

Acute Ischemic Cerebrovascular Syndrome Diagnostic Criteria

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Background—Existing diagnostic classification systems for cerebrovascular disease are based primarily on clinical impression of temporal features, clinical syndrome, inferred localization, or ischemic mechanism. Diagnostic certainty of the ischemic pathology based on supportive or refuting laboratory or radiological evidence has been of secondary importance.

Summary of Comment—*Acute ischemic cerebrovascular syndrome* (AICS) describes a spectrum of clinical presentations that share a similar underlying pathophysiology: cerebral ischemia. Diagnostic criteria for AICS incorporate prior classification systems and currently available information provided by neuroimaging and laboratory data to define 4 categories ranging from “definite AICS” to “not AICS,” which define the degree of diagnostic certainty.

Conclusions—Clinical trials testing new treatments for acute ischemic stroke or secondary stroke prevention should limit enrollment to patients with “definite” AICS whenever feasible. (*Stroke*. 2003;34:2995-2998.)

Key Words: brain imaging ■ classification ■ diagnosis

Background: Classification and Diagnostic Criteria

The purpose of a disease classification system is to delineate meaningful descriptions of clinicopathophysiological phenomena. Such a classification system provides salient diagnostic criteria that may then be employed in clinical practice to optimize patient management and in clinical investigations to categorize research subjects. Ideally, classification schemes incorporate information along 2 parallel lines: (1) characterization of syndromes based on clinical observations of symptomatology and disease progression and (2) characterization of the underlying pathophysiology and disease mechanism confirmed by pathological, laboratory, electrophysiological, genetic, or radiological data.

Existing classification systems for cerebrovascular disease are based primarily on temporal features of the symptoms (eg, completed, evolving, transient), the syndrome of clinical deficits, the inferred localization, and etiology of the stroke.¹⁻³ The degree of certainty about the diagnosis of the acute ischemic syndrome has not been addressed in these classification systems.¹⁻³ These schemes have relied primarily on bedside clinical impression, with supportive or refuting laboratory or radiological evidence relegated to secondary in importance or not incorporated at all. In recent years, as sophisticated paraclinical diagnostic techniques have developed, controversy has arisen regarding the utility and accuracy of definitions that are based solely on clinical manifestations and an arbitrarily assigned time window rather than tissue changes and pathophysiological processes.

Role of Neuroimaging and Laboratory Studies in Redefining a Disease

Advanced diagnostic techniques, including neuroimaging studies, play an ever-increasing role in the evaluation, diagnosis, and management of patients with neurological disease and in particular cerebrovascular disease. MRI in particular has become a valuable, noninvasive tool for diagnosis of brain tumors, central nervous system inflammatory processes, and cerebrovascular disorders. In the case of multiple sclerosis (MS), MRI has now become an integral component of the new diagnostic criteria for “definite MS,” “possible MS,” or “not MS.”⁴ In patients with clinically isolated syndromes suggestive of MS, the new MRI criteria more than doubled the rate of diagnosis of MS within 1 year of presentation and demonstrated a high degree of accuracy at 3 years.⁵

In the realm of cerebrovascular disease, modern neuroimaging techniques have made early paraclinical confirmation of tissue and vascular pathology possible and feasible. The introduction of CT in the 1970s transformed acute stroke evaluation, providing the first reliable method to differentiate hemorrhagic from ischemic events. In the 1990s, the clinical implementation of advanced MR techniques further revolutionized acute stroke evaluation, providing a means to rapidly identify acute ischemia as well as hemodynamic compromise with the potential to provide a practical means to identify ischemic penumbral tissue in the hyperacute stroke setting.^{6,7}

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Problem of Defining Transient Ischemic Attack and Ischemic Stroke

In the 1950s, an arbitrary distinction was made between completed stroke versus transient ischemic attack (TIA), with TIA defined as neurological symptoms of vascular etiology that resolve within 24 hours. Distinctions were based primarily on time-based resolution of symptoms and the assumption that no permanent brain injury has occurred if the clinical deficit resolves. A growing body of data from neuroimaging studies has now called into question this previous assumption and definition. In the 1970s and 1980s, a large number of studies employing CT and conventional MR sequences suggested that a subgroup of patients with transient deficits had a relevant infarct on neuroimaging studies, although a temporal link could not be definitively established.^{8–10}

In the last few years, advanced MRI techniques employing diffusion-weighted imaging (DWI) have clarified and extended these findings. Aggregate data from 7 observational studies encompassing 288 patients have clearly demonstrated that almost one half of patients with clinical TIA syndromes have a DWI abnormality (overall frequency across all studies, 49%; range, 35% to 67%).^{11–17} Although the majority of these studies suggest that the likelihood of DWI positivity increases with increasing symptom duration, this relationship is not absolute. While these lesions may resolve in some cases, the majority of patients have imaging evidence of permanent ischemic injury.¹¹ Moreover, recent studies employing MR spectroscopic techniques suggest that abnormalities can be identified in the majority of patients with transient ischemic symptoms.^{15,17} In part as a result of on these neuroimaging findings, the TIA Working Group has now called for a redefinition of TIA based on tissue pathophysiology rather than arbitrary time cutoffs.¹⁸

Not all acute focal neurological deficits are of cerebrovascular origin; in fact, a substantial proportion of transient neurological deficits are probably not ischemic in nature (eg, isolated dizziness, numbness). The risk of erroneous clinical trial conclusions from inclusion of patients without pathological confirmation has been of necessity ignored in the era before highly sensitive hyperacute brain imaging of ischemia. The fields of stroke diagnostics and clinical trials have matured to the point at which bedside inference alone is an insufficient basis of clinical trial inclusion and patient management.

Acute Ischemic Cerebrovascular Syndrome: Diagnostic Criteria

As our understanding of the underlying pathophysiology of cerebral ischemia has evolved, it has become clear that previous classification schemes and definitions may not accurately reflect the full clinicopathophysiological phenomenon. Frequently, a discrepancy emerges between historical definitions based on clinical symptomatology and new imaging or laboratory data. The findings from DWI in patients with clinical TIA syndromes provide a strong impetus to abandon rigid time-based disease definitions in favor of pathologically meaningful definitions.

While terms such as TIA retain some clinical utility, it is important to recognize that these entities represent arbitrary

categories within the continuum of ischemic cerebrovascular disease.^{10,19} The attempt to distinguish categories based on temporal profiles is confusing at best and misleading at worst. Moreover, the attempt to distinguish them on the basis of neuroimaging or laboratory findings alone may also be a moving target; as technological advances continue, blood biomarkers and neuroimaging techniques will likely be able to identify more and more subtle evidence of ischemia.

Following the lead of our cardiology colleagues, from a clinical and practical standpoint, it may be more useful to invoke a more global and encompassing term, *acute ischemic cerebrovascular syndrome* (AICS), in a manner analogous to the acute coronary syndrome.²⁰ Subcategories, ranging from “definite” to “not,” incorporate the diagnostic certainty afforded by a combination of the clinical features and the supportive diagnostic laboratory and neuroimaging data (Table).

This new classification scheme offers a number of important advantages over prior schemes and terminology. Most importantly, it incorporates the evidence-based diagnostic certainty offered by neuroimaging techniques as used in the new MS classification scheme. Previous studies have suggested that the diagnosis of cerebrovascular ischemia is often difficult, particularly for nonneurologists or if symptoms have resolved by the time of evaluation.^{21,22} This type of diagnostic certainty is important in clinical research studies, providing universally applicable and standardized definitions. For example, phase II trials or studies employing risky therapies could be limited to the “definite” or “definite” and “probable” categories, optimizing the risk/benefit ratio and increasing the power of a study to detect a meaningful benefit by including only the “definite” target population.

In addition, this classification would be useful in routine clinical stroke care. In the acute setting, it would provide a framework for patient triage and stroke team activation. It also offers the advantage of emphasizing the similar underlying etiology (risk factors), pathophysiology, and general prognosis for recurrence of any cerebral ischemic event. This is important for long-term prevention and treatment strategies.

It is important to note that this scheme should in no way supersede the importance of accurate classification and identification of the underlying mechanism and pathophysiology of each individual event; rather, the new scheme should provide a framework on which to base further investigation and description.

This new classification scheme may pose some important challenges. As technology evolves, the sensitivity and specificity of diagnostic tests will continue to improve. Over time, the “possible” and “probable” categories may no longer be necessary. Furthermore, testing the absolute sensitivity and specificity of this scheme against an independent standard may not be possible, since all available clinical and paraclinical data are used in the determinations. The validity and utility of this classification will rest heavily on its practical application and on interrater agreement. We also recognize that the term *acute* implies a time criterion, an implication somewhat opposed to the purpose of the new classification scheme. A meaningful definition of *acute* is the time period

Classification of Acute Ischemic Cerebrovascular Syndrome (AICS)

Category	Definition	Examples
Definite AICS	Acute onset of neurologic dysfunction of any severity consistent with focal brain ischemia AND imaging/laboratory CONFIRMATION of an acute vascular ischemic pathology.*	<ol style="list-style-type: none"> 1. Sudden onset of right hemiparesis and aphasia persisting for 3 hours with DWI showing acute ischemic changes. 2. Twenty-minute episode of left hemisensory loss, which resolved, with acute right thalamic ischemic lesion confirmed on DWI.
Probable AICS	Acute onset of neurologic dysfunction of any severity suggestive of focal brain ischemic syndrome but WITHOUT imaging/laboratory CONFIRMATION of acute ischemic pathology* (diagnostic studies were negative but INSENSITIVE for ischemic pathology of the given duration, severity and location). Imaging, laboratory, and clinical data studies do not suggest nonischemic etiology: possible alternative etiologies ARE ruled out.	<ol style="list-style-type: none"> 1. Sudden onset of pure motor hemiplegia that persists with normal CT at 12 hours after onset. MRI was not performed. 2. Ten-minute episode of aphasia and right hemiparesis in a patient with atrial fibrillation and subtherapeutic INR. MRI, including DWI, was negative.
Possible AICS	Acute neurologic dysfunction of any duration or severity possibly consistent with focal brain ischemia WITHOUT imaging/laboratory CONFIRMATION of acute ischemic pathology* (diagnostic studies were not performed or were negative and SENSITIVE for ischemic pathology of the given duration, severity and location). Possible alternative etiologies are NOT ruled out. Symptoms may be nonfocal or difficult to localize.	<ol style="list-style-type: none"> 1. Two-hour episode of isolated vertigo and headache in a 50-year-old man with a history of hypertension; symptoms resolved at time of imaging. MRI including DWI was negative. 2. Twenty-minute episode of isolated word finding difficulty in 85-year-old woman with a history of dementia and coronary artery disease. Head CT was negative, and MRI was not performed.
Not AICS	Acute onset of neurologic dysfunction with imaging/laboratory CONFIRMATION of NONISCHEMIC pathology* (including normal imaging/laboratory studies that are highly sensitive for ischemic pathology of the given duration, severity, and location) as the cause of the neurologic syndrome	<ol style="list-style-type: none"> 1. Sudden onset of left hemiparesis and hemineglect. MRI showed right frontoparietal intracerebral hemorrhage. 2. Thirty-year-old man with known seizure disorder found with altered mental status and right hemiplegia. Normal diffusion, perfusion-weighted MRI, and MR angiography (MRA) were acquired while symptoms were still present. EEG showed left temporal spikes.

*Imaging/laboratory confirmation includes neuroimaging studies demonstrating recent, appropriately located ischemic lesion (DWI, CT), vascular imaging demonstrating an acute arterial occlusion or stenosis appropriate to the clinical syndrome (transcranial Doppler, MRA, CT angiography, conventional angiography), or perfusion technique demonstrating a perfusion deficit in an appropriately located vascular distribution (perfusion-weighted MRI, perfusion CT, single photon-emission CT, positron-emission tomography, xenon CT). In the future, additional neuroimaging techniques such as MR spectroscopy or serum/plasma biomarkers specific to acute ischemia may be identified and could potentially provide similar laboratory confirmation.

within which occur the majority of events that might be considered for emergent intervention or treatment (proven, empirical, or investigational). In our proposal, most events referred to as *acute* will have occurred within the prior 7 days. The choice of 1 week has support from the physiological data that the decreased apparent diffusion coefficient characteristic of acute ischemic brain injury is common in the first week but rarely seen after 7 days from the time of onset.²³

Conclusions

Prior classification schemes for cerebrovascular disease, based solely on temporal features and clinical symptomatology, fail to incorporate currently available information provided by neuroimaging and laboratory data. The term *acute ischemic cerebrovascular syndrome* describes a spectrum of clinical presentations that share a similar underlying pathophysiology: cerebral ischemia. The new criteria for this syndrome define 4 categories ranging from “definite AICS” to “not AICS,” which incorporate the degree of diagnostic certainty afforded by advanced imaging and laboratory techniques. Clinical trials testing new treatments for acute ischemic stroke or secondary stroke prevention should limit enrollment to patients with “definite” or “probable” AICS. When highly sensitive diagnostic tests are routinely available within the practical constraints of the trial, enrollment should be limited to patients with only “definite” AICS.

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