Brief Communication

Biochemical Markers in Neurocritical Care

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Abstract

During the past two decades, a variety of serum or cerebrospinal fluid (CSF) biochemical markers in daily clinical practice have been recommended to diagnose and monitor diverse diseases or pathologic situations. It will be essential to develop a panel of biomarkers, to be suitable for evaluation of treatment efficacy, representing distinct phases of injury and recovery and consider the temporal profile of those. Among the possible and different biochemical markers, S100b appeared to fulfill many of optimized criteria of an ideal marker. S100b, a cytosolic low molecular weight dimeric calcium-binding protein from chromosome 21, synthesized in glial cells throughout the CNS, an homodimeric diffusible, belongs to a family of closely related protein, predominantly expressed by astrocytes and Schwann cells and a classic immunohistochemical marker for these cells, is implicated in brain development and neurophysiology. Of the 3 isoforms of S-100, the BB subunit (S100B) is present in high concentrations in central and peripheral glial and Schwann cells, Langerhans and anterior pituitary cells, fat, muscle, and bone marrow tissues. The biomarker has shown to be a sensitive marker of clinical and subclinical cerebral damage, such as stroke, traumatic brain injury, and spinal cord injury. Increasing evidence suggests that the biomarker plays a double function as an intracellular regulator and an extracellular signal of the CNS. S100b is found in the cytoplasm in a soluble form and also is associated with intracellular membranes, centrosomes, microtubules, and type III intermediate filaments. Their genomic organization now is known, and many of their target proteins have been identified, although the mechanisms of regulating S100b secretion are not completely understood and appear to be related to many factors, such as the proinflammatory cytokines, tumor necrosis factor alpha (TNF-a), interleukin (IL)-1b, and metabolic stress.

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Introduction

According to the recently published Global Burden of Disease Study (1), cerebrovascular diseases are the second leading cause of death globally and the third leading cause of premature death and disability as measured in Disability-adjusted life years (DALY) (2, 3). According to a study conducted by the World Economic Forum, the lost economic output from cerebrovascular diseases (such as ischemic,

hemorrhagic, and other non-ischemic strokes), chronic respiratory disease, cancer, and diabetes in low and middle income countries is estimated to exceed USD $7 trillion over the period 2011–2025 (4) that often result in long-term disability for survivors (3). When these cerebrovascular attacks persist for a few minutes, cerebral oxygenation levels become significantly decrease and brain cells begin to die, after a lapse of five minutes, permanent hypoxic brain injury ensues, can lead to permanent and severe disabilities.

Considering the fact, early diagnosis and treatment of acute cerebral vascular disease is a paramount important matter in clinical practice (5).

Currently, computed tomography (CT) perfusion imaging and digital subtraction angiography are frequently applied to evaluate hemodynamic changes and to visualize lesions in patients with acute cerebral vascular disease (6); moreover, with the development of CT software and hardware technology, multi-slice spiral CT has become an important diagnostic method for ischemic cerebral stroke because of its low cost, high accuracy, and ease of operation; however, CT perfusion imaging alone has some deficiencies in the diagnosis of acute ischemic cerebrovascular diseases and it is not accessible in each hospital and caring center. Furthermore, according to the paramount important role of early diagnosis and treatment of the events in preventing diseases' disability established according to the DALYs reports, some other methods like biomarkers are necessary to do better in fulfilling and covering the purpose and be accessible in urban and suburban areas.

Brief Report

Considering the issues, during the past two decades, a variety of serum or cerebrospinal fluid (CSF) biochemical markers in daily clinical practice have been recommended to diagnose and monitor diverse diseases or pathologic situations including cardiac arrest, anoxic and traumatic brain injury, and cerebrovascular accidents and diseases in neurocritical care (7); nevertheless, no biochemical markers are currently applied in clinical practice as diagnose or monitor markers in neurocritical care; although, some authors have been described a series

of biochemical markers including neuron-specific enolase, TAU protein, glial fibrillary astrocytic protein, cell-free DNA, adenylate kinase, creatinine phosphokinase isoenzyme BB, lactate, myelin basic protein, and S100B protein (8, 9).

The Biomarkers Definitions Working Group more broadly defines a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (10). The ideal peripheral biomarker will be measured noninvasively such as in an easily accessible biofluid including serum or urine. Furthermore, a panel of multiple biomarkers would likely have greater sensitivity and specificity than a single marker alone (10-13); it it while that selecting and introducing some optimal and suitable biomarkers and picking up ideal biochemical markers is highly important for both clinicians and patients.

The ideal biomarker should have specific properties such as being "inexpensive", "preferably should be performed within minutes", "have elimination within a few hours", "have a predictability of serious injury from an early sample", "should have rapidly and readily obtainable assay results", "should have rapid and significant release into blood after injury", "have central nervous specificity", "and should help clinicians in replacing advanced imaging in the patients' managing processes", "have high sensitivity and specificity, negative and positive predictive values, positive and negative likelihood ratios, and high area under the curve with the low standard errors in replacing the usual and unusual diagnostic methods", "preventing to referee patients especially acute ones to first-hand centers for better assessment and evaluation", "relationship of marker concentration to the degree of injury, quantifying the full range from subtle deficits to gross injury", and finally " predicting patients' prognosis from high to poor with relatively exact percent's" (14); however, The temporal profile of a biomarker is also important and should be noticed as a important key characteristic of each biomarker. It will be essential to develop a panel of biomarkers representing distinct phases of injury and recovery for evaluation of treatment efficacy. Based on the timing of various components of the secondary injury cascade, a

biomarker for an early post injury time point may not be appropriate for a later time point.

It would be an important development if the biomarkers in neurocritical care to be specific, standardized, and incorporated in clinical practice in helping clinicians in the early diagnosis of an evolving brain damage, monitoring and employing the most effective therapeutic agents.

Therefore, review of the literatures were elucidated among the possible biochemical markers, S100b appeared to fulfill many of the above criteria of an ideal marker (15); because has been shown to have neurotrophic effects as well as mitogenic and morphological activity on astrocytes (14) but also abundant in other cell types (16).

Protein S100β (S100β) is a 21 kDa protein with a biological half-life of 2.5 h. PS100 β was important innovation in the field of neurologic prognosis in the past decade. The biomarker has been described to increase after stroke or traumatic brain injury and is correlated with ongoing neurologic damage and prognosis (17).

Discussion

S100b has been suggested to play a part in a variety of cellular processes, primarily via binding to key synaptic proteins and inhibition of their phosphorylation (18). S100b is synthesized and secreted by astrocytes (19) and its extracellular form is physiologically implicated in the development and maintenance of central nervous system (CNS) homeostasis(16). The mechanisms of regulating S100b secretion are not completely understood and appear to be related to many factors (20, 21), such as the proinflammatory cytokines, tumor necrosis factor alpha (TNF-a), interleukin (IL)-1b (22), and metabolic stress (23). Moreover, a previous study suggested that S100b secretion involves the MAPK pathway and apparently could involve NF-kB signaling (20). Within cells, it is involved in the regulation of cell proliferation, differentiation, Ca2+ homeostasis, protein phosphorylation, transcription, enzyme activity and metabolism. When secreted into the extracellular medium, S100β exerts regulatory effects on neighboring cells including astrocytes, neurons, and microglia. At nanomolar levels, S100β has neurotrophic activity in the extracellular medium,

while at micromolar levels it stimulates apoptosis (19).

S100β protein, which is found at a high concentration in glial and Schwann cells, is considered to be a promising biochemical marker of spinal cord injury (SCI) and traumatic brain injury (TBI); however, serum S100β levels after cardiopulmonary bypass (CPB) are influenced by extracerebral contamination, increased permeability of the blood-brain barrier, and impaired renal function; because S100β levels in the cerebrospinal fluid (CSF) are unlikely to be affected by these responses to CPB, and CSF samples can be collected when CSF drainage is used, it seems reasonable to measure them as a marker of SCI and TBI (24).

The results of a study clearly demonstrated that CSF S100β levels were significantly correlated with SCI and those in the SCI group peaked 48 hours after thoracoabdominal aortic operations. Another important finding is that CSF levels seem more reliable than serum levels because CSF S100β levels of the SCI group were from 10 to 100 fold higher than serum S100β levels (24).

For traumatic brain injury (TBI), it is the most extensively studied biomarker in all severities of TBI, with well over 300 studies to date. S100B is the closest a biomarker for TBI has come to clinical use. In neuroimaging guidelines for adults with TBI, the American College of Emergency Physicians/Centers for Disease Control and Prevention state that "in mild TBI patients without significant extra-cranial injuries and a serum S-100B level less than 0.1μg/L measured within four hours of injury, consideration can be given to not performing a CT" while noting that measuring S100B levels is not an FDA approved test for clinical use (10, 25) . S100B has been implemented into clinical practice in Scandinavia where guidelines for the initial management of minimal, mild, and moderate head injury recommend that GCS 14–15 patients with no risk factors and a serum S100B b0.10 μg/L measured within six hours of injury be discharged without a CT scan, considering it a "moderate quality, strong recommendation"(10, 26). However, although acknowledging that S100B can be a sensitive indicator of brain injury, whether it adds value to clinical guidelines for TBI diagnosis has been

questioned (10).

The results of a study with the purposes determining whether elevated serum S100b correlates with neurologic complications in patients requiring hypothermic circulatory arrest (HCA) during thoracic aortic repair, and to determine the impact of retrograde cerebral perfusion (RCP) on S100b release in this setting, showed that serum S100b levels of 6.0 mg/L or higher after HCA correlates with postoperative neurologic complications. Using serum S100b as a marker for brain injury, RCP does not provide improved cerebral protection over HCA alone(27).

Conclusion

In conclusion, at the moment, it is an exciting time for development and exploration of a suitable biochemical marker in neurocritical care to play as a standardized and incorporated tool into routine clinical practice for diagnosis, determining early prognosis and other management aspects of neurocritical patients in diagnosis and detecting of ongoing brain damage; moreover, the markers can also have a helping role to define therapeutic targets and provide the diagnostic value in detecting, monitoring, and treatment efficacy of ongoing brain damage. Among the different biomarkers,   S-100b has shown to be a sensitive marker of clinical and subclinical cerebral damage, such as stroke, traumatic brain injury, and spinal cord injury.

Acknowledgment

Conflicts of Interest

The authors declare no conflict of interest.

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