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Cerebrovascular Disease and Stroke (N Rost, Section Editor)

A Diagnostic Approach to Stroke in Young Adults

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Opinion statement

Optimal diagnosis and management of stroke in young adults benefit from a multidisciplinary team, including a vascular neurology specialist. In addition to the "standard" vascular risk factors including smoking, hypertension, diabetes, and hyperlipidemia, one needs to consider alternative etiologies including substance abuse, carotid/vertebral artery dissections, and rare genetic conditions among others. Once a young patient is determined to have had a stroke, the next question a clinician should ask is *why* did this patient have a stroke? A "heart to head" diagnostic approach is recommended. A thorough history is performed, including a detailed family history with specific annotations on each family member. A thorough physical examination is necessary including a careful evaluation of the patient's general appearance, noting any joint laxity, and/or abnormalities of the skin, eyes, and heart. Findings across multiple organ systems in the patient and/or their family may indicate a genetic etiology. After an initial head CT rules out hemorrhagic stroke, additional testing should include a brain MRI, neck and cerebral vascular imaging (e.g., CTA for head and neck), transthoracic echocardiogram with a bubble study, telemetry monitoring, basic risk factor blood work (e.g., lipid panel, hemoglobin A1c, TSH, ESR, CRP, RPR, HIV, and toxicology screen), and, when appropriate, sickle screen and pregnancy test. There should be a low threshold to obtain blood cultures or a lumbar puncture. The acute treatment of ischemic stroke in young adult patients does not differ from treatment of older adults, using intravenous alteplase within 4.5 h, assuming no contraindications. In suspected proximal large artery occlusive disease, interventional clot extraction procedures should be employed in patients deemed eligible. Long-term secondary prevention strategies aimed to reduce recurrent stroke risk by targeting and modifying vascular risk factors should be instituted. The mainstay of preventative therapy

is aspirin for most etiologies; however, for atrial fibrillation, anticoagulation is recommended. Statin therapy is another pharmacologic intervention recommended in most stroke patients. Other measures employed are blood pressure reduction, smoking cessation, optimal glucose control in diabetic patients, the initiation of a healthy diet and regular exercise, and lastly, substance abuse counseling in appropriate patients.

Introduction

Stroke is among the most common and devastating diseases in the USA and worldwide. It is the leading worldwide cause of adult disability and is the fourth leading cause of death in the USA [1, 2••]. Stroke is broadly defined as a brain injury resulting from a vascular insult and can be broadly classified into two primary types, ischemic and hemorrhagic. Ischemic strokes result from insufficient blood flow to the brain leading to neuronal damage and cell death. Hemorrhagic strokes result from blood vessel rupture leading to bleeding into the brain tissue, termed an intracerebral hemorrhage, or into the surrounding brain regions, with such strokes named based on the bleeding location, including subarachnoid, intraventricular, epidural, and subdural hemorrhages.

The definition of "stroke in young" has not been uniformly implemented across many studies, with age ranges from < 44to < 55 years old. At this time, the most accepted definition is any stroke in an adult 18–49 years of age. In recent years, a concerning trend has emerged in which younger patients are having more strokes. Multiple studies have demonstrated that US stroke hospitalizations have increased for patients < 50 years old [3•, 4, 5, 6], this despite an overall decline in stroke hospitalizations and stroke-related death in recent years [3•, 4, 7–10]. Stroke in the young is particularly significant given its tremendous social and economic impact, as patients are left disabled during their peak years of productivity [11]. From an economic standpoint, the burden of young stroke on the healthcare system is thereby also growing. Notably, one study including both young and old patients recently estimated the cost (in US dollars) per hospital stay for patients affected by stroke demonstrating cost differences across stroke subtype as primarily driven by length of stay and stroke severity, ischemic stroke ($34,886), subarachnoid hemorrhage ($146,307), and intracerebral hemorrhage ($94,482) [12–14].

Young patients with stroke shift the diagnostic paradigm in clinical practice, as the etiology of ischemic stroke is different for young patients compared to older patients. The general trend with age is that the proportion of strokes due to large artery atherosclerosis and small vessel disease increase with age [15–17]. The most common identified causes of ischemic stroke in the young in the Helsinki Young Stroke Registry were cardioembolic (18.7%) and cerebral artery dissections (15.5%), small vessel disease (13.9%) and large artery atherosclerosis (8.4%) with a significant amount (33.1%) having an undetermined etiology [16, 18]. Although they were less prevalent, strokes resulting from large artery atherosclerosis or cardioembolic sources have a higher risk of death compared to other etiologies [19, 20]. One study demonstrated a 17-year mortality rate of 60% in large artery atherosclerosis in young patients [19]. Other factors associated with worse outcomes included cardiac disease and previous stroke [21], coronary artery disease [22], active tumor [22], excessive alcohol consumption [22], DM [20, 23, 24], high initial NIHSS score [25], male gender [21], and older age [20, 21]. As with stroke at older age, mortality is highest in the first month and is due to vascular reasons (recurrent stroke, cardiac or aortic causes) a majority of the time. After the first year, the mortality rates decrease significantly to 1.4–1.9% annually [20]. Younger patients with large ischemic stroke are more susceptible than older patients to malignant edema requiring hemicraniectomy and should be followed very closely through peak edema, typically up to 5 days post stroke onset.

The diagnostic workup

The strategy employed in all ischemic stroke patients is to evaluate from "heart to head". This provides a framework for clinicians evaluating all stroke patients, inclusive of young onset stroke patients. The strategy focuses on evaluation for

etiology of the stroke, which in turn, drives the immediate and long-term secondary prevention therapeutic strategies. The "heart to head" approach is usually rapidly done during an inpatient stroke evaluation and includes telemetry heart monitoring, echocardiography, CTA or MRA imaging of the head and neck vessels, and a MRI of the brain. Occasionally, patients will be referred to clinic settings after being discovered to have minor strokes, but the same diagnostic approach is applied in the outpatient setting.

The brain/head

The hyperacute phase of stroke management and evaluation is done within the first few minutes of the patient arriving to the hospital or emergency department. After the airway, breathing and circulation have been deemed to be stable; the first major steps in the evaluation can performed in parallel, including the neurologic history, NIHSS, and a non-contrast CT brain to rule out hemorrhagic stroke. More recently, patients with clinical symptomology suggestive of large vessel occlusion with cortical signs (i.e., gaze preference, aphasia, and neglect) may also undergo a stat CTA of the head and neck; this is to evaluate for interventional thrombectomy candidacy which will be discussed in a later section. After the hyperacute phase of evaluation and treatment including IV tPA in eligible patients, the aforementioned "heart to head" approach is continued. One of the major diagnostic tests performed is a brain MRI. Brain MRI illustrates the area(s) of ischemia on DWI, ADC, and FLAIR sequences and can be helpful in determining stroke etiology. For example, ischemic stroke affecting multiple vascular territories is suggestive of cardioembolic etiologies or vasculitis. The appearance on MRI may also give diagnostic clues to more esoteric causes of strokes, including mitochondrial encephalopathy lactic acidosis and stroke (MELAS) which has an MRI with multifocal infarcts that do not respect vascular territories, potentially with cortical involvement while sparing deeper white matter structures. Another example relates to the MRI finding in cerebral autosomal dominant subcortical infarcts and leukoencephalopathy (CADASIL), which reveals subcortical white matter changes in the extreme capsule, corpus callosum, and the anterior temporal poles' (O'Sullivan's sign) [26]. A watershed infarct pattern suggests a more proximal stenosis, potentially indicating atherosclerotic or dissection etiologies.

Heart

Cardioembolic sources of ischemic stroke are the most prevalent [27, 28]. In contrast to older patients whose main source of cardioembolic stroke is atrial fibrillation, the dysrhythmias are less typical offenders in young. Nonetheless, our first line screening tests of the electrical activity of the heart include a standard 12 lead electrocardiogram and telemetry monitoring to screen for dysrhythmias such as atrial fibrillation, atrial flutter, and sick sinus syndrome. Another rationale for the electrocardiograms is to look for evidence of acute myocardial infarction which can lead patients susceptible to developing a left ventricular thrombus and thus a nidus for cardioembolic ischemic stroke.

The next evaluation of the heart is the structural evaluation. Transthoracic echocardiography with bubble study evaluates for a multitude of potential stroke etiologies including left atrial or left ventricular thrombus, cardiac myxomas, infective and nonbacterial endocarditis,

rheumatic heart disease, degenerative valvular disease, cardiomyopathy, and patent foramen ovale. Bacterial endocarditis was the most common cardiac cause of stroke in young adults in the Baltimore-Washington Young Stroke [29]. Of these causes, cardiomyopathies are a major risk factor in ischemic strokes in children and young adults with estimates ranging between 10 and 100 times greater relative risk in comparison to control groups even higher than HTN and atrial fibrillation [30–32, 33•, 34]. Patent foramen ovale (PFO) is associated with ischemic stroke but management of young adults with ischemic stroke of undetermined etiology and a PFO is controversial; updated guidelines are expected following recent trials [35–37]. PFOs are estimated to be prevalent in 25% of the general population and approximately 50% in young stroke patients [11, 15].

There are clinical circumstances where a cardioembolic source is strongly considered, but a source is not identified by the above strategy. In that case, a transesophageal echocardiogram (TEE) is recommended. A recent study showed that TEE lead to changes in management 16.7% of the time with a majority being treatment of PFO but other etiologies discovered included endocarditis, aortic arch atheroma, intracardiac thrombus, pulmonary arteriovenous malformation, and valve masses [38]. Additionally, patients can be evaluated by extended cardiac monitoring both with external and internal devices. Although there are rare familial cases, atrial fibrillation is uncommon in young adults. Data from older patients suggests that through the utilization of implantable loop recorders, atrial fibrillation was detected in 25.5% of patients with stroke of undermined etiology [39••].

Blood vessels of the head and neck

It is imperative to evaluate the vasculature from the aortic arch through the intracerebral vessels in all stroke patients, especially young stroke patients as the second most common cause of stroke in the young is cervicocerebral arterial dissection accounting for 10–25% of ischemic strokes [28, 40–42]. The extracranial vertebral arteries are most commonly affected [39••]. A large proportion of dissections is spontaneous but others are associated with minor trauma such as coughing, vomiting, sudden head movement, chiropractic manipulation, and sex. Some studies have concluded that migraine, recent infection, hypertension, smoking, pregnancy, oral conceptive use, hyperhomocysteminemia, and the autumn season are predisposing factors to cervicocephalic dissection [43–52]. Carotid duplex is of limited value in evaluation of young onset stroke and CTA of head and neck is preferred initial study due to its greater resolution compared to even MRA with contrast. When cerebral venous thrombosis is suspected, delayed images, e.g., CTV, should be obtained.

Another primary reason for imaging the cerebral and neck vasculature is to evaluate for the various arteriopathies that predispose to stroke. Such entities are generally classified into inflammatory versus non-inflammatory arteriopathies. Fibromuscular dysplasia (FMD) describes a group of non-inflammatory arteriopathies that commonly affects young females causing stroke and refractory hypertension and typically affects the renal and cerebral vessels [53–55]. Angiography demonstrates the pathognomonic "string-of-beads" pattern. Another classic non-inflammatory arteriopathy that is an established

cause of stroke in young (and children) is moyamoya disease, being the cause of 6–15% of nonatherosclerotic vasculopathies [11]. Conventional angiography illustrates the well-known "puff of smoke" appearance resulting from bilateral intracranial carotid artery stenosis/occlusion with associated dilatation of lenticulostriate arteries. The other vasculopathies are listed in Table 1 with associated features to aid in identification when non-specific arteriopathies are discovered on angiography.

Large artery atherosclerosis is one of the more common etiologies in older adults that still must be considered in stroke in young, especially those in their late 30s and 40s with vascular risk factors like diabetes and smoking because large artery atherosclerosis increases after age 35–40 [15–17]. This will be less than 10% of the etiologies in stroke in young [11]. This is an important clinical consideration since the 17-year mortality rate in a recent study was 60% when LAA was determined the etiology of stroke in young [74•].

Other considerations

Concurrent with the "heart to head" evaluation, risk stratification labs are checked which include a lipid panel, HgbA1c, Utox, and TSH (if there is a clinical suspicion for atrial fibrillation) along with the standard CBC and CMP. In stroke care, it is imperative to identify the vascular risk factors in order to most appropriately prescribe a therapeutic regimen for secondary prevention. The "heart to head" method employs tactics to identify major risks of recurrence such as large artery atherosclerosis and heart failure; however, diabetes and heavy traditional risk factors are also independent risk factors of recurrent stroke or myocardial infarction [18]. More commonly encountered vascular risk factors in young are hyperlipidemia (60%), smoking (44%), and hypertension (39%) [16, 75]. Although less common, diabetes is a strong risk factor for stroke in patients younger than 55 years old [76]. In addition to the urine toxicology testing, it is imperative to take a thorough history related to alcohol consumption and recreational drug use. Drug use has been implicated in up to 12% of stroke in young [77] and overuse of alcohol has been identified as an independent risk factor for ischemic stroke in the young [78].

Gender is another factor to consider in stroke in young, with certain stroke etiologies more often associated with young women. There is an increased incidence of stroke in women younger than 30 years old compared to men which may be partially attributable to oral contraceptive use, migraine, pregnancy, and puerperium [79]. Stroke risk in female migraineurs with aura has been shown to be doubled in comparison to those without migraines, with further risk increasing in the presence of OCPs and smoking [80–83]. The triad of migraines, smoking, and OCP must be avoided, as such smoking cessation and discontinuation of OCPs must occur. Pregnancy is a rare cause of stroke but there is an increased risk in the days before birth and up to 6 weeks postpartum with a new study suggesting the increased risk may be up to 12 weeks postpartum [84]. There are other factors including venous infarcts, eclampsia, and reversible cerebral vasoconstriction syndrome (RCVS) playing a role and modulating stroke risk [85, 86].

Hypercoagulable states are an uncommon cause of stroke in young adults and, for most abnormal laboratory findings, evidence is lacking that management should be altered. One notable exception is antiphospholipid antibody

Table 1. Arteriopathies

Non-inflammatory	
Condition	**Clinical pearl**
Fibromuscular dysplasia (FMD)	String of beads sign typically carotid artery
Reversible cerebral vasoconstriction syndrome (RCVS)	Thunder clap headache(s)
	Angiographic segmental cerebral artery vasoconstriction
	Common in exposure to ecstasy, cocaine, serotonergic medications, and sympathomimetic medications
	Female predilection
Radiation-induced vasculopathy	History of radiation therapy to the head/neck
	Fibrotic large arteries
	Accelerated atherosclerosis
Moyamoya	Stenosis in terminal internal carotid arteries
	Puff of smoke appearance on angiography
Fabry disease, Ehler-Danlos type IV, Marfan syndrome, pseudoxanthoma elasticum	See Table 2
Osteogenesis imperfecta	Multiple fractures
	Blue sclera
	Severe hearing loss
	Bone deformities
Adult polycystic kidney disease (ADPKD)	Intracranial aneurysms
	Strong family history
Inflammatory	
Isolated angiitis of the CNS	Men age 50
	Headache and encephalopathy
Giant cell arteritis	Monocular vision changes
	Jaw claudication
	Age > 50
Infectious vasculitis	Related to infectious due to syphilis, tuberculosis, HIV, VZV, bacterial, and fungal
Cerebral vasculitis related to neoplasms	History of cancer especially lymphoma
Secondary CNS vasculitis	History of systemic vasculitis
Eales disease	Young Indian men
	Retinal inflammation
	Vitreal hemorrhages
Susac's syndrome	Retinocochleocerebral vasculopathy
	Young women
	Encephalopathy, vision loss, hearing loss, tinnitus
	Branch retinal artery occlusions
	Central corpus callosum microinfarcts
Acute posterior multifocal placoid pigment epitheliopathy	Chorioretinopathy
	Yellow-white placoid lesions on funduscopic exam

syndrome, with an incidence of five cases per 100,000 persons per year [11, 87]. Antiphospholipid antibody syndrome is associated with increased risk of ischemic stroke and recurrence in young adults [88]. In general, screening for hypercoagulable states in first time ischemic stroke in the young is not recommended. Inherited thrombophilias including factor V Leiden mutation, prothrombin gene mutation, protein C deficiency, protein S deficiency, and antithrombin deficiency are associated with earlier venous thrombosis but there is no clear link with ischemic stroke [89]. However, there is some evidence that these hematological factors may be associated early onset stroke risk in the setting of multiple vascular risk factors [90].

Certain clinical examination findings may suggest genetic disorders associated with ischemic stroke. Table 2 lists many of the established monogenic disorders associated with stroke, including young onset stroke. The table framework highlights many of the key-associated clinical manifestations that infer on the diagnosis. Other young onset stroke etiologies that should be considered include collagen vascular diseases, red cell disorders like sickle cell disease (SCD), platelet disorders, and atypical emboli (fat, tumor, and air cholesterol) in the setting of recent trauma or surgery.

Brief discussion of hemorrhagic strokes

Hemorrhagic stroke is a significant cause of mortality and morbidity among stroke in young patients. The incidence in patients under 45 has been estimated to be 3–6 per 100,000 per year for subarachnoid hemorrhage and 2–7 per 100,000 per year in intracerebral hemorrhage (ICH) [91, 92]. Subarachnoid hemorrhage is associated with aneurysm rupture in the overwhelming majority of cases, with arteriovenous malformations and cavernomas being less common. ICH is estimated to be 10–20% of non-traumatic strokes [93]. Lobar hemorrhage represents the majority of the intracerebral hemorrhages, many of which are hypertensive in etiology even among younger patients. Arteriovenous malformations, cavernomas, drug abuse, and bleeding disorders are other etiologies for ICH. ICH has higher mortality in its early stages and a higher morbidity in comparison to ischemic stroke. ICH mortality in the young is 6.1, 10.3, and 13.7% at 5, 10 and 20 years follow-up respectively and is independently associated with male sex and diabetes [93–97]. Although these young patients fared better than elderly counterparts in these studies, their morbidity was pronounced, with less than half of patients having employment 1 year following stroke [93, 95].

Treatment

Hyperacute therapy

Young adult patients with an ischemic stroke are recommended to be treated with intravenous alteplase (IV tPA) when they do not have any contraindications. The treatment window is 0–3 h within symptom onset per the standard-of-care and up to 4.5 h in certain situations as per AHA guidelines. The benefit from tPA is time dependent so it should be given as quickly as possible with goals traditionally being door to needle time < 60 min which will soon be

Table 2. Mendelian disorders [56–73]

Disease type	Historical pearls	Examination key findings	Inheritance and genetic defect	Diagnostic testing
Large arterial disease				
Homocystinuria	-Failure to thrive in infancy -Thrombotic events in childhood (arterial and venous) -Seizures -Mental retardation	-Marfanoid habitus -Kyphoscoliosis and/or pectus excavatum, Biconcave codfish vertebrae -Brittle and sparse hair -Crowded Teeth -Myopias, glaucoma, ectopia lentis -Foot deformitis	-AR, 21q22.3 -Deficiency of cystathione beta-synthase	-DNA testing -Homocystine is elevated in blood, CSF and urine -Methionine elevated in blood and urine
Familial hypercholesterolemia (type II-a)	-MI at young age -Family history of early MI and hypercholesterolemia	-Xanthomas (Achilles most common) -Xanthelasma -Corneal arcus	-AD, 19p13.2 -Abnormal LDL receptor	-DNA testing -Serum: elevated LDL, elevated cholesterol
Tangier disease (Familial HDL deficiency, type I)	-Early MI -Pain in extremities -Family history of early MI and dyslipidemia	-Orange tonsils -Hepatosplenomegaly -Asymmetric polyneuropathy -Lymphadenopathy	-AR, 9q22-q31	-No genetic testing -Serum: low HDL, low LDL, low cholesterol, elevated triglycerides, low phospholipids, abnormal chylomicron remnants
Moyamoya disease; Spontaneous ccclusion of the circle of Willis—several forms	-Stroke in childhood -Seizures in childhood -Hypogonadotrophic hypogonadism	-Facial dysmorphism in the MYMY4 subtype	MYMY1: AR, 3p26-p24.2 MYMY2: 17q25.3 (RNF213 gene) MYMY3: 8q23 MYMY4: XLR, Xq28 MYMY5: 10q23.31 (ACTA2 gene) MYMY6: AR, 4q32.1 (GUCY1A3)	-No genetic testing -Bilateral internal carotid artery stenosis -Conventional angiogram shows “puff of smoke”
Small vessel disease				
CADASIL—cerebral autosomal dominant; subcortical infarcts and leukoencephaly	-Migraines with aura -Early onset dementia -Mood disoders -Seizures	-Cognitive impairment sometimes with pseudobulbar affect and apathy -Focal neurologic deficits	-AD, 19p13.2-p13.1 -Notch 3 gene	-DNA testing -MRI- Confluent subcortical white matter changes that may extend to temporal lobe

Table 2. (Continued)

Disease type	Historical pearls	Examination key findings	Inheritance and genetic defect	Diagnostic testing
	-Recurrent subcortical infarcts			-MRI changes precede clinical symptoms -O'Sullivan's sign: T2 hyperintensity of the white matter of the anterior temporal poles -Other distinctive findings: extreme capsule and corpus collosum signal abnormalities
CARASIL—cerebral autosomal recessive; subcortical infarcts and leukoencephaly	-More commonly males -Childhood gait disorders due to spasticity -Progressive cognitive and motor decline	-Dementia -Alopecia (early onset in 20s) -Bone deformities especially in the spine	-AR; 10q25; reduced HTRA1 protease activity or loss of protein	-DNA testing -MRI—Diffuse white matter disease and multiple lacunar infarts
Fabry disease	-Lancinating pain especially with heat or exercise -Arthritis -Kidney disease -Delayed puberty	-Eye abnormalities: corneal opacities, tortuous retinal conjunctival vessels, crystalline conjunctival deposits -Angiokeratomas -Neuropathy and autonomic dysfunction	-X-linked, Xq21.33-q22 -Alpha-galactosidase A deficiency -Complete form in males: Males more severely affected -Incomplete form in female carriers	-Skin biopsy, culture of skin fibroblasts
Brain small vessel disease with hemorrhage	-Infantile hemiparesis -Developmental delay and mental retardation -Strokes, recurrent lacunar and hemorrhagic strokes -Seizures -Muscle cramps	-Early onset cataracts, retinal hemorrhages -Axenfeld-Rieger anomaly—developmental eye problem -Dystonia	-AD; chromosome 13q24; COL4A1; missense mutations involving glycine residues in triple helical domain	-DNA testing
Hereditary angiopathy with nephropathy, aneurysms, and	-Painful muscle contractures -Kidney disease and hematuria	-Tortuous retinal arteries and nail beds	-AD, chromosome 13q34 -Mutation cluster in 31 amino acid region of the COL4A1	-DNA testing

Table 2. (Continued)

Disease type	Historical pearls	Examination key findings	Inheritance and genetic defect	Diagnostic testing
muscle cramps (HANAC)	-Recurrent headaches -Seizures		protein encompassing integrin binding sites	
Vasculopathy, retinal, with cerebral leukodystrophy; RVCL (formerly TREX1 and HERNS spectrum)	-Seizures -Migraines -Dementia -Progressive visual impairments -Proteinuria and renal disease	-Telangiecrasias, retinopathy of optic disc, loss of central vision	-AD; 3p21.31 -TREX1 gene	-DNA testing
Early onset stroke and vasculopathy associated with mutations in ADA2 (polyarteritis nodosa, childhood-onset; PAN; ADA2 deficiency)	-Recurrent fevers -Recurrent infections -Strokes in childhood before age 5	-Central retinal artery occlusion, optic nerve atrophy, strabismus -Hepatosplenomegaly	-Autosomal recessive and spontaneous -Loss of function mutation in CERC1 encoding ADA2 protein	
Hematologic diseases				
Sickle cell disease	-Pain crises -Fevers of unknown origin -Patients of African origin	-Retinopathy -Asplenia -Scleral icterus	-AR, 11p15.5 -Missense mutation, valine for glutamate in position 6 of beta hemoglobin chain	-DNA testing -Transcranial Doppler studies: mean blood flow velocity > 200 cm/s is high risk for stroke
Protein C deficiency Protein S deficiency	-Recurrent thrombotic events	-Vitreous hemorrhages Superficial thrombophlebitis	-Protein C—AD, 2q13-q14 -Protein S—AD, 3p11.1-q11.2	-DNA testing
Factor V Leiden mutation	-DVTs		-AR, 1q23	-DNA testing
Mitochondria-based disease				
MELAS—mitochondrial encephalopathy lactic acidosis and stroke	-Seizures -Migraines -Maternally inherited diabetes -Deafness -Visual disturbances	-Short stature -Cataracts, ophthalmoplegia -Multifocal neuropathy -Deafness	-Mitochondrial -Defect in transfer RNA for leucine (A3243G and T3271C)	-Mitochondrial DNA testing -Elevated lactate and pyruvate -Muscle biopsy showing ragged red fibers

Table 2. (Continued)

Disease type	Historical pearls	Examination key findings	Inheritance and genetic defect	Diagnostic testing
	-Weakness, exercise intolerance, myalgias			
Connective tissue disorder				
Ehlers-Danlos syndrome (type IV)	-History of arterial dissections and/or rupture of aneursyms -Easy bruising	-Short stature -Alopecia gingival recession -Thin nose, lips and lobeless ears -Early loss of teeth, periodontal disease -Bladder or uterine prolapse -Hypermobile joints -Hyperextensible skin, wrinkled hands	-AD, 2q31 -Collagen III, alpha-1 gene—COL3A1	-DNA testing
Marfan syndrome	-History of arterial dissections and/or rupture of aneursyms	-Marfanoid habitus -Ectopia lentis, retinal detachments, early cataracts, glaucoma -Micrgnathia -Excessive joint laxity -Striae	-AD, 15q21.1 Fibrillin 1 gene	-DNA testing
Fibromuscular dysplasia	-Headaches -Arterial dissections -Recurrent strokes/TIAs -More common in middle aged white females	-Carotid bruits -Hypertension	-AD	-No genetic testing -Stack of coin appearance of carotid vessels on angiography
Pseudoxanthoma elasticum AD form, AR form	-Epistaxis -Hematuria -Gastrointestinal hemorrhages -Early MI	-Macular degeneration, retinal hemorrhages, angioid retinal streaks -High arched palate -Raised orange-yellow papules called “plucked chicken skin” on neck, axilla, abdomen and inguinal region	-AD and AR (rare) forms,16p13.1 -Defective transmembrane protein ABCC6 (ATP-binding cassette subfamily C, member 6 gene), substrate and function unknown	-Skin biopsy showing fragmented elastic fibers

DVT deep venous thrombosis, *MI* myocardial infarction, *AD* autosomal dominant, *AR* autosomal recessive, *ATP* adenosine triphosphate, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MRI* magnetic resonance imaging

addended to < 45 min [2••]. IV tPA dosage is weight based @ 0.9 mg/kg (maximum 90 mg) with 10% being bolused over the first minute and the remainder being infused over the next 59 min. AHA/ASA guidelines also recommend IV tPA be given to patients who have stroke symptoms 3 to 4.5 h from stroke onset with additional exclusion criteria in this time range including the following: patients > 80 years old, taking any oral anticoagulation regardless of INR, baseline NIHSS > 25, ischemia in more than one third of the MCA territory, and a history of both previous stroke and diabetes mellitus [2••]. The trials that support the use of IV tPA in this extended window are NINDS1&2, ECASS, ECASS2, ECASS3, ATLANTIS, and ATLANTIS-A [98–103]. The most recent data suggest that in the setting of large artery occlusive ischemic stroke, there is benefit of clot retrieval interventional therapies in addition to IV tPA. The recent clinical trials supporting this recommendation include MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, REVASCAT, and THRACE [104–106, 107••, 108••, 109••].

Secondary prevention

Secondary prevention focuses on stopping recurrent strokes. Even young stroke patients demonstrate a significant increase in stroke recurrence (9.4% risk at 5 years) which was attributed to modifiable risk factors [110]. The independent risk factors associated with a 5-year stroke recurrence include diabetes, heart failure, prior transient ischemic attack, large artery atherosclerosis stroke etiology, and traditional risk factors [18]. The highest recurrence risk occurs in the first year after stroke. Hence, it is important to educate patients and their families during the initial hospitalization as well as during subsequent clinic visits regarding the importance of medication compliance and behavioral compliance regarding smoking cessation, a healthy diet, and regular exercise, these among others [18].

Antithrombic therapy

Aspirin is the main therapy for secondary prevention in ischemic strokes not caused by atrial fibrillation [111, 112]. There is some data to suggest a benefit of dual-antiplatelet therapy in the setting of intracranial atherosclerosis following TIA or minor ischemic stroke for 21 and 90 days, as based on the CHANCE and SAMMPRIS studies, respectively [113, 114].

Anticoagulant therapy

Anticoagulation is indicated in the treatment of ischemic stroke due to atrial fibrillation. The recurrence rate of cardioembolic stroke due to atrial fibrillation has been shown to be approximately 8% within 1 week [115]. Studies comparing warfarin to aspirin have consistently demonstrated warfarin superiority for preventing ischemic stroke in atrial fibrillation [116]. Other novel oral anticoagulants have also been studied for prevention of ischemic stroke. Positive studies include ROCKET-AF, ARISTOTLE, and RE-LY [117, 118•, 119]. ROCKET-AF demonstrated that rivaroxaban dosed at 20 mg was not inferior to warfarin and conferred less bleeding risk except gastrointestinal bleeds [117]. ARISTOTLE evaluated apixaban dosed at 5 mg twice a day and showed superiority to warfarin in stroke

prevention with secondary outcomes demonstrating less ICH, major bleeding, and death [118•]. Dabigatran 150 mg twice a day was shown to be superior to warfarin in terms of stroke prevention and ICH risk but there was a significant risk for gastrointestinal bleed [119].

One unique consideration in stroke in young patients is empiric anticoagulation therapy. There is no robust data to guide this therapeutic consideration from a purely evidence-based perspective. However, one can consider using empiric anticoagulation in young patients with recurrent ischemic stroke of undetermined etiology. Although in young stroke patients age by definition would be scored zero, the CHA_2DS_2-VASc risk score can and should be utilized to help infer on anticoagulation use (https://www.mdcalc.com/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk). The ongoing Embolic Stroke of Unknown Source (ESUS) trial will help guide future treatment considerations [120].

Modification of vascular risk factors

Statin therapy

Statin therapy remains a mainstay in for secondary stroke prevention. This is especially true in patients with atherosclerotic risk factors as supported by the SPARCL trial [121]. Although in young stroke patients with non-atherosclerotic risk factors, this remains a topic of debate; however, statins were associated with less recurrent vascular events in young patients with stroke of undetermined etiology [122].

Blood pressure management

The AHA recommends long-term blood pressure management goals of < 140/90 mmHg in non-diabetic patients and < 130/90 mmHg in diabetic patients.

Diet and exercise

In all patients who have experienced a stroke, optimal diet and exercise habits are recommended. Patients should participate in 30 min of moderate exercise at least 3 days a week. We recommend the DASH and Mediterranean diets [123, 124]. For those with diabetes, diabetic diets with low glycemic index are recommended.

Smoking cessation

Patients are counseled during the acute stroke hospitalization, as well as at all subsequent clinical encounters, about the importance of smoking cessation for prevention of subsequent stroke. This is especially important in young stroke patients whose strokes (both ischemic and hemorrhagic) are associated with cigarette smoking [125, 126]. Regarding e-cigarettes, the short-term and long-term health effects are not well established at this time and are an area of intense research.

Diabetes management

Although diabetes is less prevalent in the young as compared to the elderly, screening for diabetes in young stroke patients should be performed. Those who do have diabetes have an estimated 2- to 6-fold increase in stroke risk emphasizing the importance of optimal glucose control [11]. NOMAS investigators found that the risk of ischemic stroke increased 3% annually and tripled in patients with diabetes more than 10 years. Therefore, such patients are referred for diabetes education and follow up with either a primary care physician or endocrinologist depending on diabetic severity.

Surgical procedures

Surgical procedures are reserved for patients with symptomatic carotid stenosis. This is defined as patients with an ischemic stroke in the distribution of an atherosclerotic internal carotid artery. Carotid endarterectomy (CEA) and/or carotid artery stenting (CAS) is recommended in patients (< 70 years old) with TIA or ischemic stroke in the setting of severe ipsilateral carotid artery stenosis defined as 70–99%, this when perioperative morbidity and mortality is 6% or less [127, 128]. Patient specific factors including age, gender, and medical comorbidities should be considered for CEA/CAS with symptomatic carotid stenosis in the 50–69% range [127, 128].

Rehabilitation

Early and intensive multidisciplinary rehabilitation is employed in all stroke patients who are physically able. Physical and occupational therapists begin the rehabilitation assessment and planning process during the acute stroke hospitalization. Following medical workup completion, patients are frequently transferred to an acute rehabilitation facility where physical, occupational, and speech therapists aim to improve the patient's functional recovery of motor, cognitive, speech, and task-related skills.

Special and pediatric treatment considerations

Sickle cell disease (SCD) is one stroke etiology that employs a disease-specific treatment regime. The landmark STOP trial demonstrated that children (2–16 years old) with elevated transcranial doppler velocities ≥ 200 cm/s should be treated with exchange transfusions for primary stroke prevention [129]. Unfortunately, in older adolescents and young adults with SCD, such clear guidelines do not exist. Typically, patients are not screened beyond the age of 16 years given the absence of data supporting the utility of TCD screening above age 16 years and the changing patterns of cerebral blood flow velocities above this age. This strategy is consistent with recommendations from several groups including the 2014 SCD guidelines from the National Heart, Lung, and Blood Institute [130] and a 2004 publication from the American Academy of Neurology [131]. Lastly, patients with Fabry disease are treated with recombinant alpha galactosidase-A replacement therapy to reduce disease-related complications, but its efficacy in stroke reduction is unclear [132].

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Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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