

Commentary

Can a simple blood test quantify brain injury?

Stephan A Mayer and Guillermo Linares

Neurological Intensive Care Unit, Milstein Hospital Building, 177 Fort Washington Avenue, Suite 8-300 Center, New York, NY 10032, USA

Corresponding author: Stephan A Mayer, sam14@columbia.edu

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See related research by Derwall *et al.*, <http://ccforum.com/content/13/2/R58>

Abstract

Despite significant advances in neurocritical care, it remains difficult to precisely measure the extent of neurological injury in patients affected by stroke, trauma, or cardiac arrest. In the intensive care unit the extent of primary and secondary injury often eludes clinicians, making prognostication imprecise and difficult. Derwall and colleagues present their findings on the dynamics of serum S-100B protein levels in out-of-hospital cardiac arrest survivors. Their study suggests that elevation of S-100B reflects the severity of the primary hypoxic-ischemic insult.

The first decade of the 21st century has witnessed explosive growth in therapies for the critically ill neurological patient. Some of these treatments, such as the use of recombinant tissue plasminogen activator for the treatment of acute cerebral infarction, target very specific pathogenic pathways. Others, such as hypothermia for the treatment of brain injury after cardiac arrest, have multiple additive and synergistic mechanisms of action that culminate in the protection of nervous tissue. To guide these treatments, technological advances in imaging and neuromonitoring can now provide a window into the metabolic and physiologic status of the injured brain, allowing us to evaluate the effect of our therapeutic interventions in real time.

Despite these promising advances, it remains difficult to precisely measure the extent of neurological injury in patients affected by stroke, trauma, or cardiac arrest. In the intensive care unit, where neurological deterioration is often obscured by encephalopathy or sedative medications, determination of the extent of primary and secondary injury often eludes clinicians, making prognostication imprecise and difficult.

For decades, researchers have sought clinically useful biomarkers of nervous system injury, and these efforts have intensified in the past few years. Early candidates for brain injury biomarkers included lactate dehydrogenase and creatinine kinase enzyme subtypes in the serum and

cerebrospinal fluid. These proved to be of little use given their lack of specificity for nervous tissue injury. The ideal biomarker would be highly sensitive and specific for neurological injury, rapidly available from the serum or other easily obtained body fluid other than cerebrospinal fluid, and released in proportion to the severity of the injury, with little variability across different diagnostic and demographic groups.

Although the ideal biomarker remains elusive, several different molecules have shown promise. Of these, neuron specific enolase, myelin basic protein, glial fibrillary acidic protein, and the S-100B protein have received the most attention.

In a recent issue of *Critical Care*, Derwall and colleagues [1] present their findings on the dynamics of serum S-100B protein levels in a prospectively studied cohort of out-of-hospital cardiac arrest (OHCA) survivors. S-100B is a constitutive protein of glial cells. Due to specificity of its cellular expression, it is considered a potentially useful marker of acute injury to the brain parenchyma and blood-brain barrier.

Sixty-eight OHCA patients were enrolled over the course of two years in five different hospitals in the city of Aachen, Germany. Sampling of serum S-100B was performed 6, 12, 24, 72 and 120 hours after the return of spontaneous circulation. About half of these patients were treated with therapeutic hypothermia and half with standard supportive care, according to the preferences of the family and treating physician. Cooling was induced to maintain core temperature at 33°C for 24 hours using refrigerated saline and body surface cooling with ice water bags.

The results of this study reflect the difficulties that typically hamper the interpretation of small non-randomized studies. No differences were detected in S-100B levels between the

OHCA = out-of-hospital cardiac arrest.

hypothermic and normothermic patients. It is our view that this should not be interpreted as lack of efficacy of hypothermia, an intervention that has been shown to improve survival and recovery after OHCA in large randomized control trials [2-5]. The lack of randomized treatment allocation makes it hard to reach any definitive conclusions regarding the effect of therapeutic hypothermia. It also remains possible that S-100B is not a useful surrogate marker for the efficacy of delayed therapeutic interventions such as hypothermia for OHCA. This may reflect the fact that most of the damage measured by S-100B elevation is related to the primary global hypoxic-ischemic insult, rather than temperature-modifiable reperfusion injury.

By contrast, this paper does suggest that S-100B may have utility as a prognostic indicator after OHCA. S-100B levels were significantly lower in patients with a favorable outcome, but only among those treated with hypothermia. It may be that the uniformly poor outcomes among those treated with normothermic supportive care reduced the ability of S-100B to discriminate between poor and favorable outcomes.

From a clinical perspective, however, the most important finding of this study is that S-100B levels were consistently the highest on admission, with a progressive decline over the next several days. These findings suggest that elevation of S-100B reflects the severity of the primary hypoxic-ischemic insult, rather than the effects of the cooling intervention.

Neuron specific enolase has been recognized in recent guidelines developed by the American Academy of Neurology as a useful prognostic indicator in comatose patients with global hypoxic-ischemic brain injury [6]. Derwall and colleagues now present data suggesting that admission S-100B levels may also be useful in this setting. The obvious challenges now are to determine whether panels of multiple biomarkers provide greater prognostic accuracy than any single measure, and to better understand how hypothermia influences the relationship between S-100B elevation, the severity of the initial insult, and long-term outcome.

Competing interests

The authors declare that they have no competing interests.

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