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Cerebrovascular Disease and Stroke (D Greer, Section Editor)

Cryptogenic Stroke—The Appropriate Diagnostic Evaluation

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Opinion statement

Ischemic strokes are a significant cause of morbidity and mortality in the United States. They may be due to large artery atherosclerosis, small vessel occlusion, cardioembolism, or other less common mechanisms such as toxins, hypercoagulable disorders, and vasospasm. Each mechanism carries its own risk of recurrence and prognosis. Strokes without an identifiable cause despite a complete work-up are described as cryptogenic. Cryptogenic stroke therefore is a diagnosis of exclusion, and one that should not be arrived at haphazardly. One must complete a thorough, and frequently challenging, stroke work-up prior to this diagnosis. Challenges in determining stroke etiology include the transient nature of precipitating events such as vasospasm or cardiac arrhythmias, variable durations of cardiac monitoring, and unclear significance of certain cardiac structural anomalies. Many consider cryptogenic stroke to be a heterogeneous combination of paroxysmal and occult conditions that create such diagnostic difficulties. The diagnosis of cryptogenic stroke itself carries with it specific outcomes and prognosis. This article will provide an overview of the definition and epidemiology, recommendations for diagnostic evaluation, and risks of recurrence of cryptogenic stroke.

Definitions and epidemiology

Stroke affects approximately 795,000 people per year (or about one person every 40 seconds) in the United States alone [1••]. Approximately one quarter of these are recurrent events. The Medical Expenditure Panel

Survey (MEPS) estimated the direct medical cost of stroke in 2010 to be $20.5 billion (including inpatient hospital stays, outpatient visits, ED visits, prescribed medication and home health care) [2]. The prevalence of stroke is highest in older adults, African Americans, those with lower levels of education, and people living in the southeastern United States [3].

One goal of inpatient hospitalization is to determine stroke etiology, thus minimizing the risk of further events. The vast majority of strokes are ischemic, and ischemic strokes are further subdivided by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. These subdivisions include large artery atherosclerosis, small artery occlusion (lacunar), cardioembolism, stroke of other determined etiology (eg, hypercoagulable state, vasculopathy), and stroke of undetermined etiology, or "cryptogenic" stroke [1••, 4].

Many studies have investigated age in relation to cryptogenic stroke. The Northern Manhattan Stroke Study (NOMASS) found that patients younger than 45 years had a higher incidence of cryptogenic stroke than those over 45 years (55 % and 42 %, respectively) [5].

As of 2010, 2.7 % of men and 2.6 % of women ≥18 years old had a history of stroke [3]. The incidence of stroke in women, however, appears to be increasing compared with men. Data gathered from the National Health and Nutrition Examination Surveys from 1999 2004 (n=17,061) found that women 45 to 54 years old were more than twice as likely to have a stroke than men in the same age group [6]. In the Framingham Heart Study, the lifetime risk of stroke for women 55–75 years old was one in five, vs 1 in 6 for men of the same age [7]. To our knowledge, however, the incidence of cryptogenic stroke does not appear to differ by gender.

The incidence of all subtypes of stroke, including cryptogenic stroke, is higher in African Americans and Hispanics than whites [8]. The Greater Cincinnati/Northern Kentucky Stroke Study measured incidence rates and trends of all strokes in a biracial population from 1993–1994, and found that cryptogenic stroke was twice as common in African Americans than in Whites (125 vs 65 per 100,000 persons) [9]. A prospective analysis of Mexican Americans, African Americans, and Caucasians with stroke found that Mexican Americans had the highest frequency of cryptogenic stroke (46 %) [10]. Interestingly, a prospective analysis comparing stroke subtypes in Hispanic patients found that cryptogenic stroke was nearly twice as common in those living in Mexico City than those in Miami (20.5 % vs 11.4 %). Those in Miami were largely of Caribbean descent, suggesting heterogeneity in the Hispanic population [11].

Appropriate stroke work-up, including brain and cardiac imaging, vessel imaging, laboratory studies, and cardiac monitoring may provide insight into stroke etiology and propensity for future events. In many cases an identifiable cause is not found, or alternatively, multiple plausible causes may be uncovered. These strokes are typically defined as cryptogenic, and constitute about 30–40 % of all strokes [9, 12, 13]. It should be noted that the extent of work-up may vary depending on the institution or practitioner, and therefore less common causes of stroke (vasospasm, vasculitis, infection, toxins) may be missed and erroneously labeled as cryptogenic. The etiology of stroke may also be transient or reversible (paroxysmal atrial fibrillation, or PAF), giving importance to the timing and duration of work-up [14]. Other potential etiologies of stroke remain controversial (patent foramen ovale, or PFO) and create ambiguity regarding management. We address these issues and others in the sections ahead.

Risk factors and evaluation

Imaging

In the evaluation of an acute stroke patient, neuroimaging is critical to rule out intracerebral hemorrhage. Computed tomography (CT) is ideal in this setting because of the rapidity in which a scan can be obtained (minutes), as well as its sensitivity for detecting acute hemorrhage. Magnetic Resonance Imaging (MRI) can be obtained in the urgent setting if there is diagnostic uncertainty (ie, acute stroke vs a stroke mimic such as seizure or migraine) or to identify subgroups that may benefit from intravenous thrombolysis or

interventional vascular treatments [15]. MRI is more sensitive than CT for ischemic stroke in the acute setting, and is typically obtained after the acute period of the evaluation to better visualize ischemic burden. MRI, however, takes more time to obtain, has more contraindications, and may not be available at all hours in some institutions.

Evaluation of the cerebral vasculature also has multiple options. Whether one is evaluating carotid occlusion from atherosclerosis or traumatic cervical artery dissection in a younger patient, it is important to know the strengths and weaknesses of the modalities available. Conventional angiography is considered the gold standard for imaging the intra- and extracranial vasculature, but this method is highly invasive, time consuming, expensive, and carries higher morbidity than other less invasive options. Computed Tomography Angiography (CTA) or MR Angiography (MRA) can be used to detect large vessel stenoses or occlusions more rapidly. CTA and MRA both have comparable sensitivity (92 %–100 % vs 86 %–97 %, respectively) and specificity (82 %–100 % vs 62 %–91 %, respectively) compared with conventional angiography [16]. CTA is easier to acquire than MRA, because of its higher availability in emergency rooms. Both CT and CTA can be done concurrently, thus avoiding the need for patient transfer and delays in therapy. It should be noted that CTA requires iodinated contrast, and therefore should be used with caution in patients with renal disease [17]. As with CT, CTA also exposes the patient to significant amounts of radiation. Carotid duplex ultrasound and transcranial Doppler (TCD) are additional noninvasive methods to evaluate the intra- and extracranial vasculature. Carotid ultrasound uses Doppler and B-mode ultrasound imaging to detect focal increases in blood flow velocity (specifically peak systolic velocity), which could indicate underlying focal vessel stenoses [18]. Carotid ultrasound is safe, inexpensive, and is 81 %–98 % sensitive in detecting significant internal carotid artery (ICA) stenoses [18, 19]. Disadvantages include a tendency to overestimate the degree of stenoses, and the quality of studies may be limited by tortuous or kinked arteries, patient body habitus, and operator variability. Peak systolic velocity may also be increased in the setting of contralateral ICA stenoses, potentially leading to overestimation of stenoses [20]. TCD measures velocity of blood flow through intracranial vessels. In stroke patients, TCD can be used to identify intracranial stenoses, to evaluate collateral vasculature, and to monitor reperfusion after thrombolysis [21–23]. TCD is a safe, inexpensive option and can be done at the bedside. Limited availability, however, due to lack of qualified ultrasonographers is a major limitation.

Large artery disease

Carotid artery atherosclerosis typically occurs at the bifurcation of the common carotid artery, and was first described in the literature by C. Miller Fisher in 1951 [24]. A growing plaque will progressively occlude a vessel (in our case extracranial carotid arteries), and can lead to a clinically significant stenoses by compromising cerebral perfusion. Sequelae of carotid stenoses include ipsilateral stroke, amaurosis fugax, or transient ischemic attack (TIA) from impaired perfusion or embolism. Carotid stenoses is more commonly seen in older patients with risk

factors such as hypercholesterolemia, hypertension, and diabetes mellitus, and less commonly in younger patients.

In the younger population, cervical artery disease (involving carotid or vertebral arteries) can occur from direct injury to the vessel wall leading to dissection. Presenting symptoms may be as nonspecific as headache and neck pain, but could also include Horner syndrome, cranial neuropathies, and long tract signs (weakness, numbness). Dissection may occur from mild to severe physical trauma, or from an underlying genetic or connective tissue disorder leading to a separation between the intima and media layers of the vessel wall. Spontaneous cervical artery dissection accounts for up to 25 % of strokes in young and middle aged patients [25, 26]. For these patients, one should consider screening for an underlying connective tissue or vascular disorder such as Ehlers-Danlos Syndrome type IV (mutation in the *COL3A1* gene (OMIM 13050), Marfan Syndrome, or Fibromuscular Dysplasia [27, 28].

A dissected vessel creates a false lumen within the wall that can lead to thrombus formation or vessel stenoses/occlusion. Diagnosis of dissection is made by vessel imaging and defined by the presence of a mural hematoma in the arterial wall; both CTA and MRA have relatively similar sensitivity and specificity in this setting [29]. CTA, as previously stated, has the advantage of quicker acquisition, with fewer contraindications and the ability to provide three-dimensional reconstructions and greater spatial resolution compared with MRA [17]. CTA should be used with caution in younger patients (especially females of child bearing age), however, as the use of ionizing radiation is concerning, and in patients with renal insufficiency because of nephrotoxic contrast dye [17]. MRA, when done concurrently with MRI, can also more readily diagnose acute stroke. Axial T1 fat-suppressed images can visualize methemoglobin of an intramural hematoma within the false lumen—commonly referred to as the "crescent sign"—which could support the diagnosis [30, 31]. Other imaging findings suggesting dissection include the "string sign" (intraluminal narrowing), "flame sign" (tapered occlusion sparing the carotid bulb), and an intimal flap. Conventional angiography may be pursued if suspicion remains high despite a negative CTA or MRA, and long-term follow-up may be performed with carotid ultrasound.

Cardioembolism

Cardiac arrhythmia and subsequent thrombus formation is a common source of cardioembolic stroke. Many patients do not have a known history of cardiac arrhythmia at initial presentation with stroke; therefore, cardiac monitoring is vital to determine long-term management and secondary prevention. Electrocardiography (ECG) is useful to rule out concomitant cardiac ischemia or to screen for cardiac arrhythmias. A standard 12-lead ECG does not rule out paroxysmal arrhythmias, such as atrial fibrillation (AF); therefore, all patients should receive continuous cardiac telemetry (CCT) during admission. The reliability of CCT, however, is inconsistent due to reader variability and inconsistent monitoring periods. Prolonged cardiac monitoring beyond the inpatient admission stage should be strongly considered, especially in patients with cryptogenic strokes that appear embolic

based on neuroimaging characteristics. Studies have shown prolonged monitoring (24–72 hours) to be superior to CCT at detecting new paroxysmal atrial fibrillation or flutter [32, 33]. A study of 56 patients with cryptogenic stroke used 21-day monitoring with mobile cardiac outpatient telemetry (MCOT) found that the median monitoring time before detection of an arrhythmia was 7 days (range 2–19 days) [34]. Another study showed that event loop recording for 7 days detected AF in 5.7 % of patients who had normal ECGs and 24-hour Holter monitoring [35]. This suggests that longer monitoring periods (>7 days) should be considered if no arrhythmia is detected with preliminary monitoring.

Small vessel occlusion/chronic disease

Common treatable risk factors for ischemic stroke include hypertension, diabetes mellitus, hypercholesterolemia and smoking [1••]. Chronic conditions such as hypertension and atherosclerotic occlusive disease predispose patients to small vessel occlusion, resulting in small subcortical (lacunar) infarcts [36–38]. Recent data has also shown that sleep apnea can increase stroke risk two-fold, independent of other risk factors [39–41]. Suggested work-up following ischemic stroke for metabolic conditions include serial blood pressure monitoring, fasting serum glucose, hemoglobin A1C, and lipid profile. Polysomnography may be pursued if there is a clinical suspicion for sleep apnea.

Other etiologies: substance abuse

Epidemiologic data has demonstrated associations between smoking, stroke risk, and mortality. Tobacco use is a well-established risk factor for all types of vascular disease, and increases the risk of both ischemic and hemorrhagic stroke [42, 43]. Men who smoke ≥20 cigarettes daily experience a two-fold increased risk of intracerebral hemorrhage and ischemic stroke, and a three-fold increased risk of subarachnoid hemorrhage compared with nonsmokers [43]. Women who smoke ≥15 cigarettes daily experience greater than two-fold increased risk of ICH and four-fold increased risk of subarachnoid hemorrhage [42]. There is strong evidence that chronic alcohol use is also a risk factor for all stroke subtypes. Most studies have shown a J-shaped association between alcohol intake and risk of stroke, with consumption of >60 g of alcohol daily increasing the risk of both ischemic and hemorrhagic stroke [44–46]. Screening for alcohol and tobacco use is therefore an essential component of primary and secondary stroke prevention.

Illicit drug use has also been associated with increased stroke risk. Brust and Richter reported stroke associated with intramuscular cocaine use in 1977 [47]. Since that time, there have been over 700 documented cases of cocaine-related stroke, either involving intranasal or intravenous use of cocaine hydrochloride or inhalation of alkaloidal “crack” cocaine [48]. Cocaine functions by blocking the presynaptic re-uptake of dopamine, norepinephrine, and serotonin. Elevated levels of these monoamines have been angiographically proven to cause cerebral artery vasoconstriction [49]. One study showed an association between cocaine use and ischemic stroke (adjusted

odds ratio 2.03; 95 % CI, 1.48–2.79) as well as ICH (adjusted odds ratio 2.33; 95 % CI, 1.74–3.11) [50]. Urine toxicology screens should be obtained in the evaluation of acute stroke, especially in younger patients, if a patient does not have other vascular risk factors, or if clinical suspicion is high in older patients.

Other etiologies: cardiac structural abnormalities

The American College of Cardiology and American Heart Association recommend obtaining a transthoracic echocardiogram (TTE) in all patients with acute stroke, especially if an embolic stroke is suspected, to rule out a cardiac source of thrombus or right to left shunt [51]. Echocardiography is also useful to uncover other cardiac structural abnormalities. Transesophageal echocardiography (TEE) is superior to TTE in this respect because of higher resolution, capacity to evaluate the aorta as well as identify small sources of emboli, and may be pursued if suspicion remains high despite a normal TTE [52]. Atrial septal abnormalities, specifically PFO or atrial septal defect (ASD), and atrial septal aneurysm (ASA) have been associated with stroke, although clear causal relationships have been difficult to prove. A higher incidence of these anomalies is found in patients with cryptogenic stroke.

Patent foramen ovale

A PFO is a flap-like valve that connects the right and left atria. It is instrumental in the fetal circulation by allowing oxygenated blood to bypass the immature lungs and pass directly into the left atrium. A PFO typically closes after birth, but may remain open in up to 25 % of adults, creating a shunt between the right and left atria [53, 54]. A meta-analysis of case control studies showed the prevalence of PFO is higher in cryptogenic stroke, specifically in patients <55 years of age but not in those 55 years of age or older [55].

A proposed mechanism of ischemic stroke in the setting of an atrial septal abnormality like PFO is paradoxical embolism from a distal source (deep vein thrombosis in the lower extremity or pelvis, or thrombi from the atrial septal defect or transient atrial arrhythmias) [56, 57]. The embolus then migrates directly into the arterial vasculature through a cardiac atrial or ventricular septal defect, essentially bypassing the pulmonary circulation. An observational study of 42 patients found a source of venous embolism in over half (24) of the patients with PFO and stroke [58]. The PELVIS study found that cryptogenic stroke patients had higher rates of deep pelvic vein thrombosis (20 %) seen with magnetic resonance venography (MRV) imaging than in patients with stroke of determined origin (4 %) [59].

The significance of uncovering a PFO in the setting of acute ischemic stroke has been widely debated. It is not known whether surgical or percutaneous closure is an effective form of secondary stroke prevention in cryptogenic stroke, and multiple trials have investigated closure vs medical therapy alone. The CLOSURE I trial (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale) provides some of

the best evidence to date regarding the role of PFO closure in stroke prevention. Adult patients ≤60 years old with PFO and cryptogenic stroke or TIA were randomly assigned to PFO closure (n=447) or medical therapy alone (n=462) [60, 61]. Those in the closure group were also placed on an aspirin plus clopidogrel regimen for 6 months followed by only aspirin, and those in the medical therapy group were given aspirin, warfarin, or both. The primary endpoint was a composite of stroke or TIA at 2 years plus 30-day mortality and neurologic mortality beyond 30 days. The results found that PFO closure failed to show superiority over medical treatment alone in preventing stroke or TIA at 2 years [61]. A limitation to this trial was inclusion of patients with transient ischemic attack (TIA). Patients with TIA do not have positive imaging to confirm an ischemic process; therefore the diagnosis is heavily dependent upon clinical judgment (creating a possibility of misinterpretation of stroke mimics such as migraine or seizure) [62]. In addition, the study included a large number of patients with lacunar stroke—which has a mechanism unrelated to PFO. Objections to the use of the STARflex system include higher rates of postoperative AF (2.4 %) vs medically treated patients (0.6 %) suggesting device arrhythmogenic potential, and a high rate of device related thrombus formation compared with other closure systems (6 % in prior studies but 1.1 % in CLOSURE I) [62, 63]. Finally, some argue that the follow-up time (2 years) was too short to truly assess PFO-related events, and that a much longer follow-up period was needed [62, 63].

The RESPECT trial (closure of a PFO with Amplatzer PFO Occluder compared with medical therapy alone) randomly assigned patients aged 18–60 with cryptogenic stroke and PFO to medical therapy alone (aspirin, clopidogrel, warfarin, or combination aspirin/dipyridamole, n=480) vs closure via the Amplatzer PFO Occluder (n=499) [60]. Closure patients were also placed on aspirin and clopidogrel for 1 month, followed by aspirin monotherapy for 5 months. The primary end point was a composite of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death after randomization, with a mean follow-up time of 2.6 years. This study excluded patients with a TIA or stroke mechanism other than paradoxical embolism (large or small vessel disease, cardioembolic source, or known hypercoagulable state were all excluded). Nine patients assigned to the device group had a recurrence of ischemic stroke compared with 16 in the medical therapy group (hazard ratio, 0.49; 95 % CI, 0.22 to 1.11; P=0.08). These results also did not find a significant benefit of surgical closure over medical therapy in the intention to treat analysis. A limitation of this study is the disproportionate dropout rate between the device group and medical therapy groups (48 vs 90, respectively), resulting in unequal exposure to the two treatment options, potentially complicating interpretation of the results.

The PC Trial investigators randomly assigned 414 patients to closure (Amplatzer PFO Occluder) or to medical therapy, and followed them for an average of approximately 4 years, and also failed to find a significant reduction in recurrent embolic events or death after closure [64]. One patient in the device group had a nonfatal stroke compared with five in the medical therapy group (hazard ratio, 0.20; 95 % CI, 0.02 to 1.72; P=0.14). The incidence of clinical atrial fibrillation increased by a factor of 10 in the CLOSURE I trial, compared with an increase by a factor of

2–3 in both RESPECT and PC Trials, suggesting a superior safety profile of the Amplatzer device compared with the STARflex device [65].

Atrial septal aneurysm

An ASA is defined as a hypermobile, redundant piece of tissue in the inter-atrial septum in the region of the fossa ovalis, and demonstrates at least 10–15 mm of excursion from the centerline during the cardio-respiratory cycle [66, 67]. Initially found in 1 % of consecutive autopsies [66], the incidence of ASA increased to 4 % in unselected patients and as high as 15 %–39 % in stroke patients using transesophageal echocardiography [67–70]. Cabanes et al found the risk of stroke to was approximately eight times higher for those with ASA >10 mm of excursion compared with those with <10 mm [67].

Aortic atheroma

Embolism from aortic atheroma has been proposed as a potential mechanism for cryptogenic stroke. A prospective case-control study of patients >60 years old with acute ischemic stroke found atheromatous plaques >4 mm in thickness in 14 % of patients compared with 2 % of controls [71]. Aortic plaques >4 mm were much more common in infarcts of unknown cause (relative risk 4.7). Using cardiac MRI, some propose that complex atheromas in the descending aorta could lead to stroke via retrograde flow [72, 73]. In one study, retrograde flow in the descending aorta reached the great vessels supplying the brain in up to 24 % of patients with cryptogenic stroke [73].

Other etiologies: hypercoagulable state

Ischemic stroke may also occur from an underlying hypercoagulable state, although literature is still limited. Coagulopathy may result from platelet dysfunction, inherited or acquired thrombophilia, or from malignancy. Hypercoagulable disorders are more often associated with venous thromboembolism rather than arterial ischemic stroke [74]. Sickle-cell disease is the most common cause of stroke in children, with rates of stroke 300 times higher than in children without the disorder [75, 76]. The highest risk of stroke is with the SS genotype [77].

Other inherited thrombophilia are less clear. A meta-analysis of 22 observational studies that included 1,526 children with ischemic stroke, 238 with cerebral venous sinus thrombosis and 2,700 test subjects, found that the hematological conditions imparting the highest risk of ischemic stroke were the presence of two or more genetic thrombophilia factors (summary odds ratio (OR) 18.6, 95 % CI 6.5–54.1) and Protein C deficiency (OR 11.0 95 % CI 5.1–23.6) [78]. Other conditions with statistical significance included the presence of antiphospholipid antibodies (OR6.95; 95 % CI, 3.67–13.14), Factor V Leiden mutation (OR 3.7; 95 % CI, 2.29–5.53), Antithrombin III deficiency (OR 3.29; 95 % CI, 0.70–15.48), and methylene tetrahydrofolate reductase (MTHFR) TT genotype (OR 1.6; 95 % CI, 1.20–2.08).

Table 1. Suggested hypercoagulable workup

Suggested hypercoagulable panel
CBC
Protein C Functional
Protein S free and total or Protein S Functional
Antithrombin III activity
Prothrombin 20210a mutation
Factor V Leiden gene mutation
Anticardiolipin antibodies (IgG and IgM)
Lupus anticoagulant tests, including dilute Russell viper venom time
Factor VIII activity
D-dimer
Homocysteine
ESR, CRP
Anti-beta-2-glycoprotein-1 antibody

MTHFR is a rate limiting enzyme in the methyl cycle, catalyzing the formation of a substrate that is required for remethylation of homocysteine to methionine [79]. A genetic mutation leading to a thermolabile variant of MTHFR leads to reduced enzyme activity and subsequently hyperhomocysteinemia. Homozygosity for the mutation (TT type) confers a 16 % higher odds of coronary heart disease compared with controls (odds ratio 1.16, 95 % CI 1.05–1.28), and is associated with an increased risk of silent ischemic infarcts (OR 1.72; 95 % CI, 1.10–2.68) [79, 80].

Antiphospholipid antibody syndrome (APS) is characterized by both arterial and venous thrombosis, with deep veins of the lower limbs and cerebral arteries being the most common sites involved [81]. APS is also associated with increased morbidity during pregnancy (pre-eclampsia, preterm delivery, and unexplained, early spontaneous miscarriage) [82]. Diagnosis requires vascular thrombosis or pregnancy morbidity with any of the following serum studies: positive lupus anticoagulant (LA), anticardiolipin antibody IgG or IgM, or anti-B2-glycoprotein-1 antibody IgG or IgM [82]. For diagnosis of APS, antibody titers should be positive on two or more occasions at least 12 weeks apart.

An excess of red blood cells (polycythemia) or platelets (thrombocytosis) increases serum viscosity resulting in sluggish flow. This can lead to an increased risk of clotting, especially in a dehydrated patient [83]. Investigation for thrombophilia should be performed in all cases of arterial ischemic stroke in children [84], spontaneous venous thrombosis, unprovoked or recurrent thrombosis at any age, positive family history for thrombosis, thrombosis during pregnancy, oral contraceptives or hormone replacement therapy, or thrombosis of unusual sites (cerebral, mesenteric, portal, or hepatic veins) [85]. Associating hypercoagulable states with ischemic stroke in older patients remains controversial, especially in patients with other known risk factors. In addition to obtaining a detailed family and birth history to rule out traumatic causes of stroke, Table 1 lists suggested studies useful to evaluate for a hypercoagulable state.

Table 2. Suggested stroke work-up

Stroke workup	Suggested studies
Neurological Imaging	CT/CTA
	MR/MRA
	Carotid Doppler
	Transcranial Doppler
	Conventional Angiography
Cardiac Workup	TTE/TEE
	Continuous Telemetry
	Serial Blood Pressure monitoring
	Holter monitoring
	Event Loop Recorder
Laboratory Studies	CBC
	Basic Metabolic Panel
	Lipid profile
	Hemoglobin A1C
	Fasting Glucose
	Urine toxicology screen
	Hypercoagulable panel
Ancillary Studies	Polysomnography
	Smoking, EtOH screens

Prognosis and outcomes

A study of functional status among patients with ischemic stroke subtypes showed that patients with cryptogenic ischemic stroke scored better on the modified Rankin scale (<2) compared with patients with large vessel atherosclerosis or cardioembolism, but worse compared with those with lacunar infarct [86]. Mortality at 1 year in cryptogenic stroke patients was higher than in those with lacunar stroke, but less than those with cardioembolic stroke [86, 87].

The short-term recurrence risk of cryptogenic stroke lies between the low risk of small vessel lacunar stroke and high risk of large vessel disease. In the NINDS Stroke Data Bank, 3 % of patients with cryptogenic stroke had recurrent events within 1 month [88]. In the NOMASS study and Oxford meta-analysis, the recurrence rates at three months were 3.7 % and 5.6 %, respectively [89, 90]. The recurrence rates at 5 years are not significantly different from other stroke subtypes [86].

Conclusions

Cryptogenic stroke is a diagnosis of exclusion, defined as an ischemic infarct not attributable to large vessel disease, small artery disease, cardioembolism, or other determined etiology. It accounts for one-third of ischemic stroke cases, and may be more prevalent in African American and Hispanic populations. A thorough evaluation (Table 2)

using historical data, vascular imaging, cardiac evaluation (acute and prolonged monitoring), toxicology screens and hematological studies must be performed before a diagnosis of cryptogenic stroke is made, as the results of these studies can dramatically alter outcomes and prognosis.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Hardik Amin declares that he has no conflicts of interest.
Dr. David M. Greer serves as a Section Editor for Current Treatment Options in Cardiovascular Medicine.

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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