Etiological Classification of Stroke in Patients with Chagas Disease Using TOAST, Causative Classification System TOAST, and ASCOD Phenotyping

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Background: Cardioembolism is considered a major pathophysiological mechanism in patients with ischemic stroke (IS) and Chagas disease (CD). However, a previous study reported that other stroke subtypes are present in more than 40% of CD patients according to the TOAST classification. Therefore, the aim of our study was to evaluate the etiologic classification of stroke in patients with CD using the Causative Classification System (CCS), the ASCOD, and the TOAST classifications in a prospective cohort of patients. *Methods:* Patients evaluated in our outpatient clinic from 2012 to 2015 with IS and CD were included and underwent full investigation for stroke etiology. TOAST, CCS TOAST, and the ASCOD classifications were compared. *Findings:* We Included 32 patients (18 men; mean age 62.7 +/−10.1 years). A total of 93.8% had at least 1 vascular risk factor; the most frequent was hypertension (87.5%). According to TOAST, we defined 87.5% as having cardioembolic stroke, being 9.4% as large-artery atherosclerotic (LAA) and 3.1% as undetermined cause. Using the CCS TOAST, 62.5% were classified as cardioaortic embolism evident and 15.6% as possible, 6.3% as small artery occlusion evident and 3.1% as probable, and 12.5% as LAA evident. When ASCOD phenotyping was applied, atherosclerosis was present in 50.1% of patients (A1 = 6.3%, A3 = 43.8%), cardiac pathology in 84.4% (C1 = 62.5%, C2 = 15.6%, C3 = 6.3%), and small-vessel disease in 66% (S1 = 9.4%, S2 = 3.1%, S3 = 3.1%). *Findings:* In conclusion, the use of the CCS and the ASCOD phenotyping in patients with CD confirmed a high frequency of cardioembolic IS but also showed that other etiologies are prevalent, such as large-artery atherosclerosis and small-vessel occlusion.
Key Words: Ischemic—stroke—Chagas—embolism.

Introduction

Ischemic stroke (IS) is a common complication of Chagas disease (CD) chronic cardiomyopathy (CCC) with a lifetime risk of 15%-64.5%.[1] Despite a significant decrease in cases of CD, there is still a large population of adults coming from endemic areas that are at risk of chronic disease.[2] The World Health Organization estimated 6-7 million infected individuals worldwide in 2015.[3]

Cardioembolism is considered a major pathophysiological mechanism in patients with IS and CCC, mainly related to the presence of apical aneurysms, heart failure,

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and arrhythmias.[4] However, other mechanisms of IS could potentially be involved in patients with CD. For example, CD is known to affect the microvascular function in the heart through microvascular spasm, reduced myocardium blood flow, increased platelet aggregation, inflammation, and myocardial fibrosis.[5,6] Therefore, it is possible that small vessels in the brain will be involved in the pathophysiology of stroke in patients with CD.[7] Actually an inflammatory imbalance (strong inflammatory response dominated by Th1 patterns) seems to be associated with an increased stroke risk in patients with chronic CD.[8] Additionally, patients with CCC often present with other cardiovascular risk factors that may overlap with the cardiomyopathy and be related to the etiology of IS.[9]

In order to better characterize the etiology of stroke in patients with CD, a previous study using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification system[10] showed that subtypes of stroke other than cardioembolism (large artery, small-vessel disease, and undetermined cause) are present in more than 40% of patients with CD, with a high frequency of stroke of undetermined etiology.[11] The TOAST system, however, identifies a single mechanism for IS, ignoring the possible interactions that can occur between 2 or more mechanisms. Indeed, IS can often be the final result of multiple abnormalities, and treatment decisions require a more comprehensive assessment, such as that provided by the Causative Classification System (CCS).[12] This system is an automated version of Stop-Stroke Study TOAST Classification (SSS-TOAST) TOAST, which was shown to have a high reliability and the ability to identify the etiology of IS.[13] The CCS can be accessed using a web-based questionnaire system (http://ccs.martinos.org or http://ccs.mgh.harvard.edu). The CCS allows for a fast analysis with great confidence, with a potential utility of improving the accuracy of the etiologic classification of IS in multicenter studies or databases where the classification of IS subtype is essential. A multicenter evaluation corroborated and ensured the accuracy of communication between different researchers and institutions.[14] A previous retrospective study evaluated the etiology of stroke in patients with IS and CD using the TOAST and SSS/CCS TOAST classification criteria and found that SSS/CCS TOAST was superior to the classic TOAST criteria in identifying a cardioembolic etiology.[15] However, retrospective TOAST subtyping based solely on medical records review has only moderate interrater reliability.[16]

The ASCOD phenotyping (A: atherosclerosis; S: small-vessel disease; C: cardiac pathology; O: other causes; D dissection) is another very useful classification for patients with IS.[17] In contrast to other classifications that lump IS in rigid groups, ASCOD grades all conditions present, describes the overlap between the diseases, and weights the potentially causal relationship between the condition detected and the IS.

Therefore, the aim of our study was to evaluate the etiologic classification of stroke in patients with CD using the CCS, ASCOD, and TOAST classifications in a prospective cohort of patients.

Methods

All patients consecutively evaluated in the outpatient stroke clinic of the Federal University of São Paulo from June 2012 to March 2015 with the clinical diagnosis of IS and a positive Chagas serology (on both immunofluorescent antibody assay and enzyme-linked immunosorbent assay tests) were included in this prospective study.

Data were collected on vascular risk factors, location of brain lesion, electrocardiography (ECG), and transthoracic echocardiography findings. All patients underwent a diagnostic protocol for stroke, including head computerized tomography (CT) and either carotid Doppler, CT angiography, or magnetic resonance angiography (MRA). Some patients underwent brain magnetic resonance imaging (MRI) and Holter monitoring at the discretion of the treating physician. All neuroimaging data were reviewed using the Synapse Picture Archiving and Communication System.

Patients were classified according to the location of their IS according to the Oxfordshire classification.[18] Stroke severity was measured using the National Institutes of Health Scale score[19] and functional outcome, with the modified Rankin Scale[20] at the time of the outpatient visit. The diagnosis of IS was obtained through clinical history, neurological examination, and neuroimaging (CT or MRI).

The etiologic classification using the TOAST criteria was carried out using data from the clinical interview and exams available through electronic medical records. The etiologic classification using the CCS algorithm and the ASCOD phenotyping were performed by a different neurologist. For the CCS, a web-based system was used: https://ccs.mgh.harvard.edu/ccs_title.php. The investigator underwent the web-based training on how to perform the CCS and completed a certification module available at the CCS website. The ASCOD classification categorized 5 predefined phenotypes: atherosclerosis (A), small-vessel disease (S), cardiac pathology (C), other causes (O), and dissection (D). Each of the five phenotypes was graded according to following categories: 1 when the disease was a potential cause of the index stroke, 2 when causality was uncertain, 3 when the disease was present but was unlikely a direct cause, 0 when the disease was absent, and 9 when the workup was insufficient to rule out the disease.

The study received institutional review board approval. All participants gave written informed consent.

Statistical Analysis

Means and standard deviations or medians and interquartile intervals were used to describe patients' char-