Cryptogenic Stroke: Clinical Consideration of a Heterogeneous Ischemic Subtype

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Background: Cryptogenic stroke can be subdivided into 3 distinct categories: stroke of no determined cause (CyNC), stroke due to multiple etiologies (Cy >1), and stroke etiology unclear due to incomplete evaluation. Although these subdivisions may be very different from one another with respect to baseline features and outcomes, they are often reported as a composite group in clinical trials. *Methods:* Patients treated at our academic institution between July 2008 and June 2013 for acute ischemic stroke were retrospectively assessed in our prospective registry. CyNC and Cy >1 patients were compared to other Trial of Org 10172 in Acute Stroke Treatment (TOAST) stroke subtypes and to each other using univariate analyses and multivariate logistic regression. The primary outcome of interest was good functional outcome, defined as a discharge modified Rankin Scale score of 0-2. *Results:* Of the 1311 included patients, 260 (19.8%) experienced a CyNC and 49 (3.7%) experienced a Cy >1. Cy >1 classification was associated with history of atrial fibrillation (odds ratio [OR], 3.17; 95% confidence interval [CI], 1.16-6.12; $P = .001$). In comparison to other TOAST classifications, CyNC strokes were more likely to have good functional outcome (OR, 1.97; 95% CI, 1.38-2.82; $P < .001$) after adjusting for baseline National Institutes of Health Stroke Scale, admission glucose, age, and intravenous tissue plasminogen activator (IV tPA). *Conclusions:* Even after adjusting for higher IV tPA treatment rates, ischemic stroke patients with no identified cause had better outcomes than other TOAST groups. Conversely, patients coded as cryptogenic with more than 1 likely cause represent a different patient subpopulation. These data argue against the consolidation of cryptogenic stroke subcategories in future investigations. **Key Words:** Ischemic stroke—TOAST—cryptogenic stroke—atrial fibrillation—management—cost.

Recognizing that acute ischemic stroke is a singular clinical condition characterized by numerous etiologies with variable pathogenesis, the Trial of Org 10172 in Acute Stroke Treatment (TOAST) proposed a classification system of ischemic stroke subtypes.[1] Circumstances in which (1) the cause of a stroke cannot be determined with any degree of confidence; (2) the presence of 2 or more potential causes complicates a parsimonious etiologic identification; or (3) the work-up performed was inadequate to evaluate the etiology are aptly denominated cryptogenic.[1] Accounting for as much as 20%-40% of the stroke population,[2-4] cryptogenic stroke has been associated with a broad spectrum of conditions,

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Received November 12, 2014; revision received December 15, 2014; accepted December 18, 2014.

There are no disclosures.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2014.12.024

including patent foramen ovale (PFO),[5] paroxysmal atrial fibrillation,[6] and congenital pathologies such as lysosomal storage diseases and primary coagulopathies.[7-9]

Cryptogenic stroke populations tend to be highly variable, making analyses difficult and potentially nonspecific.[9,10] As a result, studies regarding secondary stroke prevention and long-term outcome are often conflicting.[11,12] For example, PFO closure for the prevention of recurrent paradoxical embolism remains extensively debated,[13,14] and newer causative classification systems code patients with PFO and no other source as cardioembolic—possible.[15] Although paroxysmal atrial fibrillation may account for a significant number of cryptogenic cases,[16,17] a cost-effective and reliable method to diagnose these patients has not been defined or recommended in current guidelines.[18] The heterogeneous nature of cryptogenic stroke is further muddled by the fact that cryptogenic stroke with no clear cause and cryptogenic stroke due to multiple etiologies are often grouped together as a single composite entity. It may therefore be beneficial to distinguish these unique subtypes to provide a more precise understanding of management and prognosis. To our knowledge, no systematic evaluation of the predictors of a "cryptogenic stroke with more than 1 likely cause" designation, or the combinations of such causes, has been published.

In the present study, we report a comparative analysis of patients with cryptogenic stroke due to no known cause (CyNC), cryptogenic stroke due to more than 1 likely cause (Cy >1), and stroke according to the remaining TOAST etiologies evaluated at our center with respect to baseline characteristics, evaluation and management, and short-term outcomes.

Methods

We conducted a retrospective analysis of patients with ischemic stroke admitted from July 2008 to June 2013 to our center using a prospective registry as previously described.[19] TOAST classification was prospectively determined by a vascular neurologist and validated online at https://ccs.mgh.harvard.edu/ccs_title.php. Patients coded as cryptogenic because of incomplete work-up were excluded from the analyses. A complete work-up was defined as a minimum of brain parenchymal imaging (magnetic resonance imaging [MRI] unless contraindicated or refused), intracranial and extracranial vascular imaging, electrocardiogram (EKG) with in-hospital telemetry, and transthoracic echocardiography (TTE). We screened for cardioembolic sources using routine EKG, minimum of 24 hours of in-hospital telemetry, and TTE without transesophageal echocardiography (TEE). The use of TTE without TEE was deemed appropriate in the screening of cardioembolic sources based on definitions put forth by other larger multinational cohorts such as the Embolic Strokes of Undetermined Source global registry.[20] TEE was performed at the clinical discretion of the treating physician, and these data were also collected as part of our prospective registry. Select demographic information, clinical and radiologic data, and outcome measures were compared between patients according to acute ischemic stroke subtypes as defined by TOAST[1]: cardioembolic (CE), large vessel (LV), and small vessel, with the exception of our unique identification of (CyNC) and (Cy >1). The diagnosis of CyNC or Cy >1 was made only after complete etiologic evaluation using the aforementioned modalities. Major TOAST criteria were defined as CE, LV, or small vessel stroke. Minor TOAST included the etiologies of stroke typically classified as "other" (eg, cervical artery dissection, hypercoaguable state, vasculitis, etc). Furthermore, we compared the clinical and outcome differences between patients having CyNC strokes and patients with Cy >1 strokes.

The primary outcome of interest was good functional outcome, defined as a discharge modified Rankin Scale (mRS) score of 0-2. Secondary outcome measures included favorable discharge disposition, which we defined as discharge to home or an in-patient rehabilitation facility. Baseline characteristics between patients of different subtypes were compared using the Pearson chi-square, Fisher exact, and Wilcoxon rank-sum tests as appropriate. Multivariate logistic regression was used to evaluate the outcomes of patients according to each TOAST etiologies, including our modified Cy >1 and CyNC classification.

This study was approved by our center's Institutional Review Board with waiver of informed consent.

Results

Cryptogenic Strokes without an Identified Etiology

Of the 1311 included patients, 260 (19.8%) experienced a CyNC. Significant variation in age, gender, and race was detected comparing TOAST groups (Table 1). In comparison with Cy >1, CyNC patients displayed a lower baseline NIHSS and several significant differences in select demographics (Table 2). CyNC patients were less likely than all other patients to have a history of coronary artery disease, congestive heart failure, or a diffusion-weighted imaging (DWI)-positive lesion on MRI (Table 3). A significantly larger proportion of patients with CyNC underwent TEE as part of their etiologic work-up (42.9%) compared with patients with other etiologies of ischemic stroke ($P < .001$). Compared with other TOAST groups, patients with CyNC strokes were more likely to have good functional outcome, lower NIHSS at discharge, lower mRS at discharge, and higher proportion of patients discharged with a favorable disposition (Table 4). The relationship between CyNC and good functional outcome persisted after adjusting for NIHSS at baseline, admission glucose, age, and treatment with intravenous