REVIEW OPEN ACCESS

Clinical Approach to Genetic Cerebral Arteriopathy in the Adult Patient With Ischemic Stroke

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Neurol Genet 2024;10:e200182. doi:10.1212/NXG.0000000000200182

Abstract

Genetic arteriopathies leading to stroke in adults constitute a diverse group of cerebrovascular disorders with distinct etiologies, pathophysiologic mechanisms, and clinical presentations. As imaging modalities better delineate subtle changes in cerebral vasculature and access to genetic testing increases, the detection rate for these conditions is expected to rise, particularly among young adults with idiopathic cerebral arteriopathy and stroke. Adults with stroke in the setting of a genetic cerebral arteriopathy often present with few traditional stroke risk factors and, in certain cases, have characteristic clinical features, cerebrovascular imaging findings, and often concurrent systemic vasculopathy, such as aortopathy, which are important to recognize. Given that there are over 50 recognized genetic cerebral arteriopathies that can cause ischemic and hemorrhagic stroke in young adults, it can be a significant diagnostic challenge for the practicing neurologist when faced with a genetic cerebral arteriopathy, because clinical algorithms for a systematic approach to genetic cerebral arteriopathies are lacking. In this review, we present a phenotype-driven, clinically oriented algorithm to guide the diagnostic workup when suspecting a genetic cerebral arteriopathy in an adult patient while highlighting the genetic basis of each disease, molecular mechanisms, clinical manifestations, diagnostic approaches, and emerging therapeutic strategies. Moreover, given the lack of widely available gene panels for diagnostic germline testing for genetic cerebral arteriopathies, we propose key genes to be tested and focused on in each clinical scenario, to better decipher the underlying diagnosis in these rare conditions.

Introduction

Genetic arteriopathies account for at least 5% of strokes in adults aged 18 to 50[1]. Diagnosing these conditions is challenging due to over 50 monogenic diseases with diverse clinical and phenotypic presentations.[1] These arteriopathies are often underrecognized, poorly understood, and not routinely tested for. A family history and young age at stroke onset are often key indicators of a genetic cause, with the workup primarily driven by clinical suspicion. Strokes with unusual vasculopathy patterns and specific clinical features should prompt expanded genetic evaluations, especially when common stroke mechanisms are ruled out.

In this article, we present the clinical and diagnostic features of common genetic cerebral arteriopathies associated with stroke in adults, supported by a narrative literature review. Using a phenotype-driven approach, we categorize these conditions and propose a clinical and diagnostic algorithm to guide workup and genetic testing for this underrecognized patient population.

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Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by Cleveland Clinic.

Glossary

ADPKD = autosomal dominant polycystic kidney disease; **AGS** = Aicardi-Goutières syndrome; **AVM** = arteriovenous malformation; **CAA** = cerebral amyloid angiopathy; **CADASIL** = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; **CARASAL** = cathepsin A–related arteriopathy with strokes and leukoencephalopathy; **CARASIL** = cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; **FCL** = familial chilblain lupus; **HHT** = hereditary hemorrhagic telangiectasia; **LDS** = Loeys-Dietz syndrome; **NF1** = neurofibromatosis type 1; **PADMAL** = pontine autosomal dominant microangiopathy and leukoencephalopathy; **SLE** = systemic lupus erythematosus; **SVD** = small vessel disease; **SWS** = Sturge-Weber syndrome; **vEDS** = vascular Ehlers-Danlos syndrome.

Methods

Search Strategy

We searched PubMed for reports published between January 1980 and February 2024. A complete listing of search terms used can be found in eAppendix 1. Articles were screened by title and abstract, with priority given to recent meta-analyses/systematic reviews or rigorously conducted studies relevant to the scope of this narrative review. The reference list of relevant articles was also screened to identify additional articles that may have been missed with the search terms. The search was not restricted by language. We excluded articles without suitable English translation, conference proceedings, and non–peer-reviewed reports.

Phenotypic Grouping of Disorders

Our review identified over 50 genetic cerebral arteriopathies causing strokes in young adults, focusing on 23 key conditions based on clinical relevance, expert opinion, and frequency of observation. Using hierarchical clustering of clinical and diagnostic features, we developed a diagnostic approach for these arteriopathies. This phenotype-driven algorithm aids in the diagnostic workup for suspected genetic cerebral arteriopathy. In addition, we summarized each disease's genetic basis, molecular mechanisms, clinical manifestations, diagnostic methods, and emerging treatments.

Results

A Clinical, Phenotype-Driven, Approach to the Diagnosis of Genetic Cerebral Arteriopathy in the Adult Patient

Our approach to the clinical evaluation for the patient with genetic cerebral arteriopathy (Table 1) is based on the presence or absence of 4 key features: (1) an inflammatory CSF, (2) associated aortopathy, (3) cerebral aneurysms, and (4) cerebral small vessel disease (SVD). This approach emphasizes the importance of a standardized workup, which includes a thorough examination, CSF analysis, MRI brain and cerebrovascular neuroimaging (e.g., MRA, CTA, or digital subtraction angiography), aortic evaluation (e.g., CT aortogram or MR aortogram), and targeted genetic testing.

In the sections that follow, we describe the key features relevant to each arteriopathy for the practicing stroke neurologist.

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) should be considered a key differential diagnosis for stroke in individuals aged 20–50, particularly those with a personal or family history of intracranial aneurysms and kidney disease. With a prevalence of 1 per 1,000, ADPKD increases the risk of ischemic and hemorrhagic strokes, notably, subarachnoid hemorrhage from ruptured aneurysms (5 times higher than the general population).[2] Characterized by pathogenic variants in PKD1 or PKD2, ADPKD manifestations include bilateral renal and extrarenal cysts, along with connective tissue abnormalities such as mitral valve prolapse, thoracic aortic dissections, cerebral dolichoectasia, and intracranial aneurysms (Figure 1A).[3-5] Diagnosis is through genetic testing or renal ultrasonography, with required cyst numbers rising with age.[4] Serum microRNAs (miR-17, miR-200, miR-21) could serve as biomarkers for intracranial aneurysms.[3,6-10] No gender predilection exists for ADPKD.[11] PKD1 gene heterozygous missense mutations have been linked to epilepsy.[12] Mortality rates are high, with 18.4 deaths per 1,000 patient-years for non-ESRD patients and 37.4 per 1,000 patient-years for those with ESRD.[13]

Vascular Ehlers-Danlos Disease

Vascular Ehlers-Danlos syndrome (vEDS) should be considered in patients with recurrent spontaneous aortic, extracranial carotid, or vertebral artery dissections. With an incidence of 1 in 50,000 to 1 in 200,000, vEDS is caused by pathogenic variants in COL3A1 and differs from classical EDS by less frequent joint hypermobility and thin skin.[14,15] vEDS typically presents early, with median age of first vascular complication at 23 years.[16] The median lifespan is 51 years, with no gender predilection but potentially higher male mortality.[15,16] Imaging of the head and neck vasculature is essential to detect aneurysms or dissections. In pregnant patients, uterine rupture at delivery is a risk, emphasizing the need for early diagnosis and high-risk obstetric care.[16,17] Recent trials suggest that celiprolol, a β1 antagonist and β2 agonist, may reduce mortality and major vascular events.[18,19] Arterial dissections are managed with antiplatelet or anticoagulant therapy per dissection management guidelines and patient education on precautions to prevent recurrent dissections. We advise considering lifelong antiplatelet therapy in patients at risk of recurrent dissections.

Table 1 General Organization and Clinical Characteristics for Genetic Cerebral Arteriopathies

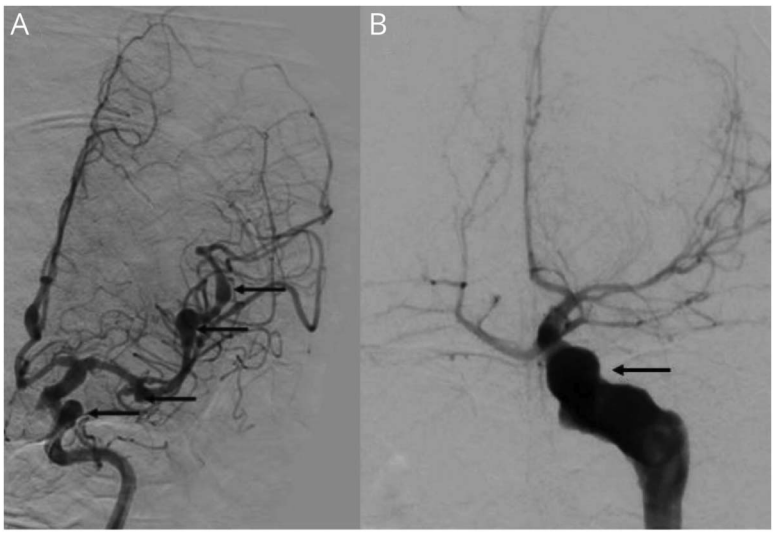
Clinical characteristics					Diagnostic consideration
Noninflammatory CSF	Aortopathy	Cerebral aneurysms more prominent	Renal cysts or renal failure		ADPKD
			Cerebral AVMs, characteristic 'velvet' skin		vEDS
			Bifid uvula		Loeys-Dietz
		Cerebral aneurysms less prominent	Moyamoya phenomenon		MYH11-related or ACTA2-related disorders
			Marfanoid appearance, ectopia lentis		Marfan syndrome
			Prominent arterial tortuosity		SLC2A10 arterial tortuosity syndrome
	No aortopathy	Cerebral small vessel disease	Claudication, peripheral neuropathy, painful crises	Nephropathy	Fabry disease
				Sagging skin, hyperpigmentation	Pseudoxanthoma elasticum
			No claudication, peripheral neuropathy, painful crises	Cognitive changes, headaches, mood disorder	CADASIL
				Cognitive changes, resistant hypertension, cerebral hemorrhage, migraines	CARASAL
				Spastic diplegia, alopecia	CARASIL
				Pontine predominance	PADMAL
				Livedo reticularis	Deficiency of ADA2
		Minimal cerebral small vessel disease or prominent intracerebral hemorrhage	Cerebral AVMs	Prominent telangiectasias	HHT
				Hemorrhage, migraines	COL4A1-related disorders
			Moyamoya phenomenon	Skin findings, optic glioma	NF1
				Systemic findings (splenic infarcts, sickle cell, Down syndrome), radiation vasculopathy, progressive intracranial atherosclerosis)	Secondary moyamoya
				Primary Moyamoya	RNF213-related disorder
			Neither cerebral AVMs nor moyamoya phenomenon	Prominent pial angiomas	Sturge-Weber
				Aneurysms, muscular weakness	Pompe disease
				Hemorrhage, dementia	Hereditary cerebral amyloid angiopathy
Inflammatory CSF	Leukoencephalopathy, retinal vasculitis, nephropathy				TREX1-related RVCL
	Encephalopathy, seizures, young age				Aicardi-Goutières

Abbreviations: ADPKD = autosomal dominant polycystic kidney disease; AVM = arteriovenous malformation; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASAL = cathepsin A–related arteriopathy with strokes and leukoencephalopathy; CARASIL = cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; HHT = hereditary hemorrhagic telangiectasia; NF1 = neurofibromatosis type 1; PADMAL = pontine autosomal dominant microangiopathy and leukoencephalopathy; vEDS = vascular Ehlers-Danlos disease.

Loeys-Dietz Syndrome

Loeys-Dietz syndrome (LDS) is characterized by skeletal, vascular, craniofacial, and cutaneous findings, including aortic root and peripheral arterial aneurysms, arterial tortuosity, cleft palate, bifid uvula, and hypertelorism. LDS is rare, and epidemiologic studies have not been conducted, so incidence, prevalence, and average lifespan remain unknown.[20,21] Patients with LDS may present in childhood with dysmorphisms and neurodevelopmental delay, but the pathophysiology of this phenotype remains uncertain.[22] LDS is marked by arterial tortuosity, most pronounced in the carotid and vertebrobasilar arterial systems, although arterial dissections and

Figure 1 Intracranial Aneurysms in ADPKD and ACTA2 Mutation–Related Disorder



(A) Digital subtraction angiography (DSA) image of a left carotid injection showing multifocal intracranial anterior circulation aneurysms (arrows) in a patient with ADPKD. (B) DSA image of a left carotid injection showing a large distal left carotid aneurysm in a young adult with ACTA2 mutation. ADPKD = autosomal dominant polycystic kidney disease.

aneurysms are also seen. Stroke at a young age, especially with arterial dilations, should increase suspicion for LDS.[23] Imaging of the aorta is recommended for pregnant patients and in the postpartum setting. Surveillance vessel imaging is recommended to monitor for intracranial aneurysms and degree of arterial tortuosity. The diagnosis is established with identification of pathogenic variants in *SMAD2*, *SMAD*, *TGFB2*, *TGFB3*, *TGFBR1*, or *TGFBR2*.[22,23]

MYH11-Related and *ACTA2*-Related Disorders

Myosin heavy chain 11 (*MYH11*)–related and actin alpha 2 (*ACTA2*)–related disorders have similar angiographic findings, sometimes described in the literature as "heritable thoracic aortic disease" along with syndromes related to variants in *TGFBR1*, *TGFBR2*, *SMAD3*, and TGFB2.[24] Both are autosomal dominant, and to our knowledge, 3 cases have been reported with *MYH11* pathogenic variants and cerebrovascular manifestations. These cases demonstrate a combination of vessel straightening ('broomstick arteriopathy'), absence of basal collaterals, and arterial stenoses—a continuum also seen with *ACTA2* pathogenic variants. Because *MYH11* specifically encodes a smooth muscle myosin, loss of its function results in vascular smooth muscle reduction, disorganization, and hyperplasia, with visceral myopathy, hypoperistalsis, and thoracic aortic aneurysms.[25] *ACTA2* pathogenic variants have been linked to infantile stroke, aortic aneurysms, aortic dissections, patent ductus arteriosus, livedo reticularis, demyelinating leukodystrophy, bicuspid aortic valves, and occasionally intracranial aneurysms (Figure 1B).[26,27] There is no known gender predilection for this disorder.[28] No epidemiologic studies exist describing either incidence, prevalence, or average lifespan for these disorders. Such patients should be monitored closely with serial thoracic aortograms (CTA or MRA) for the presence of aneurysms and referred to cardiothoracic surgery for management. We also advise monitoring occasionally for intracranial aneurysms.

Marfan Syndrome

Marfan syndrome is a multisystem disorder, with findings ranging from dilatation or dissection of the ascending aorta, pectus deformities, scoliosis, and ectopia lentis to lumbosacral dural ectasia.[29] The condition affects between 1 in 3,000 and 1 in 5,000 individuals globally.[30] Echocardiography to assess aortic, valvular, and cardiac integrity is recommended throughout life, with increased frequency to every 2–3 months in pregnancy.[29,31] Cerebrovascular complications of Marfan syndrome occur at a mean age of 40 years, without gender predilection, and include neck vessel dissection and less commonly aneurysms, based on retrospective evidence.[32-35] Marfan syndrome is diagnosed with the revised Ghent nosology, in which one criterion is a pathogenic variant in *FBN1*.[36] Morbidity is most associated with aortopathies rather than cerebral arteriopathies, but the latter are increasingly recognized as a contributor to disease burden in this condition.[37] Recent estimates suggest a lifespan of 72 years, likely related to improvements in cardiovascular surgery outcomes, and an increased detection of milder cases.[38] Genetic testing should be considered in patients with marfanoid features and cerebrovascular disease. Recurrent dissections in these patients should be treated with antiplatelet or anticoagulant therapy per dissection management guidelines.

SLC2A10 Arterial Tortuosity Syndrome

SLC2A10 encodes a glucose transporter, and mutations cause arterial tortuosity syndrome, predisposing patients to aneurysms and dissections. Typically diagnosed perinatally or early in childhood, it can present in young adulthood with cerebrovascular issues. Dysmorphic features include an elongated face, blepharophimosis, down-slanting palpebral fissures, a

beaked nose, a high-arched palate, and micrognathia. Other symptoms include hyperextensible skin and skeletal abnormalities such as arachnodactyly, pectus deformity, joint laxity, and contractures.[39] Surveillance for secondary complications involves frequent echocardiography and annual MR or CT angiography. Cerebral ischemia results from systemic vascular tortuosity and hypoperfusion.[40] Initial studies showed 40% mortality by age 4, but recent studies suggest that milder phenotypes were previously unreported.[40] No gender predilection exists. Patients with SLC2A10 mutations and type 2 diabetes may have impaired glycemic control, increasing the risk of cerebral small vessel disease.[41,42] Incidence, prevalence, and median lifespan are unknown, with only 106 cases reported.[40]

Fabry Disease

Fabry disease is characterized by an accumulation of glycosphingolipids in tissues resulting in neuropathic pain, renal damage, cerebral SVD, cardiac arrhythmias, hearing loss, and peripheral vascular disease.[43] Pathogenic variants of the alpha-galactosidase A gene (*GLA*) on the X chromosome result in deficiency of the alpha-galactosidase A lysosomal hydrolase, causing the intracellular accumulation of glycosphingolipids and globotriaosylceramide.[44] The incidence of the classical phenotype has been estimated at 1 in 50,000 to 117,000 men, although newborn screening studies estimate that 1 in 1,250 patients carries a germline GLA variant.[45,46] Most patients present with distal neuropathic pain in childhood, with white matter disease and SVD reported later at a mean of 52 years in roughly 43% of patients (Figure 2).[43,46] Secondary stroke prevention in Fabry disease involves optimization of SVD risk factors, mostly notably, hypertension, which is comorbid due to concomitant renal disease. While Fabry disease was once believed to only manifest in men, "carrier" women, due to X-inactivation, may also have varying disease manifestations.[43] Early detection of cardiac involvement is crucial for minimizing the most life-threatening sequelae, such as left ventricular hypertrophy, myocardial fibrosis, heart failure, and arrhythmias.[47] Pegunigalsidase alfa, a PEGylated covalently crosslinked form of α-galactosidase A, is an enzyme replacement therapy (ERT) recently approved by the US FDA to treat Fabry disease.[48] Before ERT, patients had an average lifespan of 50 years, but since its approval in 2001, Fabry disease is considered highly treatable.[49] While lifespan data in treated patients are not yet described, in a 2015 study, 52 ERT-treated patients had 94% overall survival at 10 years.[50]

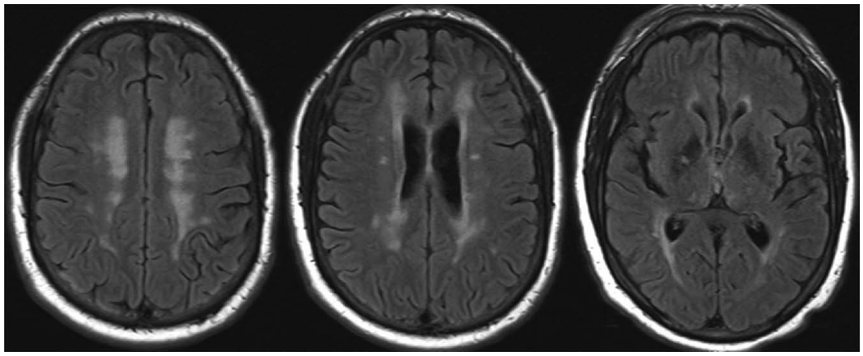
Pseudoxanthoma Elasticum

SVD has been recognized as a cerebrovascular manifestation of pseudoxanthoma elasticum (PXE), an entity characterized by progressive ectopic mineralization, primarily in the dermis, retina, and internal elastic lamina of small-sized and medium-sized arteries, resulting in peripheral arterial disease.[51] Yellow papules appear on the skin and coalesce to form leathery plaques.[52,53] Imaging studies reveal findings related to elastic fiber calcification, including microcalcifications in the liver, kidney, spleen, testis, and vessels.[54,55] PXE is caused by pathogenic variants in *ABCC6* and has also been reported to occur due to pathogenic variants in *ENPP1*.[56-58] PXE is primarily sporadic, but autosomal recessive and dominant inheritance patterns have been reported.[56] Patients are diagnosed between 8 and 12 years of age, and vascular manifestations develop several years after dermatologic signs in early adulthood.[59] A 2:1 ratio of female-to-male cases has been reported.[60] PXE is estimated to occur in 1 in 50,000 to 70,000 individuals, and patients have a normal lifespan.[59,e1] Small-molecule inhibitors of tissue-nonspecific alkaline phosphatase are being explored as a potential disease-modifying treatment in mouse models of PXE.[e2]

Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL)

Among the most well-recognized genetic causes of cerebral SVD in the adult patient is CADASIL, presenting with migraines in the third decade of life, and less commonly with subacute encephalopathy.[e3] Multifocal SVD occurs in strategic brain regions, resulting in early-onset dementia, depression,

Figure 2 MRI Brain Findings of Fabry Disease



MRI brain without contrast of a 46-year-old man with Fabry disease (receiving enzyme replacement therapy) showing diffuse (Fazekas grade 3) symmetric deep and periventricular white matter disease, in addition to bilateral remote small vessel infarcts in bilateral basal ganglia regions and diffuse cerebral atrophy.

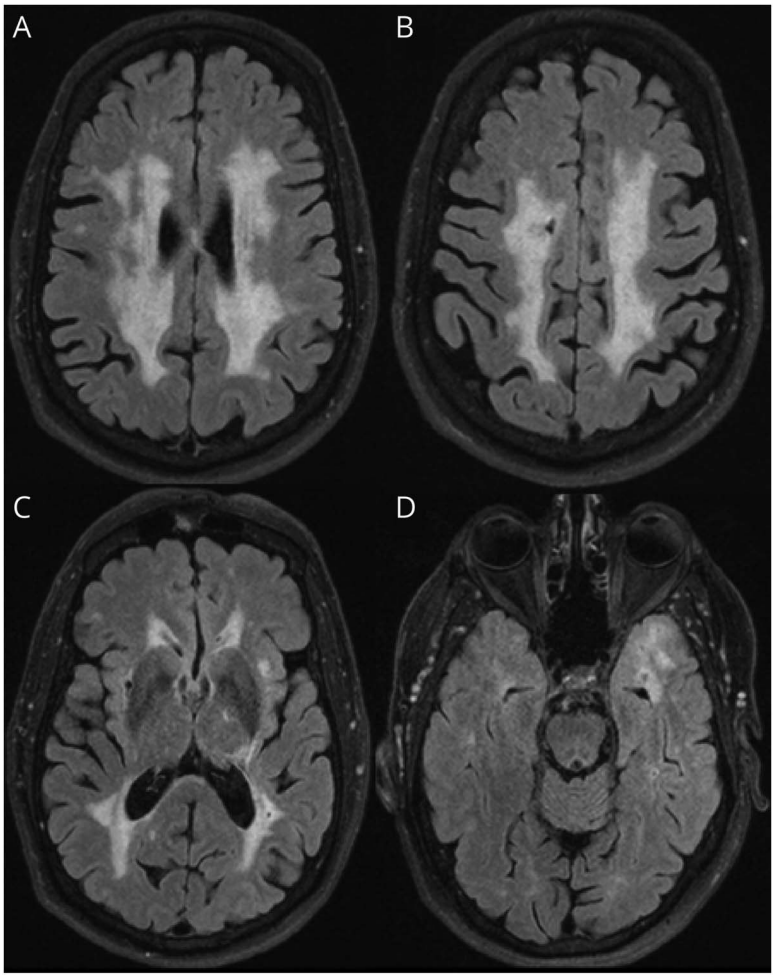
and apathy.[e3] Imaging findings include bilateral asymmetric T2/FLAIR hyperintensities in the anterior temporal lobes and external capsule, as well as lacunar infarcts, microbleeds, and subcortical infarcts (Figure 3, A–D).[e3]

CADASIL is diagnosed with the identification of a pathogenic *NOTCH3* variant.[e4] Historically, the prevalence of CADASIL was estimated at 1.3–4.1 per 100,000, although recent genomic studies have identified a much higher prevalence of pathogenic NOTCH3 variants, up to 3.4 per 1,000.[e5-e7] The mean age at onset for ischemic strokes in patients with CADASIL is 45–50 years.[e8] Women have a greater prevalence of migraines with aura and men have a greater prevalence of strokes, although these differences do not persist after the fifth decade.[e9] Neurofilament light chain is supported as a biomarker for disease progression and may represent a novel clinical trial end point for therapeutics.[e10] Testing for *NOTCH3* mutation should be considered in a patient in the third decade of life presenting with migraines, followed by subacute cognitive decline, depression, apathy, and characteristic white matter changes (Figure 3). Our review did not identify any epidemiologic studies estimating the lifespan of patients with CADASIL.

CARASAL

Cathepsin A–related arteriopathy with strokes and leukoencephalopathy (CARASAL) is an autosomal dominant arteriopathy caused by pathogenic variants in *CTSA*, encoding cathepsin A, a protease that degrades endothelin-1. Cathepsin A loss results in increased immunoreactivity of endothelin-1, leading to microangiopathy. CARASAL presents with therapy-resistant hypertension, ischemic and hemorrhagic strokes in the fourth decade of life, cognitive impairment, and depression.[e11,e12] MRI is nonspecific, with findings of multifocal SVD throughout the white matter and cortex.[e11] Only 19 patients with CARASAL have been reported, and although the disease was initially described in 5 patients from France, reported cases now include Dutch, British, Chinese, and Italian patients.[e13,e14] The rarity of cases precludes any conclusions on the clinical spectrum or estimates of incidence, prevalence, or lifespan, although migraines were reported in all 19 patients.[e14] Further research to

Figure 3 MRI Brain Findings of CADASIL



MRI brain axial T2/FLAIR images of a middle-aged man with CADASIL who presented with cognitive decline, headaches, and mood disturbance showing diffuse patchy areas of white matter hyperintensity in subcortical white matter (A), central white matter (A and B), periventricular, and basal ganglia (C) distribution, also involving bilateral anterior temporal tips (D).

characterize this disorder, its prevalence, and the potential utility of endothelin-1 as a biomarker is needed.

CARASIL

Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) is due to pathogenic variants in *HTRA1*, with fewer than 100 cases reported in the literature.[e15] Owing to its rarity, epidemiology and lifespan remain unknown.[e16,e17] Mild manifestations may be referred to as *HTRA1* cerebral SVD (*HTRA1*-CSVD), and more severe manifestations may be referred to as CARASIL.[e15] CARASIL presents with premature baldness, progressive dementia in the fourth decade of life, mood changes, and spastic gait.[e15] Recurrent ischemic strokes affect up to half of patients.[e15,e18] Imaging findings are similar to those of CADASIL.[e16,e18] While the pathophysiology of CARASIL remains uncertain, the angiotensin II receptor antagonist candesartan has been shown to normalize vessel distensibility and cerebral blood flow in mouse models.[e18,e19]

PADMAL

Pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL), due to pathogenic variants in COL4A1, has a variable age at onset, ranging from 20 to 60 years.[e20] Only 11 families have been described, so incidence, prevalence, and median lifespan remain unknown.[e21] Clinical findings include lacunar pontine stroke resulting in ataxia, hemiplegia, and hemihypesthesia.[e20,e22] Many similarities exist between PADMAL and other cerebral SVDs; however, PADMAL can be distinguished by the consistent involvement of the pons, particularly in young patients without other prominent cerebral SVD risk factors.

COL4A1-Related Disorders

COL4A1-related disorders encompass a spectrum of autosomal dominant inherited cerebral SVDs, with associated ocular defects (e.g., cataracts) and hemolytic anemia, arrhythmias, and kidney disease.[e23] These disorders include autosomal dominant familial porencephaly, autosomal dominant brain SVD with hemorrhage, and HANAC (*h*ereditary *a*ngiopathy with *n*ephropathy, *a*neurysms, and muscle *c*ramps) syndrome.[e23] Patients with germline pathogenic variants in *COL4A1* experience childhood-onset focal seizures related to porencephalic cysts.[e24] Owing to long-standing SVD from birth, microbleeds, lacunar infarcts, and calcifications can be seen.[e23] As mentioned, PADMAL is a subtype of *COL4A1*-related disorder, due to variants in the *COL4A1* 3′ UTR.[e25] *COL4A1*-related disorders may have a higher rate of hemorrhage than other hereditary SVDs.[e26] No sex-based differences have been reported. Approximately 350 cases have been reported, limiting estimates of incidence, prevalence, or lifespan.[e23,e27]

Deficiency of ADA2

Adenosine deaminase 2 deficiency (DADA2) is a monogenic recessive autoinflammatory disorder, marked by small and medium vessel vasculitis and symptoms in the first decade of life.[e28-e30] DADA2 occurs due to biallelic pathogenic loss-of-function variants in the *ADA2* gene, encoding adenosine deaminase 2, normally expressed on myeloid cells.[e30] Patients experience lacunar infarcts (located in deep brain nuclei and brainstem, sparing the subcortical white matter), nephritis, hepatic disease, aplastic anemia, hypogammaglobulinemia, and inflammatory bowel disease. The greatest carrier frequency for pathogenic variants in *ADA2* has been reported in Georgian-Jewish populations at 1 in 10, but the disorder is otherwise rare, with an estimated prevalence of 4 in 100,000.[e28] While specific lifespan estimates are not available in the literature, mortality is high, with 17% (5/29) of patients in a Dutch retrospective cohort study passing away from complications of DADA2 in the 10-year duration of the study.[e31] Because DADA2 is an autoinflammatory disease, long-term immunosuppression is the preferred treatment, with anti-TNF biologics demonstrating success in reducing progression of the inflammatory vasculopathy.[e30]

Hereditary Hemorrhagic Telangiectasia

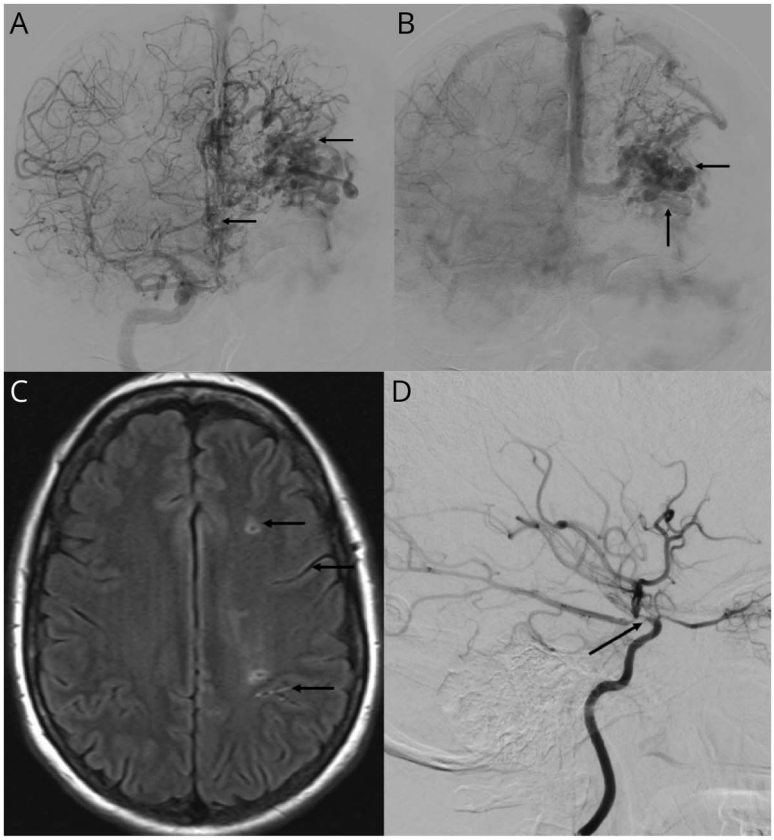
Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder associated with cerebral arteriovenous malformations (AVMs) and subarachnoid hemorrhage in young adults. The prevalence of HHT is estimated at 1 per 5,000 to 10,000 individuals.[e32,e33] Recurrent epistaxis due to nasal mucosal telangiectasias, around 12 years of age, is the most common manifestation reported, nearly universal in patients with HHT by age 40.[e34] Genetic testing for HHT entails a multigene panel for several genes: 52% related to ACVRL1 variants, 44% related to ENG variants, and others with SMAD4 variants.[e35] There is a lack of evidence supporting the prophylactic treatment of unruptured AVMs, and AVM screening remains controversial.[e36,e37] MR angiography is the primary imaging modality for AVM screening, with digital subtraction angiography (DSA) reserved for more detailed characterization (Figure 4, A and B).[e38] Brain MRI is recommended for patients with neurologic symptoms, a known history of cerebral aneurysms, or a family history of ruptured cerebral aneurysms.[e34]

Women with HHT are more likely to present with hepatic AVMs, but no sex-based differences in cerebrovascular events are reported.[e39] Transthoracic echocardiography and chest angiography may visualize lung abnormalities and pulmonary AVMs.[e40] Pulmonary AVMs, when present, may cause paradoxical emboli to the brain and subsequent stroke. Endoscopy is recommended to investigate for nose, colon, and gastric telangiectasias and AVMs.[e35,e40] Antiplatelet therapy should be used with caution in HHT, given the elevated systemic and cerebral hemorrhage risks. Although overall mortality data are sparse in the literature with no lifespan estimates available, a study in Dutch patients showed no difference in overall survival for treated HHT patients over 20 years compared with unaffected controls.[e41]

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disorder with a prevalence of 1 in 3,164 and birth incidence of 1 in 2,662, involving a highly variable

Figure 4 AVM in HHT and Cerebrovascular Findings in Moyamoya Disease



Digital subtraction angiography (DSA) images of right carotid injection in a middle-aged patient with HHT showing a large left frontal arteriovenous malformation in the arterial (A) and venous (B) phase. (C) MRI brain axial T2 FLAIR image of a middle-aged woman showing left frontal infarct (ACA-MCA borderzone) suggestive of hypoperfusion-related ischemia (upper arrow), cerebral cortical atrophy (middle arrow) because of chronic hypoperfusion, and hyperdense cortical vessels (bottom arrow) suggestive of slow flow through the left MCA branches. (D) Digital subtraction angiography image of a left carotid injection showing progressive narrowing and near-occlusion of the supraclinoid intracranial left ICA (arrow) suggestive of moyamoya disease. HHT = hereditary hemorrhagic telangiectasia; MCA =middle cerebral artery.

clinical presentation that includes pigmentary lesions, skeletal changes, benign and malignant brain tumors, and cutaneous neurofibromas.[e42-e44] Moyamoya syndrome is found in 1–6% of patients with NF1, presenting in early childhood and affecting anterior brain vasculature unilaterally (mean age of stroke 41 years).[e45-e50] T2/FLAIR hyperintensities in the thalami and medial temporal lobes are seen on routine MRI.[e46] Pathogenic variants in *NF1* exhibit variable expression but have 100% penetrance.[e51] The loss of function of the *NF1* gene product, neurofibromin, may lead to excess smooth muscle cell proliferation and alteration of the integrity of the endothelial cell layer.[e52] Overall, the median survival for patients with NF1 is 71.5 years.[e53] There is no reported gender predilection of cerebrovascular manifestations. In 2020, selumetinib, a MEK pathway inhibitor, was shown to reduce plexiform neurofibroma growth and improve quality of life in children with NF1 and became the first FDA-approved drug for NF1 treatment, but its effect on cerebrovascular disease remains unknown.[e54]

RNF213-Related Disorder (Primary Moyamoya Disease)

RNF213 (ring finger protein 213) is the major site of variants associated with primary moyamoya disease, characterized by a noninflammatory, nonatherosclerotic vasculopathy with stenosis at the cerebral origin of the distal internal carotid arteries, and moyamoya vessels, a hazy basal collateral network of angiogenesis seen on DSA (Figure 4, C and D).[e55,e56] Moyamoya disease manifests as ischemia because of vasculopathy, but seizures, hemorrhagic strokes, and cognitive impairment may also occur.[e57] Ischemic strokes are reported with a mean age of 46 years.[e58] MRA in RNF213-related disorders reveals vessels with shrunken outer diameters and concentric thickening of distal internal carotid artery vessel walls.[e59] DSA is best for observing hemodynamics and flow through occluded vessels.[e56] Patients with poor cerebrovascular reserve are at risk of ischemic stroke and should be evaluated for superficial temporal artery (STA) to middle cerebral artery (MCA) bypass, where indicated. Perfusion imaging with contrasted MRI brain, pre- and post-acetazolamide challenge is helpful in assessing cerebrovascular reserve.[e60] Surgical revascularization is also reasonable to consider for patients with hemorrhagic moyamoya disease, especially those with posterior hemorrhage.[e61]

The most frequent variant is seen in East Asian populations and is *RNF213* p.R4810K. The allelic frequency is greater in Korean and Japanese populations compared with Chinese populations (1.36% vs 0.5%), and allelic frequency in Europeans is 0.06%.[e62-e64] The female-to-male ratio of patients exhibiting a moyamoya phenotype is 2.8:1.[e65] Incidence of moyamoya disease ranges from 0.09 to 2.3 per 100,000 yearly

depending on the country, with peak incidence in the first and fourth decades of life. Prevalence ranges from 1.6 to 16.1 per 100,000. Five-year survival is reported as 92.9% for adults and 99.3% for children.[e66] Recent work in human brain epithelial cells showed that knockout of *RNF213* resulted in increased blood-brain barrier permeability due to downregulation of interendothelial junction proteins, suggesting that disease pathogenesis may relate to blood-brain barrier permeability.[e67]

Secondary Moyamoya Disease (Moyamoya Syndrome)

Secondary moyamoya, also described as moyamoya syndrome, is a phenomenon where a secondary condition causes moyamoya-like angiographic features to develop (i.e., chronic hypoperfusion from progressive distal ICA, proximal anterior cerebral artery (ACA), or middle cerebral artery (MCA) stenosis). These include sickle cell disease, accelerated atherosclerosis, radiation vasculopathy, hypothyroidism, systemic lupus erythematosus, and Down syndrome.[e68,e69] The exact incidence, prevalence, and lifespan of patients with moyamoya syndrome are unknown due to its grouping with moyamoya disease in epidemiologic studies.[e57,e70-71 e71] The management of patients with moyamoya syndrome is dependent on the status of a patient's cerebrovascular reserve. If there is impaired reserve in the setting of progressive vasculopathy, then patients should be considered for STA-MCA bypass, if feasible. However, data on the efficacy of bypass in this population are limited, and without identifying the underlying cause of the vasculopathy, bypass may only provide a temporary benefit.

Sturge-Weber Syndrome

Sturge-Weber syndrome (SWS) is a neurocutaneous disorder that presents at birth with a characteristic port-wine stain (nevus flammeus) on the upper face, in addition to capillary angiomas of the skin and cerebrovascular system.[e72] Patients may not present with cerebrovascular hypoperfusion because of leptomeningeal angiomatosis until adulthood. Neurologic involvement due to pial capillary malformations is needed for the diagnosis.[e73] Depending on the affected tissues, patients may develop cutaneous disfiguration, a predisposition to glaucoma, epilepsy, stroke-like events, and neurocognitive impairments, beginning in childhood.[e74,e75] Neuroimaging with contrast-enhanced MRI may reveal leptomeningeal angiomatosis.[e73] SWS is due to a mosaic, activating, somatic, and sporadic variant in the *GNAQ* gene.[e73,e74] SWS affects men and women of all ethnicities. Birth prevalence is estimated at up to 1 in 20,000 individuals, and most cases are not life threatening although exact lifespan data are unavailable.[e73] Despite no gender differences in incidence, men are more likely to experience ischemic episodes at a younger age.[e76]

Pompe Disease

Pompe disease, also known as acid maltase deficiency or glycogen storage disease type II (GSD II), is characterized by an autosomal recessive deficiency in lysosomal acid alpha-glucosidase (encoded by the *GAA* gene).[e77,e78] Patients with Pompe disease have buildup of glycogen in skeletal and cardiac muscles and in the CNS, leading to endothelial dysfunction that results in ischemic strokes.[e79] Pompe disease is classified based on age at onset, as either infantile (IPD) or late-onset (LOPD), and patients present with skeletal or cardiac myopathy before stroke-like symptoms.[e80,e81] Incidence is estimated at 1 in 40,000 individuals, with 75% of cases being LOPD. The median survival for patients with LOPD is 27 years after diagnosis compared with 18 months for patients with IPD.[e82,e83] CNS involvement may include sensorimotor challenges and cognitive deficits, particularly in patients with the IPD subtype.[e81,e84] Enzyme replacement therapy can be effective in treating the myopathy of Pompe disease.[e77] CT or MRI of the brain reveal ventricular enlargement or extra-axial CSF and white matter hyperintensities, more so in patients with IPD.[e84-e86] Current work with a focus on gene therapy is ongoing.[e87] Other experimental approaches include nutritional co-therapies involving ketone diets, ketone precursors, and antioxidant cocktails that aim to facilitate autophagic flux of administered GAA to the lysosome while inducing ketosis to reduce pathologic glycogen accumulation.[e88]

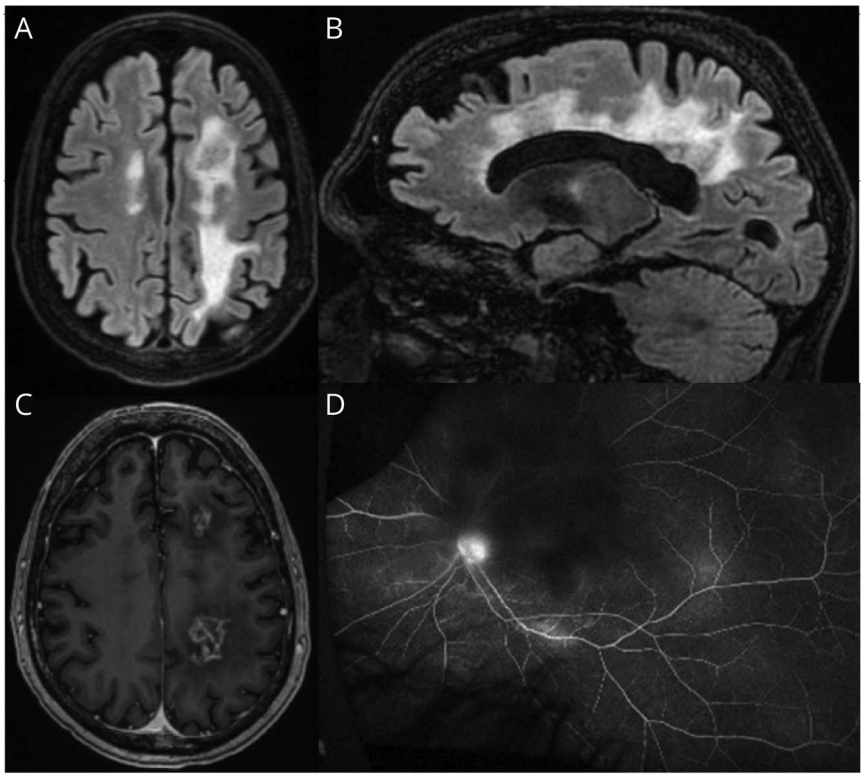
Hereditary Cerebral Amyloid Angiopathy

Patients with hereditary forms of cerebral amyloid angiopathy (CAA) have a more severe clinical course and earlier age at onset compared with those with sporadic amyloid angiopathy.[e89] In addition to intracerebral hemorrhage, patients may present with cognitive decline, related to microhemorrhage and macrohemorrhage and cerebral SVD.[e90] Hemosiderin-sensitive MRI sequences may reveal lobar hemorrhage and cortical superficial siderosis, and T2 sequences may reveal enlarged perivascular spaces, lacunar infarcts, and white matter disease.[e91,e92] Hereditary amyloid angiopathies are due to dominantly-inherited pathogenic variants in the amyloid precursor protein (*APP*) gene, the precursor of beta-amyloid.[e93] Founder mutations in *APP* for inherited amyloid angiopathy are present in the Dutch, Italian, Iowa, Flemish, Piedmont, and Arctic populations.[e93] Hereditary CAA can be further classified in Aβ and non-Aβ forms, with differing rates of lobar ICH depending on subtype. The *APOE* allele seems to have a less significant role in hemorrhage risk in hereditary CAA compared with sporadic CAA.[e93] Prevalence, incidence, and lifespan data for hereditary CAA are not available due to its rarity and genetic heterogeneity.[e90,e94]

TREX1-Related Disorder

TREX1 (3 prime repair exonuclease I)–related disorders encompass a range of autoimmune and inflammatory diseases including Aicardi-Goutières syndrome (AGS), systemic lupus erythematosus (SLE), and familial chilblain lupus (FCL).[e95-e97] Heterozygous variants of *TREX1* are also associated with retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S), a SVD that affects the retina, brain, liver, and kidneys.[e98] Although RVCL-S shares many systemic features with other arteriopathies, it may be clinically distinguished by its autosomal

Figure 5 Manifestations of TREX-1–Related Disorder



Axial (A) and sagittal (B) T2/FLAIR sequences of MRI brain of a middle-aged man with RCVL showing supratentorial progressive white matter disease most notably, in the left cerebral hemisphere with diffuse cerebral atrophy. (C) Axial T1 postgadolinium contrast study shows patchy areas of enhancement in the left frontal lobe. (D) Fluorescein angiography shows retinal vascular fluorescein leakage suggestive of retinal vasculitis.

dominant inheritance pattern, MRI abnormalities of leukoencephalopathy with contrast enhancement, multiorgan involvement, and retinal vasculitis occurring as early as 30–40 years of age (Figure 5).[e98]

Patients with TREX1-related disorders present with white matter disease, CSF lymphocytosis, intracranial calcifications, retinal vasculopathies, cutaneous lesions (e.g., chilblains), and arthralgias.[e95-e97] Patients with less cerebral involvement, such as those with FCL, may display relatively mild features on neuroimaging, such as impaired or delayed myelination.[e95,e99] At the molecular level, pathogenic *TREX1* variants lead to aberrant activation of the type I interferon response, resulting in systemic inflammation, which contributes to recurrent small vessel ischemic strokes.[e100] *TREX1* variants associated with AGS are either de novo or rare polymorphisms, with autosomal recessive transmission, with the exception of autosomal dominant inheritance in FCL.[e101] Owing to the variable phenotypes associated with this disorder, incidence and prevalence data for *TREX1* variants are not known. Mortality depends on the phenotype, with RVCL and SLE having up to 20% 10-year mortality and FCL being nonlethal.[e102]

Aicardi-Goutières Syndrome

AGS is an autosomal recessive developmental encephalopathy characterized by brain, skin, and immune manifestations, diagnosed in the neonatal period.[e103] 1 in 5 infants born with AGS, often women, will exhibit hepatosplenomegaly, thrombocytopenia, jittery movements, feeding difficulties, and intracranial vascular stenosis, potentially related to a dysregulation of the primary inflammatory stress response.[e103,e104] CT brain reveals calcification of the thalamus, periventricular white matter, and basal ganglia.[e105] MRI may

Table 2 Proposed Key Genes to be Included on Multigene Panels for the Evaluation of the Patient With Suspected Genetic Cerebral Arteriopathy

Patient subgroup	Genes
Inflammatory CSF	*TREX1, ADAR, IFIH1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1*
Noninflammatory CSF without aortopathy	*GLA, ABCC6, ENPP1, NOTCH3, CTSA, HTRA1, COL4A1, COL4A2, ADA2, ACVRL1, ENG, SMAD4, NF1, RNF213, GAA, GNAQ, APP*
Noninflammatory CSF with aortopathy	*PKD1, PKD2, COL3A1, SMAD2, SMAD, TGFB2, TGFB3, TGFBR1, TGFBR2, MYH11, ACTA2, FBN1, SLC2A10*

reveal temporal pole edema, temporal horn dilatation, and cerebral atrophy.[e106] The immune overdrive in infants with AGS may arise from the failure of nucleases to cleave endogenously produced nucleic acids.[e102,e107] While the exact prevalence is unknown, a recent study from Denmark found that the incidence of AGS was less than 0.76 per 100,000 live births annually from 2010 to 2020.[e108] With a yearly mortality rate of 19.3%, many patients with AGS do not survive into adulthood.[e103,e109]

Discussion

Evaluating patients with suspected genetic cerebral arteriopathy is complex. In this article, we reviewed these disorders and proposed a stepwise approach to help the practicing neurologist navigate genetic arteriopathy workup in adult patients, especially when common vasculopathy causes and stroke mechanisms are ruled out. This approach starts with thorough patient and family history and physical examination to identify potential genetic arteriopathies. If a genetic arteriopathy is suspected, the next steps include evaluating for aortopathy and assessing CSF for inflammation (if clinical suspicion for an inflammatory process is high), followed by stratifying conditions based on the presence of intracranial aneurysms or SVD while identifying syndrome-specific features. This systematic approach should help target genetic testing to the most likely disorders.

Although no commercial gene panels currently support high throughput testing for these conditions, we provide lists of genes to focus on for each major subset of disorder, by either a targeted panel, whole-exome sequencing, or whole-genome sequencing, based on our recommended approach (Table 2). In the absence of a targeted gene panel, we recommend whole-genome sequencing as the preferred approach. Genetic counseling before testing is crucial to discuss potential outcomes and implications. If a genetic mutation is found, targeted testing should also be offered to family members. Conditions such as HHT, Loeys-Dietz syndrome, Marfan disease, and NF1 have screening regimens; therefore, patient education on these is essential. Although disease-specific therapies exist for Fabry disease, Pompe disease, and DADA2, comprehensive vascular risk factor optimization is critical for any genetic arteriopathy. Antiplatelet therapy is recommended for stroke prevention, with cilostazol potentially being safer and more vasoprotective than aspirin or CYP212 inhibitors, although prospective studies comparing the safety and efficacy of antiplatelet agents in this population are limited.

While we aim to present a comprehensive overview of genetic cerebral arteriopathies, our review is limited to monogenic disorders, as opposed to the more common polygenic risk that modifies traditional stroke risk factors, such as familial hyperlipidemia or intracranial atherosclerosis. However, driven by the clinical phenotype, age at onset, and imaging characteristics, the systematic approach we describe provides a robust framework for the practicing neurologist to recognize a genetic cerebral arteriopathy in the adult patient and prompt appropriate genetic testing where indicated.

Study Funding

The authors report no targeted funding.

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

Received by *Neurology: Genetics* March 21, 2024. Accepted in final form June 13, 2024. Submitted and externally peer reviewed. The handling editor was Associate Editor Raymond P. Roos, MD, FAAN.

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References

1. Terni E, Giannini N, Brondi M, Montano V, Bonuccelli U, Mancuso M. Genetics of ischaemic stroke in young adults. *BBA Clin.* 2015;3:96-106. doi:10.1016/j.bbacli.2014.12.004
2. Harris PC, Torres VE. Polycystic kidney disease, autosomal dominant. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews® [online]*. University of Washington, Seattle; 1993. Accessed April 22, 2024. ncbi.nlm.nih.gov/books/NBK1246/
3. Pirson Y. Extrarenal manifestations of autosomal dominant polycystic kidney disease. *Adv Chronic Kidney Dis.* 2010;17(2):173-180. doi:10.1053/j.ackd.2010.01.003
4. Torres VE, Harris PC, Pirson Y. Autosomal dominant polycystic kidney disease. *Lancet.* 2007;369(9569):1287-1301. doi:10.1016/S0140-6736(07)60601-1
5. Perrone RD, Malek AM, Watnick T. Vascular complications in autosomal dominant polycystic kidney disease. *Nat Rev Nephrol.* 2015;11(10):589-598. doi:10.1038/nrneph.2015.128
6. Hajarnis S, Lakhia R, Patel V. MicroRNAs and polycystic kidney disease. In: Li X, ed. *Polycystic Kidney Dis [online]*. Codon Publications; 2015. Accessed September 4, 2023. ncbi.nlm.nih.gov/books/NBK373371/

7. Lee W-J, Jung K-H, Ryu H, et al. Association of autosomal dominant polycystic kidney disease with cerebral small vessel disease. *J Cereb Blood flow Metab.* 2021;41(12): 3365-3377. doi:10.1177/0271678X211037869
8. Schievink WI, Torres VE, Wiebers DO, Huston J. Intracranial arterial dolichoectasia in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol.* 1997;8: 1298-1303. doi:10.1681/ASN.V881298
9. Shigemori K, Higashihara E, Itoh M, et al. PKD1-associated arachnoid cysts in autosomal dominant polycystic kidney disease. *J stroke Cerebrovasc Dis.* 2021;30(9): 105943. doi:10.1016/j.jstrokecerebrovasdis.2021.105943
10. Lee LJ-H, Tsai L-K, Chang Y-Y, Wang J-D, Kao JT-W. Polycystic kidney disease increases the stoke incidence in Taiwan: a retrospective population-based cohort study using National Health Insurance Database. *Biomed J.* 2022;45(5):806-813. doi: 10.1016/j.bj.2021.10.005
11. Subramanian S, Ahmad T. *Polycystic Kidney Disease of Childhood. StatPearls [online].* StatPearls Publishing; 2023. Accessed September 4, 2023. ncbi.nlm.nih.gov/books/NBK537137/.
12. Wang J-Y, Wang J, Lu X-G, et al. Recessive PKD1 mutations are associated with febrile seizures and epilepsy with antecedent febrile seizures and the genotype-phenotype correlation. *Front Mol Neurosci.* 2022;15:861159. doi:10.3389/fnmol.2022.861159
13. Mladsi D, Zhou X, Mader G, et al. Mortality risk in patients with autosomal dominant polycystic kidney disease. *BMC Nephrol.* 2024;25(1):56. doi:10.1186/s12882-024-03484-3
14. Inokuchi R, Kurata H, Endo K, et al. Vascular Ehlers-Danlos syndrome without the characteristic facial features: a case report. *Medicine (Baltimore).* 2014;93(28):e291. doi:10.1097/MD.0000000000000291
15. Byers PH, Belmont J, Black J, et al. Diagnosis, natural history, and management in vascular Ehlers-Danlos syndrome. *Am J Med Genet C Semin Med Genet.* 2017;175(1): 40-47. doi:10.1002/ajmg.c.31553
16. Byers PH. Vascular Ehlers-Danlos syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews® [online].* University of Washington, Seattle; 1993. Accessed September 4, 2023. ncbi.nlm.nih.gov/books/NBK1494/.
17. Shalhub S, Byers PH, Hicks KL, et al. A multi-institutional experience in vascular Ehlers-Danlos syndrome diagnosis. *J Vasc Surg.* 2020;71(1):149-157. doi:10.1016/j.jvs.2019.04.487
18. Frank M, Adham S, Seigle S, et al. Vascular Ehlers-Danlos syndrome: long-term observational study. *J Am Coll Cardiol.* 2019;73(15):1948-1957. doi:10.1016/j.jacc.2019.01.058
19. Baderkhan H, Wanhainen A, Stenborg A, Stattin E-L, Björck M. Celiprolol treatment in patients with vascular Ehlers-Danlos syndrome. *Eur J Vasc endovascular Surg.* 2021; 61(2):326-331. doi:10.1016/j.ejvs.2020.10.020
20. Verstraeten A, Dietz HC, Loeys BL. Loeys–dietz syndrome. *Cassidy Allansons Manag Genet Syndr [online].* John Wiley & Sons, Ltd; 2021:563-576. Accessed April 22, 2024. onlinelibrary.wiley.com/doi/abs/10.1002/9781119432692.ch36.
21. Gouda P, Kay R, Habib M, Aziz A, Aziza E, Welsh R. Clinical features and complications of Loeys-Dietz syndrome: a systematic review. *Int J Cardiol.* 2022;362: 158-167. doi:10.1016/j.ijcard.2022.05.065
22. MacCarrick G, Black JH, Bowdin S, et al. Loeys-Dietz syndrome: a primer for diagnosis and management. *Genet Med.* 2014;16(8):576-587. doi:10.1038/gim.2014.11
23. Loeys BL, Dietz HC. Loeys-dietz syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews® [online].* University of Washington, Seattle; 1993. Accessed September 4, 2023. ncbi.nlm.nih.gov/books/NBK1133/.
24. Yagyu T, Noguchi T, Asano Y, et al. Association between genetic diagnosis and clinical outcomes in patients with heritable thoracic aortic disease. *J Am Heart Assoc.* 2023; 12(8):e028625. doi:10.1161/JAHA.122.028625
25. Milewicz DM, Cecchi AC. Heritable thoracic aortic disease overview. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews® [online].* University of Washington, Seattle; 1993. Accessed September 4, 2023. ncbi.nlm.nih.gov/books/NBK1120/.
26. Renard M, Callewaert B, Baetens M, et al. Novel MYH11 and ACTA2 mutations reveal a role for enhanced TGFβ signaling in FTAAD. *Int J Cardiol.* 2013;165(2): 314-321. doi:10.1016/j.ijcard.2011.08.079
27. Sabo TM, Stokes MA, Karbhari N, Veltkamp DL, Pfeifer CM. ACTA2 leukovasculopathy: a rare pediatric white matter disorder. *Radiol Case Rep.* 2020;15(8): 1285-1288. doi:10.1016/j.radcr.2020.05.031
28. Lauer A, Speroni SL, Patel JB, et al. Cerebrovascular disease progression in patients with ACTA2 Arg179 pathogenic variants. *Neurology.* 2021;96(4):e538-e552. doi: 10.1212/WNL.0000000000011210
29. Judge DP, Dietz HC. Marfan's syndrome. *Lancet.* 2005;366(9501):1965-1976. doi: 10.1016/S0140-6736(05)67789-6
30. Spencer M. Marfan syndrome. *Nursing (Lond).* 2024;54(4):19-25. doi:10.1097/01.NURSE.0001007604.09204.9a
31. Dietz H. FBN1-Related marfan syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews® [online].* University of Washington, Seattle; 1993. Accessed September 4, 2023. ncbi.nlm.nih.gov/books/NBK1335/.
32. Wityk RJ, Zanferrari C, Oppenheimer S. Neurovascular complications of Marfan syndrome: a retrospective, hospital-based study. *Stroke.* 2002;33(3):680-684. doi: 10.1161/hs0302.103816
33. Chembala J, Natarajan I, Roffe C. Thrombolysis in a stroke patient with Marfan syndrome. *JRSM Short Rep.* 2012;3(4):22. doi:10.1258/shorts.2012.012001
34. Kim JH, Kim JW, Song S-W, et al. Intracranial aneurysms are associated with Marfan syndrome: single cohort retrospective study in 118 patients using brain imaging. *Stroke.* 2021;52(1):331-334. doi:10.1161/STROKEAHA.120.032107
35. Domingo RA, Perez-Vega C, Tripathi S, et al. Intracranial aneurysms in patients with marfan syndrome: a multicenter propensity-matched analysis. *World Neurosurg.* 2021; 155:e345-e352. doi:10.1016/j.wneu.2021.08.065
36. Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. *J Med Genet.* 2010;47(7):476-485. doi:10.1136/jmg.2009.072785
37. Aubart M, Gazal S, Arnaud P, et al. Association of modifiers and other genetic factors explain Marfan syndrome clinical variability. *Eur J Hum Genet.* 2018;26(12): 1759-1772. doi:10.1038/s41431-018-0164-9
38. Silverman DI, Burton KJ, Gray J, et al. Life expectancy in the Marfan syndrome. *Am J Cardiol.* 1995;75(2):157-160. doi:10.1016/s0002-9149(00)80066-1
39. Callewaert BL, Willaert A, Kerstjens-Frederikse WS, et al. Arterial tortuosity syndrome: clinical and molecular findings in 12 newly identified families. *Hum Mutat.* 2008;29(1):150-158. doi:10.1002/humu.20623
40. Callewaert B, De Paepe A, Coucke P. Arterial tortuosity syndrome. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. *GeneReviews® [online].* University of Washington, Seattle; 1993. Accessed September 16, 2023. ncbi.nlm.nih.gov/books/NBK253404/.
41. Paz-Pacheco E, Nevado JB, Cutiongco-de la Paz EMC, et al. Variants of SLC2A10 may be linked to poor response to Metformin. *J Endocr Soc.* 2022;6(8):bvac092. doi: 10.1210/jendso/bvac092
42. Pikula A, Howard BV, Seshadri S. Stroke and diabetes. In: Cowie CC, Casagrande SS, Menke A, et al., eds. *Diabetes Am [online],* 3rd ed. National Institute of Diabetes and Digestive and Kidney Diseases (US); 2018. Accessed September 16, 2023. ncbi.nlm.nih.gov/books/NBK567972/.
43. Mehta A, Ricci R, Widmer U, et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. *Eur J Clin Invest.* 2004;34(3): 236-242. doi:10.1111/j.1365-2362.2004.01309.x
44. Bishop DF, Kornreich R, Desnick RJ. Structural organization of the human alpha-galactosidase A gene: further evidence for the absence of a 3' untranslated region. *Proc Natl Acad Sci U S A.* 1988;85(11):3903-3907. doi:10.1073/pnas.85.11.3903
45. Mehta A, Hughes DA. Fabry disease. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews® [online].* University of Washington, Seattle; 1993. Accessed April 22, 2024. ncbi.nlm.nih.gov/books/NBK1292/.
46. Tapia D, Floriolli D, Han E, et al. Prevalence of cerebral small vessel disease in a Fabry disease cohort. *Mol Genet Metab Rep.* 2021;29:100815. doi:10.1016/j.ymgmr.2021.100815
47. Pieroni M, Moon JC, Arbustini E, et al. Cardiac involvement in Fabry disease: JACC review Topic of the Week. *J Am Coll Cardiol.* 2021;77(7):922-936. doi:10.1016/j.jacc.2020.12.024
48. Wallace EL, Goker-Alpan O, Wilcox WR, et al. Head-to-head trial of pegunigalsidase alfa versus agalsidase beta in patients with Fabry disease and deteriorating renal function: results from the 2-year randomised phase III BALANCE study. *J Med Genet* 2024;61(6):520-530. doi:10.1136/jmg-2023-109445
49. Hollak CEM, Wijburg FA. Treatment of lysosomal storage disorders: successes and challenges. *J Inherit Metab Dis.* 2014;37(4):587-598. doi:10.1007/s10545-014-9718-3
50. Germain DP, Charrow J, Desnick RJ, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. *J Med Genet.* 2015;52(5): 353-358. doi:10.1136/jmedgenet-2014-102797
51. Verwer MC, Hazenberg CEVB, Spiering W, de Borst GJ. Peripheral interventions in patients with pseudoxanthoma elasticum (PXE). *Eur J Vasc endovascular Surg.* 2023; 65(1):142-148. doi:10.1016/j.ejvs.2022.08.009
52. Uitto J, Váradi A, Bercovitch L, Terry PF, Terry SF. Pseudoxanthoma elasticum: progress in research toward treatment: summary of the 2012 PXE international research meeting. *J Invest Dermatol.* 2013;133(6):1444-1449. doi:10.1038/jid.2013.20
53. Luo H, Faghankhani M, Cao Y, Uitto J, Li Q. Molecular genetics and modifier genes in pseudoxanthoma elasticum, a heritable multisystem ectopic mineralization disorder. *J Invest Dermatol.* 2021;141(5):1148-1156. doi:10.1016/j.jid.2020.10.013
54. Vanakker OM, Voet D, Petrovic M, et al. Visceral and testicular calcifications as part of the phenotype in pseudoxanthoma elasticum: ultrasound findings in Belgian patients and healthy carriers. *Br J Radiol.* 2006;79(939):221-225. doi:10.1259/bjr/20801330
55. Bercovitch RS, Januario JA, Terry SF, et al. Testicular microlithiasis in association with pseudoxanthoma elasticum. *Radiology.* 2005;237(2):550-554. doi:10.1148/radiol.2372041136
56. Bergen AA, Plomp AS, Schuurman EJ, et al. Mutations in ABCC6 cause pseudoxanthoma elasticum. *Nat Genet.* 2000;25(2):228-231. doi:10.1038/76109
57. Nitschke Y, Baujat G, Botschen U, et al. Generalized arterial calcification of infancy and pseudoxanthoma elasticum can be caused by mutations in either ENPP1 or ABCC6. *Am J Hum Genet.* 2012;90(1):25-39. doi:10.1016/j.ajhg.2011.11.020
58. Li Q, Schumacher W, Jablonski D, Siegel D, Uitto J. Cutaneous features of pseudoxanthoma elasticum in a patient with generalized arterial calcification of infancy due to a homozygous missense mutation in the ENPP1 gene. *Br J Dermatol.* 2012;166(5): 1107-1111. doi:10.1111/j.1365-2133.2012.10811.x
59. Li Q, Jiang Q, Pfendner E, Váradi A, Uitto J. Pseudoxanthoma elasticum: clinical phenotypes, molecular genetics and putative pathomechanisms. *Exp Dermatol.* 2009; 18:1-11. doi:10.1111/j.1600-0625.2008.00795.x
60. Lefthériotis G, Omarjee L, Le Saux O, et al. The vascular phenotype in Pseudoxanthoma elasticum and related disorders: contribution of a genetic disease to the understanding of vascular calcification. *Front Genet.* 2013;4:4. doi:10.3389/fgene.2013.00004

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