Editorial

Biomarkers of Stroke: Its Utility in Routine Clinical Practice

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The biomarkers are a group of chemical compounds produced in body fluid owing to various biological phenomenon in health and disease. The U.S. National Institutes of Health (NIH) working group defined 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."[1]

Stroke is still among the leading causes of death and disability across the globe despite recent therapeutic advances in the past few decades.[2] After acute cessation of blood supply to brain which eventually leads to dead ischemic core with surrounding salvageable penumbra, the latter can be saved either spontaneously or by intravenous tissue plasminogen activator (tPA) and endovascular therapy.[2] Timely diagnosis of acute stroke is very important in emergency room as the success of treatment is time dependent. However, only computed tomography (CT) and magnetic resonance imaging (MRI) reliably aid in diagnosis of stroke and able to differentiate between ischemia and hemorrhage as treatment for both differs.

Apart from high cost of tPA, lack of infrastructure for CT and MRI, financial issue, and contraindications to neuroimaging are also leading barriers in acute stroke management.[3] After acute ischemia, there is a series of biological events leading to neuronal injury and death in time-dependent manner, if untreated. Every step in this cascade is characterized by specific biochemical process and release of biomarkers which can be utilized for early diagnosis. At this juncture, the role of biomarkers of stroke come into play. If available, the ideal biomarker should readily identify the stroke type, severity, and help in prognostication and potentially capable to exclude the stroke mimics. As the brain is affected by various pathological processes, it is not feasible to get direct access to establish a tissue diagnosis. Therefore, the direct visualization of neural structures by neuroimaging and indirect diagnostic tests such as cerebrospinal fluid analysis, electrophysiological evaluation, and blood and urine analysis provide a novel method to determine the pathological alterations in brain.

The brain-derived factors are available in very less amount in blood due to integrity of blood–brain barrier (BBI); however, during acute disruption of this barriers and associated neuronal injury, they are readily available in large amount in serum. The main barrier remains the time to reach in significantly detectable level in biological fluids after crossing BBI and traversing through glymphatic system. To be more accurate, these biomarkers need to be tissue specific and independent of age, gender, drug interaction, and comorbidities.

An ideal biomarker of stroke should have high sensitivity and specificity, cost effective, and less time consuming to estimate. In addition to this, it would be widely acceptable where it is accurate enough to determine the pathological process for which it is intended to ascertain. The source of biomarker should be readily accessible and minimally invasive or noninvasive as for blood or urine and not the cerebrospinal fluid as for latter there is a potential risk of herniation, and various contraindications may prevail.

Biomarkers of Brain Injury

There is plethora of biomarker of brain injury and the list is ever increasing and research is still ongoing. Various biomarkers are available to overcome the competency of clinical decision-making and constraints in neuroimaging to improve the stroke management. So far, no biomarkers of stroke are available in routine clinical practice as a screening tool with high accuracy. It is worth mentioning few important biomarkers of neuronal injury and their role in stroke management.

S100B is an extensively studied calcium-binding protein mainly found in astroglial cells and has trophic effect at physiological limits in biological fluids, beyond which it is considered to have toxic effect. S100B is considered as a

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marker of brain injury attributable to various pathological process.[4]

Neuron-specific enolase (NSE) is a glycolytic enzyme secreted from neural cytoplasm and neuroendocrine cells. The elevated level of NSE is a sensitive indicator of neuronal damage and disruption of blood–brain barrier integrity. It has been proved to be of diagnostic and prognostic significance in stroke and the array of neurological diseases.[5]

B-type natriuretic peptide (BNP) and its derivative N-terminal fragment (NT-proBNP) are mainly synthesized and secreted from hypothalamus and stretching of cardiac myocytes. It is of special interest of researchers to investigate its potential role in the diagnosis of stroke. BNP has been studied and indicated as significant cardioembolic biomarkers with sensitivity of 72% and specificity of 69%.[6]

Glial fibrillary acidic protein (GFAP) is a cytoskeletal filament of astrocytes and Schwann cells and has a role in maintaining cellular stability and steady state. It is released quickly in the blood after intracerebral hemorrhage (ICH) and currently considered as prominent biomarker. It has sensitivity of 78% and specificity of 95%, in a pooled analysis of 12 studies with the aim to differentiate between ischemic stroke and ICH,[7] though other pathological conditions such as glioblastoma multiforme, subarachnoid hemorrhage, traumatic brain injury, and bacterial meningitis may lead to elevated levels of GFPA.[7]

Matrix metalloproteinases (MMPs) are large family of varied sized extracellular matrix degrading proteolytic enzymes secreted from astrocytes and microglia. They are indolent and protective in normal circumstances but once stimulated by activators, they instigate tissue injury, thus having dual action.[8] Their levels are increased in both ischemic and hemorrhagic strokes, but higher levels of MMP-9 correlate with NIH Stroke Scale scores and infarct volume measured by diffusion-weighted images.[9] The peak levels were associated with post-tPA and late hemorrhagic transformation.[10,11]

Another very commonly explored biomarker is D-dimer, a fibrinogen degradation product. It is an extensively studied biomarker in pulmonary embolism and deep vein thrombosis, but also has been evaluated for diagnosis of stroke and its subtype. In a recent meta-analysis assessing the role of 25 biomarkers for diagnosis of ischemic stroke, the three of them, BNP, MMP-9, and D-dimer, significantly differentiate ischemic stroke from healthy control, stroke mimics, and ICH.[12]

The recent study conducted with the aim to assess the correlation between serum level of S100B and NSE in the 60 CT scans confirmed ischemic stroke patients within 48 hours of symptom onset. The authors observed that higher levels of these two biomarkers S100B ($r = 0.61$, $p = 0.001$) and NSE ($r = 0.258$, $p = 0.047$) correlated with larger infarct volume. On multivariate analysis, the bladder and bowel involvement correlated with larger infarct volume, thus indirectly relates to the elevated level of these biomarkers.[13] However, the results of this study need further validation in a larger sample size and emergency setting to attain a wider clinical applicability.

Application in Routine Clinical Practice

The presence of a particular biomarker is not pathognomonic of a specific disease, but when interpreted in an appropriate clinical context, it makes them a valuable tool in diagnosis. Considering the acute stroke, a biomarker should discriminate between stroke and its mimics from healthy control in a time-limited manner. It must have capacity to differentiate accurately between ischemic and hemorrhagic strokes. Till now, only few biomarkers such as GFAP, S100B, and MMP-9 have shown encouraging results in clinical trials.[14] However, the future of biomarker is promising as they are making their place in diagnostic armamentarium of acute stroke care.

Conflict of Interest
None declared.

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