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Advances in the Diagnosis of Etiologic Subtypes of Ischemic Stroke

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Abstract A fundamental goal of etiologic stroke classification is to generate subgroups with discrete phenotypic, therapeutic, and prognostic features. Accurate stroke classification requires integration of multiple aspects of diagnostic stroke evaluation in a standardized manner. Diagnostic test findings can be simply organized into major etiologic groups to create a *phenotypic subtype*, or they can be reduced to a single *causative subtype* through a decision-making process. It is essential for a classification system to provide consistent results across different raters in different clinical settings. Comparability of subtype assignments is the key to valid communication of research results across the field. This article highlights important theoretical aspects of etiologic stroke classification and reviews major etiologic classification systems that have benefited from recent advances in etiologic stroke evaluation.

Keywords Ischemic stroke · Etiology · Classification

Introduction

The etiologic architecture of stroke constitutes a hierarchic structure, with frequent but less potent etiologies at the bottom and less frequent but more potent causes close to the top. The pyramid is composed of at least 100 different cardiac, arterial, hemodynamic, rheologic, and other systemic abnormalities. Assortment of patients into classes congruent with the pathophysiology is the key to understanding stroke. A functional classification system is indispensible for selecting patients for clinical trials, phenotyping in genetic and epidemiologic studies, assessing treatment response and prognosis, and interpreting research findings in simultaneous context with other parameters. Obviously, separating patients into various classes may result in the ignoring of some important qualities that characterize individuals. Nevertheless, assembling stroke features to create categories based on similarities compensates for the loss of information on an individual basis by enhancing statistical power in research studies.

Several etiologic stroke classification systems, such as the Harvard Stroke Registry [1], the Stroke Data Bank [2], the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) system [3], and the Baltimore-Washington system [4], have been described, but none has demonstrated high reliability and validity. An ideal classification system would provide a common language in the field to ensure unity among physicians and comparability among studies. The ideal system must be simple and logical. Additionally, the system should rely on the pathophysiology, use rules and criteria based on evidence rather than ideas, be flexible enough to accommodate new information as it emerges, and allow categorization of patients into the fewest possible subtypes with discrete phenotypic, therapeutic, and prognostic features. Finally, the ideal system should have proven utility in diverse clinical settings and allow categorization of individual elements of stroke in different ways according to the needs of specific research projects. The purpose of this article is to review etiologic stroke classification systems, with a particular focus on those that have incorporated the latest advances in diagnostic stroke evaluation.

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Types of Etiologic Classification: Causative Versus Phenotypic

The success of etiologic classification in stroke depends on how the individual elements of the stroke workup are organized to produce a classification system. There are two major approaches to etiologic classification in stroke. *Phenotypic subtypes* are determined based on organization of abnormal test findings into major etiologic groups. The Baltimore-Washington [4], Causative Classification of Stroke System (CCS) [5, 6••], and ASCO (*a*therothrombosis, *s*mall vessel disease, *c*ardiac causes, and *o*ther uncommon causes) [7•] are examples of phenotypic classification systems. In this type of system, a patient can be categorized into more than one etiologic subtype. For instance, a patient with carotid atheroma causing more than 50% stenosis and atrial fibrillation is classified as having "large artery atherosclerosis plus cardiac embolism." In a phenotypic classification, there are no tradeoffs among positive test findings, so there is no inadvertent loss of information. Categorizations rely, to some extent, on causal inferences; subtypes typically are determined according to the potential for each underlying etiology to cause stroke. For instance, cardiac sources of embolism are segregated into high- and low-risk groups, and atherosclerotic disease is defined according to the severity of stenosis. Phenotypic subtyping may allow the study of interactions among etiologic subtypes, patient selection in large-scale epidemiologic and genetic studies, and coding for administrative purposes. Although the concept behind phenotypic classification is a valuable one, phenotypic systems are subject to one major problem—they assign stroke patients to a vast number of categories. For example, a four-category phenotypic system in which each category is defined in four possible states (eg, major, minor, absent, unknown) might result in 256 possible subtypes (fourth power of 4). Obviously this limits the use of the phenotypic approach in most clinical research studies.

The number of etiologic subtypes inversely correlates with statistical power in research studies; the fewer the etiologic subtypes, the less patients must bear the burden of research participation. This, in turn, translates into lower costs and a shorter study duration. Therefore, it is imperative to integrate diagnostic test results and clinical stroke features to identify the most likely *causative subtype* for each patient. TOAST [3] and CCS [5, 6] are examples of causative systems. Unlike phenotypic classification, designation of the causative subtype is a decision-making process requiring integration of multiple aspects of ischemic stroke evaluation, including symptom characteristics, vascular risk factors, and diagnostic test findings. For instance, for a patient with atrial fibrillation and significant carotid stenosis, a decision in favor of large artery atherosclerosis may be made when there is imaging evidence of multiple infarcts of different ages exclusively in the hemisphere ipsilateral to the stenotic artery.

Causation is difficult to infer in the absence of a gold standard. Causative subtypes frequently are assigned based on a presumed mechanism of stroke, rather than on direct demonstration of the cause by a gold standard such as pathologic verification of the suspected mechanism. Therefore, the ability of classification systems to assign the cause of stroke unambiguously is limited (validity). Subtype assignments can be made with a high level of confidence only if a particular etiology in a given patient is the sole potential mechanism. Current diagnostic technologies allow frequent identification of multiple coexisting etiologies. The process of causative subtyping, therefore, also is subject to an important investigator bias (reliability). The issue of reliability and validity in causative classification is discussed further in the following section.

Reliability and Validity of Etiologic Stroke Classification

Interrater reliability is an important measure for evaluating the quality of a classification system. The interrater reliability coefficient (kappa) indicates the percentage agreement among raters corrected for chance [8]. Deviations from perfect reliability introduce "measurement error" or "misclassification error" to stroke research; this, in turn, makes it hard to apply classification results to patient care or to compare studies from different investigators [9]. The variance introduced by misclassification error reduces the statistical power of clinical studies. Depending on the study design and variability in outcome parameter, an improvement in kappa value from 0.50 to 0.80 would permit a reduction in sample size by up to 40% to achieve the same study power [10]. Attainment of high interrater reliability in stroke classification therefore is essential to ensure the validity of research studies.

Accurate interpretation of reliability requires understanding of the factors that lead to disagreement among raters in etiologic stroke classification. Disagreements usually occur from the ambiguities in patient data, the differences in knowledge and experience of raters, and the classification system. Disagreement is likely to be greater in larger and unselected cohorts, in cohorts with diverse etiologies, and in settings in which multiple raters (more than two) are involved. Additionally, reliability tends to decrease as the proportion of patients with multiple competing etiologies or an incomplete diagnostic workup increases in a given cohort. Subtype assignments in such patients often are made based on the physician's best guess in the absence of well-defined criteria to identify the most likely mechanism.

Validity in etiologic stroke classification refers to whether categorizations are operational in terms of predicting hard

stroke outcomes. Published evidence suggests that major stroke subtypes defined by the TOAST criteria are modest but independent predictors of recurrent ischemic stroke [11], short- and long-term outcome [12–16], and mortality [17, 18]. The type of preventive treatment [19, 20] and the prevalence of coexisting coronary artery disease [21] also differ by stroke subtype. Newer classification systems with higher reliability may enhance the validity of etiologic stroke classification by eliminating misclassification error and variance in stroke research.

Etiologic Classification Systems

Several etiologic classification systems have been devised for ischemic stroke. Some failed to revise their rules according to the needs of the time and therefore have expired [1, 2, 21]. Others have attained limited acceptance and use by the community [4, 22]. The following section provides a background on the most modern and commonly applied classification systems.

The TOAST System

The TOAST system was developed for use in a therapeutic acute ischemic stroke trial in the early 1990s [3]. The system is based primarily on clinical features but also uses existing diagnostic information from CT, MRI, transthoracic echocardiography, extracranial carotid ultrasonography, and, when available, cerebral angiography. The TOAST system is composed of five major subtypes (Table 1): large artery atherosclerosis, cardiac embolism, small artery occlusion, stroke of another determined cause, and stroke of an undetermined cause. There are two possible states (probable or high risk and possible or low risk) for the first four categories, whereas the last category is broken down further into cursory evaluation, unknown group, and patients with two or more potential causes. These categories give rise to an 11-subtype system. Details of the definitions of each category may be found in the original publication [3].

Compared with earlier classification systems [1, 2, 21], the TOAST system uses more objective criteria for subtype diagnoses. The diagnosis of large artery atherosclerosis requires vascular imaging evidence of an atherosclerotic lesion causing more than 50% stenosis. Cardiac causes are arbitrarily divided into high-risk and medium-risk sources based on their relative potential to cause stroke. The diagnosis of lacunar infarction is confirmed based on the size (>1.5 cm in diameter) and location (brainstem, subcortical white matter) of the ischemic lesion on brain imaging. Additionally, this classification system incorporates the completeness of diagnostic investigations into subtype assignments; a "probable" subtype is diagnosed only if diagnostic evaluation findings exclude other etiologies. A "possible" diagnosis is made if there is evidence of one subtype, but diagnostic studies for other subtypes are not done.

Although the TOAST system has been used as the gold standard classification system for almost two decades, it is becoming apparent that it has important limitations. The TOAST system assigns patients with more than one etiology to a distinct category (two or more causes or unclassified category). Although this approach is intended to enhance the accuracy of assignments to other etiologic categories, frequent detection of multiple competing etiologies with a present-day stroke workup results in categorization of approximately half of all stroke patients into the "unclassified" group [5, 23, 24]. Likewise, because diagnostic investigations in routine clinical practice often are stopped when a positive test finding is obtained, etiologic subtypes frequently are assigned a low level of confidence ("possible") in the TOAST system. Decisions regarding subtype assignments based on raters' personal opinions rather than published TOAST rules result in a reduction in the size of "unclassified" and "possible" categories, but at the expense of reliability. Several studies have assessed the TOAST system's reliability. Despite the initially reported high interrater reliability in the original publication [3], subsequent studies from independent investigators have consistently demonstrated a moderate reliability for the TOAST system, with kappa values ranging from 0.42 to 0.54 [25–29]. A computerized algorithm using the TOAST rules slightly improved the reliability (kappa=0.68), yet the 95% confidence intervals around the point estimate for kappa were large (0.44–0.91) and the reliability assessment was performed by only two raters [26].

The CCS

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. The system attempts to accomplish its goal by developing a framework that is well defined, easily replicable, and fully evidence based [6••]. It incorporates multiple aspects of present-day diagnostic stroke evaluation (diffusion-weighted imaging, perfusion-weighted imaging, CT and magnetic resonance angiography of extracranial and intracranial arteries, transthoracic and transesophageal echocardiography, and Holter monitoring) in a regulated manner to identify both causative and phenotypic subtypes.

The CCS categorizes ischemic stroke into major etiologic groups similar to those of the TOAST system (Table 1). However, the definitions for the subtypes are slightly different from those of TOAST: large artery

Table 1 Important characteristics of etiologic classification systems for ischemic stroke

Characteristic	TOAST	CCS	ASCO
Year of publication	1993	2005, 2007	2009
Type	Causative	Causative and phenotypic	Phenotypic
Subtypes, *n*			
Major	5	5 for causative and 96 for phenotypic CCS	625
Extended	7	8	–
Extended with confidence levels	11	16	–
Subtypes	Large artery atherosclerosis (probable, possible)	**Causative type**	Atherothrombosis (absent, definite, likely, unlikely, unknown)
	Cardiac embolism (probable, possible)	Large artery atherosclerosis (evident, probable, possible)	Cardiac embolism (absent, definite, likely, unlikely, unknown)
	Small artery occlusion (probable, possible)	Cardio-aortic embolism (evident, probable, possible)	Small vessel disease (absent, definite, likely, unlikely, unknown)
	Stroke of another determined cause (probable, possible)	Small artery occlusion (evident, probable, possible)	Other uncommon causes (absent, definite, likely, unlikely, unknown)
	Stroke of undetermined cause (cursory evaluation, unknown, two or more causes or unclassified)	Other uncommon causes (evident, probable, possible)	
		Undetermined (unknown, unclassified, incomplete evaluation, cryptogenic embolism)	
		Phenotypic type	
		Large artery atherosclerosis (evident, possible, absent, unknown)	
		Cardiac embolism (evident, possible, absent, unknown)	
		Small artery occlusion (evident, absent, unknown)	
		Other uncommon causes (evident, absent)	
Important features	Is widely accepted and simple	Uses rules and criteria that are all based on published evidence	Integrates completeness of diagnostic evaluation into the level of confidence for subtype assignments
	Is validated by independent groups for predicting hard stroke outcomes	Assigns the most likely mechanism when multiple potential causes exist	Itemizes the diagnostic criteria required to identify or rule out a stroke etiology
	Incorporates degree of diagnostic certainty into subtype assignments	Uses objective criteria to stratify cardiac sources of embolism into high- and low-risk groups	Integrates causally unrelated conditions into subtype assignments
		Integrates degree of diagnostic certainty and completeness of diagnostic evaluation into the level of confidence for subtype assignments	
		Has a web-based automated version (http://ccs.mgh.harvard.edu)	
		Demonstrates excellent reliability, which is achieved with a small "unclassified" group	
		Is validated for predicting early risk of recurrent stroke	
Limitations	Has poor to moderate interrater reliability	Depends on the availability of brain and vascular imaging	Lacks reliability and validity data
	Assigns patients with more than one etiology to the "unclassified" group, inflating the "undetermined" category	Is based on evidence from diverse studies	May cause confusion in interpreting classification results because of the combination of causative and noncausative factors
	Does not accommodate recent major advances in diagnostic technology	Has too many phenotypic subtypes (n=96) for most research studies	Depends on the availability of brain and vascular imaging
			Has too many phenotypic subtypes (n=625) for most research studies
			Has a restrictive definition for atherothrombosis (>70% stenosis), which may leave out patients with 50–70% stenosis who may benefit from carotid endarterectomy

ASCO atherothrombosis, small vessel disease, cardiac causes, other uncommon causes, *CCS* Causative Classification of Stroke System, *TOAST* Trial of ORG 10172 in Acute Stroke Treatment

atherosclerosis is defined as either occlusive or stenotic (ie, ≥ 50% diameter reduction or <50% diameter reduction with plaque ulceration or thrombosis, or plaque with ≤50% diameter reduction at the site of the origin of the penetrating artery supplying the region of an acute lacunar infarct) vascular disease judged to be the result of atherosclerosis in the clinically relevant extracranial or intracranial arteries. Cardiac sources of embolism are segregated into high- and low-risk categories with reference to an objective 2% primary stroke risk threshold. The diagnosis of small vessel occlusion is considered when there is imaging evidence of a single, clinically relevant acute infarction less than 20 mm in greatest diameter within the territory of basal or brainstem penetrating arteries in the absence of any focal pathology in the parent artery at the site of the origin of the penetrating artery (eg, focal atheroma, parent vessel dissection, vasculitis, vasospasm). As in the TOAST system, the "undetermined" category in the CCS is broken into subcategories: unknown, incomplete evaluation, unclassified stroke (more than one etiology), and cryptogenic embolism. The last subgroup, cryptogenic embolism, is a new category aiming to identify patients with angiographic evidence of an abrupt cutoff in an otherwise normal-looking artery or subsequent complete recanalization of a previously occluded artery. Segregation of such patients into a distinct category may give researchers the opportunity to study new emboli sources in a more refined way.

Major subtypes in the CCS are defined in three grades according to the weight of causal evidence: evident, probable, and possible. An etiology is deemed evident only if it is the sole potential mechanism that carries a high risk for stroke. A mechanism is classified as possible if there is no evident cause of stroke. A possible mechanism is associated with either low or uncertain risk for stroke. When there is more than one evident stroke etiology, a probable stroke mechanism is assigned based on the presence of clinical qualities that make a particular mechanism a more likely cause of stroke. The weight of causal evidence is determined according to quantitative primary stroke risk estimates associated with each cause. These risk estimates are used to rank multiple stroke mechanisms to identify the most probable cause. Additionally, specific clinical or imaging features that make one mechanism more probable than others (eg, internal watershed infarcts for large artery atherosclerosis, multiple acute infarcts in both anterior or both anterior and posterior circulations for cardio-aortic embolism, and stereotypic lacunar transient ischemic attacks within the preceding week for small vessel disease) also are used to determine the strength of causal relationships. The CCS identifies the certainty around causal associations by taking into account the comprehensiveness of the diagnostic evaluation. The influence of a missing diagnostic test on the final subtype classification is determined on a patient-by-patient basis depending on other diagnostic test findings and clinical stroke features. For example, the absence of echocardiography does not change subtype assignment in a patient with atrial fibrillation (cardio-aortic embolism), may lower the level of confidence in a patient with large artery atherosclerosis (possible large artery atherosclerosis), and prevents the assignment of large artery atherosclerosis as the cause in a patient with concurrent systemic embolism (incomplete evaluation). Finally, in the CCS, the weight of causal evidence for each etiology is graded according to the presence of a spatial relationship between the brain infarct and its cause (eg, multiple acute infarcts in both hemispheres, indicating a cardio-aortic source) and a temporal relationship between a specific event and the brain infarct (eg, stroke following cardiac or vascular surgery, acute myocardial infarction, and acute arterial dissection).

An automated system incorporating all the rules used in the CCS classifies the cause of stroke based on an analytic weighting of all the identified stroke etiologies and the strength of the evidence supporting them. It is a web-based tool available for free at http://ccs.mgh.harvard.edu for academic use. The automated CCS intends to limit interexaminer variability in interpreting stroke-related characteristics and to ensure consistency in data entry, thereby maximizing interexaminer reliability in stroke classification. The interrater reliability of the CCS for causative subtyping has been assessed in three studies. An internal assessment by two raters revealed excellent reliability (kappa=0.90) for five major subtypes [5]. A subsequent external assessment by five raters from four centers also demonstrated excellent reliability (kappa = 0.86) [6••]. A third international multicenter study confirmed the earlier findings on reliability [30]. The percentage of patients assigned to the unclassified group in these reliability studies ranged from 0% to 12%, suggesting that the automated system reliably classifies patients into known subtypes without expanding the unclassified category.

The ASCO Classification of Ischemic Stroke

ASCO is a typical phenotypic system that categorizes stroke patients according to a combination of their etiologic characteristics [7•]. Its definitions for subtypes are based largely on expert opinion and are slightly different from those in other systems. A definite diagnosis of atherothrombosis is considered when there is atherosclerosis in the clinically relevant artery causing more than 70% stenosis or less than 70% stenosis with attached luminal thrombosis, or mobile thrombus in the aortic arch. A definite diagnosis of small vessel disease requires the demonstration of a deep infarct with a diameter less than 15 mm plus the presence of old lacunar infarct or

leukoaraiosis or recent, repeated, similar transient ischemic attacks. Cardiac sources of embolism are stratified arbitrarily into various risk groups based on their relative potential to cause stroke.

ASCO incorporates the quality of diagnostic evaluation in its subtype assignments in different grades: 0 for conditions in which diagnostic evaluation reveals no abnormality, 1 for the presence of a definite cause based on direct demonstration by a gold standard test, 2 for the presence of an uncertain cause based on evidence from tests with imperfect sensitivity and specificity, 3 for circumstances in which disease is present but not likely a direct cause of stroke, and 9 for the inability to perform relevant diagnostic tests for a given subtype. Overall, the system classifies ischemic stroke into 625 phenotypic subtypes. According to the ASCO system, a patient with large artery atherosclerosis, atrial fibrillation, and lacunar infarction is classified as having "large artery atherosclerosis + small vessel disease + cardiac embolism," or A1-S1-C1-O0.

The ASCO system takes into account certain stroke features that are not necessarily causally related to the event of stroke, such as leukoaraiosis, chronic microbleeds, Virchow-Robin spaces, and clinically irrelevant atherosclerotic disease. Accounting for factors that correlate with baseline burden of vascular disease may facilitate patient selection for large studies in which phenotype is more important than the underlying cause. For instance, in a study exploring genetic determinants of small vessel disease, it may be justified to study patients with leukoaraiosis even when the index stroke is caused by nonlacunar mechanisms. Because some of the concurrent conditions are quite prevalent in a typical stroke cohort and they usually are subject to significant interrater disagreement, the overall impact of including concurrent features on the system's validity and reliability remains to be seen. According to the published ASCO rules, a patient with a cryptogenic M1 embolism with large hemispheric infarction and leukoaraiosis is classified as having "small vessel disease present" (A0-S3-C0-O0), which, once again, highlights the importance of interpreting phenotypic and causative subtypes in a completely different context.

Conclusions

Etiologic classification systems retain important information toward understanding the etiopathogenetic framework of stroke. The TOAST system has been a reflection of the way neurologists have thought about recognizing and understanding stroke for almost two decades. Nevertheless, it suffers from moderate reliability. The automated CCS carries on the TOAST tradition. It is a more complex system, but it provides causative subtype assignments with higher reliability. The CCS and ASCO system allow stratification of stroke patients based on their phenotypic characteristics, promising utility in large epidemiologic studies. Further studies are needed to assess the utility of stroke subtypes in the clinical management of stroke, including their ability to aid in treatment decisions. Further evaluation of available systems also is necessary to characterize their reliability in different clinical settings so that they can be used interchangeably by different investigators from different geographic and professional backgrounds.

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