

Embolic Stroke of Undetermined Source: A Primer for Nursing

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ABSTRACT

BACKGROUND: Cryptogenic stroke has been used to identify ischemic strokes with no identified cause; however, this classification is limited by the lack of a standardized and thorough evaluation. Embolic Stroke of Undetermined Source is used to define those strokes with no identified cause after a standardized diagnostic workup. **METHODS:** We conducted a literature review from January 1, 2014, to July 31, 2020 including the term “ESUS.” **RESULTS:** Embolic stroke of undetermined source accounts for approximately 25% of ischemic strokes and is used to classify patients with no identified cause of stroke despite routine brain imaging, noninvasive vascular imaging of the head and neck, a minimum of 24 hours of cardiac monitoring, and echocardiography. Studies have shown that these strokes may be caused by occult atrial fibrillation, occult malignancy, and other hypercoagulable states but are often identified after hospital discharge. The risk of recurrent stroke in ESUS patients remains high at 4.5% per year on single antiplatelet therapy. Ongoing research aims to identify biomarkers that can identify ESUS subgroups who may benefit from alternative antithrombotic therapies. **CONCLUSION:** Because of the complexity of the evaluation and the uncertainty associated with an unknown cause of stroke, neuroscience nurses caring for these patients should be familiar with ESUS and educate the patient about the condition and the importance of complying with all prescribed treatments, tests, and subsequent follow-up appointments after discharge.

Embolic stroke of undetermined source (ESUS) is a relatively new term that is used to characterize cryptogenic stroke with an undetermined cause after completing a specified workup that excludes lacunar, atherosclerotic, and other known causes of embolic stroke. Approximately 25% of ischemic strokes do not have a specific cause identified despite a thorough diagnostic workup. The workup and diagnosis of this type of stroke involves a variety of tests, including prolonged heart monitoring for atrial fibrillation (AF) post hospitalization.^{1,2} Ongoing studies are evaluating medication treatments for secondary stroke prevention in ESUS as will be reviewed. Given the unknown cause of stroke at the time of discharge, patients may find frustration with not having a clearly determined explanation for their stroke. In addition, patients with this diagnosis may have relatively minor strokes.

The lack of a definitive diagnosis coupled with less disability than other stroke subtypes may affect patients' medication adherence and compliance with follow-up testing needed to solidify the cause of their stroke and reduce their overall recurrent stroke risk. We conducted a literature review from January 1, 2014, to July 31, 2020 including the term “ESUS.”

Causes of Cryptogenic Stroke

Imaging has shown that the pattern of these infarctions related to cryptogenic strokes seems to result from distal emboli rather than an arterial occlusion.³ One potential risk factor for this type of stroke is paroxysmal AF that was present before the stroke occurred but remained undiagnosed.^{2,3} There is recent evidence to suggest that the same pathology that contributes to AF may also result in thromboembolism even before AF manifests.³ For this reason, a more comprehensive workup is suggested to assist clinicians in identifying occult AF as a potential cause of cryptogenic stroke.⁴

The diagnostic workup for cryptogenic stroke includes a minimum of 24 hours of continuous electrocardiography monitoring;² however, longer-term monitored cardiac outpatient telemetry and/or implantable cardiac monitor has been shown to increase the detection of occult AF in patients with cryptogenic stroke.⁵ In a study looking at the rate of AF in cryptogenic stroke patients with an implantable cardiac monitor, AF was detected after 6 months in approximately 8.9% of patients.²

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Comparatively, during the same period, AF was detected in 1.4% of patients who did not have an implantable cardiac monitor.² These data suggest that long-term cardiac monitoring with an implantable cardiac monitor is more effective than conventional follow-up for the detection of AF in cryptogenic stroke patients.²

Other causes of cryptogenic stroke may include coagulation abnormalities such as underlying malignancy, paradoxical embolism secondary to venous thromboembolism, and other hypercoagulable states (HS).⁶ A recent study examined the incidence of these risk factors using the MOCHA profile, which examined markers of coagulation and hemostatic activation.⁶ The MOCHA profile consists of the following blood tests: serum D-dimer, prothrombin fragment 1.2, thrombin-antithrombin complex, and fibrin monomer.⁶ During a follow-up of 10 months in 132 patients, this test identified either new malignancy (21%), venous thromboembolism (9%), or HS (11%) in 23% of those patients.⁶ The results of this study suggest that the use of the MOCHA profile may be useful as part of the follow-up evaluation in cryptogenic stroke patients to aid in the identification of the cause.⁶

Diagnosis

The full workup recommended for diagnosing ESUS includes brain imaging, noninvasive vascular imaging of the head and neck, a minimum of 24 hours of cardiac monitoring, and echocardiography.⁷ If hypercoagulability is suspected during the hospital stay, the patient may have laboratory tests performed during hospitalization; however, some of these tests may take several days to result and may not be completed before the patient is discharged from the hospital and thereby require outpatient follow-up. This can result in the patient being discharged without having a specific cause of their stroke yet identified. Because patients are often eager to know the cause of their stroke, the lack of a specific cause may affect compliance with follow-up appointments, medication adherence, and testing needed to accurately diagnose this condition.

Recurrent Stroke Risk

Single antiplatelet therapy remains the standard of care for secondary stroke prevention in patients with ESUS.^{8,9} Although this medication has been shown in clinical trials to reduce recurrent stroke risk in those patients with cryptogenic stroke,^{9,10} the risk of recurrent stroke in this population remains relatively high, with approximately 4.5% per year.^{11,12} Contributing factors to recurrent stroke in this population include unidentified occult AF, underlying malignancy, and other HS.^{2,3,6}

Current Evidence

Recently published trials have compared the use of direct oral anticoagulants versus acetylsalicylic acid for

Nurses positively impact patient outcomes by providing understanding of the disease process.

secondary stroke prevention, with studies of rivaroxaban and dabigatran showing no significant benefit on recurrent stroke rates compared with acetylsalicylic acid in an unselected group of ESUS patients.^{8,9} Ongoing studies are evaluating apixaban versus acetylsalicylic acid for recurrent stroke prevention in ESUS and the use of biomarkers to identify a subset of patients who may benefit from anticoagulation.³ For example, the ARCADIA (AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) trial is evaluating whether left atrial cardiopathy biomarkers based on electrocardiography, echocardiography, and serum amino terminal pro-B-type natriuretic peptide levels may identify ESUS patients who are at a high risk of recurrent stroke and may benefit from anticoagulation therapy versus acetylsalicylic acid.³ The ATTICUS (Apixaban for Treatment of Embolic Stroke of Undetermined Source) trial is also currently evaluating apixaban versus acetylsalicylic acid to prevent recurrent stroke risk in an unselected cohort of ESUS patients.¹³

Given that anticoagulation therapy is superior to antiplatelet therapy in patients with AF for secondary stroke prevention and that ESUS patients who undergo implantable loop recorders for outpatient cardiac monitoring can have AF detected in up to 30% of patients after 3 years of monitoring, identification of ESUS patient subgroups who may benefit from anticoagulation is the focus of ongoing studies.^{2,3}

Medical Management

The CHANCE (Clopidogrel in High-Risk patients with Acute Nondisabling Cerebrovascular Events) trial found that short-term antiplatelet therapy was superior over acetylsalicylic acid alone in preventing recurrent stroke at 90 days in patients with ischemic stroke or high-risk transient ischemic attack who presented early after the onset of symptoms and had minor stroke symptoms.¹⁴ These patients should be given a loading dose of clopidogrel, 300 mg, followed by 75 mg of clopidogrel daily with low-dose acetylsalicylic acid for 21 days.¹⁴ At the end of 21 days, the patient should be placed on single antiplatelet therapy.¹ Single antiplatelet therapy remains the standard of care for long-term secondary stroke prevention in patients with ESUS.^{8,9} Although this medication has been shown in clinical trials to

reduce recurrent stroke risk in those patients with ESUS,^{9,10} the perceived benign nature of the drug may further contribute to low medication adherence in this stroke population.

Conclusion

Because of the complexity of the evaluation and the uncertainty associated with an unknown cause of stroke, it is important for neuroscience nurses caring for these patients to be familiar with ESUS and to educate the patient about the condition and the importance of complying with all prescribed treatments, tests, and subsequent follow-up appointments after discharge. The patient may be very overwhelmed and fearful during their hospital stay. It is helpful to explain to the patient that, although the cause of their stroke may not be known at the time of discharge, outpatient neurology will continue work to help identify the cause of their stroke to determine the best treatment options to prevent subsequent strokes. Nurses can positively impact the patients' outcomes by assisting the patients in understanding their disease process and empowering them to make pertinent decisions related to their poststroke care.

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