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REVIEW

Classifying Ischemic Stroke, from TOAST to CISS

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SUMMARY

Ischemic stroke classification is critical in conducting basic research and clinical practice. A precise analysis of stroke subtypes requires the integration of clinical features, findings from diagnostic tests, and knowledge about potential etiologic factors by competent diagnostic investigators. We performed a literature review of the published stroke classification systems and examined each for its benefits and limitations in the evaluation of the stroke etiology. Two major approaches to etiologic classifications of ischemic stroke are currently being used: the causative and phenotypic subtyping. The most widely used causative system is the Trial of Org 10172 in acute stroke treatment (TOAST) classification. With the advances in modern diagnostic technology, new stroke subclassification systems, such as the causative classification system (CCS) and Chinese ischemic stroke subclassification (CISS) system, have been developed to enhance the accuracy of TOAST. The A-S-C-O (**A**therosclerosis, **S**mall-vessel disease, **C**ardiac source, **O**ther cause) phenotypic classification system makes efforts to identify the most likely etiology but not neglecting the possibility of other potential multiple causes. We conclude that the ideal stroke classification system needs to be valid, easy to use, evidence-based, and incorporate new information as it emerges.

Introduction

Stroke is a complex disease that can be caused by multiple potential etiologies. Advances in diagnostic technology have allowed us to identify the potential underlying causes of stroke in stroke patients. The fundamental goals of ischemic stroke classification are to make a correct diagnosis, enable prompt treatment, and predict future risks in subgroups of certain discrete features. There are two major approaches to etiologic subclassification of ischemic stroke. Phenotypic subtyping uses primarily clinical and diagnostic test findings and organizes this information into major etiologic groups. According to this system, a patient can belong to more than one etiologic subtype. On the other hand, causative subtyping classifies stroke patients into a single etiologic subtype through a decision-making process. Such process involves the integration of clinical features, vascular risk factors, and diagnostic test findings. With the development of modern neuropathology and neuroradiology, there have been many new etiologic stroke classification systems described. Currently, the most widely accepted ischemic stroke subtyping system internationally is the TOAST (Trial of ORG 10172 in acute stroke treatment) classification scheme [1]. Here, we intend to provide a comprehensive review of these stroke classification systems.

Stroke Classification Systems before the Era of TOAST

1. Thirty years ago, cranial computed tomography (CT) in the diagnosis of stroke was in its infancy [2]. The major diagnostic tool at that time was cerebral angiography and only a few epidemiological studies regarding stroke had been conducted. The Harvard Cooperative Stroke Registry was the first computer-based diagnostic program using a prospective published database for stroke subclassification [3]. With only 3% had CT scans, the diagnosis of stroke in half of those patients was based on clinical information; the others were diagnosed by cerebral angiography [4]. Patients studied in the Harvard Stroke Registry were predominantly white and from a

single institution. A government-sponsored stroke registry was then proposed. Derived from the Harvard Stroke Registry, the Stroke Data Bank was created and funded by the National Institute of Neurological Disease and Stroke [5]. At that time of patient enrollment into this Stroke Data Bank, the diagnostic technology had changed again. Nearly all patients had brain CT scans and many had echocardiography. The introduction of CT technology allowed more accurate determination of the location and the extent of ischemic stroke.

2. The Oxfordshire Community Stroke Project (OCSP) clinical classification system was a simple tool. It was based on the clinical symptoms alone, or in combination with CT scan findings [6]. Because of its simplicity, it has been used in routine clinical practice, large-scale observational studies and clinical trials. This classification addressed the severity and outcome of the stroke but not the causes [7]. However, OCSP classification had some limitations: (1) The site of the brain infarction was not specific enough for a particular stroke etiology. (2) This classification failed to investigate potential risk factors of stroke. (3) The discrimination between lacunar and small-volume cortical infarcts was not accurate, especially when only the clinical criteria was used [8].

TOAST

The purpose of the TOAST classification system was to better categorize stroke patients for the purpose of investigating any potential efficacy of the anticoagulant danaparoid for treatment of various types of ischemic strokes [1]. This system was primarily based on clinical features plus any information from neuroimaging, echocardiography, neurosonography, and cerebral angiography. Even though the trial failed to show any efficacy of using danaparoid, the TOAST classification system has been used extensively for other purposes, such as identifying new genetic markers and risk factors [9,10]. The TOAST system was composed of five major subtypes: large artery atherosclerosis (LAA), cardioembolism (CE), small artery occlusion (SAO), stroke of other determined cause (SOC), and stroke of undetermined cause (SUC; Table 1). SUC was further divided into (1) no cause was found despite an extensive workup or (2) two or more plausible causes were found. Compared to the other previously described systems, the TOAST system used more objective criteria for stroke subtyping. It was thought to be a simple, logical, and useful system. It incorporated level of diagnostic certainty into subtype assignments, and was validated by independent groups for predicting "hard" stroke outcomes, such as functional dependency or death. Since then, this classification system has been widely used for over 2 decades. The TOAST investigators noted that stroke prognosis, risk of recurrence, and choice of management were influenced by ischemic stroke subtypes. However, whether the TOAST criteria were appropriate for a mechanism-oriented classification system remained unsettled. It also had several important limitations: (1) SAO was defined by the clinical syndrome and the size of the infarct (≤15 mm in diameter). Consequently, a single larger deep infarct could be classified as SUC rather than a more appropriate diagnosis of SAO [14]. (2) TOAST would categorize approximately 40% of all strokes into the SUC group, including those patients with potential multiple etiologies or had incomplete diagnostic work-up. (3) Some subtype definitions relied only on users' opinion or interpretation. As a result, the TOAST classification system only had moderate interrater reliability [15–17].

Causative Classification System (CCS)

Because the TOAST classification of acute ischemic stroke was dependent upon patient's clinical feature and baseline CT scan findings, which were often unrevealing, there was a need for a better classification of stroke subtypes that would incorporate new technological advances and the levels of diagnostic evidences. In the 10 years after the introduction of the TOAST system, stroke can be better diagnosed with new neuroimaging technology, such as diffusion-weighted magnetic resonance imaging (MRI) and magnetic resonance angiography [18]. Different diffusion-weighted MRI patterns are associated with specific stroke causes. For example, in a case of acute ischemic stroke in which both symptomatic internal carotid artery stenosis and atrial fibrillations are present, clinicians may use diffusion-weighted MRI to determine the most probable etiological mechanism. Furthermore, LAA or CE may suggest if there are multiple lesions in the region supplied by a clinically relevant artery or bilateral lesions [14].

The CCS project was launched in 2003 by a group of physicians interested in developing an evidence-based etiologic classification scheme for acute ischemic stroke [19,20]. It was a web-based classification system based on TOAST, which categorizes ischemic stroke into potentially five major subtypes (Table 1). It is available free for academic use at http://ccs.mgh.harvard.edu. The CCS was devised to overcome the major limitations of the TOAST system. The primary goal was to achieve high reliability without inflating the "unclassified" category. To achieve this goal, the CCS classifies stroke based on published evidence, and by integrating results of multiple diagnostic stroke evaluation (diffusion-weighted MRI, CT angiography and magnetic resonance angiography, echocardiography, and Holter monitoring). In this system, if multiple potential causes existed, the patient would be assigned to a subtype based on the most likely mechanism. The objective criteria used in TOAST are updated in the CCS, to allow stratification of cardiac sources of embolism into high- and low-risk groups, with reference to an objective 2% primary stroke risk threshold. The CCS also revised the conventional definition for lacunes and included lesions of up to 20 mm in diameter. The "undetermined" category in TOAST was broken into several subcategories in the CCS: unknown, incomplete evaluation, unclassified stroke (more than one etiology), and cryptogenic embolism (angiographic evidence of an abrupt cutoff in an otherwise normal-looking artery or subsequent complete recanalization of a previously occluded artery). Making cryptogenic embolism into a distinct category may give researchers the opportunity to study new embolic sources in a more refined way [11].

The current CCS Version 2.0 provides both causative and phenotypic stroke subtypes. It relies on five sources of data: clinical evaluation, brain imaging, extracranial and intracranial vascular survey, heart evaluations, and work-up for uncommon causes of stroke. In addition, the author has made several revisions and

Table 1 Characteristics of major etiologic classification systems for ischemic stroke [11,12,13]

	TOAST	CCS	A-S-C-O	CISS
Publication year	1993	2007	2009	2011
Type of system	Causative	Causative and phenotypic	Phenotypic	Causative
Major subtypes	1. Large artery 2. Cardioembolism 3. Small vessel occlusion 4. Other determined etiology 5. Undetermined etiology	1. Supra-aortic large artery atherosclerosis 2. Cardio-aortic embolism 3. Small artery occlusion 4. Other causes 5. Undetermined causes	1. Atherosclerosis 2. Cardioembolism 3. Small vessel disease 4. Other causes	1. Large artery atherosclerosis 2. Cardiogenic stroke 3. Penetrating artery disease 4. Other etiologies 5. Undetermined etiology
Advantages	Worldwide use Simple, logic and easy to use Validation by independent groups Predicting prognosis and risk of stroke recurrence	Rules and criteria based on published Evidence Updated criteria to stratify cardioembolism into high- and low-risk groups Web-based automated version available Reducing the ratio of "undetermined" category	Integration of diagnostic evaluation into the level of confidence for subtype assignments Clarified diagnostic criteria to identify or rule out a stroke etiology Integration of noncausative factors into subtype assignments	Incorporation of the etiology and underlying mechanism into stroke subclassification Creating a new subtype of PAD Large artery atherosclerosis further subclassified into four categories
Disadvantages	Only moderate inter-rater reliability Oversized "undetermined" etiology Not fit to recent advances in diagnostic technology	Depending on the availability of modern diagnostic technology Based on evidence from diverse studies Aortic arch atherosclerosis belonging to cardio-aortic embolism	Further reliability and validity data needed Interpretation cautiously with the combination of causative and noncausative factors Depending on the completeness of diagnostic tools Too many phenotypic subtypes (n = 625) for research studies Too restrictive definition to diagnose atherosclerosis and small vessel disease	Lacking reliability and validity data Depends on the availability of brain and vascular imaging Future imaging technology needed to verify the concept of PAD

ASCO, atherosclerosis, small vessel disease, cardiac causes, other uncommon causes; CCS, Causative Classification of Stroke System; CISS, Chinese Ischemic Stroke Subclassification; PAD, penetrating artery disease; TOAST, Trial of ORG 10172 in acute stroke treatment.

clarifications to the terms and definitions in CCS from the feedback of members and users of the previous version. Evidence showed that the CCS had good to excellent intrarater and interrater reliability [21]. However, CCS also had some drawbacks: (1) It was based on the evidence from diverse studies. (2) It depended on the availability of brain and vascular imaging. (3) The author decided to include aortic atherosclerosis in the category of CE, contrary to other classification systems [22].

Atherosclerosis, Small-Vessel Disease, Cardiac Source, Other Cause

The A-S-C-O (**A**therosclerosis, **S**mall-vessel disease, **C**ardiac source, **O**ther cause) phenotypic stroke classification system was proposed by an international group of leading stroke experts [23] (Table 1). Unlike the TOAST system, the A-S-C-O system assigned a level of likelihood to each potential cause and reflected the most likely etiology without ignoring other unrelated vascular conditions [12]. With the A-S-C-O classification, patients who had atherosclerotic disease were assigned an A subtype without considering the causality. An atherosclerotic disease definitely related to the index stroke was classified as A1, uncertain causality as A2, and atherosclerosis present but unlikely related to the index stroke as A3. In the absence of atherosclerosis the grade was A0, and in case of insufficient work-up the grade was A9. This was the main concept of the A-S-C-O classification. The rater should know the definition of each subtype clearly and every patient would receive a phenotypic score (e.g., A3-S3-C1-O0). This system was designed for a variety of purposes, such as describing patient demographics in clinical trials, grouping patients in epidemiological studies, phenotyping in genetic studies, and classifying patients for therapeutic options in clinical practice. For example, if we plan to analyze genetic polymorphism or a new risk factor in patients with LAA, we can take all A1 to A3 cohorts identified by the A-S-C-O system, whereas in TOAST only the small proportion of patients classified as LAA can be selected.

Compared to TOAST, A-S-C-O is more stringent in its definitions of LAA (i.e., A1 in A-S-C-O) and SAO (i.e., S1 in A-S-C-O). To be assigned a A1, the A-S-C-O system requires a criteria of >70% stenosis or <70% stenosis but with attached luminal thrombus. This criterion would exclude patients with 50–70% stenosis for whom that more aggressive therapy may be of benefit. To diagnose S1, a deep infarct with a diameter <15 mm must be present along with the presence of an old lacunar infarct or leukoaraiosis, or recent, repeated, similar transient ischemic attacks. Overall, this system classifies ischemic strokes into 625 phenotypic subtypes, integrates features unrelated to the event into stroke subtype assignments, and relies on the availability of brain and vascular imaging studies. A study designed to assess the reliability and validity of the A-S-C-O system showed that it had good-to-excellent agreement with TOAST, and that the A-S-C-O grade 1 interrater reliability was good to excellent for A1, C1, and O1, but only moderate for S1 [24].

Chinese Ischemic Stroke Subclassification

The principle of the Chinese Ischemic Stroke Subclassification (CISS) system was conceived at a neurology discussion forum (http://www.rhammer.cn/), where several neurologists discussed the pathophysiology of SAO and LAA. CISS has two steps. The first step aims at etiological classification and the second step at further classifying the underlying mechanism of ischemic stroke. At the first step, CISS classified stroke into five categories based on the concept of TOAST, but the SAO subtype was renamed as penetrating artery disease (PAD) [13] (Table 1). PAD was defined as an acute isolated infarct in the clinically relevant territory of one penetrating artery, regardless of the size of infarct. CISS proposed that PAD was caused by atherosclerosis at the proximal segment of the penetrating artery or lipohyalinotic degeneration of an arteriole. With the advent of new imaging technology, such as high resolution magnetic resonance angiography, the wall of the penetrating artery could be directly visualized and further PAD subclassifications have now become possible [25]. In addition, aortic arch atherosclerosis is classified into LAS, which makes it more consistent with real pathological changes. At the second step, CISS further classifies the underling mechanism of ischemic stroke from intracranial and extracranial LAA into four categories according to the modern imaging technology: parent artery (plaque or thrombus) occluding penetrating artery, artery-to-artery embolism, hypoperfusion/ impaired emboli clearance, and multiple mechanisms. Actually, CISS has introduced a classification system that considers both etiological and pathophysiological causes. Although the reliability and validity of CISS have not been studied, it represents an innovative classification system that more faithfully reflects the pathophysiology of stroke.

Conclusion

Etiologic classification of stroke is primarily a research tool. With the advent of modern diagnostic technologies and the improved understanding of underlying mechanisms of ischemic stroke, new classification and subclassification systems of stroke need to be reliable, valid, ease to use, evidence-based, and incorporate new information as it emerges. A good stroke classification system is key to select patients for genetic phenotyping, conduct epidemiological studies, and make treatment decisions and prognostic predictions.

Conflict of Interest

The authors declare no conflict of interest.

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