Genetic Stroke Syndromes

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ABSTRACT

Purpose of Review: This review describes the clinical and radiographic features, genetic determinants, and treatment options for the most well-characterized monogenic disorders associated with stroke.

Recent Findings: Stroke is a phenotype of many clinically important inherited disorders. Recognition of the clinical manifestations of genetic disorders associated with stroke is important for accurate diagnosis and prognosis. Genetic studies have led to the discovery of specific mutations associated with the clinical phenotypes of many inherited stroke syndromes.

Summary: Several inherited causes of stroke have established and effective therapies, further underscoring the importance of timely diagnosis.

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INTRODUCTION

Ischemic stroke is a heterogeneous disorder with variable clinical presentations and a multitude of risk factors and causative mechanisms. In many cases, despite a comprehensive evaluation, the stroke mechanism is not clearly elucidated. In cryptogenic stroke and in patients with a family history of stroke, it is particularly important to consider inherited syndromes in the differential diagnosis. Recognition of clinical phenotypes associated with monogenic disorders known to cause ischemic stroke can lead to specific testing for inherited syndromes. Establishing a definitive diagnosis has both prognostic and therapeutic implications for affected patients and their families.

MONOGENIC DISORDERS ASSOCIATED WITH STROKE Fabry Disease

The cerebrovascular manifestations of Fabry disease include ischemic stroke at an early age, often involving the

vertebrobasilar circulation, dolichoectasia of cerebral vessels (**Figure 9-1**¹), and white matter abnormalities on brain MRI.² Other CNS manifestations include TIA, vertigo, hearing impairment, tinnitus, and cognitive disturbances. Peripheral nervous system involvement manifests as small fiber peripheral neuropathy with painful acroparesthesias, hypohidrosis, impaired temperature sensation, and intestinal dysmotility. Sensory and motor nerve conduction studies and EMG are typically normal.³ Major systemic manifestations include cardiac conduction disturbances, cardiomyopathy, renal failure, angiokeratomas, and corneal dystrophy. Radiographically, hyperintensity in the pulvinar region on T1-weighted MRI sequences has been described in addition to white matter abnormalities (**Figure 9-2**⁴).⁵ MRI or magnetic resonance (MR) angiography can show tortuosity and dilatation of cerebral vessels.

Fabry disease is caused by genetic mutations that result in deficient activity of the lysosomal hydrolase α -galactosidase A (GLA) (**Case 9-1**).

KEY POINTS

- The cerebrovascular manifestations of Fabry disease include ischemic stroke at an early age, often involving the vertebrobasilar circulation, dolichoectasia of cerebral vessels, and white matter abnormalities on brain MRI.
- Fabry disease is caused by genetic mutations that result in deficient activity of the lysosomal hydrolase α -galactosidase A.

FIGURE 9-1

Vertebrobasilar dolichoectasia in Fabry disease. *A*, Magnetic resonance angiography demonstrating tortuosity of the vertebrobasilar system. *B*, T2-weighted MRI through the dolichoectatic vertebral-basilar junction (arrow).

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More than 300 distinct mutations have been identified. Inheritance is X-linked, with men harboring the major disease manifestations and women being mildly affected carriers. Fabry disease is categorized as a lysosomal storage disorder with GLA inactivity resulting in progressive accumulation of glycosphingolipids, such

as globotriaosylceramide, in vascular endothelium, smooth-muscle cells, and autonomic and dorsal root ganglia. Lipid deposits probably contribute to vessel occlusion and tissue ischemia; however, the exact pathogenetic mechanism of cerebral infarction has yet to be elucidated. Dolichoectasia of the larger cerebral

FIGURE 9-2

Pulvinar sign in Fabry disease. Magnetic resonance findings in the posterior thalamus (pulvinar). T1-weighted images through the thalamus in three patients with mild (*A*), moderate (*B*), and marked (*C*) hyperintensity.

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Case 9-1

A 21-year-old man presented to the emergency department reporting bilateral blurry vision. The visual symptoms began abruptly 2 days earlier and were preceded by a thunderclap headache the week before. The patient admitted to using marijuana daily. The neurologic examination was notable for uncorrected near visual acuity of 20/30 bilaterally. A right homonymous hemianopia was found on confrontational visual field testing. He was not able to read simple or complex sentences. Writing, fluency, repetition, comprehension, and object naming were intact. Examination showed normal gait and motor, sensory, and cerebellar function.

The abrupt onset of symptoms prompted consideration of a vascular cause, such as ischemic or hemorrhagic stroke. The heralding thunderclap headache raised the possibility of subarachnoid hemorrhage, cervicocephalic dissection, cerebral venous thrombosis, or reversible cerebral vasoconstrictive syndrome. Primary or secondary complications related to marijuana or other illicit substance abuse were also considered. Laboratory testing was remarkable for a serum creatinine of 1.2 mg/dL, and ECG demonstrated a right bundle branch block. Brain MRI revealed multifocal areas of acute infarction predominantly involving the vertebrobasilar circulation (**Figure 9-3**). Serum α -galactosidase A (GLA) activity was found to be zero, strongly suggestive of Fabry disease.

Comment. This patient had multisystem manifestations of Fabry disease, including abnormal cardiac conduction, cerebrovascular involvement, and early renal dysfunction. At follow-up, additional family history revealed that the patient's sister had developed progressive visual deterioration and painful acroparesthesias during adolescence. A maternal half uncle developed renal failure requiring hemodialysis at 32 years of age.

The patient was later able to recall a personal history of painful acroparesthesia beginning in middle school. He was referred to a genetics counselor; molecular testing was not believed to be necessary given the family history and undetectable GLA activity. He was referred for hematologic, ophthalmic, cardiologic, nephrologic, and dermatologic evaluations. Enzyme replacement therapy was recommended.

FIGURE 9-3 Fabry disease. Axial diffusion-weighted MRI sequence obtained at the level of the thalami. Multifocal, bihemispheric regions of restricted diffusion are seen with notable involvement of the calcarine cortex and splenium of the corpus callosum. Infarction of the splenium resulted in the disconnection syndrome alexia without agraphia, evident on neurologic examination.

KEY POINTS

- Recombinant α -galactosidase A is available as enzyme replacement therapy for Fabry disease and should be considered for affected individuals.
- Sickle cell disease is complicated by stroke in 25% of affected individuals before the age of 45 years.
- Sickle cell disease is caused by a point mutation that results in substitution of valine for glutamic acid in position number 6 of the β -polypeptide chain of hemoglobin.

vessels may result from mechanical weakening of the vessel wall due to glycosphingolipid deposition.

Measurement of leukocyte GLA activity can be used for diagnosis and is a standard enzymatic test in most laboratories. Sensitivity and specificity of the GLA activity assay approaches 100% in men, but only identifies about 50% of female carriers, where levels range from normal to low. Molecular genetic testing can be used to diagnose women or men who have marginal GLA activity. Skin biopsy or culture of skin fibroblasts can help establish the diagnosis if other means are not available. A diagnosis of Fabry disease should be considered when evaluating stroke in the young, particularly if the patient has a family history of stroke and the posterior circulation is involved. Once a diagnosis is established, additional studies should include urinalysis for proteinuria, measurement of renal function, and an ECG to evaluate for cardiac involvement.

Recombinant GLA is available as enzyme replacement therapy for Fabry disease and should be considered for affected individuals. Replacement therapy has been shown to decrease left ventricular mass, reduce pain, and increase quality of life.⁶ Reduction of stroke risk, progression of disease, or mortality has not been established. Enzyme replacement therapy is typically started as soon as possible after diagnosis and administered as an IV infusion (agalsidase alpha 0.2 mg/kg or agalsidase beta 1 mg/kg) every 2 weeks and continued indefinitely. Treatment is expensive, with estimates of retail cost exceeding \$200,000 per year.

Cost-effectiveness of enzyme replacement therapy compared with standard medical care has been evaluated recently in a Dutch cohort of patients with Fabry disease.⁷ In this cohort, treatment had limited effect on quality of life and progression to end-organ damage and was

associated with costs per additional quality-adjusted life-year ranging from €5.5 million to €7.5 million (US \$7,377,700 to \$10,060,500). Identification of those patients most likely to benefit from enzyme replacement therapy could potentially enhance cost-effectiveness.

Clinicians must have a high index of suspicion for Fabry disease because of its vague and variable presentation with multiorgan system dysfunction requiring the need for comprehensive multispecialty care for optimal management.

Sickle Cell Disease

Sickle cell disease is complicated by stroke in 25% of affected individuals before the age of 45 years.⁸ Ischemic stroke is most common when stroke onset occurs before the age of 20 years; hemorrhagic stroke is more common when stroke occurs after the age of 20 years. The initial peak incidence of stroke occurs between 2 years and 5 years of age. Recurrent stroke risk is high and occurs in about two-thirds of patients within 2 years of the index event.⁹ A nonatherosclerotic cerebral vasculopathy causing stenosis and occlusion of the proximal cerebral vessels can be identified with noninvasive vascular imaging techniques, including MR angiography, CT angiography, and transcranial Doppler (TCD) ultrasonography. In some patients, a network of lenticulostriate collaterals develops, creating a moyamoya appearance on conventional angiography. Cognitive and behavioral changes may occur as a result of silent cerebral infarction. Systemic manifestations include vaso-occlusive crises causing chest, back, and extremity pain, compensated hemolytic anemia, and jaundice.

Sickle cell disease is caused by a point mutation that results in substitution of valine for glutamic acid in position number 6 of the β -polypeptide chain of hemoglobin. The point mutation results

in abnormal aggregation of hemoglobin, causing changes in red blood cell shape and rheology. Polymerization of deoxygenated hemoglobin, changes in red blood cell membrane structure and function, disordered cell volume, and increased adherence to vascular endothelium play a role in the pathophysiology of sickle cell disease.¹⁰ Inheritance is autosomal recessive, and the disease is most prevalent in individuals of African or African American descent.

Measurement of mean blood flow velocity in the proximal middle cerebral artery or distal internal carotid artery by TCD can identify children at high risk for stroke. Mean blood flow velocity greater than 200 cm/sec is associated with increased stroke risk. The Stroke Prevention Trial in Sickle Cell Anemia study randomized children without a history of stroke and with TCD velocities greater than 200 cm/sec to observation or prophylactic transfusion therapy targeted to a hemoglobin S fraction of less than 30%.¹¹ The study was terminated after enrollment of 130 patients demonstrated a 92% reduction in stroke risk ($P < .001$) in the transfusion group. Transfusion therapy also reduced the risk of new silent cerebral infarction and stroke in a subgroup with evidence of prior silent infarction on the initial brain MRI. A follow-up study found six additional stroke cases, with five occurring in the group that stopped transfusion therapy.¹² The main risk associated with chronic transfusion therapy is iron overload that can be effectively managed with iron chelation therapy.

Children with sickle cell disease should be routinely screened with TCD, and those with mean flow velocities greater than 200 cm/sec should receive exchange transfusion therapy to reduce the hemoglobin S fraction to less than 30%. In practice, screening is often performed annually beginning at age 2 years. If blood flow velocities exceed

200 cm/sec, rescreening in 2 to 4 weeks can identify children with persistently elevated velocities that benefit from prophylactic transfusion therapy.

A retrospective cohort study of children with sickle cell disease and acute stroke (less than 24 hours from symptom onset) compared simple transfusion with exchange transfusion at the time of clinical stroke and found that children receiving simple transfusion had a five-fold greater relative risk of recurrent stroke than those receiving exchange transfusion therapy.¹³ Hydroxyurea, which increases fetal hemoglobin production, has been utilized empirically as an alternative to chronic transfusion therapy for secondary prevention. The Stroke with Transfusions Changing to Hydroxyurea trial randomized children with sickle cell disease and stroke with evidence of iron overload from chronic transfusion to treatment with either continued transfusion and iron chelation or hydroxyurea and phlebotomy.¹⁴ No strokes occurred in the 66 subjects assigned to transfusion and chelation therapy compared with seven strokes in the 67 subjects assigned to hydroxyurea and phlebotomy. Based on these results, simple or exchange transfusion with chelation remains the optimal way to manage children with sickle cell disease, stroke, and iron overload. Discontinuation of transfusion therapy in children with sickle cell disease causes high rates of reversion to abnormal intracranial blood flow velocities and stroke.¹⁵ A challenge in managing these cases is that it is not known when, or if, children grow out of the need for transfusions.

Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Recurrent subcortical brain infarction and TIA are common in cerebral

KEY POINT

- Children with sickle cell disease should be routinely screened with transcranial Doppler, and those with mean flow velocities greater than 200 cm/sec should receive chronic transfusion therapy to reduce the hemoglobin S fraction to less than 30%.

KEY POINTS

- T2 hyperintensities involving the white matter of the anterior temporal poles (O'Sullivan sign) are seen in 90% of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is associated with mutations in the *NOTCH3* gene on chromosome 19p13.2-p13.1, which codes for a large transmembrane protein necessary for vascular smooth muscle differentiation and development.
- False-negative results can occur with genetic analysis and should prompt skin biopsy to evaluate for granular osmophilic material in the vascular basal lamina, a finding highly specific for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and occur in up to 85% of symptomatic individuals. A retrospective cohort study found that median age at stroke onset was 51 years in men and 53 years in women.¹⁶ Ischemic stroke may present with classic small vessel lacunar syndromes, including pure motor stroke, pure sensory stroke, dysarthria-clumsy hand, and ataxic-hemiparesis. Recurrent stroke can lead to cognitive decline, dementia, gait abnormalities, urinary incontinence, and pseudobulbar affect. Migraine with aura occurs in about 30% of cases and is an early sign with onset often in the third decade of life (Case 9-2).¹⁷ Stroke and vascular cognitive impairment are the major causes of morbidity and mortality.

Although symptom onset typically occurs in adulthood, brain MRI abnormalities precede the onset of symptoms and are a useful screening tool for diagnosis for both symptomatic and presymptomatic carriers. T2 hyperintensities involving the white matter of the anterior temporal poles (O'Sullivan sign) are seen in 90% of patients with CADASIL. A similar pattern of regional involvement is uncommon in small vessel ischemia due to hypertension or other traditional cerebrovascular risk factors.¹⁸ Signal abnormalities in the extreme capsule and corpus callosum are also distinctive of CADASIL. Many patients with CADASIL have cerebral microbleeds.¹⁹ Gradient-recall echo sequences on brain MRI can identify these areas of hemosiderin deposition with high sensitivity; however, microbleeds are not unique to CADASIL as they occur in patients with cerebral amyloid angiopathy and hypertensive vasculopathy. The MRI finding that correlates best with clinical impairment in CADASIL is brain atrophy.²⁰ Atherosclerotic

changes in the medium and large cervicocephalic vessels are typically minimal or absent.

CADASIL is associated with mutations in the *NOTCH3* gene on chromosome 19p13.2-p13.1, which codes for a large transmembrane protein necessary for vascular smooth muscle differentiation and development. Inheritance is autosomal dominant, with affected family members in successive generations evident on pedigree analysis. More than 80 different *NOTCH3* mutations, the majority occurring in the extracellular region of the receptor within an epidermal growth factor-like repeat domain, have been identified in patients with CADASIL.²¹ The underlying mechanism through which *NOTCH3* mutations result in the clinical phenotype has not been fully elucidated. Transgenic mice expressing a vascular *NOTCH3* mutation or knockout mutation demonstrate enhanced cortical spreading depression, which may explain the co-prevalence of migraine with aura in patients with CADASIL.²² Molecular genetic testing can establish the diagnosis in patients with a family history of stroke or dementia and clinical and radiographic features suggestive of CADASIL. False-negative results can occur with genetic analysis and should prompt skin biopsy to evaluate for granular osmophilic material in the vascular basal lamina, a finding highly specific for CADASIL.

Specific treatment for CADASIL is not currently available. Aggressive management of cerebrovascular risk factors such as hypertension, hyperlipidemia, and diabetes mellitus is likely valuable given that CADASIL is primarily a small vessel arteriopathy. Antiplatelet therapy and migraine prophylaxis have been utilized in clinical practice, but neither has been clearly established as beneficial in CADASIL.

Case 9-2

A 29-year-old woman presented for a second neurologic opinion for her history of recurrent neurologic symptoms and stroke. Three years before presentation, she developed intermittent headaches characterized by sharp, stabbing, and burning pain. Her headaches were occasionally accompanied by nausea and impairment of peripheral vision bilaterally. She had an episode of right-sided weakness that occurred 9 months ago. Six months ago, she suddenly began to vomit while washing dishes at home. This was followed by headache and left-sided weakness, predominantly involving the arm and hand. She also reported difficulty with concentration, memory, and multitasking at that time. She was hospitalized and diagnosed with an ischemic stroke. Her mother and brother both had a history of stroke. Neurologic examination demonstrated a left hemiparesis, reduced sensation on her left side, and hyperreflexia in the left upper and lower extremities. Review of the brain MRI performed during her hospitalization was remarkable for changes consistent with acute ischemic stroke. Additionally, T2 abnormalities involving the anterior temporal poles were seen, highly characteristic of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (Figure 9-4). Molecular genetic testing revealed a DNA sequence variation in the *NOTCH3* gene.

FIGURE 9-4 Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Axial fluid-attenuated inversion recovery (FLAIR) MRI in a 29-year-old woman demonstrating T2 signal abnormalities in the temporal polar white matter (A, B [arrows], C) and lateral ventricular margins (D, E, F) exceeding what would be expected for a patient of this age.

Comment. The progression of symptoms from migraine with aura to TIA and stroke in a young person, followed by symptoms of cognitive dysfunction, should lead to consideration of CADASIL, particularly in patients with a family history of stroke or dementia. Missense mutations identified in the *NOTCH3* gene resulting in gain or loss of a cysteine residue within one of the 23 exons encoding the 34 epidermal growth factor–like repeat domains of the protein have been associated with 90% of CADASIL cases.

KEY POINTS

- Stroke with onset in the third decade, and dementia with onset in the third through fifth decade, are characteristic of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy. Systemic manifestations include premature alopecia with onset in the teen years and cervical or lumbar spondylosis in the second and third decades of life.
- Vision and memory loss, seizures, hemiparesis, apraxia, and dysarthria with onset in the fourth decade of life followed by death 5 to 10 years after clinical presentation is the typical disease progression in retinal vasculopathy with cerebral leukodystrophy.

Cerebral Autosomal Recessive Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Stroke with onset in the third decade, and dementia with onset in the third through fifth decade, are characteristic of cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL). Systemic manifestations include premature alopecia with onset in the teen years and cervical or lumbar spondylosis in the second and third decades of life. Hypertension is not associated with development of subcortical infarction in CARASIL. Linkage analysis has identified mutations in the high-temperature requirement A serine peptidase 1 (*HTRA1*) gene on chromosome 10q as the cause of CARASIL.²³ *HTRA1* binds and cleaves the prodomain of pro-transforming growth factor β -1 (pro-TGF- β 1), and the cleaved product is degraded by the endoplasmic reticulum. This mechanism regulates the amount of mature TGF- β 1.²⁴ No disease-specific therapy for CARASIL is available at this time.

Retinal Vasculopathy With Cerebral Leukodystrophy

Retinal vasculopathy with cerebral leukodystrophy (RVCL) has also been called cerebroretinal vasculopathy syndrome; hereditary vascular retinopathy; or hereditary endotheliopathy, retinopathy, nephropathy, and stroke (HERNS). Vision and memory loss, seizures, hemiparesis, apraxia, and dysarthria with onset in the fourth decade of life followed by death 5 to 10 years after clinical presentation is the typical disease progression in RVCL. The retinopathy is characterized by neovascularization of the optic disc, retinal hemorrhages, and macular edema. In about 50% of patients,

brain MRI demonstrates an enhancing tumorlike lesion with cortical sparing that may resemble a primary CNS malignancy. Small white matter lesions have also been described, which may resemble demyelinating lesions. Anecdotally, spontaneous regression of the tumorlike lesions has been observed (Figure 9-5).²⁵

Mutations in the *TREX1* gene have been associated with RVCL. *TREX1* encodes a DNA exonuclease, and patients with RVCL have frame-shift mutations affecting the C-terminal domain that result in a truncated protein product that prevents normal translocation into the cell nucleus.²⁶ The molecular pathophysiology has yet to be elucidated; however, clinical manifestations are the result of a cerebral and retinal microvasculopathy. Inheritance is autosomal dominant, with affected family members evident in successive generations. The proliferative retinopathy may respond to intravitreal bevacizumab.²⁷

Mitochondrial Encephalopathy, Lactic Acidosis, and Strokelike Episodes

Cerebrovascular manifestations of mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS) are characterized by stroke, often with onset before the age of 40 years, resulting in hemiparesis, hemianopia, or cortical blindness. Other neurologic signs and symptoms include focal and generalized seizures, dementia, recurrent migrainelike headaches, and muscle weakness. Systemic manifestations include short stature, hearing loss, recurrent vomiting, and diabetes mellitus. MELAS often presents in childhood after normal development, and the clinical course can be relapsing-remitting with eventual development

FIGURE 9-5 Retinal vasculopathy with cerebral leukodystrophy. Sequential axial MRI showing an ovoid T2-hyperintense (A) and gadolinium-enhancing (B) lesion adjacent to the frontal horn of the right lateral ventricle. At 6 months, a larger lesion with surrounding edema occupied the right frontal lobe with a central zone of presumed necrosis and gadolinium enhancement (C, D). At 12 months, the lesion had reduced in size with persistent enhancement (E, F). At 18 months (not shown), the lesion further decreased in size with near resolution of the surrounding edema. Fluorescein and indocyanine green angiography with corresponding color photographs of the retina show views of the macula of the right eye (G–I). Periarterolar narrowing and sheathing, focal leakage, telangiectasias, and cotton wool spots are present.

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KEY POINT

■ The mitochondrial encephalopathy, lactic acidosis, and strokelike episodes disorder often presents in childhood after normal development, and the clinical course can be relapsing-remitting with eventual development of progressive neurologic disability.

of progressive neurologic disability.²⁸ Early diagnostic criteria included stroke before the age of 40 years, encephalopathy characterized by seizures or dementia, and blood lactic acidosis or ragged red fibers on Gomori trichrome staining of skeletal muscle.²⁹ It has become increasingly apparent

that a broader range of clinical phenotypes exists, including stroke onset after the age of 40 years.³⁰ MRI abnormalities involve the cerebral cortex and may cross vascular territories with sparing of the deep white matter.³¹

MELAS is a maternally inherited mitochondrial disorder, with 80% of cases

KEY POINTS

- The mitochondrial encephalopathy, lactic acidosis, and strokelike episodes syndrome is a maternally inherited mitochondrial disorder, with 80% of cases associated with the A3243G mutation in the gene encoding transfer RNA^{LEU(UUR)}.
- The classic angiographic appearance of moyamoya is stenosis and occlusion of the bilateral distal internal carotid arteries and proximal middle/anterior cerebral arteries accompanied by a network of abnormal lenticulostriate collateral vessels that has the appearance of a puff of smoke.

associated with the A3243G mutation in the gene encoding transfer RNA^{LEU(UUR)}. Additional mitochondrial mutations affect respiratory chain enzymes, particularly complex I. Treatments for MELAS have focused on reducing oxidative stress and include coenzyme Q10 (ubiquinone), levocarnitine, L-arginine, and B vitamins.^{32,33} Definitive disease-modifying therapy has yet to be established. Valproate should be avoided as anti-epileptic therapy for recurrent seizures because severe paradoxical convulsions have been reported.³⁴ Statins should also be avoided, if possible, because they may precipitate or exacerbate myopathy in MELAS mutation carriers.^{35,36}

Moyamoya Disease

Moyamoya disease is associated with recurrent TIA, ischemic stroke, and hemorrhagic stroke. In children with moyamoya disease, ischemic stroke and TIA are more prevalent and may be triggered by exercise, crying, coughing, fever, or hyperventilation; in adults, intraparenchymal and intraventricular hemorrhage is more prevalent.

Hemiparesis, aphasia, altered mentation, and visual disturbance are common stroke sequelae.³⁷ In addition to cerebrovascular events, epilepsy occurs as an additional neurologic manifestation. The incidence of moyamoya disease is highest in Japanese and other East Asian populations. The classic angiographic appearance of moyamoya is stenosis and occlusion of the bilateral distal internal carotid arteries and proximal middle/anterior cerebral arteries accompanied by a network of abnormal lenticulostriate collateral vessels that has the appearance of a puff of smoke. Conventional arteriography is considered the gold standard for diagnosis, but the vascular abnormalities may be visualized with noninvasive modalities, including CT and MR angiography.

Familial forms of moyamoya, which account for about 15% of cases, have

been associated with mutations in the *RNF213* gene on chromosome 17q25.3.³⁸ In most families, inheritance is autosomal dominant with incomplete penetrance, but other modes of transmission have been described.³⁹ Moyamoya disease is a nonatherosclerotic, noninflammatory vasculopathy histopathologically characterized by intimal hyperplasia, smooth muscle cell proliferation, and disruption of the internal elastic lamina, which results in progressive stenosis and occlusion of affected large vessels. Irregular collateral networks in the basal ganglia develop in response to progressive luminal narrowing.⁴⁰ Moyamoya disease shares associations with other nonatherosclerotic large vessel arteriopathies, including cervical artery dissection, fibromuscular dysplasia, and intracranial aneurysms.⁴¹ Progressive stenosis and occlusion of the terminal internal carotid arteries and proximal middle/anterior cerebral arteries with irregular collateral networks may develop secondary to atherosclerosis, radiation, sickle cell disease, or other causes and has been termed moyamoya syndrome.

There is a paucity of randomized clinical trials of specific treatment for moyamoya disease. In clinical practice, antiplatelet therapy has been used to prevent recurrent ischemic events. To augment blood flow, surgical procedures that have been done include direct revascularization by extracranial-intracranial bypass and indirect revascularization by several techniques, including encephaloduroarteriosynangiosis (EDAS) and encephaloduroarteriomyosynangiosis (EDAMS). EDAS is performed by attaching the dissected superficial temporal artery to the edges of a linear dural incision, which promotes neovascularization of the ischemic hemisphere. EDAMS is an extension of the EDAS technique that uses the superficial

Case 9-3

A 50-year-old woman was hospitalized with recurrent transient neurologic symptoms. Four months before presentation, she began having episodes of slurred speech accompanied by numbness of the left side of her face and left hand lasting 2 to 3 minutes followed by spontaneous improvement. On the day of admission, she developed a 5-minute spell of left-sided paresthesia, facial droop, and slurred speech. Her neurologic examination was normal. Noncontrasted head CT showed an area of chronic encephalomalacia in the right parietal lobe. CT perfusion study demonstrated reduced cerebral blood flow in the right hemisphere, with a prolongation of the mean transit time in the right middle cerebral artery distribution. Conventional angiography was performed to further evaluate the cerebral circulation. The supraclinoid segment of the right internal carotid artery and proximal middle cerebral and anterior cerebral arteries demonstrated hemodynamically significant occlusive lesions. Abnormal lenticulostriate collateral vessels were evident (**Figure 9-6**), suggestive of moyamoya disease.

FIGURE 9-6 Moyamoya disease. Cerebral angiogram of the right internal carotid artery with oblique (A) and lateral (B) projections demonstrating severe tapering stenosis of the right carotid terminus (arrows) as well as severe stenosis of the M1 segment of the right middle cerebral artery with multiple small hypertrophied collateral branches extending from the region of stenosis (arrowheads).

Comment. Patients with moyamoya disease are at risk for hemodynamic TIA and stroke involving the watershed areas of the anterior, middle, and posterior circulation. This patient continued to have symptoms despite permissive hypertension and IV normal saline for maintenance of intravascular volume. A right craniotomy with superficial temporal artery to middle cerebral artery bypass with encephaloduroarteriosynangiosis was performed to augment blood flow to the ischemic hemisphere. The patient remained asymptomatic after the procedure.

temporal artery in addition to the deep temporal artery of the temporalis muscle and middle meningeal artery to promote neovascularization (**Case 9-3**).⁴²

CONCLUSION

Several monogenic disorders with clinical phenotypes that include ischemic stroke have been well characterized.

Accurate diagnosis has therapeutic implications in Fabry disease and sickle cell disease. Recognition of the cerebrovascular, neurologic, systemic, and radiographic manifestations of these inherited disorders can lead to disease-specific diagnostic testing in selected patients with cryptogenic stroke or a family history of stroke.

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