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Serum Markers of Severe Traumatic Brain Injury: Are They Useful?

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Learning Objective: To present new, additional means of assessing, monitoring, and managing ongoing brain damage in order to limit the development of secondary brain damage in intensive care patients suffering from severe traumatic brain injury.

Abstract

S100B, neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP) are the most well-known and most-used serum markers at present. NSE and S100B may have some utility if properly interpreted and tracked, but have significant limitations in terms of single measurements and lack of specificity. GFAP appears to be much more helpful, with much higher specificity. Nevertheless, GFAP needs to be validated in larger studies, and correlated with outcomes. It is conceivable that future intensivists will be using a panel of markers to assess primary brain injury, detect ongoing secondary brain injury, and possibly even assess the benefits of neuroprotective drugs.

Background

Before attempting to answer whether or not serum markers are "useful," let us first briefly consider the pathophysiology of severe traumatic brain injury (TBI) as we see it in the trauma intensive care unit. One of the main problems is the development of secondary brain damage triggered by both primary trauma and increased intracranial pressure, decreased mean arterial pressure, and decreased cerebral perfusion pressure.¹ One of the main difficulties the intensivist is faced with is monitoring and managing patients to provide continuous effective critical care and to limit the development of secondary brain damage. Obviously, the more severely injured the patient is, the more difficult monitoring and management may become; i.e., although patients with severe isolated TBI are sometimes difficult to manage, patients with additional multiple trauma can pose an even greater challenge. In recent years, improved intracranial pressure monitoring and modern neuroimaging techniques such as computed tomography and magnetic resonance imaging have contributed greatly to the assessment and care of patients with TBI.² Nevertheless, for all their accuracy, both techniques are expensive, and not always available. Above all, they are associated with stress for patients with TBI (transport to the CT and monitoring en route) and thus cannot be considered suitable for frequent follow-ups. Thus, assessment, monitoring, and management of TBI remain difficult for the intensivist and often stressful for the patient. A serum test measuring one or more markers to determine the status quo of brain damage would no doubt be welcome in the setting of severe TBI. Such markers would be useful indeed in guiding critical care and evaluating the prognosis of patients with severe TBI.

Similar to tests for damage to other organs (i.e., troponin for damage to the heart), a test for damage to the brain might well be based on the measurement of one (or more) serum marker(s). Ideally, markers of brain damage should be measurable quickly and simply, and should be measurable in serum, since serum is more readily available than cerebrospinal fluid.³ Above all, however, ideal markers of brain damage should be both highly brain-specific and sensitive.⁴

Since the early 1980s, there has been an increasing amount of research on markers of brain damage. Easily detectable substances derived from neurons and glia were measured by commercially available assays and studied as

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markers of brain damage in various clinical settings ranging from stroke⁵ and cardiac arrest⁶ to traumatic brain injury.⁷ This review will focus on the three most well-known serum markers, neuron-specific enolase (NSE), S100B, and glial fibrillary acidic protein (GFAP).

Neuron-Specific Enolase (NSE)

NSE is a glycolytic enzyme with a molecular mass of 78 kD and a biologic half-life of 48 hours.⁸ NSE is found primarily in the cytoplasm of neurons, but also in peripheral neuroendocrine cells and in certain rare tumors associated with amine precursor uptake, such as small-cell lung cancer, neuroblastoma, and melanoma. NSE is found in platelets and erythrocytes as well.⁹ NSE is passively released by cell destruction only; it is not actively secreted into the extracellular space. Serum NSE levels over 10 mcg/L are considered abnormal.³

We conducted a prospective clinical study on trauma patients admitted to our institution within the first 8 hours after trauma.¹⁰ On the one hand, we found that NSE remained slightly to markedly elevated in the nonsurvivors suffering from TBI, and rose to a peak 24 to 96 hours before death, showing a relationship to outcome after TBI. On the other hand, we found that NSE was elevated within the first 48 hours after trauma in patients with multiple trauma but without TBI, verified by computed tomography on admission to the hospital. After the first 48 hours, NSE dropped back to normal values and remained normal in all multiple-trauma patients *without* TBI. Since these multiple-trauma patients without TBI all survived, we cannot say whether NSE would have risen to a peak before death as it did in the nonsurvivors of TBI.

In experimental studies on rats, we have also found that NSE was increased without any brain damage whatsoever after hemorrhagic shock, open femur fracture, and local ischemia and reperfusion of the liver, gut, and kidney. NSE has the advantage of being the only marker found primarily in neurons rather than in glia. However, apart from the previously mentioned problems associated with multiple trauma, NSE has one serious drawback: it is found in erythrocytes and is thus released into the blood during hemolysis,¹¹ i.e., hemolysis may cause a false-positive NSE increase.

S100B

S100B is a calcium-binding protein with a molecular mass of 10-12 kD and a biologic half-life of about 1 hour.³ S100B is found primarily in the cytoplasm of astroglia and Schwann cells, but also in non-nervous cells such as adipocytes, chondrocytes, and melanoma cells. In contrast to other markers, S100B can be both actively secreted into the extracellular space and passively released by cell death.¹² It was termed "S100" because it is partially soluble in a 100% saturated solution of ammonium sulphate.¹² Serum S100B levels over 0.2 mcg/L are considered abnormal.³

In the past, S100B was considered to be a reliable marker of brain damage and a good indicator of outcome.¹³ Recently, however, evidence has been increasing that S100B is not necessarily a reliable marker of brain damage in every setting: S100B increases have been found without brain injury after both cardiac surgery¹⁴ and trauma.¹⁵ In a prospective study of 55 trauma patients (Injury Severity Score [ISS], >23; Glasgow Coma Scale [GCS] score, <8) classified by radiography,

computed tomography, ultrasound, and neurology as TBI without multiple trauma, TBI, with multiple trauma or multiple trauma without TBI, we measured S100B initially after trauma and daily for a maximum of 21 days.¹⁶ We found that both survivors and nonsurvivors had markedly increased S100B levels for 24 to 48 hours after trauma. S100B levels returned to normal within the first 48 hours after trauma in all survivors. In contrast, we found that all nonsurvivors of isolated TBI had S100B values that either increased consistently or dropped and then increased again after the initial posttraumatic increase. We did not find any relationship whatsoever between S100B and localization, pattern, or severity of TBI. According to receiver operating characteristic curve analysis and calculation of the area under the curve, S100B is equally accurate for mortality prediction at 24, 48, and 72 hours after trauma and most accurate >84 hours after trauma. We found that sensitivity/specificity for mortality prediction was more accurate in TBI without multiple trauma than in TBI with multiple trauma. In other words, although S100B may be a reliable marker of brain damage in TBI without multiple trauma 24 hours after trauma and thereafter, it appears to be less reliable in TBI with multiple trauma.

Experimentally, we have verified that hemorrhagic shock induces a significant S100B increase in serum and that the S100B increase is associated with the severity of shock in rats: S100B is significantly higher in severe shock than in moderate shock.¹⁷ Further experimental studies in rats have shown that S100B is significantly increased early after bilateral femur fracture¹⁸ and after local ischemia and reperfusion of the liver, the gut, and the kidney.¹⁹ These findings clearly indicate that S100B is not a reliable marker of brain damage in the early posttraumatic setting, which is frequently associated with hemorrhagic shock, local ischemia, and/or open fractures.

Glial Fibrillary Acidic Protein (GFAP)

GFAP is a filament protein with a molecular mass of approximately 45 kD. GFAP is found primarily in the astroglial cytoskeleton and was therefore formerly known as astroprotein.²⁰ In contrast to S100B and NSE, GFAP is not found outside the central nervous system and is thus considered to be highly brain-specific.²¹ Moreover, in contrast to S100B, which is a marker of *activation* but not necessarily of cell *damage*, GFAP does indeed appear to be a marker of actual cell damage.²² Serum GFAP levels over 0.033 mcg/L are considered abnormal.³

Clinically, we investigated the brain specificity and relationship of GFAP to brain damage and outcome after TBI. In a prospective study of patients with TBI or with multiple trauma without TBI (verified by computed tomography), we measured serum GFAP at admission and daily during intensive care, and documented computed tomography, daily highest intracranial pressure, lowest cerebral perfusion pressure, lowest mean arterial pressure, and 3-month GOS. After TBI, we found that GFAP was significantly higher in nonsurvivors than in survivors and higher in patients with GOS 1 (death) than GOS 4-5 (moderate to good recovery). Interestingly, we also found that GFAP, in contrast to S100B and NSE, remained completely normal in multiple-trauma patients without TBI. GFAP showed a relationship to the pattern of TBI in computed tomography and was significantly higher in cases of more severe TBI. From these findings, we conclude that GFAP is not only brain-specific, but also related to the severity of brain injury and to outcome after TBI.²³

Summary

In the course of the last decade, hopes were soaring that quick, simple, and inexpensive measurement of S100B and NSE might prove to be a laboratory technique capable of partially replacing expensive and tedious neuroimaging procedures. Recently, however, measurement of GFAP has become possible in serum. Clinical and experimental studies have shown that things are clearly not quite as simple as they once appeared to be.

- Individual NSE and/or S100B levels measured on any given day are of very limited value. The course of NSE and S100B monitored on a day-to-day basis is required to judge the development of secondary brain damage.¹⁶
- Although preliminary studies indicate that GFAP, the newest and most promising of the serum markers of brain damage, is highly specific for the central nervous system and thus particularly well-suited as a marker for clinical practice,²³ further clinical research will be required to support this evidence.³
- Last, but not least, one of the main limitations in measuring serum markers is time. S100B and NSE assays require approximately 2 hours until results are ready. Clinical routine relies heavily on simple, quick assays that provide instant results. Although such instant assays are not available on the market yet, the industry has risen to the challenge and there is hope that instant assays will be commercially available before too long.³ A new GFAP assay (BioVendor Inc., Heidelberg, Germany) is currently undergoing clinical validation and is expected to be commercially available later this year. In the United States, NSE, S100B, and GFAP can be measured in clinical trials, but routine use is awaiting approval by the Food and Drug Administration.

Conclusion

Although no single brain-specific marker has yet been unanimously established for traumatic brain in routine clinical practice, there is overwhelming evidence that serum markers of TBI are useful in neurointensive care. Presently, S100B is the most widely acknowledged marker, and is definitely useful, provided the intensivist is aware of its strengths and weaknesses.¹³ It is conceivable that GFAP will become a widely acknowledged marker as well²² and that future intensivists will perhaps be using a panel of markers to assess primary brain injury, detect ongoing secondary brain injury, and possibly even to assess the benefits of neuroprotective drugs.³

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