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Cerebrovascular Disease and Stroke (N Rost, Section Editor)

Etiologic Stroke Subtypes: Updated Definition and Efficient Workup Strategies

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Opinion statement

Stroke affects approximately 16.9 million individuals per year worldwide and is the second leading cause of death. Stroke represents a family of related, but distinct subtypes. Classifying stroke subtypes must take into account various aspects of a standardized stroke workup to allow optimization of treatment and prevention strategies. Secondary prevention and pharmacologic treatment is tailored based on stroke mechanism. Additionally prognostication and recurrent risk also depends on stroke etiology. Efficient workup of stroke relies on a thorough history, clinical examination, imaging studies, and putative mechanism of stroke that lead the treating physician to a particular etiological path. Here , we provide the reader with updated definitions of etiologic ischemic stroke types as well as efficient workup strategies.

Introduction

Stroke affects approximately 16.9 million per year worldwide and is the second leading cause of death [1, 2]. In the United States alone, annual incidence approaches 800,000 strokes per year, and a quarter of these are recurrent strokes. Recurrent stroke has a higher mortality rate than first-ever stroke and contributes to a greater cognitive decline [3]. In recent years, advances in lifestyle modifications, neurolog-

ical imaging, and pharmacological and surgical interventions for secondary stroke prevention have reduced stroke mortality, but the overall burden of cerebrovascular disease continues to grow with the aging of the US population. Risk factors (modifiable and non-modifiable), clinical presentations, imaging findings, and treatments vary based on specific stroke subtypes [4]. Diagnosis and workup of stroke focuses on establishing and classifying stroke etiology as it relates directly to stroke etiology classification systems. In this review article we aim to provide the reader with updated definitions of etiologic ischemic stroke types as well as efficient workup strategies.

Stroke definition

In the 1970s, the World Health Organization (WHO) defined stroke as "rapidly developing clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin" [5]. This standard definition, which continues to be widely accepted, includes cerebral infarction, primary intracerebral hemorrhage, and subarachnoid hemorrhage. Since 1978, our knowledge of the natural history of stroke, risk factors, and neuroimaging has advanced substantially. Such growth in knowledge has urged us further to understand the stroke types based on clinical presentation, risk factors, and lab and imaging results.

Ischemic vs. hemorrhagic stroke

The first and most important step in stroke classification is to differentiate ischemic versus hemorrhagic stroke. Ischemic stroke accounts for 80 % to 85 % of all strokes within the Western population [6]. Regional loss of cerebral blood flow due to stenotic or occluded cerebral vasculature causes ischemic stroke. Even though hemorrhagic strokes only account for 15 % to 20 % of all strokes, they result in significantly higher morbidity and mortality rates compared to ischemic strokes. Hemorrhagic strokes are caused by rupture of cerebral vasculature. Broadly, we classify hemorrhagic strokes into two types: subarachnoid and intracerebral. One can also divide hemorrhagic stroke into extraparenchymal and intra-parenchymal hemorrhage. Subarachnoid, subdural, and epidural hemorrhage comprise the extra-parenchymal arm. The three etiological types of intracerebral hemorrhage include hypertensive (typically deep), amyloid angiopathy (typically lobar), and structural (typically related to a vascular malformation or tumor). While certain clinical characteristics may aid in the diagnosis and classification of hemorrhagic stroke, for the purposes of the rest of this review we will limit ourselves to the discussion of ischemic stroke subtypes.

Efficient workup of stroke relies on a thorough history, clinical examination, imaging studies, and putative mechanism of stroke that lead the treating physician to a particular etiological path. Herein we provide the

reader with updated definitions of etiologic ischemic stroke types as well as efficient workup strategies.

Ischemic stroke classification systems

Classifying ischemic stroke subtypes allows optimization of treatment and prevention strategies. For example, management of risk factors such as hypertension and dyslipidemia greatly reduces risk of recurrent small vessel ischemic infarcts. A recent study on Secondary Prevention of Small Subcortical Strokes (SPS3) found a decrease in recurrent strokes with systolic blood pressure maintained below 130 mmHg. (HR 0.81, $p=0.08$) [7]. Similarly, those with stroke secondary to moderate to severe carotid stenosis benefited from carotid endarterectomy within 2 weeks of the index event [8]. Secondary prevention and pharmacologic treatment is tailored based on stroke mechanism. Additionally, prognostication and recurrent risk are also highly dependent on stroke etiology. Thus, ischemic stroke subtyping relies on a comprehensive and somewhat standardized stroke workup.

Two different general approaches to stroke classification include a phenotypic and causative. Phenotypic classification systems [Baltimore-Washington system, Causative Classification of Stroke (CCS), and the Atherothrombosis, Small Vessel disease, Cardiac causes, and Other uncommon causes (ASCO)] divide patients into more than one etiologic category. While this is helpful for administrative and coding purposes, its clinical use has limitations given that the causal mechanism of the stroke cannot be deduced from this classification [9–12]. In contrast to the phenotypic system of classification, the causative system integrates patient history, examination, imaging findings, comprehensive workup, and premorbid risk factors to determine the most probable cause of stroke. The most commonly used causative etiologic classification systems in current stroke literature are the Trial of Org 10172 in Acute Stroke Treatment (TOAST) and the CCS [10, 13]. Table 1 describes the major categories within different classifications. A third approach using more of an anatomical classification such as the Oxfordshire Community Stroke Project Classification (OCSP) can predict the site and extent of infarct [14], but performs less well determining the mechanism of stroke [15].

Ischemic stroke subtypes and workup strategies

There are five major categories of stroke subtype that are identified by both the CCS and TOAST classifications; however, the difference lies in the degree of certainty of the identification of the mechanism of stroke. These five major types are large artery atherosclerosis, cardiac embolism, small artery occlusion, stroke of another determined cause/uncommon causes, and stroke of undetermined cause/cryptogenic stroke. While both systems generate similar categories, recent data suggest that the systems are not capturing exactly the same populations [16].

CCS is currently available as a web-based tool (http://ccs.mgh.harvard.edu) and takes into account the extent and completeness of evaluation. The causative category is further subdivided into evident, probable, and possible subtypes,

Table 1. Etiologic stroke classification systems

Etiological stroke classifications	Categories	Characteristics
TOAST [13]	Large artery atherosclerosis, Cardiac embolism, Small vessel occlusion, Stroke of another determined cause, Stroke of undetermined cause	Causative type classification Simple to use, accepted internationally and used in a large number of clinical trials. Inter-rater reliability is poor and over-estimates the cryptogenic stroke subtype. Does not take into account the diagnostic innovations. Levels of confidence within etiologic types are designated as probable or possible. When two or more mechanisms are possible, the stroke etiology is classified as undetermined.
CCS [10]	Large artery atherosclerosis, Cardio-aortic embolism, Small artery occlusion, Other uncommon causes, Undetermined	Causative and phenotypic type classification Relies on accuracy and completeness of stroke workup to categorize stroke mechanism. Good inter-rater reliability. More complex in structure, but online tool is easy to use. Levels of confidence within etiologic types are designated as evident, probable, or possible. When two or more mechanisms are possible, the most likely stroke etiology is identified.
ASCO [12]	Atherothrombosis, Cardiac embolism, Small vessel disease, Other uncommon causes	Phenotypic type classification Relies on a thorough diagnostic evaluation. Insufficient reliability data available. Difficult to use in research protocols due to the large number of phenotypic subtypes. Levels of confidence within etiologic stroke types are designated as absent, definite, likely, unlikely and unknown.

thereby providing a level of confidence to the user [10].

TOAST, on the other hand, categorizes the five types into probable and possible and is simpler to use. However, the simplicity of the classification may result in overestimation of cryptogenic stroke as this category in the original study also included patients with competing mechanisms [13]. Here, we describe the five major categories and efficient workup strategies for each stroke type (Table 2).

Cardiac-aortic embolism

Cardioembolism results in significant morbidity and mortality and carries a high recurrence risk. It is associated with a worse prognosis than other stroke types [17]. The potential sources of embolism include a dilated left atrium in

Table 2. Ischemic stroke subtypes, definition, radiological features, and diagnostic workup

Stroke subtype	Definition	Radiological features	Diagnostic workup
Cardioembolism	Includes patients with large vessel or branch vessel occlusions due to a cardiac source of embolism	Wedge shaped cortical infarct, or multiple areas of diffusion restriction in different vascular territories	MRI of the brain, Head and neck CTA/MRA, EKG, TTE, TEE, Cardiac monitoring – Holter/Loop recorders
Large artery atherosclerosis	Clinical findings and imaging suggests >50 % stenosis of a large artery secondary to atherosclerosis	Watershed infarction between two vascular territories	MRI of the brain, CTA/MRA, Carotid ultrasound. Catheter angiography may be necessary. Advanced plaque imaging and monitoring of HITS with TCD is also possible.
Small vessel disease	Small brainstem or subcortical infarct with no identifiable cardiac or large artery source of embolism/thrombosis	Small <2 cm subcortical or deep infarct. Most common areas are pons, thalamus, basal ganglia and cerebellum	MRI of the brain, Head and neck MRA/CTA to exclude large vessel pathology. Hemoglobin A1c, lipid panel, screening for tobacco and drug use.
Uncommon causes	Stroke due to rare causes such as non-atherosclerotic vasculopathies and hypercoagulable conditions	Imaging varies by etiology. Vasculitis may appear as small cortical and subcortical infarcts of different ages.	Standard stroke workup*. Lumbar puncture and catheter angiography. In some cases brain biopsy may be necessary.
Cryptogenic stroke	Stroke of no clear etiology despite an exhaustive evaluation	Cryptogenic embolism may appear as an embolic infarct – wedge shaped, cortical with no clear underlying source.	Standard stroke workup*. Remainder of the workup is guided by the putative mechanism. TEE, Holter monitoring, DVT ultrasound, MRI of pelvic veins, cardiac MRI are some additional investigations.

*Standard stroke workup defined as MRI of the brain, CTA or MRA of the head and neck, TTE, Evaluation of risk factors – hypertension, diabetes, and dyslipidemia.

the setting of atrial fibrillation or other arrhythmias, a weak left ventricle, mechanical heart valves, infective endocarditis resulting in vegetations, and aortic arch atherosclerosis. History and physical examination often raise suspicion about this type of stroke. Presence of pedal edema, raised jugular venous pressure, and an irregularly irregular heartbeat may point towards a cardiac source of clot. Neuroimaging studies such as CT/MRI scanning suggest embolism from a proximal source such as the heart or aorta when a cortical wedge shaped infarct or infarcts in multiple vascular territories are seen in the absence of significant large vessel disease.

Workup of a potential cardioembolic stroke entails careful evaluation of the anatomic and physiologic function of the heart. A thorough history and physical examination should include history of cardiac disease, measurement of temperature, auscultation of heart and lungs, and examination of skin and eyes for any findings suggestive of endocarditis. In addition to CT/CTA or MRI/MRA for brain and vascular structures, a detailed cardiac evaluation should be performed. A routine EKG should be followed by in-house cardiac telemetry. If the suspicion for atrial fibrillation is high, long-term cardiac monitoring by means of

30-day event monitors or implantable loop recorders should be considered [18•, 19]. A transthoracic echocardiogram must be performed and a transesophageal echocardiogram (TEE) is needed if pathology of the aortic arch, valve, atrial septum, and left atrial appendage is in question [20].

TEE has been considered the gold standard test for diagnosis of patent foramen ovale (PFO) and in identifying high-risk characteristics such as septal excursion and the presence of an atrial septal aneurysm in patients with a suspected paradoxical embolism. A recent meta-analysis of TEE studies for identification of PFO found a sensitivity and specificity of 89.2 % and 91.4 %, respectively [21], thereby highlighting that complementary testing with transcranial Doppler (TCD) may be necessary to increase the diagnostic yield.

Atrial fibrillation is the most common cause of cardioembolic stroke and carries a risk of 5 % per year [22]. Patients with atrial fibrillation and TIA/stroke are at high risk for recurrence and often warrant anticoagulation with warfarin or newer oral anticoagulants. Simple scores such as the CHADS2 or CHA2D2-Vasc can help determine annual stroke risk. Each patient's hemorrhagic risk has to be carefully evaluated prior to anticoagulation [23–25].

New innovations in the field of electrophysiology have led to the development of implantable cardiac monitors in recent years. These are as small as a thumb drive and can be implanted in the subcutaneous tissue in the 4th intercostal space by a simple bedside procedure under local anesthesia. These devices carry a long battery life and are MRI compatible. Although they carry a higher initial cost, they are cost-effective in the long run and decrease the need for prolonged and multiple noninvasive tests. The Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL- AF) study demonstrated the superiority of one such device in detecting paroxysmal atrial fibrillation in patients with cryptogenic stroke who underwent cardiac monitoring [19]. In the authors' opinion this device may have a role in patients for whom the suspicion for atrial fibrillation is high and a 30-day cardiac monitoring has been unrevealing.

Large artery atherosclerosis

Large artery atherosclerosis comprises carotid and vertebral artery disease as well as intracranial atherosclerosis. Cigarette smoking, older age, dyslipidemia, and hypertension are major risk factors for development of atherosclerosis [26]. Symptomatic carotid stenosis of >70 % has a 10 – 15 % annual recurrent stroke rate if untreated [26]. Potential mechanisms of stroke are artery to artery embolism or in situ thrombosis. The lack of good collateral flow results in hypoperfusion of the supplied territory particularly at the border zone areas. A history of retinal ischemia, loss of vision in one eye, or transient postural limb shaking episodes warrant evaluation for carotid disease. Vertebrobasilar symptoms such as alternating hemiparesis, double vision, ataxia, dizziness, dysarthria, and dysphagia should prompt thorough evaluation of the posterior circulation. Infarcts in watershed zones on neuroimaging warrant evaluation of intra- and extracranial vasculature by means of CTA/MRA imaging. A diagnostic cerebral angiogram may be necessary to quantify the degree of vascular stenosis and the anatomy of the culprit lesion.

A large vessel thrombosis should prompt workup for cardioembolic causes if other large vessels have no signs of atherosclerotic disease. In the

rare scenario that a patient is unable to get a MR or CT angiogram due to contraindications, TCD imaging for intracranial vessels and a carotid ultrasound for extracranial vessels can be employed. TCD is helpful in identifying high intensity transient signals (HITS) in patients with ongoing embolism. HITS represent solid or gaseous emboli that break off from the culprit lesion and are a marker of high risk for recurrent stroke [27]. In recent times, TCD has also been used intraoperatively during cardiac and carotid surgeries to monitor for distal emboli [28, 29].

Advances in radiology have helped characterize carotid plaques and identify anatomic features that increase stroke risk. Imaging with dynamic contrast-enhanced MRI has elucidated that thickness of the fibrous cap and lipid core, as well as intraplaque hemorrhage, are markers of impending plaque rupture and thrombosis. The authors believe that such imaging needs broader validation in larger, independent cohorts before adoption as a screening tool. A patient subset that might benefit from dynamic contrast-enhanced MRI might be the asymptomatic carotid stenosis group where high risk features might prompt early intervention [30•].

Small vessel disease

Small vessel disease causing lacunar infarcts results from risk factors such as diabetes, hypertension, dyslipidemia, and smoking. TOAST classification defines a lacunar infarct as a brainstem or subcortical hemispheric lesion less than 15 mm in diameter with no evident cardiac cause or large artery atherosclerosis [13]. In contrast, the CCS classification uses a lesion size of <20 mm in diameter [10]. The pathophysiology of small vessel disease includes lipohyalinosis, microatheromata, and ostial disease [31]. The presence of vascular risk factors and classic presentation of a lacunar syndrome helps localize the lesion. Classic lacunar syndromes are pure motor hemiparesis, pure sensory syndrome, ataxic-hemiparesis, and clumsy hand dysarthria that do not have any associated cortical signs such as neglect, vision changes, or speech changes.

MRI of the brain with diffusion weighted imaging is the first step in confirming the location and size of the infarct. An MRA of the head and neck performed simultaneously can provide evidence of large vessel atherosclerosis, if any, that may secondarily cause perforator blockage by embolism or occlusion of ostia. Gradient echo imaging or T2* weighted imaging helps identify prior lacunar hemorrhages that are a hallmark of longstanding small vessel disease secondary to hypertension [32]. Blood tests such as hemoglobin A1c and lipid panel help assess the status of metabolic risk factors. Continuous blood pressure monitoring to evaluate and treat hypertension, and smoking assessment and counselling are important during the hospitalization.

Uncommon causes of stroke

As noted above, the most common causes of stroke, particularly among the adult population, are atherosclerosis and cardiac embolization. There are a number of less common causes that, if not completely worked up, could be erroneously classified as undetermined as per the TOAST classification. Such uncommon causes include but are not limited to 1) non-

inflammatory vasculopathies such as fibromuscular dysplasia, vasospasm, and moyamoya disease; 2) inflammatory vasculopathies that are a result of autoimmunity, post infectious causes, or may result from toxins and neoplasm; 3) coagulopathies associated with cerebral venous sinus thrombosis (CVT); and 4) hypercoagulable states associated with malignancy. As with all possible causes of stroke, clinical history, risk factors, and age all play a role in determining etiology. If clinical history and imaging suggest a stroke, but etiology is unknown, there are a number of additional investigations to consider in each of these presumed etiological scenarios.

For both non-inflammatory and inflammatory vasculopathies, vascular imaging such as MRA, CTA, TCD, carotid Doppler, and conventional cerebral angiography play a crucial role in determining possible etiology. The appearance and location of vascular abnormalities help to differentiate among the many causes. For example, in a young adult with ischemic stroke, stenosis of distal internal carotid artery with collateralization that gives a puff of smoke appearance on cerebral angiography suggests moyamoya disease. In a patient with non-inflammatory vasculopathy where revascularization is being considered, an 18-fluorodeoxyglucose PET scan or a single photon emission computed tomography (SPECT) scan may be necessary to determine the brain perfusion [33].

In patients where an inflammatory vasculopathy such as vasculitis is being considered based on history of multifocal infarcts at a young age and vessel irregularities, a lumbar puncture may be necessary to evaluate for inflammatory markers and antibodies. Important laboratory studies to consider in such a case include erythrocytic sedmentation rate (ESR); C-reactive protein (CRP); angiotensin-converting enzyme (ACE); ds-DNA antibodies; complement; anti-RO and anti-La antibodies; c- and pANCA/MPO; anti-endothelial antibodies; electrophoresis; serologic tests for syphilis, Borreliosis, hepatitis B and C, and HIV; blood cultures; and serum drug screen. It is also important to review a patient's medication list for possible medication-induced vasculitis [34].

Cerebral venous sinus thrombosis (CVT) typically presents with headache, seizures, or depressed consciousness. Acquired hypercoagulable states such as pregnancy, post-partum state, and oral contraceptive use should arouse suspicion for CVT. There is a strong body of literature supporting the role of hypercoagulable states in cerebral venous thrombosis. Workup needed when evaluating for possible venous hypercoagulability includes protein C, protein S, factor V Leiden and activated protein-C (APC) resistance, anti-thrombin III, heparin cofactor II, and prothrombin gene mutation. Factor V and prothrombin gene mutation are more commonly seen in Caucasians as compared to African Americans and Hispanics. If no clear cause of hypercoagulability is established through laboratory testing, screening for an underlying malignancy may be necessary in a patient by employing CT of the chest, abdomen, and pelvis or a whole body PET scan [35].

Cryptogenic stroke

Cryptogenic stroke is variably defined by the different classification systems. As highlighted earlier, the TOAST classification identifies a stroke of un-

determined etiology if two or more plausible causes are identified or if the evaluation is negative and/or incomplete [13]. CCS subclassifies the undetermined category into unclassified stroke, incomplete evaluation, and cryptogenic embolism. This category of cryptogenic embolism comprises patients with embolic appearing infarcts that have no identifiable source despite an exhaustive workup [10]. A thorough evaluation by means of brain MRI, noninvasive angiography of the head and neck (MR or CT), TTE, and cardiac monitoring is the first step in identifying the source of clot. Further workup is tailored according to the putative mechanism. Several different possibilities are considered based on patient age and history.

a) Paradoxical embolism and hypercoagulable states.

If the suspicion is high for a paradoxical embolism workup should include a TEE to evaluate for a PFO. Features such as septal excursion, presence of a shunt at rest, and size of the PFO are indicative of high risk for recurrent stroke [36]. A DVT ultrasound would identify the presence of a thrombus in the deep veins, and tests for hypercoagulability such as factor V Leiden, prothrombin gene mutation, protein C or S deficiency, or lupus anticoagulant may need to be obtained in patients less than 50 years old [37•].

b) Aortic atherosclerosis

Several prospective studies have identified that atherosclerotic plaques in the aortic arch that are greater than 4 mm in size, mobile, and ulcerated independently predict recurrent stroke. The best way to evaluate for these plaques as a source of embolism is by performing a TEE [38, 39]. However, the optimal secondary stroke prevention remains undetermined [40].

c) Arrhythmias

Paroxysmal or occult arrhythmias such as atrial fibrillation are often difficult to capture during a brief hospitalization. If cryptogenic embolism secondary to an occult arrhythmia is suspected, prolonged Holter monitoring or the newer loop recorders can be employed. Detection of atrial fibrillation has been as high as 25 % in patients with extended (30 or more days) of monitoring [41].

Conclusion

Identifying stroke subtypes and etiology is considered standard of care as it dictates outcome and recurrence after an index event. While the TOAST classification is the most widely used classification system worldwide, the CCS has increasingly found favor with stroke physicians due to its completeness and integration of all parts of a stroke evaluation from history to investigations, as well as the computer assisted capture of the primary data underlying the subtype classification [42]. Standard workup of stroke comprises comprehensive MRI as well as vascular imaging, evaluation for diabetes and dyslipidemia, and cardiac monitoring. Further investigations are guided by presumed stroke mechanism. With the evolution of technology newer devices and imaging modalities are being used to help delineate stroke etiolo-

gy with certainty. Despite challenges and pitfalls associated with the new innovations, we are slowly, but surely improving our ability to provide strategic and specific stroke care.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Mehndiratta: None

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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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