

Embolic Stroke of Uncertain Source: An Entity Slowly Coming Into Focus

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“Happy who had the skill to understand nature’s hid causes”

— Virgil, *The Georgics*

Antithrombotic therapy for ischemic stroke prevention has been complicated by multiple, nonexclusive potential causes for the incident event, imprecise definitions of pathogenetic categories, and a therapeutic window narrowed by the potential for intracerebral hemorrhage. Paradoxically, the risk of hemorrhage is highest soon after a stroke in a period that has the potential for the greatest benefit from effective secondary prevention. Readily available markers of pathogenesis in this early time frame are needed. Currently, stroke neurologists first confirm the absence of hemorrhage on cerebral imaging to establish the presence of an ischemic stroke. Cause is classified broadly into large-artery, small-vessel disease, cardioembolic, cryptogenic, and unusual causes that include genetic, infectious, and paraneoplastic states. Subsequent investigations are driven by the need to establish the presence of conditions with specific accepted therapy: significant carotid stenosis necessitating surgery or stenting, a major risk cardioembolic source requiring anticoagulation, or uncommon sources such as bacterial endocarditis. Most individuals with stroke who do not fit into these categories are treated with antiplatelet therapy, usually low-dose aspirin. Cryptogenic stroke, which makes up about 25% of ischemic stroke, has proven to be particularly resistant to advances in therapeutics because of conflicting definitions, an evolving diagnostic armamentarium with the potential to identify multiple possible causes in a single patient, and the failure of trials

to demonstrate a benefit for strategies other than aspirin in specific potential causes such as aortic arch atheroma, intracranial stenosis, and until recently patent foramen ovale.¹

One approach to the optimization of prevention is to increase the complexity and number of the initial investigations.² This approach is expensive, not accessible to individuals and health systems without advanced imaging capability and, in the absence of specific therapy for identified sources, has not been widely embraced. In addition to identifying a candidate for specific treatments, a pathogenetic classification can provide a prognosis and diagnostic certainty that prevent additional investigations that are futile, unrewarding, or harmful.

The power of the Embolic Stroke of Uncertain Source (ESUS) construct is in acknowledging the difficulty in identifying the source in a given patient and focusing efforts on the dominant pathophysiology—embolization into the cerebral vasculature. This provides focus and direction to the otherwise dispiriting effort to identify specific therapies for numerous potential causes of emboli, with insufficient criteria to implicate a particular source in a specific patient. ESUS has been operationally defined as a nonlacunar stroke not associated with significant stenosis in a feeding artery in the absence of a high-risk cardioembolic source or other known cause. A significant advance is the elaboration of a pragmatic set of investigations required to meet the definition by the Cryptogenic Stroke/ESUS Working Group.¹ The construct has generated interest for the potential to illuminate the otherwise murky concept of cryptogenic stroke, and while some would argue that concept remains fuzzy, some clarity is emerging.^{3–5} Pooled estimates from cohorts totaling over 1600 individuals suggest that ESUS represents at least 17% of ischemic stroke and probably closer to 20% when accounting for incomplete investigations. Patients with ESUS tend to be younger with lower rates of traditional vascular risk factors than other stroke subtypes, have minor strokes with a mean National Institutes of Health Stroke Scale of 5, but retain a significant risk for recurrent stroke (4.5% per year) and death (3.9% per year).³

In this issue of *JAHA*, Merkler and colleagues report an association between cardiac troponin (cTn) and ESUS.⁶ They

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examined a large single-center cohort including 512 patients with ESUS or ischemic stroke caused by large- or small-vessel disease and who had a cTn measured within 24 hours of admission. An elevation of troponin was defined as a value above the 99th percentile for the laboratory (0.04 ng/mL). Stroke subtype was retrospectively determined using the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria and correlated with cTn levels by logistic regression with adjustment for known associations of cTn such as stroke size, renal failure, and involvement of the insula. Elevation of cTn was twice as likely in individuals with ESUS as with small- or large-vessel strokes (17.7% versus 8.9%), with an adjusted odds ratio of 3.3 (95% confidence interval, 1.2–8.8, $P=0.017$). The association was robust with consistent results noted on multiple sensitivity analyses including analyses using only dynamic changes in cTn as the outcome variable, excluding individuals who had atrial fibrillation (AF) noted on postdischarge long-term monitoring and analyses that treated cTn as a continuous variable. The authors appropriately note several limitations including the single-center origin of the cohort and incomplete ascertainment of cTn. These factors may explain some unusual features of their population including a relatively high proportion of ESUS compared with other noncardioembolic subtypes and the high proportion of women. The relative prevalence of cryptogenic stroke observed in other studies compared with the arterial subtypes included in this study suggests that ESUS should make up about one third of the sample rather than the 47% observed.¹ Similarly, pooled cohort studies demonstrate a female proportion of 42% in ESUS compared with the slight predominance of women observed (51.9%).³

What explains the association between ESUS and elevated cTn? Cardiac injury as a consequence of stroke is possible in a subset of individuals but seems unlikely to be the predominant mechanism in this population of small strokes (mean National Institutes of Health Stroke Scale 3) after accounting for involvement of the insula, which has been associated with neurogenic cardiac injury. Small foci of myocardial injury that generate cerebral emboli is an intriguing mechanism raised by this work. Consistent with this is the recent finding that emboli extracted from the brains of individuals with ESUS during acute stroke treatment show features consistent with cardiogenic emboli.⁷ AF is associated with elevated troponin and subclinical AF has been suggested as the cause underlying cryptogenic stroke.^{8,9} The elimination of patients later found to have AF from the analysis cohort did not substantially change the strength of the association, and long-term monitoring of cardiac rhythm has demonstrated that a minority of ESUS patients have AF on follow-up. Atrial myopathy/dysfunction in the absence of AF has been suggested as a cause of embolic stroke and the association

between this, as yet incompletely understood, condition and cTn remains to be explored.

The association of elevated cTn in the setting of ESUS has the potential to advance the understanding of this entity and needs to be replicated in other cohorts, preferably in a prospective study enrolling consecutive patients with determination of outcomes of individuals with ESUS and elevated cTn. Elevated cTn in other stroke subtypes is associated with worse prognosis, and a similar determination in this relatively milder stroke population would have implications for care.

Three randomized trials comparing anticoagulants with aspirin in individuals with ESUS are under way: Rivaroxaban Versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients With Recent Embolic Stroke of Undetermined Source (ESUS) (NAVIGATE ESUS), Randomized Evaluation in Secondary Stroke Prevention Comparing the Thrombin Inhibitor Dabigatran Etexilate Versus Aspirin in Embolic Stroke of Undetermined Source (RESPECT ESUS), and Apixaban for Treatment of Embolic Stroke of Undetermined Source (ATTICUS). If successful, these efforts will greatly simplify secondary stroke prevention by reducing the impetus to identify specific sources of stroke in each individual. These trials are ongoing with results anticipated in 2018. The work of Merkler et al supports the hypothesis underlying these trials that anticoagulation will provide a reduction in the risk of recurrence over aspirin and further assists in understanding this new construct: ESUS.

Disclosures

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