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Stroke biomarkers in clinical practice: A critical appraisal

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ABSTRACT

Biomarkers provide critical mechanistic insights to key biologic processes that occur during cerebral ischemia which, when carefully applied, can improve clinical decision-making in acute stroke management. The translation of a blood-based biomarker in ischemic stroke to clinical practice is challenging, in part, due to the complexity of ischemic stroke pathogenesis and the presence of a blood-brain barrier that restricts the release of brain-specific markers into the circulation. The pathologic and clinical aspects of ischemic stroke are described in this review, where a non-exhaustive list of biomarkers that interrogate different aspects of ischemic stroke such as oxidative damage, inflammation, thrombus formation, cardiac function and brain injury are described. The potential roles of these biomarkers are further examined under different clinical scenarios aimed at (1) averting the risk of hemorrhagic transformation, (2) identifying individuals at risk of early neurologic deterioration and malignant infarction, (3) aiding in the diagnosis of ischemic stroke and its differentiation from other stroke mimics, (4) guiding the search for stroke etiology, and (5) assessing stroke risk within the community. Researchers should explore the roles of stroke biomarkers to enhance clinical decision-making that is presently largely based on intuition and subjective reasoning.

Contents

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1. Introduction

By 2050, more than 1.5 billion people in the world will be aged 65 years and older, and a silent epidemic of stroke is imminent (Feigin et al., 2014). Stroke represents the second leading cause of death for people older than 60 years, the most important cause of permanent disability, and uses approximately 3-7% of the total healthcare expenditure in high-income countries (Feigin et al., 2014).

The pathophysiology of cerebral ischemia has played a key role in guiding biomarker research in ischemic stroke. Substantial data indicate that atherosclerosis is a life course disease that begins insidiously with the evolution of risk factors, giving rise to a subtle subclinical disease that culminates in overt cerebrovascular illnesses (Kuller et al., 1995; Psaty et al., 1999). Ischemic stroke is a consequence of atherosclerosis that affects the large intra- and extracranial arteries and small vessels, as well as a result of an embolic phenomenon of blood thrombus from the heart or aorta, resulting in an interruption and severe reduction of blood flow within the cerebral circulation (Lo et al., 2005). Depending on the degree of hypoperfusion, an area with complete absence of flow can result, namely the infarct core, where neuronal death occurs within a few minutes, and a surrounding area called the penumbra which suffers from a moderate reduction of blood flow and contains functionally impaired but semi-viable brain tissues (Astrup et al., 1981). In the ischemic core region, brain cells undergo necrotic cell death producing an area that is electrically, metabolically and functionally inactive. By contrast, neurons in the ischemic penumbra are thought to be metabolically active, but electrically and functionally compromised. The penumbra has a variable outcome. If blood flow is not restored within a relatively short time, the penumbra undergoes the same destiny as the core region (Lo et al., 2005).

Central to the acute treatment of ischemic stroke are arterial recanalization and reperfusion by means of intravenous recombinant tissue plasminogen activator (TPA) (NINDS rt-PA Stroke Study Group, 1995) and endovascular treatment (through device-driven retrieval or aspiration of blood thrombus) (Powers et al., 2015). Early reperfusion can potentially salvage ischemic brain tissues and, in clinical trials, is associated with a 5-fold increase in the likelihood of a good functional recovery (Powers et al., 2015). Upon reoxygenation, reactive oxygen species (ROS) and early inflammatory cells are rapidly recruited and numerous non-enzymatic oxidation reactions take place in the cytosol and/or cellular organelles (Khatri et al., 2012). The ischemic cascade is characterized by the following biochemical events - bioenergetics failure, ionic imbalance, acidosis, excitotoxicity, oxidative stress and inflammation, before culminating in cell death via necrosis or apoptosis (Khatri et al., 2012). In practice, the benefits of arterial recanalization and reperfusion are weighed against the dreaded risk of intracranial hemorrhage that is associated with early neurologic deterioration, malignant infarction and a high mortality (Seet and Rabinstein, 2012).

The ability to identify high-risk stroke patients is desirable for clinicians to accurately triage patients to specialized stroke units for closer monitoring, individualize treatment in anticipation of stroke-related complications, and accurately inform long-term prognosis. Current methods to identify such high-risk individuals depend largely on clinical intuition that is derived from an assessment of neurologic and neuroimaging features, and initial treatment response. The use of biological signatures of cerebral ischemia that takes into account the complex biology of stroke is appealing to clinicians as this facilitates an objective assessment of benefits and risks under different clinical scenarios.

This review provides an overview of the mechanistic basis of a non-exhaustive list of biomarkers that interrogate different aspects of stroke pathogenesis (e.g. oxidative damage, inflammation, thrombus formation, cardiac function and brain injury) and describes their potential applications to guide clinical decision-making at critical time-points in stroke management. This review focuses on biomarkers that are measurable in blood, a material that is widely accessible in human stroke. We searched medical databases such as MEDLINE, PubMed and Ovid for publications that highlight the use of blood-based biomarkers in clinical scenarios where comparisons between biomarkers are made with outcomes such as hemorrhagic transformation, early neurologic deterioration and malignant infarction (see Table 1 and Table 2).

2. What is a biomarker?

Biomarkers are objectively-measured biological signatures of normal and pathologic processes that can serve a wide range of purposes such as risk stratification, therapeutic assessment strategies, clinical trial design and drug development (Biomarkers Definitions Working Group, 2001). Simply, a biomarker has good clinical acceptance if the biomarker is accurate, is acceptable to the patient, is easy to interpret by clinicians, has a high sensitivity and specificity for the outcome it is expected to identify, and explains a reasonable proportion of the outcome independent of established predictors consistently across multiple studies. Biomarkers also provide an avenue for researchers to gain a mechanistic understanding of the differences in pharmacological responses to drugs in preclinical and human models, and improve the design of clinical trials by tightening the selection criteria to better target the application of a particular compound of interest (Muir, 2002).

As clinical events take time to develop (sometimes years), the