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Review Article

A Systematic Approach to the Definition of Stroke

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Abstract

The 24-hour time-line for symptoms in the current definition of stroke is arbitrary. Moreover, this definition does not include silent stroke, encourage acute stroke therapy and consider dramatic recovery after successful therapy. Silent stroke, which is five times more common than symptomatic stroke, is a risk factor for future stroke and is associated with adverse neurological and cognitive functions. Whilst pathological confirmation remains the gold standard in defining stroke and its underlying etiology, widely available neuroimaging has greatly obviated the need for post-mortem examination. Modern multimodal neuroimaging permits confirmation of infarction and/or hemorrhage in the central nervous system, reveals the location and size of the vascular lesion, excludes the stroke mimics and evaluates the relevant cerebrovascular anatomy. Nevertheless, neuroimaging may be limited to an unenhanced computed tomography of the brain. Furthermore, stroke symptoms may resolve either spontaneously or upon successful thrombolysis despite development of new infarction or hemorrhage. It was timely for the American Heart Association and American Stroke Association to publish an updated definition of stroke in July 2013. This updated definition of stroke incorporates both clinical and tissue criteria and comprises of ten possible definitions of stroke. The latter include silent infarction and silent hemorrhage. One problem of the updated definition is major overlaps among the definitions. Another problem is the non-systematic nature of the definitions. This editorial proposes a comprehensive and systematic approach to the definition of stroke by incorporating the following factors: level of certainty, presence and nature of symptoms, duration of symptoms, pathological types, and underlying etiologies.

Keywords: Cerebral Hemorrhage; Cerebral Infarction; Silent Stroke; Stroke; Stroke Definition; Transient Ischemic Attack

Abbreviations

AHA: American Heart Association; ASA: American Stroke Association; CNS: Central Nervous System; CT: Computed Tomography; CVT: Cerebral Venous Thrombosis; ICH: Intracerebral Hemorrhage; MRI: Magnetic Resonance Imaging; SAH: Subarachnoid Hemorrhage; TIA: Transient Ischemic Attack.

Current Definition of Stroke

Stroke is a non-traumatic, focal vascular-induced injury of the central nervous system (CNS) and typically results in permanent damage in the form of cerebral infarction, intracerebral hemorrhage (ICH) and/or subarachnoid hemorrhage (SAH). Stroke is a leading cause of death and disability worldwide. "Apoplexy" is derived from "apoplexia", which is a Greek word meaning "a striking away". Hippocrates of Cos used "apoplexy" to describe very acute, often fatal, non-traumatic brain injuries at 400 BC [1]. In 1689, William Cole first used "stroke" to denote "apoplexy" [2]. "Transient ischemic attack" (TIA) was introduced in 1950s to describe a temporary episode of vascular-related brain dysfunction not qualifying as stroke. The current definition of stroke was introduced by the World Health Organization in 1970 as "rapidly developing clinical signs of focal or global disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" [3]. TIA was defined in 1975 as "temporary and focal dysfunction of vascular origin of a variable duration up to 24

hours" [4]. Conceptually stroke will lead to irreversible CNS damage with persistent symptoms unless promptly and successfully treated, whereas TIA should not produce either CNS damage or persistent symptoms. Indeed the 24-hour cut-off line for symptoms was arbitrarily chosen to demarcate stroke from TIA. Advances in basic neuroscience, neuropathology and neuroimaging in the past four decades have casted serious doubt about the validity of the current definitions of stroke and TIA.

Insofar stroke is a manifestation of non-traumatic vascular disease of the CNS, the ischemic or hemorrhagic tissue injury can be located in the brain, spinal cord and/or retina. Functional consequences, if any, are not limited to cerebral symptoms; symptoms of stroke may be due to involvement of the spinal cord or retina, e.g. central cord syndrome, Brown Séquard syndrome, complete cord syndrome, monocular blindness, scotoma. Symptoms mimicking stroke can be due to traumatic vascular disease and non-vascular diseases. Thus, stroke mimics must be considered and excluded by appropriate investigations.

Unless the brainstem or bilateral cerebral hemispheres is/are severely affected by the stroke process or stroke is complicated by markedly raised intracranial pressure, symptoms of stroke should be focal rather than global in nature. Thus, symptoms and signs of stroke should be consistent with the location and nature of vascular-induced CNS injury. The vascular process of occlusion or rupture may involve the artery, capillary, vein and venous sinus, including

atherothrombosis, cardioembolic arterial occlusion, artery-to-artery embolism, small vessel disease, aneurysm, arteriovenous malformation, cortical vein thrombosis, venous sinus thrombosis, and dural arteriovenous fistula. Underlying disease process and risk factors should be evaluated to help select our preventive measures.

The 24-hour criterion for symptoms of stroke is misleading because modern neuroimaging, especially diffusion weighted imaging of magnetic resonance imaging (MRI), reveals that CNS infarction can develop much sooner. On the other hand, CNS tissue can survive without infarction for up to days of moderate ischemia. Despite spontaneous resolution of symptoms of stroke within 24 hours of onset, small new cerebral infarction, intracerebral hemorrhage or subarachnoid hemorrhage can be documented on neuroimaging. Indeed neuroimaging studies, especially using MRI, on stroke patients and people without a prior history of stroke have revealed silent cerebral infarction and/or silent hemorrhage, which are five times more common than stroke with symptoms [5]. Moreover, successful recanalization of the arterial occlusion plus timely revascularization of the ischemic CNS tissue can achieve complete resolution of symptoms within 24 hours with or without new infarction on neuroimaging [6]. Thus, duration of stroke symptoms should be a secondary consideration when tissue information is absent or insufficient.

Updated Definition of Stroke

It was timely for the American Heart Association (AHA) and American Stroke Association (ASA) to publish an updated definition of stroke in July 2013. This updated definition of stroke comprises of ten possible scenarios: CNS infarction, ischemic stroke, silent CNS infarction, ICH, stroke caused by ICH, silent cerebral hemorrhage, SAH, stroke caused by SAH, stroke caused by cerebral venous thrombosis (CVT), and not otherwise specified stroke [7]. As pathological confirmation of stroke is generally lacking and computed tomography (CT) is widely available, AHA/ASA emphasized that stroke is a clinical and radiological diagnosis. Symptoms and signs should be interpreted according to our knowledge of neuroanatomy, vascular anatomy and vascular pathology, i.e. the lesion location, affected blood vessel and disease mechanism. The latter is related to general systemic diseases and family history of illnesses, and non-vascular processes causing stroke mimics must be considered unlikely. Modern multimodal MRI or CT neuroimaging permits confirmation of infarction and hemorrhage in the CNS, reveals the location and size of the vascular lesion, excludes the stroke mimics and evaluates the relevant cerebrovascular anatomy [8]. Nevertheless, multimodal neuroimaging is time consuming and therefore counterproductive in minimizing any delay in revascularization treatment for acute ischemic stroke.

CNS infarction refers to ischemic cell death in the brain, spinal cord or retina in a defined vascular territory based on objective, i.e., pathological, imaging or other, evidence or pure clinical evidence, i.e., with either symptoms of neurological dysfunction lasting ≥ 24 hours or a rapidly fatal outcome. Other etiologies should be excluded. Explicit inclusion of spinal cord and retina is an advantage of this definition. Another advantage is the use of either objective or pure clinical evidence of ischemic damage. This definition also includes type I and II hemorrhagic infarctions. Hemorrhagic infarctions are

hemorrhages without mass effect within the infarctions; type I is characterized by discrete petechiae and type II by confluent petechiae.

Ischemic stroke refers to an episode of neurological dysfunction, i.e., clinical evidence, due to focal cerebral, spinal or retinal infarction; infarction is based on objective evidence. In other words, stroke is characterized by symptoms, and the 24-hour time line is not mandatory if there is objective evidence of CNS infarction. On the other hand, silent ischemic stroke is not considered by this definition.

Silent CNS infarction refers to objective evidence of CNS infarction without any clinical evidence. In other words, there are no relevant symptoms of stroke.

ICH refers to a focal collection of blood within the brain parenchyma or ventricles not due to trauma. Unlike other definitions of stroke, this does not include non-traumatic hemorrhage within the subarachnoid space, spinal cord and retina. This definition also includes type I and II parenchymal hemorrhages after cerebral infarction. Unlike type I and II hemorrhagic infarctions, mass effect is present; type I is limited to $\leq 30\%$ of the infarction and type II $>30\%$.

Stroke caused by ICH refers to an episode of neurological dysfunction, i.e., clinical evidence, due to ICH. In other words, this is symptomatic ICH.

Silent cerebral hemorrhage refers to an asymptomatic focal collection of old blood within the brain parenchyma, ventricles or subarachnoid space not due to trauma. In other words, this is asymptomatic old ICH or SAH.

SAH refers to bleeding into the subarachnoid space of the brain or spinal cord. As trauma is not specifically excluded, this definition may include both traumatic and non-traumatic SAH.

Stroke caused by SAH refers to an episode of neurological dysfunction, i.e., clinical evidence, and/or headache due to non-traumatic SAH. In other words, this is symptomatic non-traumatic SAH.

Stroke caused by CVT refers to CNS infarction or hemorrhage due to thrombosis of a cerebral venous structure. Neurological dysfunctions, i.e., clinical evidence, caused by reversible edema alone are insufficient.

Not otherwise specified stroke refers to pure neurological dysfunction, i.e., clinical evidence, with insufficient information to allow classification into one of the above AHA/ASA definitions of stroke. Presumably there is no pathological, imaging or other objective evidence of stroke.

As summarized above, the AHA/ASA definition of stroke addresses many deficiencies of the current definition and includes silent infarction and hemorrhage. Nevertheless, the updated definition of stroke does not address all the limitations of the current definition [7]. The 24-hour arbitrary time-line is still required as part of the clinical evidence for the diagnosis of stroke unless there is objective, i.e., pathological, imaging or other, evidence. Despite the slogan of 'time is brain' in stroke management, the AHA/ASA definition does not encourage acute stroke therapy or consider dramatic recovery after successful therapy. This is also the case for stroke caused by CVT. Presence of neurological dysfunctions attributable to CVT

should justify commencement of anticoagulation, treatment of the underlying cause and other supportive treatment [9]. If prompt and appropriate treatment of CVT prevents the development of CNS infarction and hemorrhage, the updated definition of stroke would not regard the event as stroke caused by CVT. According to the AHA/ASA definition, this event is either a not otherwise specified stroke or not a stroke at all [7].

The updated definition of stroke is not as clear as the current definition on some aspects [7]. One problem of the updated definition is major overlaps among the ten scenarios. The definition of CNS infarction may include silent CNS infarction, but the latter is separately defined. At the same time, there is a separate definition of ischemic stroke as symptomatic CNS infarction. The definition of ICH includes type I and II parenchymal hemorrhages after cerebral infarction but excludes type I and II hemorrhagic infarctions. In the absence of a prior documentation of cerebral infarction, however, it is impossible to distinguish between parenchymal hemorrhage and ICH. Moreover, this definition of ICH may include silent ICH because clinical symptom is not specified; yet silent cerebral hemorrhage is separately defined. At the same time, there is a separate definition of stroke caused by ICH as symptomatic ICH. Similarly the definition of SAH does not specify any clinical symptom, but silent SAH is included in the definition of silent cerebral hemorrhage. In addition, there is a separate definition for stroke caused by SAH.

In general, the AHA/ASA definition of stroke uses the term 'stroke' to emphasize clinical evidence and the terms 'infarction' and 'hemorrhage' to emphasize objective evidence from pathology and/or radiology [7]. Yet the chosen terminology is rather non-systematic, vague and non-equivalent. The definition of not otherwise specified stroke is an example. In the absence of pathological or imaging information, it is not possible to distinguish between ischemic and hemorrhagic strokes and to exclude stroke mimics. Another example is the definition of stroke caused by CVT. This definition does not include silent CVT and symptomatic CVT without infarction or hemorrhage. In addition, it is not clear how infarction or hemorrhage in the spinal cord, which is part of CNS, can be caused by thrombosis of a cerebral venous structure in stroke caused by CVT.

A Systematic Approach to the Definition of Stroke

As pointed out by AHA/ASA, the purpose of an updated definition of stroke is for diagnosis in clinical practice, in clinical research and in assessments of the public health [7]. This editorial proposes a comprehensive and systematic approach by incorporating the following factors: level of certainty, presence and nature of symptoms, duration of symptoms, pathological types, and underlying etiologies. These principles are used in the diagnostic definitions of many neurological conditions, e.g. migraine, tension-type headache, Alzheimer's disease, vascular dementia, multiple sclerosis, and Creutzfeldt-Jakob disease [10-14].

As a non-traumatic focal vascular-induced injury of the CNS with a potential consequence of cerebral, spinal or retinal infarction and/or hemorrhage, the definition of stroke should include both clinical and tissue criteria [7]. Symptoms and signs, if any, should be compatible with the location and nature of tissue damage. Duration of symptoms,

such as 24 hours or longer, is irrelevant when tissue damage is present or upon successful implementation of revascularization in acute ischemic stroke. Spontaneous resolution of stroke symptoms within 24 hours justifies the terminology of reversible stroke instead of TIA. Appropriate investigations should be performed to confirm the location and nature of tissue damage and vascular lesion, exclude the stroke mimics and evaluate the underlying etiology. In the absence of tissue confirmation, such uncertainty warrants the terminology of possible stroke. CNS venous thrombosis is a recognized cause of infarction, hemorrhage or both. Edema may not be distinguishable from infarction especially upon prompt initiation of anticoagulation. Thus the following scenarios are included in the proposed definition of stroke.

Possible stroke refers to a clinical syndrome of neurological dysfunction due to presumed non-traumatic vascular cause of focal cerebral, spinal or retinal infarction or hemorrhage. Relevant symptoms should be 24 hours or longer unless the outcome is rapidly fatal. Confirmation of location and nature of tissue damage is unavailable. Under the circumstance, stroke mimics cannot be reliably excluded; the underlying etiology is either uncertain or merely assumed from the known history of vascular risk factors.

Possible reversible stroke refers to a clinical syndrome of neurological dysfunction due to presumed non-traumatic vascular cause of focal cerebral, spinal or retinal infarction or hemorrhage. Relevant symptoms should spontaneously and completely resolve within 24 hours. Confirmation of location and nature of tissue damage is unavailable. This is equivalent to TIA with inadequate work up but a small hemorrhage with transient symptoms is a possibility. Under the circumstance, stroke mimics cannot be reliably excluded; the underlying etiology is either uncertain or merely assumed from the known history of vascular risk factors.

Ischemic stroke refers to a clinical syndrome of neurological dysfunction due to presumed non-traumatic vascular cause of focal cerebral, spinal or retinal infarction. Relevant symptoms should be 24 hours or longer unless the outcome is rapidly fatal or the fast resolution of symptoms is attributed to a dramatic response to acute revascularization. CNS hemorrhage is excluded. Confirmation of location of CNS infarction may be available. Acute CNS infarction may not be discernable when neuroimaging is limited to an urgent unenhanced CT brain. In addition, new CNS infarction may be absent because of an excellent response to acute revascularization. Under the circumstance, stroke mimics can be reliably excluded. Depending on thoroughness of investigations, the underlying etiology may be elucidated or assumed from the known history of vascular risk factors.

Reversible ischemic stroke refers to a clinical syndrome of neurological dysfunction due to presumed non-traumatic vascular cause of focal cerebral, spinal or retinal infarction. Relevant symptoms should spontaneously and completely resolve within 24 hours. CNS hemorrhage is excluded. Confirmation of location of CNS infarction may be available but CNS infarction may not be discernable when neuroimaging is limited to an urgent unenhanced CT brain. This is equivalent to TIA with adequate work up. Under the circumstance, stroke mimics can be reliably excluded. Depending on thoroughness of investigations, the underlying etiology may be elucidated or

assumed from the known history of vascular risk factors.

Silent ischemic stroke refers to detection of focal cerebral, spinal or retinal infarction of presumed non-traumatic vascular cause. Relevant symptoms cannot be recalled or documented. Depending on thoroughness of investigations, the underlying etiology may be elucidated or assumed from the known history of vascular risk factors. Co-existing silent CNS hemorrhage is possible. It is envisaged that silent spinal infarction may not be distinguishable from demyelinating or cystic lesions on pure neuroimaging ground.

Hemorrhagic stroke refers to a clinical syndrome of neurological dysfunction due to presumed non-traumatic vascular cause of focal cerebral, spinal or retinal hemorrhage. Relevant symptoms should be 24 hours or longer unless the outcome is rapidly fatal. Confirmation of location of CNS hemorrhage, i.e., intracerebral, intraventricular, subarachnoid, intraspinal or retinal, is available. Under the circumstance, stroke mimics can be reliably excluded. Depending on thoroughness of investigations, the underlying etiology may be elucidated or assumed from the known history of vascular risk factors. Hemorrhagic stroke can be a complication of ischemic stroke especially following acute revascularization.

Reversible hemorrhagic stroke refers to a clinical syndrome of neurological dysfunction due to presumed non-traumatic vascular cause of focal cerebral, spinal or retinal hemorrhage. Relevant symptoms should spontaneously and completely resolve within 24 hours. Confirmation of location of CNS hemorrhage, i.e., intracerebral, intraventricular, subarachnoid, intraspinal or retinal, is available. Under the circumstance, stroke mimics can be reliably excluded. Depending on thoroughness of investigations, the underlying etiology may be elucidated or assumed from the known history of vascular risk factors. Reversible hemorrhagic stroke can be a complication of ischemic stroke especially following acute revascularization.

Silent hemorrhagic stroke refers to detection of old focal cerebral or spinal hemorrhage of presumed non-traumatic vascular cause on T2*-weighted or gradient echo MRI [8]. Relevant symptoms cannot be recalled or documented. Confirmation of location of previous CNS hemorrhage, i.e. intracerebral, periventricular or intraspinal is available. Co-existing silent ischemic stroke is possible. Depending on thoroughness of investigations, the underlying etiology may be elucidated or assumed from the known history of vascular risk factors.

Concluding Remarks

Stroke is a clinical and tissue diagnosis of great global impact and implications. Clinical diagnosis of stroke without further information or confirmation of non-traumatic vascular damage should be allowed. Complete resolution of symptoms can occur spontaneously or in response to successful revascularization. In case of spontaneous and complete recovery, it is preferable to call it a reversible stroke rather than a TIA. Tissue definition of stroke is mainly based on neuroimaging data because pathological confirmation is generally lacking. Non-traumatic vascular tissue damage is sufficient but not necessary for the diagnosis of stroke. Unlike acute myocardial ischemia, sensitive and specific laboratory or electrical diagnostic tests for stroke are not available. Whilst advanced multimodal neuroimaging can provide

comprehensive and diagnostic information for stroke, this is time consuming, expensive and unavailable in the developing world. A comprehensive and systematic approach to the definition of stroke is warranted. The proposed definition of stroke would consider the level of certainty, presence and nature of symptoms, duration of symptoms, pathological types, and underlying etiologies. Adoption of the proposed definition will facilitate diagnosis of stroke in clinical practice, in clinical research and in assessments of the public health. When stroke is suspected because of relevant symptoms, prompt and timely investigations and treatment are indicated. Detection of silent stroke would justify assessment and management of vascular risk factors for stroke prevention. Clinical trials and stroke databases will drive our future advances in epidemiology, pathophysiology, acute intervention and prevention of stroke. Nevertheless, these studies should adopt a standardized definition of stroke. Public health assessment is the systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice. A revised definition of stroke will inevitably change the incidence, prevalence and mortality of stroke. Allowance of different levels of certainty and variations in thoroughness of investigations would bring a global perspective to public health surveillance of stroke.

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