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Etiologic classification of ischemic stroke: Where do we stand?

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ABSTRACT

Despite major technological advances in ischemic stroke diagnostic techniques, our current understanding of stroke mechanisms and etiology continues to remain unclear in a significant percent of patients. As a result, several etiological ischemic stroke classifications have emerged during the last two decades but their reliability and validity is far from perfect and further world-wide research is needed in order to achieve the so much needed "standard reference language". An ideal ischemic stroke classification should both comprise all underlying pathologies that could potentially concur to an index event and emphasize the most likely etiological and pathophysiological mechanism. Currently available approaches to ischemic stroke classification are either phenotypic or causative in nature, a multitude of criteria being published by different authors. Phenotypic classifications are targeted towards describing the concurring underlying pathologies, without highlighting the most probable ischemic stroke etiology, while causative classifications focus on establishing the most likely cause, neglecting other associated diseases. A judicious use of this two different concepts might improve clinical research as well as daily clinical practice.

1. Introduction

Stroke is nowadays one of the major global health problems, comprising 75.2% of deaths and 81.0% of stroke-related disability adjusted life years lost in developing countries [1]. Up to 87% of the global burden of stroke is attributed to ischemic stroke, which is a heterogeneous disorder with more than 100 pathologies implicated in its pathogenesis [2]. Therefore, a reliable and precise etiologic classification of this disease is highly important for both daily clinical practice and research purposes [3–5]. Currently available approaches to ischemic stroke classification are either causative or phenotypic in nature, several criteria being published by different authors [3]. This paper aims to review currently used etiological classification systems and to emphasize the importance of a reliable stroke classification system.

2. Methods

A systematic literature review was done using PubMed to identify studies and papers published in English between 1st of January 1990 and 1st of January 2017, using the keywords: "ischemic stroke", "classification system", "etiological classification". Papers were considered for inclusion based on relevance of title and abstract and were excluded if the papers didn't fit the topic of interest. References cited in relevant papers were also examined and included if deemed important.

3. Discussion

3.1. History

Etiologic subgroups of ischemic stroke were first described in 1958 by the National Institute for Neurological Disorders and Blindness Report on cerebrovascular diseases. Ischemic stroke etiological subgroups were at that time designated "thrombosis with atherosclerosis", "cerebral embolism", "other causes" and "cerebral infarction of undetermined origin". The main goal of this initial report was stated by Milikan as follows: " Our ultimate objectives are to obtain greater clarity of thinking [in regard to cerebrovascular diseases], to compose a generally acceptable classification, to establish reliable criteria for diagnosis" [6]. Until the early 1970s ischemic stroke classification was mainly based on clinical grounds and autopsy studies. The 1970s were marked by the introduction of computerized brain tomography, the more frequent use of catheter angiography and by the well known description of lacunar syndromes by Miller Fischer [7–9]. The scarce available data of various clinical findings in different subtypes of stroke prompted a group of authors led by J.P. Mohr and L.R. Caplan to

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develop the Harvard Cooperative Stroke Registry. The Harvard Registry was the first prospective computer based registry on any medical condition. Patients with ischemic stroke were classified in three subgroups: "large artery thrombosis", "lacunar infarcts" and "embolism" [10,11]. In the meantime, 17 years after the initial NINDB communication, Milikan referring to ischemic stroke subtypes emphasized a perennial truth: "It continues to be evident that in such a complex set of clinical-pathophysiological phenomena some standard reference language or set of definitions should be used, or the literature of investigation will be uninterpretable" [12].

The explosive growth of interest and knowledge about stroke was driven by the introduction of echocardiography, ambulatory cardiac rhythm monitoring, B-mode, continuous wave and pulsed-wave Doppler technology, as well as by high-energy bidirectional pulsed-Doppler systems for intracranial ultrasound, which were all available in the late 1980s [13]. The Stroke Data Bank Registry and later on, the TOAST project (Trial of ORG 10172 in Acute Ischemic Stroke) included the information achieved through these investigations in the criteria used for the etiologic classification of ischemic stroke [14,15].

Nowadays, novel and refined imaging data, as well as prolonged rhythm monitoring techniques provide a vast amount of potential findings implicated in stroke etiology. With the more frequent implementation of international registries and wide-scale population studies, the need for reliable and comprehensive classification systems emerged. This led to the implementation of the updated TOAST classification (SSS-TOAST), the Causative Classification System (CCS) and of a comprehensive phenotypic ischemic stroke classification (ASCOD) [16–18]. Different etiological classification systems are listed in Table 1.

3.2. Key concepts in stroke classification systems

3.2.1. Reliability and validity of classification systems

The subject of stroke classifications systems cannot be thoroughly approached without explaining the importance of reliability and validity. Reliability is the extent to which an experiment, test or measuring procedure yields the same results on repeated trials while validity is usually defined as the degree to which a research measures what it intends to measure [19].

The reliability of an ischemic stroke classification system refers to the reproducible classification of an index ischemic stroke by the same and by different examiners. It is thus, mainly defined by its interrater agreement (inter observer agreement) which is measured in any situation in which two or more observers evaluate the same thing [19]. The result is expressed as the kappa (κ) coefficient, which is derived from the difference between the observed agreement compared to the agreement expected by chance alone [20]. There are no strict benchmarks for interpreting κ values, a value of 0 usually indicating agreement equivalent to chance, while a value of 1 indicates perfect agreement. Kappa values between 0.61 and 0.8 are a measure for substantial interrater agreement while values above 0.81 are considered to show almost perfect agreement [21]. Assessment of the reliability of a classification system is a suitable measure to evaluate the message communicated between clinicians and researchers world-wide and an important determinant in the conception of clinical trials. Improvement of the reliability of a classification system from 0.5 to 0.8 might reduce the sample size of a clinical study by around 40% [22]. A classification system might be reliable if it yields the same results, irrespective of their validity.

Validity is examined by three separate points – criterion, construct and content. Criterion validity is measured with sensitivity, specificity and positive predictive value and implies a comparison with a "gold standard" [23]. However stroke research lacks a gold standard for etiological diagnosis since there is a declining interest in autopsy studies [24]. Thus, most classification criteria rely on current diagnostic technologies and clinical patterns. Even with the use of modern ancillary tests and imaging techniques it is sometimes still debatable whether the mechanism underlying an ischemic stroke was embolic, atherothrombotic or hemodynamic. Construct validity is determined by comparing new classification systems with the old approved ones. Content validity measures the extent to which an instrument of measure includes all relevant dimensions of what it intends to measure [23].

3.2.2. Phenotypic versus causative classifications

Two main categories of classifications are currently being used for establishing the etiology of ischemic strokes [3]. Phenotypic classifications record all abnormal test findings, stratify them based on certain evidence grades without weighting towards the most likely cause. A phenotypic classification will assign a degree of probability for every possible stroke etiology. This feature makes phenotypic classifications like ASCOD [2], ASCO [25], CCS [16] and Baltimore-Washington [26] ideal for large scale epidemiologic and genetic studies, as well as for ischemic stroke registries [27].

Causative classification systems assign patients with ischemic stroke in a single category based on available clinical, epidemiological and diagnostic data. These classifications usually rely on a set of criteria constructed with the help of an estimated risk of stroke attributed to different conditions in large population based studies. Thus, patients are classified in mutually exclusive categories, thereby reducing the number of subtypes. However, causality is not easily demonstrated [28]. Examples of causative systems include: TOAST [15], CCS [16] and CISS [29]. An overview of the most used ischemic stroke classification systems is presented in Table 2.

Etiology of ischemic stroke is often multifactorial and therefore an ideal ischemic stroke classification should both comprise all underlying pathologies that could potentially concur to an index event and emphasize the most likely etiological and pathophysiological mechanism. Phenotypic classifications are targeted towards describing the concurring underlying pathologies, without highlighting the most probable etiology, while causative classifications focus on establishing the most likely cause in a given patient, usually neglecting other associated diseases. A judicious use of this two different concepts might improve clinical research as well as daily clinical practice.

3.3. Main classification systems

3.3.1. TOAST classification

The TOAST classification is the most widely used system for establishing ischemic stroke etiology. It was implemented in 1993 by Adams et al. in order to be used in the Trial of Org 10172 in Acute Stroke Treatment [15]. Although this trial was negative [30], the TOAST classification was further used for a large number of epidemiologic [5], intervention [30], risk factor assessment [31,32] and prognosis [33] studies for both stroke and transient ischemic attacks [34]. Furthermore, important ischemic stroke risk factors [35], early and long term recurrence [4] as well as survival [35] were all found to differ between TOAST subtypes.

Being fairly simple to use, the TOAST classification provides the basic skeleton for ischemic stroke classification for clinicians and

Table 1
Ischemic stroke classification systems.

National Institute for Neurological Disorders and Blindness (NINDB), 1958 [6]
Harvard Cooperative Stroke Registry, 1978 [10]
Stroke Data Bank, 1988 [113]
Trial of ORG 10172 in Acute Stroke Treatment (TOAST), 1993 [15]
Baltimore Washington, 1995 [26]
Stop-Stroke Study TOAST (SSS-TOAST), 2005 [46]
Modified-TOAST by Han et al., 2007 [77]
Causative Classification System (CCS), 2007 [16]
ASCO, 2009[25]
Chinese ischemic stroke classification (CISS), 2011 [29]
ASCOD, 2013 [2]
SPARKLE, 2014 [61]