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Review Article

S-100β protein as a biomarker in acute hemorrhagic stroke

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ABSTRACT

Acute hemorrhagic stroke, a subtype of acute stroke is one of the leading causes of death and disability throughout the world. At present, the diagnosis of acute hemorrhagic stroke is mainly based on Computer Tomography (CT) or Magnetic Resonance Imaging (MRI) but till now no biomarkers are routinely used in acute hemorrhagic stroke management. This article is a critical and descriptive review on the role of S100β protein as a biomarker in acute hemorrhagic stroke. Plasma S-100β level increases significantly in acute hemorrhagic stroke patients when compared to the normal subjects. Beside, the plasma S-100β can be correlated to the volume of hemorrhage in brain measured by plane CT scan. Plasma S-100β is an useful biomarker in acute hemorrhagic stroke and can be used for estimation of volume of hemorrhage in brain in acute hemorrhagic stroke patients. Thus, S-100β can be useful as an alternative to CT scan/MRI in diagnosis and in taking therapeutic decision in acute hemorrhagic stroke management.

Keywords: S-100β, Acute hemorrhagic stroke, Biomarker

INTRODUCTION

Acute hemorrhagic stroke, a subtype of acute stroke is one of the leading causes of death and disability throughout the world. The incidence of this disease is increasing with the gradual increase in obesity, diabetes mellitus, hyperlipidemia, hypertension and some other cardiac problems. Stroke may be broadly classified into ischemic and hemorrhagic stroke.[1] In hemorrhagic stroke, the injury of neuronal tissue is caused by compression of tissue from expanding hematomas. In addition, pressure may lead to loss of blood supply causing infarction.[2] Hypertension or any other factors which causes endothelial lining of vessel weak leads to the rupture of the blood vessel of a focal region of brain and collection of blood in brain parenchyma. Collected hematoma or hemorrhage then cause mass effect on the surrounding neurons, adjacent structures and increase the intracranial pressure and may cause even death by brain herniation.[1]

At present, diagnosis of stroke is mostly based on CT scan (Computer Tomography) or MRI (Magnetic Resonance Imaging). CT scan is sensitive to acute blood and thus mostly diagnostic and sensitive to acute hemorrhagic stroke.[2] Although various plasma biomarkers have been found to rise in response to acute hemorrhagic stroke, but no blood biomarkers are routinely used till now for early diagnosis, clinical prognostication and taking therapeutic decisions in acute stroke management.[3]

S-100β is a member of S-100 super family of proteins. This family of proteins is called so because they are 100% soluble in ammonium sulfate. S-100 is an acidic protein and has a molecular weight of 21 kilodalton. It consists of two subunit α chain and β chain. It is known that combination of these subunits is different from the location in human body. S-100β is located in glial cell and schwann cell, S-100αβ in glial cell, and S-100αα in

striated muscle, heart and kidney. S-100β is a Ca^{2+} binding protein with four calcium binding sites.[4] Out of all varieties of S-100 protein, S-100β is glial specific and thus can be a brain specific protein marker. It is expressed primarily by astrocytes that unsheathe blood vessels and NG-2 expressing cells. Physiologically S-100β protein functions in neurite extension, stimulation of calcium influxes, inhibition of PK-C mediated phosphorylation, astrocytosis and axonal proliferation, inhibition of microtubule assembly etc. In developing CNS, it is a neurotropic factor and neuronal survival protein. In adult human, it is usually elevated due to nervous system damage which makes it potential clinical marker.[5] S-100β was the first member of S-100 protein family to be measured in various body fluids to test its usefulness as an index of brain damage in children and adults. S-100β concentration is correlated well with the extent of brain damage occurring in brain hemorrhage, traumatic brain injuries, focal vascular insults, and strokes following cardiac surgeries. S-100β was also suggested by some researchers to be a non-invasive marker for blood-brain barrier function.[6] Because of its predominant location in astroglial cells, CNS (central nervous system) insults like as in traumatic injuries of head, cerebral hemorrhage, hemorrhagic stroke etc which can damage astroglial cellular structure causes leakage of S-100β into extracellular matrix and into CSF and finally further into blood stream. Thus measurement of S-100β protein can be used for monitoring traumatic brain injury, cerebral hemorrhage, stroke etc. and in giving diagnosis and prognosis of the clinical outcome.[4] S-100β protein can be detected in very low amount in blood in normal healthy individuals. Increased S-100β concentration in CSF (cerebrospinal fluid) is an index of active phase of cell injury. Since S-100β (96%) predominates in the brain, its concentration is elevated in neuronal injuries like brain hemorrhage and elevated S-100β in CSF can be an useful marker for the diagnosis of the degree of brain damage. Another recent study also shown that increasing S-100β in blood can be well correlated to the degree of brain damage after cerebral hemorrhage and severe head injury.[7] The current article has been presented with a primary objective to focus on the S-100β protein as a biomarker in acute hemorrhagic stroke.

MATERIALS AND METHODS

This article is a critical and descriptive review on the role of S100β protein as biomarker in acute hemorrhagic stroke. The articles so collected from various research databases had been reviewed and analyzed extensively.

RESULTS AND DISCUSSION

Plasma S-100β level in healthy individuals ranges from 0.02 to 0.15 µg/l (i.e. 20-150 pg/ml) as determined by immunoluminometric analytic method and the reference value for S-100β protein depends on the race of the individuals.[8] According to a group of researcher, the plasma S-100β level in the intracerebral hemorrhage patients rises significantly compared to that in control group (178±74.2 vs 63.2±23.0 pg/ml; P<0.001).[9] Similarly, Q Liao[10] in his study also observed that serum protein S100β concentration was significantly elevated in patients with intracerebral hemorrhage (ICH) (0.54±0.41 µg/l), as compared to controls (0.17±0.04 µg/l, P<0.01). This may be due to the rise of S-100β following intracerebral hemorrhage.[11] Beside, another study confirmed the role of S-100β protein as an early marker of cerebral damage and peri-operative cerebral complications such as stroke, delayed awakening and confusion etc. following cardiac bypass surgery.[12] Andreas Raabe[13] also suggested that serum S-100β protein might be a promising biochemical marker of brain injury and outcome after severe head injury.

Various neurovascular research studies have focused on the correlation of the plasma S-100β to the volume of hemorrhage and lesion in hemorrhagic stroke. Pilar Delgado et al[14] in their study in intracerebral hemorrhage (ICH) patients observed positive significant correlation between the plasma S-100β and the baseline ICH volume (r=0.45; P< 0.0001). Another study also reported the high association between both plasma and CSF (cerebrospinal fluid) S-100β level in acute basal ganglia hemorrhagic stroke patients with the volume of hemorrhage (P<0.05) in both cases.[9] Similarly, a research group also reported that serum S-100β level in acute intracerebral hemorrhage may reflect the volume of hemorrhage significantly.[10] Beside, a study in rat models also reported similar findings.[15] This may be because of the good correlation between the release pattern of S-100β and the volume of vascular lesion.[16] Beside, one interesting fact is that, plasma S-100β which contributes to inflammatory changes in brain can also predict the neurological outcome after spontaneous intracerebral hemorrhage.[17,18] Elevated serum S100β level before thrombolytic therapy has also been found to be an independent risk factor for hemorrhagic transformation in patient with acute stroke.[19] Although neuroimaging is useful in differentiating ischemic from hemorrhagic stroke in the Emergency Department, a wide-available rapid combination of biomarkers including S100β seems promising to achieve a rapid biochemical diagnosis and differentiation of ischemic versus hemorrhagic stroke within the first hours of symptoms onset.[20] Similarly, a group of researcher also suggested that a combination of plasma biomarkers including S-100β can be used for differentiating ischemic and hemorrhagic stroke.[21]

CONCLUSIONS

Plasma S-100β rises in response to the acute neuronal injury and acute hemorrhagic stroke. From the above discussion it can be concluded that plasma S-100β level which increases significantly in acute hemorrhagic stroke compared to the normal healthy subjects, can be correlated to the volume of brain lesion in acute hemorrhagic stroke patients. Beside, plasma S-100β can also predict the neurological outcome after acute

hemorrhagic stroke. However, the role of S-100β in differentiating acute ischemic and hemorrhagic stroke needs further research. But, till now costly imaging techniques like CT or MRI are used as gold standards in diagnosis and monitoring the acute stroke patients. S-100β estimation which is much cheaper when compared to imaging technology can be used as an alternative to CT scan or MRI in a setup where costly imaging technologies are lacking.

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