

Pathophysiology and genetic factors in moyamoya disease

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Moyamoya disease is an uncommon cerebrovascular condition characterized by progressive stenosis of the bilateral internal carotid arteries with compensatory formation of an abnormal network of perforating blood vessels providing collateral circulation.

The etiology and pathogenesis of moyamoya disease remain unclear. Evidence from histological studies, proteomics, and endothelial progenitor cell analyses suggests new theories underlying the cause of vascular anomalies, including moyamoya disease.

Familial moyamoya disease has been noted in as many as 15% of patients, indicating an autosomal dominant inheritance pattern with incomplete penetrance. Genetic analyses in familial moyamoya disease and genome-wide association studies represent promising strategies for elucidating the pathophysiology of this condition.

In this review, the authors discuss recent studies that have investigated possible mechanisms underlying the etiology of moyamoya disease, including stem cell involvement and genetic factors. They also discuss future research directions that promise not only to offer new insights into the origin of moyamoya disease but to enhance our understanding of new vessel formation in the CNS as it relates to stroke, vascular anomalies, and tumor growth. (DOI: 10.3171.2009.1.FOCUS08302)

KEY WORDS • moyamoya disease • moyamoya syndrome • stroke •
bypass surgery • pathophysiology • genetics

In this review, we discuss recent investigations in moyamoya disease, including stem cell involvement in the pathophysiology of moyamoya disease and genetic factors underlying the etiology of moyamoya disease. We also discuss future directions, which promise not only to offer new insights into the pathogenesis of moyamoya disease but to enhance our understanding of new vessel formation in the central nervous system as it relates to stroke, vascular anomalies and tumor growth as well.

Moyamoya Disease

Epidemiology

Originally thought to affect primarily individuals of Asian descent, moyamoya disease has been increasingly reported throughout the world in all major demographic groups.^{3,16,73,75,80} A nation-wide Japanese survey of 2075 patients with moyamoya disease found an annual incidence of 0.35 and annual prevalence of 3.16 per 100,000.⁷⁵ Age at onset demonstrated a bimodal distribution with

Abbreviations used in this paper: AVM = arteriovenous malformation; bFGF = basic fibroblast growth factor; EPC = endothelial progenitor cell; HIF-1 = hypoxia-inducing factor-1; MMP = matrix metalloproteinase; SDF-1 = stromal cell-derived factor-1; SMC = smooth-muscle cell; SNP = single nucleotide polymorphism; VEGF = vascular endothelial growth factor.

the largest peak at 5 years of age (onset was < 10 years of age in 48% of patients) and a second smaller peak at 45–49 years of age.⁷⁵ However, a more recent regional analysis of 267 newly registered patients with moyamoya disease in Hokkaido, Japan, found a markedly increased annual incidence of 0.94 and annual prevalence of 10.5 per 100,000.³ Interestingly, there was a dramatic decrease in pediatric presentations, with the percentage of patients < 10 years of age at onset decreasing to 15.1% from 48% previously, and the largest peak now occurring at 45–49 years of age.³

The authors of an analysis of the western US (California and Washington) identified 298 patients with moyamoya disease (prevalence 0.086 per 100,000),⁷³ significantly lower than the 0.35 reported in the nationwide Japanese survey. However the incidence rate among Asian-Americans in California in the study was comparable at 0.28, with a greater than 4-fold increased incidence of the disease in Asian-Americans relative to Caucasian Americans.⁷³ Similarly, an analysis performed in Hawaii, where the majority of the cohort was made up of Asian and Pacific Islanders, found incidence and prevalence rates that were higher than those in the US overall.¹⁶

The existing data on racial differences in susceptibility to moyamoya disease support a role for genetic predisposition. However, given recent evidence suggesting a significant change in the detection rate of adult moy-

amoya disease in Japan,³ further studies are needed on the natural history and clinical features, especially comparing North American to Asian moyamoya disease.

Pathophysiology: Histology to Proteomics

Progressive bilateral stenosis or occlusion of the internal carotid artery with frequent involvement of the proximal anterior and middle cerebral arteries is characteristic of moyamoya disease. Histopathological studies of affected internal carotid artery segments in moyamoya disease demonstrate eccentric fibrocellular thickening of the intima, proliferated SMCs, prominently tortuous and often duplicated internal elastic lamina, with no inflammatory or atheromatous involvement.^{14,44,78} Vessel occlusion results from excessive accumulation of SMCs and thrombosis within the lumen. It is hypothesized that in the setting of arterial stenosis or occlusion, hypoxic regions of the brain induce collateralization through the formation of dilated and tortuous perforating arteries. Histopathologically, the moyamoya collateral vessels display thinned media with fibrin deposition in the vessel walls, fragmented elastic laminae, and microaneurysm formation.^{14,25,35,50,78,81} This native revascularization strategy is orchestrated by the expression of various growth factors involved in angiogenic signaling cascades, including HIF-1, VEGF, bFGF, transforming growth factor- β_1 , hepatocyte growth factor, and MMPs.^{24,43,50,70,81} Taken together these studies indicate the existence of a proangiogenic intracranial milieu in patients with moyamoya disease. Future investigations are needed that focus on high-throughput proteome-wide approaches that go beyond individual molecules to provide a better insight into global pathways and interactions at play in moyamoya disease and that correlate expression levels to extent of disease on neuroimaging (for example, correlation of angiogenic factors in CSF, serum, and urine to extent of collateralization seen on cerebral angiography and measurements of cerebral blood flow and blood volume on perfusion MR imaging/SPECT/PET). Future studies will also aim to develop genetic and serum biomarkers that can be used as predictors of outcomes after initial presentation. Biomarkers reflective of changes in the proangiogenic intracranial milieu after direct and indirect revascularization procedures will help clinicians monitor disease evolution in patients with moyamoya disease.

Accumulation of SMCs in Vascular Lesions

The excessive accumulation of SMCs and abnormal production of extracellular matrix components seen in moyamoya disease are also characteristic pathological entities in a number of other vascular diseases. Previously, it was assumed that pathological SMC accumulation derives from the adjacent medial SMC layer of the vascular wall, which regulates vascular tone and blood flow.^{55,57} However, neointimal SMCs differ from medial SMCs in phenotype and gene-expression pattern.⁸³ Migration of SMCs from the media across the internal elastic lamina is not commonly observed,^{55,57} and neointima can be formed in the absence of medial cells,⁶⁰ suggesting neointimal SMCs differed in origin from medial SMCs.

Recent evidence now suggests that bone marrow–derived vascular progenitor cells have the potential to home in on diseased vessels and differentiate into neointimal SMCs and endothelial cells in models of postangioplasty restenosis, transplant-associated graft vasculopathy, and hyperlipidemia-induced neointimal hyperplasia.⁶¹ Angioplasty is known to cause direct vessel wall injury, which induces SMCs to proliferate with subsequent overproduction of extracellular matrix.^{12,21} Transplant-associated vasculopathy occurs secondary to immunological targeting of the allograft by the recipient.^{5,17,56} Atherogenic substances (for example, oxidized low-density lipoprotein, homocysteine, angiotensin II, and lipopolysaccharides) can induce apoptosis and abnormal vascular wall remodeling, resulting in neointimal formation.^{57,62,72} Similar mechanisms have been proposed for the development of stenosis or occlusion in moyamoya disease—that is, direct vessel wall injury, immunological targeting, and caspase-3–mediated apoptosis.^{40,65,71,74,76}

Endothelial Progenitor Cells in Vascular Anomalies

The majority of moyamoya disease research has focused on abnormal angiogenesis—that is, endothelial cell sprouting from existing vessels, in the underlying pathogenesis of moyamoya disease.³⁹ However, adult vasculogenesis is increasingly being understood as the pathway for adult neovascularization.^{2,6,7} Vasculogenesis differs from angiogenesis in that new blood vessels arise from circulating bone marrow–derived EPCs rather than from local endothelial cells.² Vasculogenesis begins during tissue ischemia with increased expression and stabilization of the transcription factor HIF-1, which promotes local production of SDF-1 and VEGF-A by hypoxic endothelial cells.^{6,7} It is hypothesized that release of SDF-1 ligand results in reversal of a marrow/periphery gradient that normally inhibits EPC migration.⁷ As a result, EPCs can mobilize to the periphery where they are preferentially recruited to SDF-1–expressing ischemic tissue during adult vasculogenesis.^{6,7,20,37,77}

There is recent evidence that circulating stem and progenitor cells and aberrant vasculogenesis may contribute to the development of other vascular abnormalities. Children with proliferating infantile hemangioma harbor increased levels of mobilized EPCs³⁴ and surgical specimens of infantile hemangioma specimen are positive for progenitor-specific markers including CD34, AC133, and VEGF.³³

Consistent with aberrant vasculogenesis as a shared final common pathway among vascular anomalies, moyamoya disease has been associated with co-occurrence of other vascular malformations, including cerebral cavernous malformations³¹ and brain AVMs (Fig. 1).^{1,10,15,18,30,38,48,51,64,66,67} The paracrine chemical bFGF stimulates endothelial cell growth and promotes angiogenesis⁵³ and is found in histochemical association with cerebral cavernous malformations.^{32,42} Elevated levels of bFGF have been observed in the CSF of patients with moyamoya disease,^{43,81} which is one proposed mechanism explaining the co-occurrence of cerebral cavernous malformation with moyamoya disease.³¹ Brain AVMs associated with moyamoya disease have been reported in patients ranging

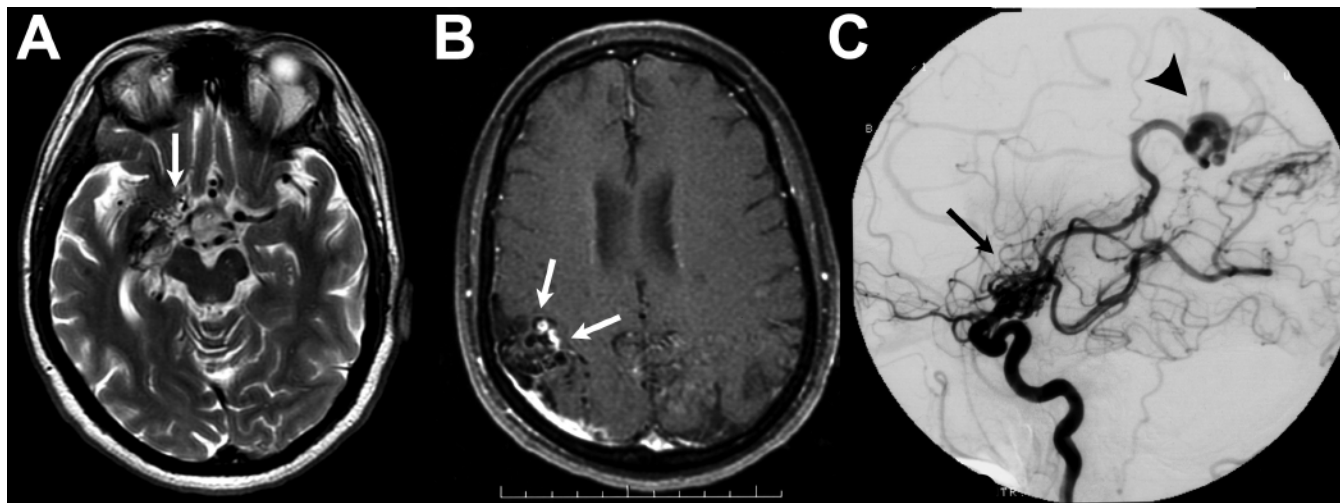


Fig. 1. Imaging studies acquired in a 47-year-old woman who suffered a hemorrhage from a right parietal AVM. A and B: Axial T2-weighted (A) and a T1-weighted (B) MR images obtained after contrast agent injection. C: Lateral cerebral angiogram. Flow voids are detected on the T2-weighted image (arrow in A), which correlate with the finding of moyamoya vessels and occlusion of the middle cerebral artery on the cerebral angiogram (arrow in C). The right parietal AVM is detected on the contrast-enhanced image (arrows in B) and correlates with the AVM on the angiogram (arrowhead in C) with an early draining vein. The patient was first treated for the AVM after the hemorrhage occurred and then underwent right superficial temporal artery–middle cerebral artery bypass surgery.

in age from 8 to 54 years, occurring in both unilateral and bilateral disease.^{1,10,15,18,30,38,48,51,64,66,67} Fuse et al.¹⁵ have reported the diagnosis of a brain AVM in a 9-year-old girl 4 years after undergoing indirect bilateral revascularization surgery for a diagnosis of moyamoya disease. The exact mechanism for this rare de novo brain AVM formation is unknown. The authors proposed decreased cerebral perfusion pressure and hypoxia in the setting of moyamoya disease as one possible mechanism, acting through elaboration of angiogenic cascades. However, this seems less likely given that revascularization was deemed effective on pancerebral angiography. It may be more likely that de novo brain AVM formation occurred in the setting of an increased angiogenic environment⁸² induced by the bilateral indirect revascularization surgery.

The co-occurrence of brain AVM with moyamoya disease may support the theory of a shared final common pathway in the pathogenesis of these 2 diseases. Indeed, similar angiogenic factors are expressed in both diseases, including increased expression of HIF-1, VEGF, and VEGF receptors.^{19,69,81} It has been shown that MMP-9 is responsive to hypoxia²³ and may result in release of EPCs by cleavage of membrane-bound kit ligand in the bone marrow.²² Interestingly, MMP-9 has been shown to be increased in patients with moyamoya disease as well as in those with a brain AVM.^{8,9} Of note, a SNP in the gene encoding TIMP-2, a candidate SNP within a location identified in linkage studies of familial moyamoya, has been implicated as a genetic predisposing factor for familial moyamoya.²⁹ However, subsequent studies have been unable to replicate this finding.⁴⁶

Recently, Jung et al.²⁸ provided the first demonstration of aberrant vasculogenesis in moyamoya disease, although future studies are needed to enumerate circulating EPCs in moyamoya disease patients in vivo using

FACS¹¹ and to perform blood genomic analysis on these and other circulating cell populations.^{41,68} Data are lacking on progenitor-specific markers and SDF-1 expression in cerebrovascular disease tissue and on levels of circulating EPCs and other markers of vasculogenesis in the peripheral blood of patients with cerebrovascular disease, including moyamoya disease. Future studies to define basal EPC profiles in moyamoya disease and other cerebrovascular diseases, changes in EPC profiles after stroke or intracerebral hemorrhage, as well as changes in EPC profiles following revascularization procedures (direct versus indirect), will aid in the understanding of vascular stem cell biology, validate the utility of EPCs as a marker of moyamoya disease progression, and shed light on novel therapeutic strategies for the medical management of cerebrovascular disease.

Genetic Analyses: Current Concepts and Future Directions

Genetic analysis has the potential to uncover underlying pathogenic mechanisms of moyamoya disease that could enhance our understanding of vascular disease and identify novel targets for therapeutic intervention. Furthermore, genetic screening in Japan is of interest given the increased incidence of moyamoya disease in that population and undiagnosed asymptomatic moyamoya disease carrying an estimated annual risk of either ischemic or hemorrhagic stroke that exceeds 3%.^{36,45}

A number of genome-wide linkage studies have been carried out in Japanese families with diagnoses of familial moyamoya that suggest linkage to at least 5 different chromosomal regions: 3p24.2-p26,²⁶ 6q25,²⁷ 8q23,⁵⁹ 12p12,⁵⁹ and 17q25.^{46,79} The differences in loci identified by these linkage studies may represent locus heterogeneity. However, it is worth noting that linkage analyses involving affected siblings or relative pairs have only

limited statistical power and are often susceptible to false-negative results.⁵⁴ Further compounding the situation, Mineharu et al.⁴⁷ have reported that the mode of inheritance in Japanese families with familial moyamoya is autosomal dominant with incomplete penetrance. These authors suggest that penetrance is in part age dependent and influenced by genomic imprinting.⁴⁶ The significance of this observation is that at-risk carriers of a pathogenic gene defect may be disease free at the time of clinical assessment, making it difficult to accurately identify segregation of pathogenic gene defects among affected family members in pedigrees of familial moyamoya. For these reasons, no pathogenic gene mutation has yet been identified and studies have largely been unable to identify replicable loci.

However, recent works provide new hope that a pathogenic gene mutation may soon be identified. Yamauchi et al.⁷⁹ used microsatellite markers to interrogate chromosome 17 given the association between moyamoya disease and neurofibromatosis Type 1, for which the causative gene (*NFI*) has been identified on chromosome 17q11.2. Using an affected member-only approach, the authors suggest a candidate locus at 17q25.⁷⁹ Evidence in support of this finding came recently when Mineharu et al.⁴⁶ carried out a separate analysis in 15 extended Japanese families using genome-wide parametric linkage analysis and identified a candidate locus at 17q25.3. Collectively, these data provide compelling evidence that a pathogenic gene associated with familial moyamoya might be found on chromosome 17q25. Future efforts will focus on comprehensively sequencing each gene and performing copy number analysis at this locus.

Another approach with significant potential to elucidate genetic factors associated with moyamoya disease is genome-wide association studies that involve the use of high-density SNP arrays. This approach was recently exemplified by an elegant study from Gunel's group⁴ into the pathogenesis of intracranial aneurysms. It has been previously noted that siblings of intracranial aneurysm probands are at 4-fold increased risk of hemorrhage from intracranial aneurysm, suggesting a genetic component to risk.⁶³ However, similar to moyamoya disease, genome-wide linkage studies of intracranial aneurysms in familial cases have been unable to identify a replicable loci and case-control candidate gene studies have failed to produce replicable results.^{13,49,52,58} These considerations motivated Gunel's group to undertake multistage genome-wide association studies to identify common variants that contribute to intracranial aneurysm in 3 large cohorts: a Finnish cohort of 920 cases and 985 controls, a Dutch cohort of 781 cases and 6424 controls, and a Japanese cohort of 495 cases and 676 controls.⁴ This pivotal effort resulted in the identification of common SNPs on chromosomes 2q, 8q, and 9p that show significant association with intracranial aneurysm with odds ratios of 1.24–1.36.⁴ Genome-wide association study approaches are now being applied in moyamoya disease with the hope of uncovering the underlying pathogenic mechanisms of moyamoya disease.

To date, reports on familial moyamoya have been limited to Asian families. Given considerable evidence of

differing genetic susceptibility between Asian and North American populations,^{16,73,75} future studies are needed to clarify inheritance patterns in North American pedigrees of familial moyamoya and to replicate linkage analyses within these patients.

Conclusions

Moyamoya disease is an important cause of stroke in children and young adults. Further investigations are needed to identify the underlying cause of moyamoya disease. High-throughput proteome-wide approaches promise to provide a better insight into global pathways and interactions at play in moyamoya disease. Studies on EPC function represent a promising new area of research that may provide insights into the mechanism of new vessel formation in moyamoya disease and other cerebrovascular diseases. Genetic analysis of familial moyamoya has the potential to uncover the underlying mechanisms triggering the aforementioned pathways and to identify novel targets for therapeutic intervention. Furthermore, genome-wide association studies in moyamoya disease may help overcome limitations of previous genetic investigations in familial cases only.

Data from proteomics, progenitor cell research and genetic investigations in moyamoya disease will not only be important for the development of novel therapies specific to moyamoya disease but will also have the potential to enhance treatment options for a wide variety of disorders of the CNS, including stroke, hemorrhage, vascular malformations, and CNS tumors.

Disclosure

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