Cryptogenic Stroke
Anatomy of the Stroke Work-Up

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KEYWORDS

• Cryptogenic stroke • Embolic Stroke of Undetermined Etiology (ESUS)
• Ischemic stroke • Diagnostic testing • Cardiac monitoring • Hypercoagulable
• Imaging

KEY POINTS

- There are a variety of stroke definitions, advancements in diagnostic technologies, differing thoughts on appropriate etiologic investigations, and more than 200 known causes of ischemic stroke (IS) requiring elimination.
- It is important to determine the cause of cryptogenic stroke (CS) to understand the functional prognosis and eliminate the risk of stroke recurrence by providing appropriate secondary stroke prevention.
- In clinical practice, the diagnosis of CS is considered, when the diagnostic assessment is not complete, when a single cause cannot be determined for there are several potential causes, or there is no identifiable cause despite an extensive evaluation.

INTRODUCTION

The diagnosis of cryptogenic stroke (CS) is made by exclusion. There are a variety of stroke definitions, advancements in diagnostic technologies, along with differing thoughts on appropriate etiologic investigations, and there are more than 200 known causes of ischemic stroke (IS) requiring elimination.[1] Despite an extensive evaluation the cause of CS cannot be determined in 30% to 40% of cases.[2] It is important to determine the cause of CS to understand the functional prognosis and eliminate the risk of stroke recurrence by providing appropriate secondary stroke prevention.

In clinical practice, the diagnosis of CS is considered when the diagnostic assessment is not complete, when a single cause cannot be determined because there are several potential causes, or there is no identifiable cause despite an extensive evaluation.[5]

Understanding stroke subtype is essential for managing acute interventions and secondary prevention. One prominently used classification system, designed for the TRIAL of ORG-10172 for Acute Stroke Treatment (TOAST), defined an undetermined stroke as a "brain infarction that is not attributable to a cardio-embolic source, large

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Crit Care Nurs Clin N Am 32 (2020) 37–50
https://doi.org/10.1016/j.cnc.2019.11.008
ccnursing.theclinics.com

Stroke Mechanism

Thrombotic (20%)[3]
- Arterial plaque as a result of atherosclerosis

Cardioembolic (20%)
- Blood clot from faulty heart valve or atrial fibrillation (AF)
- Results when a clot dislodges and travels to an area of decreased circulation

Lacunar (25%)
- Small-vessel disease
- A vessel is coated with a lipid compound, a process known as lipohyalinosis, which causes the lumen to thicken and restricts blood flow
- Associated with hypertension

Cryptogenic (30%)
- No cause found for stroke

Other (5%)
- Coagulopathies
- Vasculitis
- Drug abuse
- Infections[4]

artery atherosclerosis, or small-vessel disease, despite an extensive vascular, cardiac and serologic evaluation."[5] As such, the definition is thought of in negative terms, based on the absence of findings.

TOAST classification of acute IS denotes five subtypes[5]:

- Large-artery atherosclerosis (thrombosis/embolus)[a]
  - Carotid/vertebral, intracranial/extracranial, aortic arch
  - Stenosis, dissection, vasculitis
- Cardioembolism (high risk/medium risk)[a]
  - AFib, dilated cardiomyopathy, patent foramen ovale (PFO), endocarditis
- Small-vessel occlusion (lacune)[a]
  - Hypertension
- Stroke of other determined etiology[a]
  - Hypercoagulable states, iatrogenic, carotid/vertebral dissection
- Stroke of undetermined cause
  - Two or more causes identified
  - Negative evaluation
  - Incomplete evaluation

EMBOLIC STROKE OF UNDETERMINED SOURCE (ESUS)

Another definition, based on infarct topography,[6] is the inference being that all nonlacunar IS are caused by embolism.[7] In 2014, the clinical construct of embolic stroke of undetermined source (ESUS) was introduced to identify patients with nonlacunar CS in whom embolism was the likely stroke mechanism.[8]

[a] Possible or probably depending on results of ancillary studies.

The main rationale for such an approach has been to define this group of patients in a positive manner, to enable a clearer definition for conduct of randomized controlled trials, and by extension, implications for clinical practice. Developing a consensus definition for CS requires agreement on what is considered to be an extensive or adequate evaluation and which findings are considered etiologic (**Box 1**).[9]

Box 1
Criteria for diagnosis of Embolic Stroke of Undetermined Source (ESUS)

1. IS detected by computed tomography or MRI that is not lacunar
2. Absence of extracranial or intracranial atherosclerosis causing greater than 50% luminal stenosis in arteries supplying the area of ischemia
3. No major risk of cardioembolic source of embolism
4. No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, and drug abuse)[10]

INDIVIDUAL RISK FACTORS

Age

A patient's age is indicative to the likelihood of a variety of stroke causes. In young adults 18 to 30 years of age, dissection is the most common, but congenital cardiac disease and thrombophilia are also notable causes. In those 31 to 60 years of age, early onset atherosclerosis and acquired structural cardiac diseases are increasingly common. As the population ages, the likelihood of specific stroke subtypes is also expected to change. In patients older than 60 years of age, occult atrial fibrillatin (AFib) becomes more frequent.[11] AFib is the most common source of cardiogenic embolism, and increases from 1.5% in 50 to 59 year olds to 23.5% in those aged 80 to 89 years.[12] Understanding the changing patterns of stroke subtypes is important for anticipating the appropriate allocation of preventive and treatment resources and their cost implications for the health care system.[13]

Medical History

The evaluation of a patient with IS should include a careful history regarding symptom onset, progression, associated symptoms, and medical history. A history of neck injury and headache at the time of onset can suggest dissection as a cause, and associated palpitations or chest pain might suggest a cardioembolic source.[14] Patients should be screened for modifiable risk factors: hypertension, diabetes (by serum glucose or hemoglobin A_{1C}), hyperlipidemia (by serum lipids), heart disease (ASCVD calculator), obesity (body mass index [BMI]), smoking (PPD x years), and excessive alcohol use (drinks per day per week).[15]

Comorbidities and In-hospital Stays

In-hospital strokes are considered a complication of an illness that resulted during a hospitalization, or an iatrogenic consequence related to the withdrawal of a protective therapy (anticoagulation), or of therapeutic interventions during hospitalization. Common mechanisms may be related to a direct complication of vessel manipulation (catheterization), brain ischemia from systemic hypoperfusion (an occluded or subocclusive vessel, hypotension), or a thromboembolic event (deep vein thrombosis [DVT], cancer, stroke), or caused by stasis (bedrest) along with events induced by comorbid

illness or surgery.[16] Underlying risks may be increased by withdrawal of antithrombotic or anticoagulant therapy because of bleeding, inability to take oral medications, or invasive procedures. Hospitalized patients may experience any combination of these factors, which may help to explain the increase in risk for stroke in patients hospitalized compared with those in the community.[17]

Baseline Stroke Work-Up

Stroke patients admitted to the intensive care unit (ICU) typically have an initial workup completed in the emergency department (ED), or at an outside hospital (OSH) prior to transfer. Hence, stroke patients arriving to the ICU often present with a presumed initial stroke diagnosis.

Patients transferred for ICU care from an OSH should arrive with documentation of the initial evaluation, including presenting symptoms, laboratory results, and care provided, along with imaging done prior to transfer (imaging on disk should accompany transferred patients) to avoid repetition of studies. If a patient received intravenous (IV) alteplase prior to arrival, drug bolus and infusion dosage, along with time initiated, should be clearly documented. Approximately 15% to 20% of patients with IS will require care in an ICU.[18]

There is no agreement about the baseline clinical investigation of CS, but recent studies note the investigation should include obtaining a brain computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, 12-lead EKG, cardiac monitoring for 24 hours (Holter), transthoracic echocardiogram (TTE), screening for a prothrombotic (hypercoagulable) state in patients younger than 55 years, CT angiography (CTA) or MRI angiography (MRA) or cervical and intracranial digital angiography, and ultrasonography (US) Doppler of cervical and vertebral arteries.[19,20]

Neuroimaging

The initial evaluation of patients with suspected stroke includes a head CT without contrast. Head CT is widely available, rapidly obtained, and less expensive than other imaging modalities, such as brain (MRI), although not as sensitive detecting small infarcts that may be important to characterize stroke mechanism. Although CT and MRI have the same sensitivity in excluding hemorrhage, brain MRI is superior to CT in detecting acute infarction.[20–22]

The topographic characteristics of stroke (infarct location and volume) are determined by brain MRI, including diffusion sequences (DWI and ADC), which are more sensitive to small lesions (lesions in the cerebellum and brainstem). These topographic features provide important etiologic information, such as infarcts in multiple brain territories suggest emboli from a proximal aortocardiac source; infarcts of different ages in a single territory suggest emboli of arterial origin; infarcts along the borders between brain artery territories suggest systemic hypotension or multiple emboli; and a small, deep infarct along with white-matter hyperintensities suggests intrinsic small-vessel disease.[11]

Intracranial (brain) and cervical (neck) vasculature (vessels) are investigated by MRA (vessels), CTA (vessels), or digital subtraction angiography (fluoroscopy). Time of flight (TOF) MRA (uses a measure of blood flow as opposed to contrast) and may exaggerate the degree of stenosis in comparison with CTA or carotid ultrasound (US) (decreased flow may give the impression of a decreased lumen caliber). If MRA and CTA are not available (or contraindicated), the carotid arteries are assessed with Doppler Ultrasound (US) to look for stenosis or dissection.[15]

Cardiac Monitoring

A single electrocardiogram (EKG) is not likely to detect AFib or flutter in 24 hours of cardiac telemetry.[23] Outpatient cardiac monitoring for occult AFib is now the standard of care after CS, for the detection of AFib leads to initiating anticoagulation therapy that is superior to antiplatelet therapy.[24] Studies have shown that the longer patients are monitored, the more likely AFib will be detected.[25] There is a chance, however, that some of the AFib detected may not be causative of the stroke event.

The most cost-effective approach to cardiac monitoring has yet to be determined. It may be prudent to begin with noninvasive 30-day cardiac monitoring initially, especially in patients with a high index of suspicion for AFib, and a high likelihood of compliance with 30-day monitoring. An unrevealing 30-day monitor does not exclude the presence of AFib, and these patients should be considered to undergo an implantable cardiac monitor for longer monitoring.[26]

The heart should be assessed by TTE to evaluate for thrombus, left atrial dilatation (which may be associated with AFib), and valvular vegetation (although transesophageal echocardiogram [TEE] is more sensitive to assess for vegetation).[15] Several studies have shown TTE and perhaps TEE are useful in identifying a potential cardiac source in patients with CS.[14]

An agitated saline (bubble) study is done during the TTE to look for patent foramen ovale (PFO), typically in those aged less than 65. If a PFO is found, a search for deep vein thrombosis (DVT) is undertaken with Doppler US of the lower extremities, and pelvic MR venography to evaluate for thrombosis of the pelvic veins, which may be caused by May-Thurner syndrome (iliac vein thrombosis caused by compression of the left common iliac vein, by the right common iliac artery).[15] Migraine associated with paradoxical embolism via PFO (more common in young patients) is thought caused by a presumed loss of filtration of microemboli or toxic substances via right-to-left shunting.[27,28]

The advantage that TEE possesses relative to TTE is that the US probe is placed in the esophagus and positioned directly behind the heart. This permits the use of higher frequencies because the US beam has a shorter distance to travel. This higher frequency allows a better resolution of images. TEE may have an advantage over TTE in evaluating for bacterial endocarditis, the functioning of prosthetic heart valves, and severe mitral regurgitation caused by ruptured chordae tendineae.

TEE identifies potential causal sources of embolus in patients with CS that leads to changes in management and outcomes at least 3% of the time. Other findings, particularly aorta atherosclerosis, are identified much more commonly but the causal link to stroke is uncertain, thus changes in management in these cases is variable and data describing resulting outcomes are lacking.[29] The utility of TEE and its superiority with respect to TTE is still the subject of discussion.[30]

Other Diagnostic Modalities

Carotid duplex monitoring for microembolism can detect high-risk patients with asymptomatic carotid stenosis, and assist in identifying mild degrees of symptomatic carotid stenosis in patients with CS. Recently, three-dimensional US and contrast-enhanced US have been used to assess vulnerable plaque at risk for rupture in patients with carotid atherosclerotic disease.[31,32]

In ICU management of cerebrovascular disease, transcranial Doppler (TCD) has typically been used to detect vasospasm after subarachnoid hemorrhage (SAH).[33] It has also been a reliable tool in detecting occlusions of the main intracranial vessels,

such as the middle cerebral artery (MCA), or the basilar artery (BA). As the emergency treatment of acute IS evolves, TCD can play an important role because it rapidly, noninvasively, and objectively identifies patients with occlusion of major intracranial arteries who could be candidates for thrombolytic treatment. In addition, it is a reliable tool for the detection of spontaneous or medically induced reperfusion in a previously occluded vessel.[34,35]

Agitated saline TCD monitoring is based on intracranial detection of IV injected microemboli. The size and functional relevance of right-to-left shunting is readily assessed using TCD, with similar sensitivity and specificity with TEE.[35] The reasons that TCD is more sensitive than TEE for detecting PFO, includes the ability to perform a more vigorous Valsalva maneuver in the absence of sedation and the loud and obvious signal that is produced by bubbles on TCD.[34]

LABORATORY WORK-UP

- Serum lab testing can take on a life of it's own. Basic serum testing would include; glucose, HbA1c, electrolytes, renal function tests, CBC including platelet count, prothrombin time (PT), international normalized ration (INR), activated partial thromboplastin time (aPTT), and HCG for women of child bearing age.
- Other labs to consider; lipid profile, LFTs, TSH with reflex, CRP, ESR, Troponin and CK.
- C-reacdtive protein (CRP), a biomarker for inflammation: elevated level in patients with AFib compared with those who do not have AFib history; patients with persistent AFib have higher CRP levels than those with paroxysmal AFib.[36]
- Brain natriuretic peptide (BNP): assessing cardiac stretch and heart failure, may harbor an underlying or occult cardioembolic mechanism
- Troponin: early positive troponin after IS may be independently associated with a cardiac embolic source
- D dimer: acutely elevated after stroke suggests embolic phenomenon; may implicate a hypercoagulable state due to an occult malignancy
- Fibrinogen (factor I): protein essential for blood clot formation
- Thyroid stimulating hormone (TSH): hyper thyroid can be related to AFib, hypo thyroid can be related to progression of athero
- Homocysteine: amino acid produced as the body digests protein
- Lipoprotein (a): molecule of "bad" cholesterol with an extra protein attached; interferes with blood's natural clot busters
- Venereal disease research laboratory (VDRL): screen for syphilis.

HYPERCOAGULABLE PROFILE

Evaluating for a hypercoagulable state includes antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant, β_2 glycoprotein antibody) and genetic mutations (protein C or S deficiency, antithrombin III deficiency, factor V Leiden, prothrombin gene mutation). Of these, only the antiphospholipid antibodies are associated with arterial and venous thromboembolism, and so could potentially cause a stroke if a PFO or other shunt between the venous and arterial circulation is present.[15]

Serum testing for acquired antiphospholipid syndrome may be considered in the presence of a history of prior venous thromboembolism, second trimester abortion, or rheumatologic disorder. The diagnosis requires the persistence of high titers of autoantibodies of the IgG or IgM isotype (for >12 weeks), detected by enzyme-linked immunosorbent assay for anti-β2-glycoprotein I or anticardiolipin antibodies or by lupus-anticoagulant assays.

Other conditions associated with an acquired hypercoagulable state include pregnancy, hormonal contraceptive use, exposure to hormonal treatments (eg, anabolic steroids or erythropoietin), nephritic syndrome, and cancer. Patients with cancer may have distinctive D dimer levels (a marker of coagulopathy, >20 times higher than those without cancer) and infarct patterns (multiple lesions in multiple vascular territories).[37]

IS may be caused by inherited thrombophilia. Tests for thrombophilia have high costs and low diagnostic accuracy. Their results can fluctuate, and repeated assessment is needed or genetic testing should be done where possible. Clues for a hypercoagulable state include a history of DVT or multiple miscarriages.[38]

Inherited or acquired hypercoagulopathies are not a well-studied cause for IS and thought to only contribute to a small proportion of IS. Generally, hypercoagulable work-up for antiphospholipid syndrome and coagulopathies is indicated in select patients, particularly those who are young, with a PFO and possibly at risk of paradoxical embolism, with history of unprovoked venous thromboembolism.[39] To contrast, some recent reports suggest there is little benefit to advanced testing for hypercoagulable states in CS, even in young patients and those with PFOs.[40] Furthermore, identification of hypercoagulable patients may not yield risk reduction in recurrent stroke despite therapy.[41] As a result, many clinicians argue that thrombophilia work-up in stroke is an unjustified cost that can lead to unnecessary anticoagulation.[40] Furthermore, in the setting of an acute stroke, some markers of hypercoagulability are transiently or falsely elevated, and the tests may need to be repeated. Therefore, it is often more cost-effective to perform hypercoagulability testing after other tests have been performed, perhaps in the outpatient rather than the hospital setting. (**Box 2**).

Box 2
Hypercoagulable testing considerations

Antiphospholipid antibodies (APLA) are acquired and associated with both arterial and venous thromboembolism.

- Antiphospholipid antibodies (Anticardiolipin antibodies)
- Lupus anticoagulant
- Beta-2 glycoprotein antibody

  Repeat confirmatory testing needed in 6 months due to false positives.

Genetic mutations (abnormal upfront [may be inherited])

- Not Commonly Associated with Stroke
  - Protein C or S deficiency
  - Antithrombin III deficiency
  - Factor V Leiden mutation
  - Prothrombin gene mutation

Primarily associated with venous thromboembolism, could only potentially cause a stroke if a PFO or other shunt between the venous and arterial circulation if present.

EVALUATION FOR MALIGNANCY

Two of the most common causes of death among the elderly are cancers and IS and the associations between them have been described.[37,42,43] The frequency

of stroke in patients with cancer is nearly 7%,[44] most of which develop in the first few months after a cancer diagnosis. This is most likely related to hypercoagulability through alterations of the homeostatic cascade, the integrity of the endothelium, and platelet function.[45–47] Stroke mechanisms in patients with known cancer may differ from those that occur in the general population,[42,48] with CS subtype being the most common and associated with reduced survival.[49]

Because of advances in cancer medicine and the growing elderly population, the number of people living with cancer is increasing. As a consequence, the number of patients who have cancer is expected to increase among patients with stroke, especially in those without other stroke pathologic processes. Certain cancers, such as lung cancer (especially adenocarcinoma), and gastrointestinal malignancies secrete substances, such as cysteine proteases, tissue factor, and sialic acid moieties of mucin, and exhibit procoagulant activity, resulting in the activation of factors X and VII.[50,51] Aggressive antitumor therapy may increase the risk of thrombosis.[52] Anticoagulation can effectively prevent cancer-related stroke; hence, early identification of this stroke mechanism is important and requires additional studies.

Once other potential stroke mechanisms are excluded, an evaluation for occult malignancy as a cause of CS should be considered, especially in older patients with systemic symptoms suggestive of a cancer diagnosis, such as unexplained weight loss. Cerebral infarcts involving multiple vascular territories are more common in patients with cancer.[53] There should be a low threshold of diagnostic testing when looking for an occult malignancy in the absence of systemic symptoms suggestive of cancer. Additional testing commonly performed includes age-appropriate cancer screening modalities; serum inflammatory markers, such as erythrocyte sedimentation rate (ESR); and CT scan of the chest, abdomen, and pelvis.[42]

GENETIC CONSIDERATIONS FOR CRYPTOGENIC STROKE

This topic cannot be adequately addressed in this article. The following is a brief overview of considerations.

Hereditary factors contribute to stroke risk, although teasing apart risk because of genetic mutations and because of shared familial exposures remains challenging. The task has been complicated by the heterogeneity of stroke, the multitude of conventional risk factors that cause stroke, and the variability among populations and studies.[54]

Genetic variability may however, contribute to stroke risk through several potential mechanisms. First, specific rare single-gene disorders may contribute to individual familial syndromes for which stroke is the primary or unique manifestation (eg, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Second, single-gene disorders may cause a multisystem disorder of which stroke is just one manifestation (eg, sickle cell anemia). Third, some common variants of genetic polymorphisms have been associated with stroke risk, although the individual contribution of such polymorphisms is regarded as modest (eg, variants in 9p21).[55] Fourth, genetic causes of conventional stroke risk factors, such as AFib, diabetes mellitus, and hypertension, are also associated with risk of stroke.[56] Emerging evidence suggests that genetic studies could help to distinguish stroke subtypes and even contribute to patient management. For example, there is an association between gene variations that confer an increased risk of AFib and IS. This raises the possibility that genetic tests could help to make the diagnosis of strokes likely to be because of AFib.[55]

Genetic causes related to stroke

- CADASIL - Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- MELAS - Mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes
- MTHFR - Methylenetetrahydrofolate reductase
- FHM - Familial hemiplegic migraine
- APLA - Antiphospholipid antibody
- Moyamoya disease (abnormal net-like blood vessels)
- Ehlers-Danlos syndrome (connective tissue disorders)
- Fabry disease (enzyme alpha-galactosidase A. deficiency)

SUBSTANCE USE AND ABUSE

Substance abuse, notably cocaine abuse, is an important risk factor in stroke. In a large population-based study, cocaine use was associated with a 5.7-fold increase in the odds of having an IS in young adults.[57] Furthermore, de los Ríos and colleagues[58] recognized an increased frequency of cocaine abuse as a cause of stroke among 35- to 54-year-old patients with stroke. These observations generate a strong case for aggressive community-based education regarding increasing cocaine abuse and risk for stroke.

Illicit drug use has been associated with increased stroke risk. Cocaine, amphetamines, and heroin substantially increase the risk of hemorrhagic stroke and IS. Adjusting for other risk factors, there is a 7- to 14-fold increase in stroke among drug abusers. Pathogenesis is likely multifactorial. Hypertension, vasospasm, intravascular thrombosis caused by platelet activation and vasculitis. Cocaine functions by blocking the presynaptic reuptake of dopamine, norepinephrine, and serotonin. Elevated levels of these monoamines have been angiographically proven to cause cerebral artery vasoconstriction.[59–61]

In one of the earliest studies looking at the cardiovascular effects manifested by cannabis, Mittleman and colleagues[62] reported a nearly five-fold increased risk of myocardial infarction (MI) within an hour of consuming cannabis. Several mechanisms by which cannabis negatively impacts the cardiovascular system has been hypothesized in case reports.[63] These include orthostatic hypotension, cardiac arrhythmias, and intimal hyperplasia (response of a vessel to injury). In addition, a prospective study of 48 young patients with IS demonstrated a strong temporal association of cannabis consumption and reversible cerebral vasoconstriction syndrome (RCVS).[64] An Australian cohort of young patients with stroke revealed that cannabis users had a 2.3-fold higher risk for developing IS even when adjusted for all other covariates including tobacco use.[65]

Similarly, a population-based study used the US nationwide inpatient sample and demonstrated that smoking cannabis was independently associated with the occurrence of stroke. The mean age at stroke was 33.1 years.[66] In contrast, a Swedish study failed to identify this independent relationship among young adults.[64] With the societal drift for increased cannabis legalization for medical and recreational use, its use may not be as harmless as otherwise thought of, and more research is needed to explore the potential relationship between cannabis use and stroke.

INFECTIOUS CONSIDERATIONS

The association of stroke with infectious entities, such as infectious endocarditis, has been well described,[67] but direct infectious causes outside the realm of infectious endocarditis continues to be an area of debate. This becomes more relevant in strokes deemed as cryptogenic or of undetermined cause.[68]

Consider lumbar puncture (LP) to look for signs of an infectious, inflammatory, or neoplastic valvular lesion; atrial clot; or aortic atherosclerosis. In certain clinical settings, such as immunosuppressed patients or those with high exposure risk, and in patients with evidence of multifocal infarcts, infectious etiologies, such as viruses (varicella-zoster virus, herpes simplex virus, and cytomegalovirus), syphilis, and tuberculosis, should be considered and confirmed by serum and cerebrospinal fluid (CSF) testing.[14] Obtain blood cultures if there is concern for infectious endocarditis. Procalcitonin and BioFire testing may be prudent to consider.

Infections increase the susceptibility to stroke by causing local inflammation of the cerebral parenchyma and meninges, through systemic inflammation, by promoting atherosclerosis, causing coagulation and endothelial dysfunction, and in some cases directly inducing ischemia.[69,70] Another proposed mechanism describes a direct pathogenic invasion of the vascular wall with smooth muscle cell proliferation or increased cytokine production, or a combination of both.[71] Inflammation seems to be a common pathway in stroke causation with infection. Persistent inflammatory activity even after a resolved infection has been shown to increase stroke risk years later.[72]

Infectious causes of stroke are underrecognized, but are important to consider in pediatric patients, young adults with no apparent vascular risk factors, immunocompromised patients, and in patients with cryptogenic ischemic or hemorrhagic stroke. Inflammation in the setting of infection seems to increase the risk of cerebrovascular events. Identifying infectious causes is challenging, hence a high index of suspicion and a low threshold for obtaining additional nontraditional stroke investigations is necessary, especially in the aforementioned high-risk patients. These investigations can include contrast cerebral imaging, cerebrospinal fluid analysis, and high-resolution vessel imaging modalities that may facilitate an early diagnosis and prompt initiation of targeted antimicrobial therapy.[73]

Preventive and therapeutic interventions through the use of vaccinations and antibiotic therapy along with having a low threshold for infectious evaluation in select patients may, help in reducing the stroke incidence.[73]

SUMMARY

The specific cause of stroke in a large number of patients continues to challenge clinicians despite efforts to arrive at a CS diagnosis. Approximately 30% to 40% of ischemic strokes do not have a definitive cause despite specialized, costly testing, that often results in diminishing yield. Understanding the pathogenic mechanism of stroke, lack of Class I evidence, the workup and treatment strategies often vary considerably. CS incorporates a heterogenous group of patients leading to therapeutic implications based on the potential mechanism. In the absence of AFib, antiplatelet therapy continues to be the mainstay of treatment, though scientific evidence to support this is limited. In addition, risk factor management and lifestyle modifications, lead to improved stroke prevention strategies in patients with CS.

DISCLOSURE

The author has nothing to disclose.

REFERENCES

1. Bogousslavsky J, Caplan LR. Uncommon causes of stroke. Cambridge: Cambridge University Press; 2001.
2. Sacco RL, Ellenberg J, Mohr J, et al. Infarcts of undetermined cause: the NINCDS stroke data bank. Ann Neurol 1989;25(4):382–90.
3. Hart RG, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. Stroke 2001;32(3):803–8.
4. Ryan D. Handbook of neuroscience nursing: care of the adult neurosurgical patient. New York: Thieme; 2019.
5. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. definitions for use in a multicenter clinical trial. TOAST. trial of org 10172 in acute stroke treatment. Stroke 1993;24(1):35–41.
6. Etherton MR, Rost NS, Wu O. Infarct topography and functional outcomes. J Cereb Blood Flow Metab 2018;38(9):1517–32.
7. Liberman AL, Prabhakaran S. Cryptogenic stroke: how to define it? how to treat it? Curr Cardiol Rep 2013;15(12):423.
8. Hart RG, Diener H, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol 2014;13(4):429–38.
9. O'Donnell M, Kasner SE. Cryptogenic stroke. In: Grotta J, Albers G, Broderick J, et al, editors. Stroke. 6th edition. New York: Elsevier; 2016. p. 707–15.
10. Hart RG, Catanese L, Perera KS, et al. Embolic stroke of undetermined source: a systematic review and clinical update. Stroke 2017;48(4):867–72.
11. Saver JL. Cryptogenic stroke. N Engl J Med 2016;374(21):2065–74.
12. Goldstein LB, Bushnell CD, Adams RJ, et al. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42(2):517–84.
13. Ovbiagele B, Goldstein LB, Higashida RT, et al. Forecasting the future of stroke in the United States: a policy statement from the American Heart Association and American Stroke Association. Stroke 2013;44(8):2361–75.
14. Yaghi S, Elkind MS. Cryptogenic stroke: a diagnostic challenge. Neurol Clin Pract 2014;4(5):386–93.
15. Berkowitz A. Lange clinical neurology and neuroanatomy: a localization-based approach. New York: McGraw-Hill Education; 2016.
16. Kelley RE, Kovacs AG. Mechanism of in-hospital cerebral ischemia. Stroke 1986;17(3):430–3.
17. Azzimondi G, Nonino F, Fiorani L, et al. Incidence of stroke among inpatients in a large Italian hospital. Stroke 1994;25(9):1752–4.
18. Singh V, Edwards NJ. Advances in the critical care management of ischemic stroke. Stroke Res Treat 2013;2013:510481.
19. Rubens JR, Selvaggio G, Lu TK. Synthetic mixed-signal computation in living cells. Nat Commun 2016;7:11658.
20. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2018;49(3):e46–99.
21. Chalela JA, Kidwell CS, Nentwich LM, et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. Lancet 2007;369(9558):293–8.
22. Merino JG, Warach S. Imaging of acute stroke. Nat Rev Neurol 2010;6(10):560.

23. Liao J, Khalid Z, Scallan C, et al. Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. Stroke 2007;38(11):2935–40.
24. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364(9):806–17.
25. Sanna T, Diener H, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370(26):2478–86.
26. Choe WC, Passman RS, Brachmann J, et al. A comparison of atrial fibrillation monitoring strategies after cryptogenic stroke (from the cryptogenic stroke and underlying AF trial). Am J Cardiol 2015;116(6):889–93.
27. Diener H, Weimar C, Katsarava Z. Patent foramen ovale: paradoxical connection to migraine and stroke. Curr Opin Neurol 2005;18(3):299–304.
28. Dao CN, Tobis JM. PFO and paradoxical embolism producing events other than stroke. Catheter Cardiovasc Interv 2011;77(6):903–9.
29. Christiansen ME, Van Woerkom RC, Demaerschalk BM, et al. What is clinical efficacy of transesophageal echocardiography in patients with cryptogenic stroke? A critically appraised topic. Neurologist 2018;23(1):30–3.
30. de Bruijn SF, Agema WR, Lammers GJ, et al. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. Stroke 2006;37(10):2531–4.
31. Madani A, Beletsky V, Tamayo A, et al. High-risk asymptomatic carotid stenosis: ulceration on 3D ultrasound vs TCD microemboli. Neurology 2011;77(8):744–50.
32. Partovi S, Loebe M, Aschwanden M, et al. Contrast-enhanced ultrasound for assessing carotid atherosclerotic plaque lesions. Am J Roentgenol 2012;198(1):W13–9.
33. Sloan MA, Alexandrov AV, Tegeler CH, et al. Assessment: transcranial Doppler ultrasonography: report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. Neurology 2004;62(9):1468–81.
34. Kulkarni AA, Sharma VK. Role of transcranial Doppler in cerebrovascular disease. Neurol India 2016;64(5):995–1001.
35. Mitsias P. Ischemic stroke management in the critical care unit: the first 24 hours. J Stroke Cerebrovasc Dis 1999;8(3):151–9.
36. Chung MK, Martin DO, Sprecher D, et al. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001;104(24):2886–91.
37. Kim SJ, Park JH, Lee M, et al. Clues to occult cancer in patients with ischemic stroke. PLoS One 2012;7(9):e44959.
38. Berlit P. Diagnosis and treatment of cerebral vasculitis. Ther Adv Neurol Disord 2010;3(1):29–42.
39. Reynolds HR, Jagen MA, Tunick PA, et al. Sensitivity of transthoracic versus transesophageal echocardiography for the detection of native valve vegetations in the modern era. J Am Soc Echocardiogr 2003;16(1):67–70.
40. Morris JG, Singh S, Fisher M. Testing for inherited thrombophilias in arterial stroke: can it cause more harm than good? Stroke 2010;41(12):2985–90.
41. Kolominsky-Rabas PL, Weber M, Gefeller O, et al. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. Stroke 2001;32(12):2735–40.
42. Seok JM, Kim SG, Kim JW, et al. Coagulopathy and embolic signal in cancer patients with ischemic stroke. Ann Neurol 2010;68(2):213–9.

43. Kim SG, Hong JM, Kim HY, et al. Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. Stroke 2010; 41(4):798–801.
44. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine (Baltimore) 1985;64(1):16–35.
45. Caine GJ, Stonelake PS, Lip GY, et al. The hypercoagulable state of malignancy: pathogenesis and current debate. Neoplasia 2002;4(6):465–73.
46. Dammacco F, Vacca A, Procaccio P, et al. Cancer-related coagulopathy (trousseau's syndrome): review of the literature and experience of a single center of internal medicine. Clin Exp Med 2013;13(2):85–97.
47. Sack GH, Levin J, Bell WR. Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic, and therapeutic features. Medicine (Baltimore) 1977;56(1):1–37.
48. Schwarzbach CJ, Schaefer A, Ebert A, et al. Stroke and cancer: the importance of cancer-associated hypercoagulation as a possible stroke etiology. Stroke 2012;43(11):3029–34.
49. Navi BB, Singer S, Merkler AE, et al. Recurrent thromboembolic events after ischemic stroke in patients with cancer. Neurology 2014;83(1):26–33.
50. Bick RL. Cancer-associated thrombosis. N Engl J Med 2003;349(2):109–11.
51. Rickles FR, Patierno S, Fernandez PM. Tissue factor, thrombin, and cancer. Chest 2003;124(3):58S–68S.
52. Li S, Chen W, Tang Y, et al. Incidence of ischemic stroke post-chemotherapy: a retrospective review of 10,963 patients. Clin Neurol Neurosurg 2006;108(2):150–6.
53. Giray S, Sarica FB, Arlier Z, et al. Recurrent ischemic stroke as an initial manifestation of an concealed pancreatic adenocarcinoma: Trousseau's syndrome. Chin Med J 2011;124(4):637–40.
54. Boehme AK, Esenwa C, Elkind MS. Stroke risk factors, genetics, and prevention. Circ Res 2017;120(3):472–95.
55. Gretarsdottir S, Thorleifsson G, Manolescu A, et al. Risk variants for atrial fibrillation on chromosome 4q25 associate with ischemic stroke. Ann Neurol 2008;64(4): 402–9.
56. Bevan S, Traylor M, Adib-Samii P, et al. Genetic heritability of ischemic stroke and the contribution of previously reported candidate gene and genomewide associations. Stroke 2012;43(12):3161–7.
57. Cheng Y, Ryan KA, Qadwai SA, et al. Cocaine use and risk of ischemic stroke in young adults. Stroke 2016;47(4):918–22.
58. de los Ríos F, Kleindorfer DO, Khoury J, et al. Trends in substance abuse preceding stroke among young adults: a population-based study. Stroke 2012;43(12): 3179–83.
59. Amin H, Greer DM. Cryptogenic stroke: the appropriate diagnostic evaluation. Curr Treat Options Cardiovasc Med 2014;16(1):280.
60. Ionita CC, Xavier AR, Kirmani JF, et al. What proportion of stroke is not explained by classic risk factors? Prev Cardiol 2005;8(1):41–6.
61. Kaufman MJ, Levin JM, Ross MH, et al. Cocaine-induced cerebral vasoconstriction detected in humans with magnetic resonance angiography. JAMA 1998; 279(5):376–80.
62. Mittleman MA, Lewis RA, Maclure M, et al. Triggering myocardial infarction by marijuana. Circulation 2001;103(23):2805–9.
63. Wolff V, Armspach J, Lauer V, et al. Cannabis-related stroke: myth or reality? Stroke 2013;44(2):558–63.

64. Falkstedt D, Wolff V, Allebeck P, et al. Cannabis, tobacco, alcohol use, and the risk of early stroke: a population-based cohort study of 45 000 Swedish men. Stroke 2017;48(2):265–70.
65. Hemachandra D, McKetin R, Cherbuin N, et al. Heavy cannabis users at elevated risk of stroke: evidence from a general population survey. Aust N Z J Public Health 2016;40(3):226–30.
66. Kalla A, Krishnamoorthy PM, Gopalakrishnan A, et al. Cannabis use predicts risks of heart failure and cerebrovascular accidents: results from the national inpatient sample. J Cardiovasc Med 2018;19(9):480–4.
67. Silver B, Behrouz R, Silliman S. Bacterial endocarditis and cerebrovascular disease. Curr Neurol Neurosci Rep 2016;16(12):104.
68. Yaghi S, Bernstein RA, Passman R, et al. Cryptogenic stroke: research and practice. Circ Res 2017;120(3):527–40.
69. Manousakis G, Jensen MB, Chacon MR, et al. The interface between stroke and infectious disease: infectious diseases leading to stroke and infections complicating stroke. Curr Neurol Neurosci Rep 2009;9(1):28.
70. Bergh C, Fall K, Udumyan R, et al. Severe infections and subsequent delayed cardiovascular disease. Eur J Prev Cardiol 2017;24(18):1958–66.
71. Fugate JE, Lyons JL, Thakur KT, et al. Infectious causes of stroke. Lancet Infect Dis 2014;14(9):869–80.
72. Ihara M, Yamamoto Y. Emerging evidence for pathogenesis of sporadic cerebral small vessel disease. Stroke 2016;47(2):554–60.
73. Jillella DV, Wisco DR. Infectious causes of stroke. Curr Opin Infect Dis 2019;32(3):285–92.