making it an important cause of pediatric cerebrovascular disease. However, the true prevalence is likely underestimated, as multiple studies have reported incidental diagnoses in patients undergoing imaging for unrelated reasons, with some remaining asymptomatic for months or years [13, 14]. Additionally, in non–East Asian countries, limitations in diagnostic coding—such as the inability to distinguish moyamoya disease from moyamoya syndrome in ICD-based studies like

that of Uchino, et al. [15]—have further complicated efforts to delineate disease burden and etiology.

The disease typically follows a bimodal age distribution, with a pediatric peak between 5 and 10 years and a second peak in adults in their 40s[16-19]. A female predominance is consistently observed, with a 2:1 female-to-male ratio in most cohorts[16, 17, 20].

Geographically, East Asia reports the highest incidence, with 0.3–1 per 100,000 in Japan[16, 17], where moyamoya is the most common pediatric cerebrovascular disorder[1]. Incidence is similar in Korea and slightly lower in China[21]. Outside East Asia, reported rates are lower but vary: 0.3/100,000 in Europe [22] and 0.1/100,000 in the United States, where incidence rate ratios are elevated for Asians (4.6) and African Americans (2.2), and reduced for Hispanics (0.5) compared to White individuals[15]. Regional disparities are also evident in smaller studies: a Tunisian series found moyamoya in 18% of pediatric AIS cases [23], while in Sudan, 96% of children with sickle cell disease (SCD) and stroke who underwent vascular imaging were diagnosed with moyamoya [24].

Autoimmune comorbidities have also been associated with moyamoya. In the United States, patients with moyamoya, particularly those of White ethnicity, have significantly higher rates of autoimmune disorders compared to the general population, including type 1 diabetes mellitus (8.5% vs. 0.4%) and thyroid disease (17% vs. 8%) [25]. These findings suggest that, beyond genetic predisposition, systemic inflammatory or autoimmune mechanisms may contribute to disease susceptibility.

Genetic factors likely underpin some of the observed racial and geographic differences in incidence. Over 50% of Asian Americans with moyamoya harbor a founder mutation in the RNF213 gene, compared to 3.6–29% of non-Asian patients [26]. RNF213 is currently the best-studied susceptibility gene for moyamoya, with both common and rare variants implicated, particularly among East Asian populations.

While many pediatric cases are idiopathic, a growing number are recognized as moyamoya syndrome, occurring in association with underlying genetic or systemic disorders. Among these, sickle cell disease (SCD), Down syndrome (Trisomy 21), and neurofibromatosis type 1 (NF1) are the most well-characterized. In the largest national analysis of pediatric moyamoya admissions in the United States, Titsworth et al.[27] found that 16% of cases had SCD, 8.6% had Down syndrome, and 6.4% had NF1, underscoring their relevance within the hospitalized population.

SCD carries the highest reported prevalence. Prevalence rates vary depending on the availability of transcranial Doppler (TCD) screening and prophylactic therapy, with 20–35% reported in angiographic studies. In one Sudanese cohort, where such resources were limited, 96% of imaged children with stroke were found to have moyamoya changes [23, 24, 20]. Neurofibromatosis type 1 (NF1) is associated with a lower, though still significant, risk, with moyamoya reported in approximately 0.6% of pediatric patients, particularly in centers where neuroimaging is routinely used for surveillance. Children with Down syndrome (Trisomy 21) also demonstrate a markedly increased risk, with a prevalence estimated at 0.3–0.6% (approximately 1 in 250) [28]. While the general population prevalence may appear lower than in NF1, the greater frequency of Down syndrome in the population and its strong overrepresentation among moyamoya admissions make it a key risk group in clinical practice.

NEUROLOGICAL PRESENTATION AND SYMPTOMS

Recent studies have highlighted that the initial presentation as well as the clinical and radiological progression of MMA varies based on genotype and comorbidities[29-31].The most common clinical presentations of moyamoya in children are ischemic strokes (31-68%) and TIAs (13-40%). TIAs are often triggered by hyperventilation, which may occur during crying, physical activity, playing wind instruments, or in response to anxiety or pain. Other clinical presentations include hemorrhagic strokes (2.7%) headaches (5.7-6%), seizures (1.3-23.9%), cognitive alteration (3.3-19.3%) and movement disorders (3.6-4%)[32-38].The reported prevalence of these symptoms varies widely due to differences in study designs. Additionally, patients frequently presents with overlapping symptoms. In an Italian cohort, 26% patients reported multiple symptoms[39].

The progressive stenosis of cerebral arteries in moyamoya leads to chronic cerebral hypoperfusion and loss of cerebrovascular reserve. Consequently, in children, ischemic events can be triggered by factors such as hyperventilation, crying, exercise, coughing, the Valsalva maneuver, or fever [40]. The most common symptoms associated with moyamoya include hemiparesis and speech impairment, both of which reflect the frequent involvement of the anterior and middle cerebral vascular territories in ischemic events [1]. Posterior circulation involvement often represents disease progression from the anterior territories, and it occurs in up to 30% of pediatric cases[41, 42]. A subset of patients may present with posterior symptoms early in the disease course. Although often asymptomatic, posterior involvement may present with symptoms such as visual disturbances, dizziness, or ataxia, depending on the extent of ischemia. In addition to motor and speech symptoms, children with moyamoya may experience seizures, often associated with ischemic or hemorrhagic brain injury. Seizures are relatively common, with up to 40% of affected children eventually developing epilepsy [43, 44].Headaches, which often resemble migraines, are another frequent symptom, although other headache types have also been reported[45]. Movement disorders, though less common, can be present, particularly chorea, which is most frequently observed[46]. Dystonia and paroxysmal movement disorders have also been reported but are rarer.

Cognitive impairment is a common feature of pediatric moyamoya, with deficits often accumulating over time. Even in the absence of overt strokes, children may show impairments in working memory, verbal comprehension, perceptual reasoning, and processing speed, indicating that abnormal cerebral hemodynamics may impair brain function early on[47, 48]. Cognitive outcomes tend to be worse in children who do not undergo revascularization surgery[49], while post-surgical improvements in memory, attention, and impulsivity highlight the surgery's positive effect on frontal lobe function[50, 51].

The wider availability of MRI and the emergence of disease-specific screening have increased the incidence of asymptomatic cases of MMA encountered. It is not clear if these asymptomatic cases are detected in their pre-clinical period or if they constitute a milder form of the arteriopathy[13].

NON-NEUROLOGICAL FEATURES

As mentioned previously, MMA primarily affects the intracranial arteries. However, there can also be extra-cranial involvement, although this is less common. Extra-cranial involvement may include arteries of the neck (carotid, vertebral), chest (pulmonary, coronary) and/or abdomen (renal, superior mesenteric, celiac). Screening studies in young adults with MMD showed that approximately 17% had significant stenosis in the coronary, superior mesenteric, celiac, renal and internal iliac arteries [52]. A higher prevalence of systemic vasculopathy has been seen in the presence of MMD due to RNF213

variant[52], which has been proposed to be used as an effective biomarker for systemic screening [53]. Of these, renal artery involvement has been the most frequently reported. In reports including both pediatric and adult patients with MMD the prevalence of renal artery involvement is 5-8%, with only 2-5% having clinical manifestation of hypertension[54-56]. While in adults this finding may be confounded by the presence of atherosclerotic disease causing renal artery stenosis, a pediatric limited cohort showed that advanced stages of MMD were associated with renal artery stenosis[56]. Findings of renal artery stenosis have been reported in patients with previously healthy renal arteries suggesting that these changes can occur de novo and without any clear genetic predisposition[57]. Recent evidence suggests that the histopathological changes observed in extracranial vascular involvement of moyamoya differs from intracranial findings. Whereas intracranial moyamoya vasculopathy is characterized by fibrocellular intimal thickening, attenuation of the media, and disruption of the internal elastic lamina, extracranial lesions often lack these classical features and instead exhibit distinct patterns such as preserved media and elastic lamina, suggesting a potentially different pathophysiological mechanism [58]. Further studies are required to understand this difference. Clinical signs and symptoms may vary depending on the extracranial arteries involved but may include headache, vertigo/dizziness, systemic hypertension, and pulmonary hypertension.

Additionally, hypertension has been reported in MMD without an associated renal artery stenosis in up to 29% in a cohort of pediatric MMD patients[59]. Age at diagnosis, evidence of posterior circulation involvement, BMI and years since surgery were found to correlate with evidence of systemic hypertension. However, the pathophysiology of hypertension in childhood MMD is not fully understood.

GENOTYPE-PHENOTYPE CORRELATION

Susceptibility gene discovery, disease awareness and improved phenotyping allowed refinement of clinical phenotypes associated with MMA. Characterized entities and their features are described below.

Neurofibromatosis Type 1-related Moyamoya

Neurofibromatosis Type 1 (NF1) is the most common inherited neurocutaneous disorder associated with moyamoya syndrome (MMS).[60] In comparison to other causes of MMS, MMS-NF1 is considered to have a milder phenotype and is often asymptomatic at presentation with arteriopathy as an incidental finding.[29] Low stroke burden was identified in a study with predominately unilateral disease.[30] A retrospective single centre study of 19 cases combined with a literature meta-analysis reported stroke or TIA was the presentation in at least 32% of paediatric MMS-NF1 cases.[61] Cerebrovascular events were more common in children under the age of 4 years than in older children and were associated with bilateral anterior circulation involvement.[61] This subset of younger, more aggressive MMS-NF1 phenotype requires further investigation.

Trisomy 21-Related Moyamoya

A nationwide study reported that the T21 population has a 26-fold greater prevalence of coexisting moyamoya compared with the prevalence of T21 among live births.[34] A retrospective single centre study reported five cases of MMS-T21 which presented with stroke and bilateral MMS.[29] In these 5 cases, the five year recurrence rate was 80%, which was the highest recurrence rate when compared to sickle cell disease (SCD) and NF1. A single surgical

centre noted MMS-T21 cases tended to be older than the average pediatric moyamoya patient with an average age at diagnosis of 8.4 vs 6.5 years.[62]

Sickle Cell Disease-Related Moyamoya

Sickle cell disease (SCD) is the most common cause of paediatric stroke world-wide. Within this group, a subset develops MMS-SCD which increases the risk of recurrent stroke up to 50% at 5 years.[29, 63] The majority of MMS-SCD affect the middle cerebral and anterior cerebral arteries, with a potential 2.4-fold increased risk of recurrent stroke associated with moyamoya collaterals.[64] Secondary prevention of stroke in SCD includes chronic exchange transfusion, but this does not stabilise the progression of MMS. There are reports of successful reversal of vasculopathy with curative hematopoietic stem cell transplant.[65]

RNF213-related Moyamoya

Genome wide association studies in East Asians with moyamoya disease identified an association with RNF213, particularly with the founder variant p.R4810K (c.14576G>A), not found in Caucasians.[66, 67] RNF213 encodes an E3 ubiquitin ligase thought to regulate angiogenesis and endothelial stability, although its precise function remains under investigation. Homozygous variants of p.R4810K have been reported to have early onset bilateral disease, posterior circulation predominance, symptoms of stroke or TIA and rapid progression but is also seen in unaffected individuals.[68, 69] In a European paediatric cohort study, other RNF213 likely pathogenic variants were associated with a younger age at presentation, predominance of posterior circulation arteriopathy and multi-territorial strokes.[70] The variability in the clinical phenotype has led to an interest in endothelial gene variants and epi-genetic factors that may modulate RNF213 expression, including pro-inflammatory cytokines.[71, 72] Immune biomarkers of MMA in CSF, serum and urine are relevant for developing targeted surveillance programs and therapies.[73-75]

Although less extensively characterized, monogenic forms of moyamoya involving genes such as ANO1, BRCC3, and GUCY1A3 appear to define distinct clinical phenotypes. GUCY1A3-related moyamoya is associated with early-onset hypertension and achalasia[76], while BRCC3 mutations lead to an X-linked moyamoya syndrome with short stature and delayed puberty in males[77]. ANO1 variants have been reported in syndromic moyamoya with systemic vascular anomalies, potentially linked to smooth muscle dysfunction[78].

These emerging insights highlight a growing recognition that the traditional distinction between moyamoya disease (MMD) and moyamoya syndrome (MMS) may no longer adequately capture the biological diversity of the condition. Increasingly, a genotype- and mechanism-driven classification is being favored—one that better reflects the underlying pathophysiology and heterogeneity in clinical course. As research continues to uncover genetic and immunologic contributors, moyamoya arteriopathy is being reframed as a spectrum of mechanistically distinct vasculopathies, each with unique implications for surveillance and treatment strategies[58, 79, 80].

CLINICAL EVOLUTION AND PROGNOSIS

The clinical evolution of moyamoya is complex, marked by significant phenotypic variability. It is characterized by new symptomatic strokes, silent infarcts detected during follow-up imaging, transient ischemic attacks, and cognitive decline. Symptoms may or may not coincide with radiographic progression of the angiopathy, which can be ongoing and remains difficult to predict. While early evidence suggests a higher recurrence of ischemic events

in patients of Asian ancestry compared to those of European ancestry[30], the role of ethnic and genetic factors in recurrence rates has not been thoroughly studied. Furthermore, no effective methods or biomarkers exist to accurately assess stroke risk or the progression of arteriopathy.[81].

The overall recurrence rate for ischemic events has been reported to range between 20% and 39%.[12, 29, 39, 82, 83]. This recurrence, along with the risk of disease progression, appears inversely correlated with age, with younger children facing a higher risk of both progression and stroke recurrence. [83, 84]. Even in asymptomatic cases, moyamoya is not a benign condition. Up to 46% of children show progression of arteriopathy on vascular imaging within five years, with 45% of these children becoming symptomatic during that time, and 12-25% suffering from a stroke.[13, 30]

Although surgical revascularization improves outcomes, it does not fully halt disease progression. The risk of late ischemic and hemorrhagic events following surgery in pediatric moyamoya ranges from 1.7% to 6.3% and 1.7% to 12%, respectively, with an overall stroke incidence of 0.10-0.85% per year[85-90].Funaki et al[85] reported a hemorrhagic stroke rate of 0.3% per year in a cohort followed over 30 years, a lower rate than the estimated 2.5-3% rate of de novo hemorrhages in adult moyamoya patients.[91, 92]. This suggests that revascularization surgery offers long-term protection against hemorrhages in children who undergo the procedure. However, the risk of hemorrhage increases with time[85] remains the leading cause of mortality in adulthood, with intracranial hemorrhages accounting for up to 53% of deaths in adults who initially presented with juvenile moyamoya [49, 85-88].

APPROACH TO CLINICAL CHARACTERIZATION

Clinical characterization of moyamoya arteriopathy (MMA) requires a structured and comprehensive approach that integrates presenting features, risk stratification, imaging, and longitudinal monitoring. Given the heterogeneity of clinical presentation and underlying etiologies, especially in pediatric patients, early recognition and systematic evaluation are essential for timely diagnosis and individualized care.

Although several professional organizations have issued disease-specific guidelines (Table 1), there is currently no unified or consensus-based framework for the clinical evaluation of children with moyamoya across comorbid conditions. Screening recommendations are most clearly outlined for patients with sickle cell disease, while in conditions like neurofibromatosis type 1 (NF1) and Trisomy 21, the guidance is less explicit and largely based on expert opinion or institutional practice.

Clinical and Screening Recommendations for Moyamoya Disease and Syndrome

TABLE 1

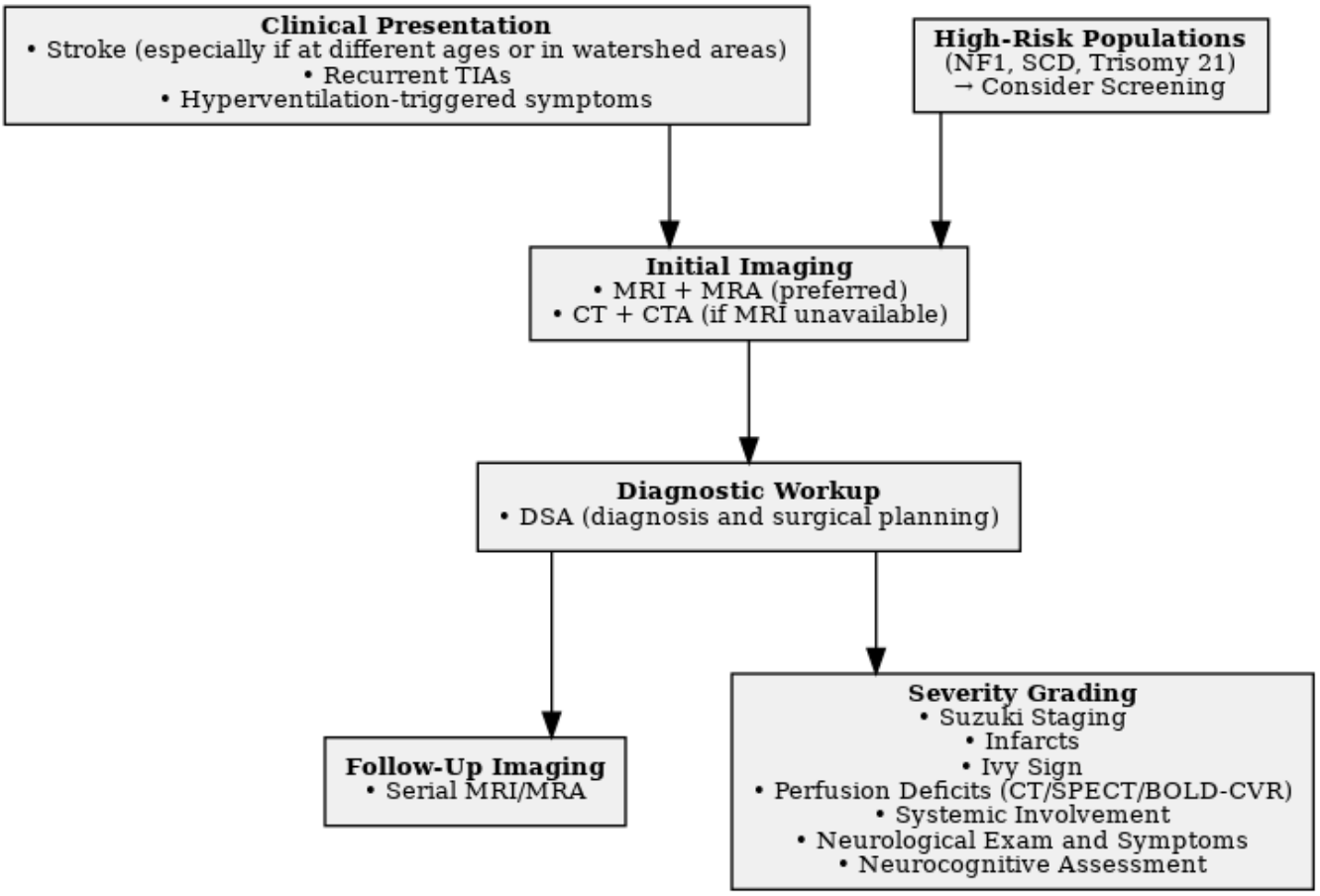
Guideline	Organization	Target Population	Clinical and Screening Recommendations
AHA/ASA Scientific Statement (2021)[93]	AHA/ASA	Adults with Moyamoya Disease	- Antiplatelet therapy may be reasonable for preventing ischemic events. - Cilostazol may improve outcomes but requires further validation.

TABLE 1			
ASH Guidelines for Sickle Cell Disease (2020)[94]	ASH	Children and adults with SCD and Moyamoya Syndrome	- Revascularization surgery suggested in addition to transfusion for patients with stroke/TIA.
ESO Moyamoya Guidelines (2023)[95]	ESO	Patients with Moyamoya Angiopathy	- Hemodynamic assessment recommended in diagnostic workup. - Revascularization surgery suggested in symptomatic patients.
Japanese Guidelines for Moyamoya Disease (2021)[37]	Japan Stroke Society	Patients with Moyamoya Disease	- Antiplatelet therapy may be considered for ischemic cases. - Revascularization recommended for symptomatic patients.
AAP Health Supervision for Children with Down Syndrome (2022)[96]	AAP	Children with Down Syndrome	- No specific moyamoya screening recommendations. - High index of suspicion in symptomatic patients.
Neurofibromatosis Type 1 French Guidelines (Expert opinions)[97]	NF France Network	Patients with NF1	- No universal recommendation for moyamoya screening. - Imaging considered in cases with neurologic symptoms or optic glioma.

This table summarizes current recommendations regarding the clinical management and screening of moyamoya arteriopathy (MMA) in both isolated and syndromic contexts, based on national and international guidelines. Abbreviations: AHA – American Heart Association, ASA – American Stroke Association, ASH – American Society of Hematology, ESO – European Stroke Organisation, AAP – American Academy of Pediatrics, SCD – Sickle Cell Disease, TIA – Transient Ischemic Attack, NF1 – Neurofibromatosis Type 1

To address this gap, we propose a practical framework that supports systematic evaluation and clinical decision-making in both syndromic and non-syndromic moyamoya. Figure 2 presents a diagnostic workflow, beginning with symptom recognition and high-risk populations, proceeding through imaging and angiographic confirmation, and leading into longitudinal monitoring. This is complemented by Table 2, which provides a structured framework for clinical phenotyping and severity grading. The table outlines key domains—including history, physical examination, laboratory investigations, imaging, and neurocognitive evaluation—and links them to actionable or prognostic findings. The goal is to support reproducible clinical

Figure 2. Clinical Approach to Pediatric Moyamoya Arteriopathy Diagnosis. This flowchart outlines the recommended diagnostic pathway for evaluating moyamoya arteriopathy in children. Moyamoya should be suspected in the presence of stroke (particularly in watershed territories or at multiple ages), transient ischemic attacks (TIAs), and hyperventilation-triggered events. High-risk populations—such as those with neurofibromatosis type 1 (NF1), sickle cell disease (SCD), or Trisomy 21—should be considered for screening even when asymptomatic. MRI/MRA is the preferred initial imaging modality, with CT/CTA as an alternative, although collateral assessment is limited with this modality. Digital subtraction angiography (DSA) remains the gold standard for confirmation and surgical planning, However, it may not be necessary in cases where the diagnosis is unequivocal on non-invasive imaging and surgery is not being considered. Follow-up imaging typically involves serial MRI/MRA every 6 to 12 months, tailored to the



patient's clinical status. Severity grading integrates multiple factors: Suzuki staging, infarct burden, ivy sign, perfusion deficits (via CT perfusion, SPECT, or BOLD-CVR), systemic vascular involvement, neurological findings, and neurocognitive status.

assessment and harmonize practice across disciplines and institutions.

Together, these tools are designed to improve the early recognition of MMA, particularly in complex or syndromic cases, and to standardize communication across clinical, surgical, and research settings.

Clinical Phenotyping in Pediatric Moyamoya: Structured Framework

TABLE 2

Aim	Evaluation Methods	Key Findings & Clinical Relevance
A. Identification of Causes, Risk Factors, and Comorbidities	Medical History: – Ethnic background – Family history (stroke, moyamoya) – Prior cranial/spinal radiation – CNS infection history – Known genetic syndromes (e.g., NF1, T21) – Autoimmune disease – Cognitive or learning concerns – Vaccination history	– East Asian ancestry → Associated with RNF213 variant – Family history → Suggests familial form (Actionable: consider sibling screening) – History of radiation/infection → Known acquired causes – NF1, T21 → Well-established syndromic risk factors (Actionable: prompts vascular imaging) – Known autoimmune disease (e.g., SLE, AAV) → May present as moyamoya syndrome – Learning or cognitive issues → May reflect chronic ischemia (Actionable: refer for neuropsych evaluation and school adaptation)
	Physical Examination: – Blood pressure – Cardiovascular and neurological exams – Skin/dysmorphic features – Fundoscopy – Beighton score	– Hypertension → Suggests renovascular or systemic vasculopathy – Neurological signs (e.g., hemiparesis, dystonia) → Common presenting symptoms – Café-au-lait spots → Suggest NF1 (Actionable: confirm diagnosis and screen vasculature) – Hyperlaxity → May suggest a connective tissue disorder – Retinal changes → Indicator of systemic vascular burden
	Laboratory Investigations: Genetic testing: • RNF213 sequencing in all pediatric MMA cases • Vasculopathy gene panel or WES/WGS depending on institutional protocols Immunologic/Inflammatory workup: • ESR, CRP, ferritin, LDH • ANA, ENA, dsDNA, ANCA • C3, C4 • Antiphospholipid antibodies • Immunoglobulins A, M, G, E • Thyroid function and antibodies • Urinalysis • Optional: CSF (WBC, RBC, protein, glucose, IFN-α) Thrombophilia/Metabolic workup: • INR, PT, PTT, fibrinogen • Homocysteine, lipoprotein(a)	– RNF213 mutation (e.g., p.R4810K) → Core susceptibility gene – Other selected monogenic causes: • GUCY1A3 – AR moyamoya with achalasia and hypertension • SAMHD1 – AGS-associated vasculopathy (interferonopathy) • BRCC3 – X-linked moyamoya with short stature and hypogonadism • ANO1 – Moyamoya with early posterior involvement and aneurysms formation – Positive ANA, dsDNA, ANCA → Suggest autoimmune vasculitis (e.g., SLE, AAV) – Low C3/C4, elevated CRP/ESR → Reflects systemic inflammation – Positive APLA → Antiphospholipid syndrome – Elevated IgE → May suggest hyper-IgE syndrome (e.g., DOCK8, STAT3) – Hyperhomocysteinemia, protein C/S/ATIII

TABLE 2

Aim	Evaluation Methods	Key Findings & Clinical Relevance
	• Protein C, S, antithrombin • Factor V Leiden, Prothrombin G20210A Renal panel (urea, creatinine, electrolytes, eGFR)	deficiency → Thrombophilia – Renal dysfunction → Suggests systemic vasculopathy
B. Characterization of Disease Severity and Extent	Neuroimaging*: – MRI and MRA of the brain – Digital subtraction angiography (DSA) – Perfusion imaging: CT perfusion, SPECT, BOLD-CVR MRI	– ICA/ACA/MCA stenosis → Diagnostic hallmark – Suzuki staging → Defines disease progression – Posterior circulation involvement → More frequent in RNF213-positive and advanced disease – Silent infarcts or chronic hypoperfusion → May warrant urgent revascularization – Ivy sign → Associated with increased ischemic injury risk – Impaired BOLD-CVR → Indicates reduced cerebrovascular reserve
	Systemic Imaging: – ECG, echocardiography – Ophthalmologic exam – CT angiography or Doppler (renal, aortic, mesenteric, peripheral vessels)	– Cardiomyopathy or congenital heart disease → Often seen in syndromic moyamoya – Retinal changes → May reflect systemic vasculopathy – Renal, mesenteric, or aortic artery stenosis → Associated with RNF213, BRCC3, and ANO1 variants
	Neurocognitive Evaluation: – Formal neuropsychological testing	– Executive dysfunction, attention deficits, processing delays → May occur even without overt stroke – Learning difficulties → Suggest ischemic burden (Actionable: refer for neuropsychology and academic accommodations)

This table outlines a systematic approach to identifying underlying causes, risk factors, and disease severity in children with moyamoya. It integrates history, examination, and targeted investigations to support diagnostic clarification and personalized care. Investigations are further discussed in the Clinical Management, Genetics, and Neuroimaging chapters. Abbreviations:AAV – ANCA-associated vasculitis; ACA – anterior cerebral artery; ACTH – antithrombin III; AGS – Aicardi-Goutières syndrome; ANA – antinuclear antibodies; ANCA – antineutrophil cytoplasmic antibodies; ANO1 – anoctamin 1; APLA – antiphospholipid antibodies; BRCC3 – BRCA1/BRCA2-containing complex subunit 3; CBC – complete blood count; CRP – C-reactive protein; CSF – cerebrospinal fluid; CT – computed tomography; DSA – digital subtraction angiography; dsDNA – double-stranded DNA; ECG – electrocardiogram; eGFR – estimated glomerular filtration rate; ENA – extractable nuclear antigen; ESR – erythrocyte sedimentation rate; GUCY1A3 – guanylate cyclase 1, soluble, alpha 3; IgA/IgM/IgG/IgE – immunoglobulin A/M/G/E; LDH – lactate dehydrogenase; MCA – middle cerebral artery; MRI – magnetic resonance imaging; MRA – magnetic resonance angiography; NF1 – neurofibromatosis type 1; PT/PTT/INR – prothrombin time / partial thromboplastin time / international normalized ratio; RNF213 – ring finger protein 213; SAMHD1 – SAM domain and HD domain-containing protein 1; SLE – systemic lupus erythematosus; SPECT – single-photon emission computed tomography; T21 – Trisomy 21 (Down syndrome); WBC/RBC – white blood cells / red blood cells; WES – whole-exome sequencing; WGS – whole-genome sequencing. *Investigations are further discussed in the clinical management, genetic and neuroimaging chapter

CONCLUSION

Moyamoya arteriopathy is associated with significant morbidity in the pediatric population and represents a clinically and biologically heterogeneous condition. Its diverse causes and associations impact not only initial presentation but also long-term evolution and outcomes. This variability underscores the need for a comprehensive and systematic clinical assessment to identify underlying risk factors, syndromic associations, and comorbidities that may influence prognosis and management.

Despite growing understanding of genetic and radiographic contributors, several major challenges remain. There are currently no validated clinical or biological biomarkers to stratify disease severity or predict progression, especially in asymptomatic or minimally symptomatic children. It remains difficult to determine which patients will benefit most from surgical revascularization and, crucially, to identify the optimal timing for intervention. These limitations hinder risk-based follow-up strategies and personalized care pathways. Advancing the field will require large-scale, prospective efforts to link clinical phenotypes with molecular and radiological profiles—toward more precise and predictive models of disease.

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