Reliability of S100B in predicting severity of central nervous system injury

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Abstract  S100B is a protein biomarker that reflects CNS injury. It can be measured in the CSF or serum with readily available immunoassay kits. The excellent sensitivity of S100B has enabled it to confirm the existence of subtle brain injury in patients with mild head trauma, strokes, and after successful resuscitation from cardiopulmonary arrest. The extent of S100B elevation has been found to be useful in predicting clinical outcome after brain injury. Elevations of S100B above certain threshold levels might be able to reliably predict brain death or mortality. A normal S100B level reliably predicts the absence of significant CNS injury. The specificity of S100B levels as a reflection of CNS injury is compromised by the findings that extra-cranial injuries can lead to elevations in the absence of brain injury. This potential problem can most likely be avoided by measuring serial S100B levels along with other biomarkers and carefully noting peripheral injuries. Serum markers GFAP and NSE are both more specific for CNS injury and have little to no extra-cranial sources. Sustained elevations of S100B over 24 h along with elevations of GFAP and NSE can more reliably predict the extent of brain injury and clinical outcomes. In the future, S100B measurements might reliably predict secondary brain injury and enable physicians to initiate therapeutic interventions in a timelier manner. S100B levels have been shown to rise hours to days before changes in ICP, neurological examinations, and neuroimaging tests. S100B levels may also be used to monitor the efficacy of treatments.

Key phrases  S100B Protein · Biomarker for brain injury · Clinical outcomes prediction · Neuron specific enolase (NSE) · Glial fibrillary acidic protein (GFAP) · Secondary brain injury · Assessment of CNS injury

Introduction

It is important for physicians in neurological intensive care units (NICU) to be able to predict the presence and severity of central nervous system (CNS) injury. An accurate appreciation of the severity of CNS injury can help predict outcomes and rationally help to decide when the application of aggressive therapeutic interventions would be appropriate [1].

In patients with little or no chance for a meaningful recovery intensivists can appropriately initiate comfort measures and avoid subjecting the majority of patients to a severely debilitating survival. At the same time, they can allocate limited vital health care resources to patients with better chances for meaningful recovery. Patients with neurological injuries from a variety of causes are at risk of secondary injuries from pathophysiological mechanisms such as increased intracranial pressure, vasospasm, stroke, and seizures. The timely application of aggressive medical and surgical interventions in the NICU can frequently mitigate the clinical impact of secondary injury to the brain.

Standard methods to prognosticate the severity of initial brain injury and anticipate the onset of secondary injury have included the neurological examination, neuroimaging studies, intracranial pressure monitors, electrodiagnostic testing, and transcranial dopplers. These tests have limited reliability in critically ill patients who are frequently given sedatives, analgesics, and muscle relaxants, or are not
S100 proteins are a family of dimeric cytosolic calcium binding proteins made up of an alpha and a beta isomer. S100 proteins are found in abundance in astroglial and Schwann cells and have been found in a few tumors such as schwannoma, gliomas, melanoma, and neuroblastoma [12–16]. The alpha and beta isoforms have also been called S100A1 and S100B respectively. There are also other rare A types numbering over 6. Most S100 proteins are found as dimmers, which are combinations of isomers in a molecule. Three types of dimers are usually found. A homodimer consisting of two S100A1 isomers has been labeled S100A1A1. Likewise, a homodimer of two S100B isomers has been labeled S100BB. One heterodimer combining the alpha and beta isomers has been found and is called S100A1B [17]. All three heterodimers have been found in glial cells, astrocytes, ependymal cells, oligodendrocytes, and Schwann cells in the central and peripheral nervous system [18–22]. The S100BB dimer is 21 kDa in size and is predominantly represented in glial and Schwann cells [21–23]. Unless specifically noted, all references in this monograph to the S100BB homodimer should be considered equivalent to S100B.

S100 family members have been found in the following locations outside of the nervous system: melanocytes, adipocytes, chondrocytes, and epidermal Langerhans cells [24–27]. The Beta isomer of S100 has also been found in skeletal muscle, skin, and in both white and brown fat [22, 25].

Investigations have noted that various mechanisms can release S100B protein from glial cells into the extracellular space [28]. Astrocytic activation has been found to immediately follow primary brain injury [29]. S100B protein is involved in the astrocytes reaction to injury by regulating the Calcium influxes and stimulating astrocytic proliferation via interaction with transcription factors [30–33].

Serotonin can enhance the release of S100B via stimulation of astroglial 5-HT1A receptors [34]. Corticotropin-like intermediate-lobe peptide and adrenocorticotropic hormone (ACTH) have both been found to release S100B [35]. Activation of A(1) adenosine or mFlu3 metabotropic glutamate receptors has been shown to lead to the rapid release of S100B proteins [36].

S100B may be involved in the cellular response to ischemia. Extracellular Adenosine levels are found to be elevated shortly after stroke and traumatic brain injury due to rapid intracellular ATP depletion. S100 proteins were found to be released within one hour after the extracellular adenosine levels rose [37–39]. S100 family proteins appear to be released from proliferating astrocytes [40]. Experimental injury to the brain via trauma or stroke has been found to induce a reactive gliosis with a peak around 3–4 days after the injury [41, 42].

S100B appears to be released into the extra-cellular space near the injured tissue and can enter into the serum from the brain through a disrupted blood brain barrier or into the CSF and then into the blood via the arachnoid villi [43]. S100B is removed from the serum by renal clearance with a serum half-life of 20–25 min [44]. Serum concentrations of S100B are not influenced by hemolysis because S100B was found to be absent in red blood cells [45].

S100B measurement techniques

Various methods have been developed to measure the S100B levels in serum including a radioimmune assay...