Biochemical changes in the injured brain

Seelora Sahu, Deb Sanjay Nag, Amlan Swain, Devi Prasad Samaddar

Biochemical changes in the injured brain

Brain metabolism is an energy intensive phenomenon involving a wide spectrum of chemical intermediaries. Various injury states have a detrimental effect on the biochemical processes involved in the homeostatic and electrophysiological properties of the brain. The biochemical markers of brain injury are a recent addition in the armamentarium of neuro-clinicians and are being increasingly used in the routine management of neuro-pathological entities such as traumatic brain injury, stroke, subarachnoid haemorrhage and intracranial space occupying lesions. These markers are increasingly being used in assessing severity as well as in predicting the prognostic course of neuro-pathological lesions. S-100 protein, neuron specific enolase, creatinine phosphokinase isoenzyme BB and myelin basic protein are some of the biochemical markers which have been proven to have prognostic and clinical value in the brain injury. While S-100, glial fibrillary acidic protein and ubiquitin C terminal hydrolase are early biomarkers of neuronal injury and have the potential to aid in clinical decision-making in the initial management of patients presenting with an acute neuronal crisis, the other biomarkers help in long-term prognosis. Cerebral microdialysis has established itself as a novel way of monitoring brain tissue biochemical metabolites such as glucose, lactate, pyruvate, glutamate and glycerol while small non-coding RNAs have presented themselves as potential markers of brain injury for future.

Key words: Biomarkers; Brain injuries; Brain ischemia; Epilepsy; Subarachnoid hemorrhage

© The Author(s) 2017. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The biochemical markers of brain injury are being increasingly used to assess the severity and prognosis in the injured brain. While S-100, glial fibrillary acidic protein and ubiquitin C terminal hydrolase have been used as early biomarkers to aid in clinical decision-making and initial management, other biomarkers help in long-term prognosis. Cerebral microdialysis is a novel way of monitoring brain tissue biochemical metabolites and each component gives an idea about the severity and type of pathologic process in the brain. In addition, small non-coding RNAs have presented themselves as potential markers of brain injury for future research.
INTRODUCTION

The brain is one of the most energy intensive organs of the body, utilizing around 60% of the available energy for the fulfillment of electrophysiological function, and the remaining 40% is expended in the homeostasis of the internal milieu of the brain cells[1]. Brain metabolism is an energy intensive phenomenon involving a wide spectrum of chemical intermediaries and their consequent usage in brain energy production.

The evolution of techniques to monitor brain metabolism started in the late 19th century[2]. However, major strides in the understanding of the cerebral metabolic processes have happened only in the last 50 years and have greatly contributed to our understanding of the processes governing the myriad and complex activities of the central nervous system in general and the brain in particular.

In this editorial we focus on the basics as well as perturbations of brain metabolism in the different clinical scenarios of neurological injury such as traumatic brain injury (TBI), stroke and subarachnoid hemorrhage (SAH). The aim of this review is also to discuss the means at our disposal to monitor such deviations and the practical clinical applications of such techniques[2].

BRAIN METABOLISM AND BIOCHEMISTRY

As mentioned earlier, brain metabolism is peculiar for being a highly energy intensive process. Although it contributes approximately (only) 2%-2.5% of the total body weight, it receives approximately 20% of the total blood supply and 25% of the total oxygen supply[3].

The biochemical processes in the brain exhibit various peculiarities with ramifications in brain injury. First is the presence of a blood brain barrier formed by endothelial cell layers of the brain vessels[4-6], which plays an important role in the maintenance of homeostasis in relation to the electrolytes and energy substrates such as glucose, glutamate and ketone bodies[7,9]. Nerve impulse propagation is the key function within the brain and is basically an amalgamation of electrical and chemical processes. The electrical processes are responsible largely for impulse propagation within a neuron whereas chemical reactions influence signal transmission from one neuron to another as well as at the effector cells and axon ends in the synapse[10]. The synapses perform the critical function of transferring electrical impulses across the synaptic cleft or for further impulse propagation on to another neuron or muscle for a particular desired action. Impulse transmission through a synaptic cleft is a complex biochemical process involving neurotransmitters like glutamate and γ-aminobutyric acid as well as the activation of various ion channels. Sodium and potassium are the major ions involved in the generation of action potentials, especially in the process of hyperpolarization and depolarization of neurons[11-14]. The enormity of the biochemical processes involved in the signal transduction of neural impulse can be gauged from the fact that while a single neuron has 1000 to 20000 synapses, there are around 90 billion neurons in an adult human brain[15].

Brain injured states such as stroke and head injury have a detrimental effect on the biochemical processes involved in the aforesaid homeostatic and electrophysiological properties of the brain.

BIOCHEMISTRY OF THE INJURED BRAIN

The biochemical basis of brain injury can be explained on the basis of either one or a combination of the following broad pathological mechanisms[16]: Ischemia; traumatic brain injury; epileptogenesis.

Ischemic brain injury

Ischemia and resultant hypoxia lead to the derangement of energy intensive processes critical to homeostasis in the brain. Dysfunctional ATP dependent ion pumps result in consequent disequilibrium in sodium, calcium and potassium ion homeostasis, culminating in the release of excitatory amino acids such as glutamate[17,18]. Glutamate plays a pivotal role in the ensuing excitotoxicity by activating α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, N-methyl-D-aspartic acid (NMDA) and metabolic receptors. Calcium, free radicals and phospholipase activation also contribute significantly in the cellular damage of the brain.

An important aspect of ischemic injury in the brain is the nature of ischemia. Global ischemia of the brain follows events such as cardiac arrest, whereas focal ischemic changes are seen after events such as episode of stroke. In focal ischemia there exists a penumbra region which is responsive to brain resuscitation measures albeit within a critical time frame of a few minutes. In the scenario of ongoing global ischemia, the severity of brain damage is dependent on the time until re-establishment of brain circulation as well as the differential susceptibility of the various regions of the brain to hypoxia[19,20].

Traumatic brain injury

Primary injury following trauma to the brain consists of direct concussional neuronal damage, herniation of important structures as well as ischemic injury because of damage to blood vessels. Reversal of primary injury is impossible. However, amelioration of secondary effects is possible. The biochemical processes detailed previously play a pathologic role in traumatic brain injury and calcium is an important ion implicated in traumatic brain injury at the cellular level[21,22].

Sahu S et al. Biochemical changes in the injured brain

Sahu S, Nag DS, Swain A, Samaddar DP. Biochemical changes in the injured brain. World J Biol Chem 2017; 8(1): 21-31 Available from: URL: http://www.wjgnet.com/1949-8454/full/v8/i1/21.htm DOI: http://dx.doi.org/10.4331/wjbc.v8.i1.21
Epileptogenic injury
Epilepsy is defined as sudden and excessive electrical discharge from neurons and occurs from a plethora of causes such as electrolyte and metabolic perturbations, temperature disturbances, and structural insults such as tumors, trauma and infections. The mechanism of epileptiform damage resembles ischemia and involves the previously detailed sequences culminating in glutamate excitotoxicity and NMDA and metabotropic nerve activation [23,24].

The ongoing process of cellular injury in the injured brain leaves in its wake a multitude of biochemical markers. An ideal marker for injury should be specific to the brain, pick up brain injury within a reasonable and defined time frame and exhibit low variation with age and sex [25,26]. However, the search for such a marker remains elusive till date.

BIOCHEMICAL MARKERS OF BRAIN INJURY

The biochemical markers of brain injury are a recent addition in the armamentarium of neuro-clinicians and are being increasingly used in the routine management of neuro-pathological entities such as traumatic brain injury, stroke, SAH, and intracranial space occupying lesions. The use of such markers in the brain via-a-vis their use in the heart had been limited by various factors such as the heterogeneity of different cell types in the brain, the differential integrity of the blood brain barrier as well as the multimodal mechanisms contributing to neuronal death. However, they are recently being increasingly used in assessing severity as well as in predicting the prognostic course of neuropathological lesions. S-100 protein, neuron specific enolase (NSE), creatinine phosphokinase isoenzyme BB (CPK-BB) and myelin basic protein (MBP) are some of the biochemical markers which have been proven to have prognostic and clinical value in the brain injury and are dealt henceforth in a detailed perspective.

S-100 PROTEIN

S-100 is a calcium binding protein with a molecular weight of 21 kDa and is present in two isoforms - "α" (25%) and "β" (75%). While S-100 "α" protein is found in melanocytes, S-100 β isoform is found predominantly in glial cells and Schwann cells of the peripheral nervous system and central nervous system. Although the β isoform is found in adipocytes and chondrocytes, the concentration of S-100 β in non-neural tissue (100-200 ng/mg of soluble brain protein) is minimal as compared with glial and Schwann cells (3500 ng/mg of brain protein) [26,27].

S-100 β protein is metabolized and excreted by the kidneys, has a t½ of 2 h and a mean serum level of 0.050 ± 0.081 g/L [28]. S-100 β protein levels have been found to increase especially following brain tissue injury in various experimental models [29].

S-100 β in head injury: Elevated levels of S-100 β have been found in patients after minor and major head injury [26,30-36]. In patients with mild head injury (GCS 13-15) where initial computed tomography (CT) scans of their brain do not exhibit any abnormality, S-100 β levels have been found to be high, especially in the golden hour following trauma [26]. Elevated levels of S-100 β in serum following head injury have also been associated with impaired cognition score [37].

In severe head injury an increased serum S-100 β level of > 2 g/L just after and during evolution of TBI has been found to be associated with a high mortality rate. Persistent elevations of S-100 β have shown an association with ongoing secondary brain damage following the primary insult. S-100 β has exhibited correlations with CT pathologies, with lower values being more common in diffuse type I and type II injuries. As a marker of clinical outcome following TBI, S-100 β has shown promising results [33-36,38-42].

Hence S-100 β in TBI can be concluded to be of clinical utility in assessing the extent of primary and secondary brain injury. It also has a role in predicting the time course of recovery and probability of an improved clinical outcome.

S-100 β protein in SAH: Plasma concentration of S-100 β in patients with SAH has shown a correlation with the severity of hemorrhagic affliction in the early phase of the disease as well as with the incidence of delayed cerebral ischemic events. There is also evidence correlating S-100 β levels with the severity of long-term neurological impairment as well as Glasgow outcome scores. Similar results have been observed with ventricular cerebrospinal fluid (CSF) S-100 β concentrations. There is significant evidence to suggest that S-100 β in CSF may show a superior correlation with CT and single-photon emission CT findings in addition to being predictive for outcome in patients with cerebral aneurysm [43-46].

NSE

As an isoenzyme of enolase enzyme involved in glycolysis, NSE was thought to be a relevant marker of neuronal injury [47]. However, it has also concurrently evolved as a marker for neuro-endocrine malignancies such as small cell lung cancer and neuroblastoma and hence its specificity for neural tissues is doubtful [48]. Serum levels are in the range of 5-12 ng/mL and CSF levels normally are less than 2 ng/mL [49].

NSE in TBI: In experimental model studies on cortical contusion, the highest concentration of NSE was observed at around 7.5 h following injury. This coincides with the primary mechanism of injury to the brain parenchyma and could be explained on the basis of extrusion of the cytoplasmic protein into the CSF from damaged neuronal and glial tissue. A secondary peak in the NSE levels was observed at around 1.5 d and in all probability reflects secondary ischemic damage to the contused...
biochemical changes in the injured brain. An experimental TBI model in rats clearly demonstrated that CSF NSE is a more accurate motor of ongoing neuronal damage than serum NSE levels. There have been a plethora of studies on the correlation of serum and CSF NSE levels with head injury as well as their prediction of long-term outcome. Serum NSE levels showed a significant correlation with an identifiable contusion on CT scan and also predicted the incidence of long-term mortality and persistent vegetative state in patients with TBI. NSE in SAH NSE in SAH patients had been found to be an excellent predictor of delayed cerebral ischemic events and poor perioperative outcome. However, the correlation of serum NSE levels with the clinical grade of SAH patients at the time of admission is a contentious issue with various studies giving different levels.

NSE in stroke Experimental studies in cerebral ischemia models and animal studies have unequivocally demonstrated that NSE levels in CSF correlate with the degree of severity of cerebral ischemia. In addition they have been found to be increased before irreversible brain cell damage, hence offering the promise of being used as a marker of guidance of cerebro-protective measures in stroke. In human studies examining the correlation of CSF with serum NSE levels, NSE has been found to have a positive correlation with infarct size and volume. In a study by Cunningham et al, serum NSE levels in patients with ischemic stroke were higher when compared with hemorrhagic stroke, and the highest levels in ischemia was observed at 48 to 96 h. NSE had also been found to correlate with and help in differentiation between reversible and irreversible brain damage in survivors of cardiac arrest. In such patients, serum NSE levels post resuscitation care are a reliable predictor of neurologic outcome and they also aid in prognostication of such patients.

CPK-BB Of the three isoenzymic forms of creatinine phosphokinase, the CPK-BB isoform is found in the brain. CPK-BB levels in various pathological entities of brain injury such as stroke, TBI, post cardiac arrest and SAH have shown a correlation with the extent of injury and have also shown to be able to predict outcome.

MBP MBP originates from oligodendroglial cells and binds with myelin. In TBI it is released into CSF and serves as a useful marker predicting the clinical course and outcome. In addition there are various other proteins which are less established via a-vis their role in predicting severity and outcome in the brain injured states.

TAU PROTEIN Tau is a protein arising from the microtubules, which offers theoretical promise as a marker of brain injury and has been especially studied in TBI states. However, recent evidence has been very conflicting and the evidence on the diagnostic and prognostic value of tau protein and its correlation with abnormal CT findings in TBI has been very limited.

GLIAL FIBRILLARY ACIDIC PROTEIN As a major component of astroglia, glial fibrillary acidic protein (GFAP) offers the promise of exclusivity to the central nervous system. There have been numerous studies in TBI sub-population such as severe or moderate TBI wherein GFAP concentration has shown a positive correlation with severity of injury, outcomes as well as CT and MRI findings. In a study comparing GFAP and S-100, GFAP exhibited characteristics of being a more sensitive marker of neural injury. It also had higher value for predicting return to work via a-vis S-100 especially in patients with severe head injury.

UBIQUITIN C TERMINAL HYDROLASE Ubiquitin c terminal hydrolase (UCH-L1) is a neuron specific protein comprising 1%-5% of total brain protein, which has been implicated in neuron repair in pathological and degenerative conditions of the brain. There has been a release of UCH-L1 into CSF and blood in brain injury and elevated levels have exhibited a correlation with severity and outcome in TBI populations.

WHICH BIOMARKER TO CHOOSE AND WHEN? The preceding discussion indicates that the different biomarkers in brain injury do not exactly fit into the “one size fits all” algorithm. Evidence in the field is an evolving process and it seems increasingly probable that neuro-clinicians will rely more and more on a combination of different biomarkers as an aid in diagnosis, severity scoring, prognostication and interventional decisions in brain injured patients. S-100, GFAP and UCH-L1 are early biomarkers of neuronal injury and have the potential to aid in clinical decision-making in the initial management of patients presenting with an acute neuronal crisis such as stroke, TBI and SAH. The other biomarkers are of value in predicting long-term complications and prognosis in such patients.

INTRICACIES OF SAMPLE COLLECTION AND ANALYSIS While CSF levels of biomarkers reflecting CNS injury are more accurate, in acute settings such as TBI and stroke, collection of blood samples represents a more convenient
and practical approach. In recent times there have been enormous strides in the field of standardization of methods by which samples are being collected for the measurement of the neuronal biomarkers. Recently, there have been attempts to isolate the aforementioned biomarkers from urine and saliva of patients to preclude non-invasiveness and ease collection.

**LIMITATIONS**

The widespread use of neuro-pathological markers is limited by variability and discrepancies in the values indicating significant levels of these biomarkers. The results of various studies paint a very inconsistent picture and this could be attributed to flaws and variation in study design as well as non-standardization of techniques in collection, handling and assay of such biomarkers. To summarize, the data till date on biomarkers of the injured states such as TBI, SAH, brain tumors, stroke and epilepsy. Table 3 illustrates the clinical implications of cerebral microdialysis in various scenarios.

**NEW DEVELOPMENTS**

In addition to serum and CSF assays of biomarkers of brain injury, there has been a variety of neuro-chemical methods which have been of use in brain tissue biochemistry. These methods have gradually progressed from analysis of post mortem samples to advent of newer and sophisticated methods such as cerebral microdialysis (CMD).

CMD was a modification of the push-pull cannula technique and was invented by Delgado et al. with subsequent modifications and popularization by Ludwig et al. and Ungerstedt et al. It is a novel way of monitoring brain tissue biochemical metabolites such as glucose, lactate, pyruvate, glutamate and glycerol wherein the monitoring of each component gives an idea about the severity and type of pathologic process in the brain. Table 1 summarizes all the commonly used serum and CSF biomarkers of cerebral injury with their clinical implications. Table 2 summarizes components monitored by cerebral microdialysis and their clinical implications.

**NEW DEVELOPMENTS**

In addition to serum and CSF assays of biomarkers of brain injury, there has been a variety of neuro-chemical methods which have been of use in brain tissue biochemistry. These methods have gradually progressed from analysis of post mortem samples to advent of newer and sophisticated methods such as cerebral microdialysis (CMD).

CMD was a modification of the push-pull cannula technique and was invented by Delgado et al. with subsequent modifications and popularization by Ludwig et al. and Ungerstedt et al. It is a novel way of monitoring brain tissue biochemical metabolites such as glucose, lactate, pyruvate, glutamate and glycerol wherein the monitoring of each component gives an idea about the severity and type of pathologic process in the brain. Table 1 summarizes all the commonly used serum and CSF biomarkers of cerebral injury with their clinical implications. Table 2 summarizes components monitored by cerebral microdialysis and their clinical implications.

**NEW DEVELOPMENTS**

In addition to serum and CSF assays of biomarkers of brain injury, there has been a variety of neuro-chemical methods which have been of use in brain tissue biochemistry. These methods have gradually progressed from analysis of post mortem samples to advent of newer and sophisticated methods such as cerebral microdialysis (CMD).

CMD was a modification of the push-pull cannula technique and was invented by Delgado et al. with subsequent modifications and popularization by Ludwig et al. and Ungerstedt et al. It is a novel way of monitoring brain tissue biochemical metabolites such as glucose, lactate, pyruvate, glutamate and glycerol wherein the monitoring of each component gives an idea about the severity and type of pathologic process in the brain. Table 1 summarizes all the commonly used serum and CSF biomarkers of cerebral injury with their clinical implications. Table 2 summarizes components monitored by cerebral microdialysis and their clinical implications.

**NEW DEVELOPMENTS**

In addition to serum and CSF assays of biomarkers of brain injury, there has been a variety of neuro-chemical methods which have been of use in brain tissue biochemistry. These methods have gradually progressed from analysis of post mortem samples to advent of newer and sophisticated methods such as cerebral microdialysis (CMD).

**NEW DEVELOPMENTS**

In addition to serum and CSF assays of biomarkers of brain injury, there has been a variety of neuro-chemical methods which have been of use in brain tissue biochemistry. These methods have gradually progressed from analysis of post mortem samples to advent of newer and sophisticated methods such as cerebral microdialysis (CMD).

**NEW DEVELOPMENTS**

In addition to serum and CSF assays of biomarkers of brain injury, there has been a variety of neuro-chemical methods which have been of use in brain tissue biochemistry. These methods have gradually progressed from analysis of post mortem samples to advent of newer and sophisticated methods such as cerebral microdialysis (CMD).
the novel biomarker profiles identified in these studies as being associated with TBI has been validated in independent studies using unrelated, non-proteomic or genomic techniques. Exciting preliminary data on the expression profiles of small non-coding RNAs in peripheral blood mononuclear cells from military personnel exposed to mild TBI have been reported; three small RNAs seem to be primarily associated with mild TBI, but the results require replication.

CONCLUSION
To conclude, biochemical markers of brain injury have witnessed major developments in acquisition and processing of samples, with cerebral microdialysis and expression of non-coding RNAs being the most recent modality to analyze such changes. Use of such biomarkers, while not as popular as their cardiac counterparts, is slowly but surely being established both in the realms of basic research as well as in management, severity scoring and prognostication of patients with neurological injury. There is abundant potential in the regular use of such biomarkers and efforts are underway to integrate such biomarkers into clinical practice in TBI, SAH and stroke.

REFERENCES
1. Patel PM, Drummond JC, Lemkuil BP. Cerebral physiology and the effects of anaesthetic drugs. In: Miller RD, editor. Miller’s Anaesthesia. 8th ed. Philadelphia: Elsevier; 2015: 387-409
2. Finlay JM, Smith GS. A Critical Analysis of Neurochemical Methods for Monitoring Transmitter Dynamics in the Brain. 2000. Available from: URL: http://www.acnp.org/g4/GN401000004/CH004.html
3. Schoenemann PT. Evolution of the size and functional areas of the human brain. Annu Rev Anthropol 2006; 35: 379-406 [DOI: 10.1146/annurev.anthro.35.081705.123210]

4. AllopG, Gamble HJ. An electron microscopic study of the pericytes of the developing capillaries in human fetal brain and muscle. J Anat 1979; 128: 155-168 [PMID: 422476]
5. Ballabh P, Braun A, Nedergaard M. Anatomic analysis of blood vessels in germinal matrix, cerebral cortex, and white matter in developing infants. Pediatr Res 2004; 56: 117-124 [PMID: 15128918 DOI: 10.1203/01.PDR.0000130472.30874.FF]
6. Cristante E, McArthur S, Mauro C, Maggioli E, Romero JA, Wylezinska-Arridge M, Couraud PO, Lopez-Tremoleda J, Christian HC, Weksler BB, Malaspina A, Solito E. Identification of an essential endogenous regulator of blood-brain barrier integrity, and its pathological and therapeutic implications. Proc Natl Acad Sci USA 2013; 110: 832-841 [PMID: 23277546 DOI: 10.1073/pnas.1209362110]
7. Löscher W, Potischka H. Blood-brain barrier active efflux transporters: ATP-binding cassette gene family. NeuroRx 2005; 2: 86-98 [PMID: 15717060 DOI: 10.1602/neurorx.2.1.86]
8. Yin B, Loike JD, Kako Y, Weinstock PH, Breslow JL, Silverstein SC, Goldberg IJ. Lipoprotein lipase regulates Fc receptor-mediated phagocytosis by macrophages maintained in glucose-deficient medium. J Clin Invest 1997; 100: 649-657 [PMID: 9239412 DOI: 10.1172/JCI119576]
9. Seyfried TN, Kiebish MA, Marsh J, Shelton LM, Huysentruyt LC, Mukherjee P. Metabolic management of brain cancer. Biochim Biophys Acta 2011; 1807: 577-594 [PMID: 20804725 DOI: 10.1016/j.bbadis.2010.08.009]
10. Marieb EN, Hoehn K. Human Anatomy & Physiology, 8th ed. San Francisco, CA: Benjamin Cummings, 2010: 385-428
11. Murali T, Müller U, Werheid K, Sorger D, Reuter M, Becker T, von Cramon DY, Barthel H. In vivo evidence for differential association of striatal dopamine and midbrain serotonin systems with neuropsychiatric symptoms in Parkinson’s disease. J Neuropsychiatry Clin Neurosci 2001; 13: 222-228 [PMID: 11449029 DOI: 10.1016/S1556-2772(00)00005-0]
12. Hajjawi OS. Human Brain Biochemistry. Ame J BioS 2014; 2: 122-134 [DOI: 10.11648/j.bioj.20140204.13]
13. Sherwood L. Human Physiology from Cells to Systems. 8th ed. Stanford, CT: Cengage Learning, 2012: 105-115
14. Marois R, Ivanoff J. Capacity limits of information processing in the brain. Trends Cogn Sci 2005; 9: 296-305 [PMID: 15925809 DOI: 10.1016/j.tics.2005.04.010]
15. Crick FHC. The Astonishing Hypothesis: The Scientific Search for the Soul. New York, NY: Macmillan Publishing Company,
In the study titled "Biochemical changes in the injured brain" by Sahu et al., the authors explore the impact of biochemical markers such as S-100 protein in the context of brain injury. The study highlights the significance of S-100 protein in assessing the severity of head injury and its correlation with clinical outcomes. The research findings contribute to a better understanding of neuroinflammation and cerebral edema, which are critical aspects in the management of traumatic brain injury (TBI). Through the analysis of serum and cerebrospinal fluid (CSF) S-100 protein levels, the study provides valuable insights into the mechanisms underlying brain injury and the potential for improved diagnostic and therapeutic strategies. The inclusion of S-100 protein in clinical protocols could aid in the early detection of brain damage, leading to better patient outcomes and enhanced quality of life. 

Key findings include:
1.Increased serum S-100 protein levels correlate with the severity of brain injury.
2. S-100 protein levels can predict neurological impairment and functional outcome after TBI.
3. Serial measurements of S-100 protein can be used to monitor the progression of brain injury.

The study underscores the importance of biochemical markers in the evaluation of brain injury and suggests the potential for S-100 protein measurement to play a significant role in the management of traumatic brain injuries.
annual meeting of Japanese society of surgery for stroke, 2000

schoeberl w, kittler h, sterz f, behringer w, holzer m, frossard m, spitzauer s, lagger an. time course of serum

specific enzyme in patients resuscitated from cardiac arrest. stroke 1999; 30: 1598-1603 [pmid: 10436107 doi: 10.1161/101.31.0.1598]

ikeda y, mohichuki y, nakamura y, dohi k, matsumoto h, jinbo h, hayashi m, matsumoto k, yokisaka t, murase h, sato k. protective effect of a novel vitamin e derivative on experimental traumatic brain edema in rats—preliminary study. acta neurochir suppt 2000; 76: 343-345 [pmid: 11450400]

maranos pj, schmeichel de. neuron specific enzyme, a clinically useful marker for neurons and neuroendoctrine cells. annu rev neurosci 1987; 10: 269-295 [pmid: 3551759 doi: 10.1146.anurev.
env.030187.001413]

uzan m, hanci m, guzel o, sarioğlu ac, kuday c, ozlen f, haye e, wakayama y, okayasu h, takahashi h, shibuya s. levels of serum and cerebrospinal fluid enzyme in patients with cerebral vascular disease and other neurologic diseases. stroke 1988; 10: 313-318 [doi: 10.3959/jstroke.10.313]

eriksson l, reiber h. clinical relevance of increased neuron

specific enzyme concentration in cerebrospinal fluid. clin chim acta 1985; 157: 49-54 [pmid: 3052937 doi: 10.1016/0009-8881(85)

8890306-3]

kawasaki h, wakayama y, okaya h, takahash h, shibuya s. levels of serum and cerebrospinal fluid enzyme in patients with cerebral vascular disease and other neurological diseases. stroke 1988; 10: 313-318 [doi: 10.3959/jstroke.10.313]

veurnytten k, lotvellen a, karcher d. detection of neuron

specific enzyme concentration in cerebrospinal fluid with patients with neurological disorders by means of a sensitive enzyme

immunoassay. clin chim acta 1990; 187: 69-78 [pmid: 2317937 doi: 10.1016/0009-8881(90)90332-m]

mokuno k, kato k, kawai m, matsuoka y, yanagi t, soubi i. neuron-specific enzyme and s-100 protein levels in cerebrospinal fluid of patients with various neurological diseases. j neurosurg 1993; 80: 443-451 [pmid: 6355398 doi: 10.1065/jnns.1993.10150x(83) 90155-7]

cunningham rt, watt m, winder j, mckinstry s, lawton j, johnston cf, hawkins sa, buchanan kd. serum neuron-specific enzyme as an indicator of stroke volume. ejr j clin invest 1996; 26: 298-303 [pmid: 8732487 doi: 10.1046/j.1365-2362.1996.129282.x]

daubertschmidt r, linsmeyer j, mrochen h, meyer m. changes of neuron-specific enzyme concentration in plasma after cardiac arrest and resuscitation. mol chem neuropathol 1991; 14: 237-245 [pmid: 1958265 doi: 10.1007/bf03195939]

stelzl t, von bose mj, hogl b, fuchs hh, fliegel ka. a comparison of the prognostic value of neuron-specific enzyme serum levels and somatostatin evoked potentials in 13 reanimated patients. eur j Emerg med 1995; 2: 24-27 [pmid: 9422176 doi: 10.1007/100063110-19950300-00006]

martens p, raabe a, johnson p. serum s-100 and neuron-specific enzyme for prediction of regaining consciousness after global cerebral ischemia. stroke 1998; 29: 2363-2366 [pmid: 9804649 doi: 10.1161/01.str.29.11.2363]

fogel w, krieger d, veith m, adams hp, hund e, storh-hagen-locher b, buggle f, mathias d, hacke w. serum neuron-specific enzyme as early predictor of outcome after cardiac arrest. crit care med 1997; 25: 1133-1138 [pmid: 9233737 doi: 10.1097/00003246-199707000-00012]

tirschweil dl, longstreth wt, rauch-matthews me, challenger wl, rothstein t, wray l, eng lj, fine j, copass mk. cerebrospinal fluid creatine kinase bb isoenzyme activity and neurologic prognosis after cardiac arrest. neurology 1997; 48: 352-357 [pmid: 9040720 doi: 10.1212/2363-2366 [pmid: 9804649 doi: 10.1161/01.str.29.11.2363]

pfeiffer fe, homburger ha, yanagihara t. creatine kinase bb isoenzyme in csf in neurologic diseases. measurement by radioimmunoassay. arch neurol 1983; 40: 169-172 [pmid: 6830458 doi: 10.1001/archneur.1983.04005003603102]

ikeda y, nakazawa s, tsuji y, mori h. [sequential changes in serum creatine phosphokinase isoenzyme activity and correlation with prognosis in patients with acute head injuries]. neurol med chir (tokyo) 1987; 27: 90-96 [pmid: 2441365 doi: 10.2176/ nmc.27.90]

cooper pr, chalif dj, ramsey jf, moore rj. radioimmunoassay of the brain type isoenzyme of creatine phosphokinase (ck-bb): a new diagnostic tool in the evaluation of patients with head injury. neurosurgery 1983; 12: 536-541 [pmid: 6866236 doi: 10.1227/01.neu.122707-0006123-198300500-00010]

skogseid jm, nordby h, urdal p, pau a, lieless f. increased serum creatine kinase bb and neuron specific enzyme following head injury indicates brain damage. acta neurochir (wien) 1992; 115: 106-111 [pmid: 1605707 doi: 10.1007/bf01406367]

coolin mw, longstreth wt, lam am, challenger wl, mayberg ts, fine js, witt hr. cerebrospinal fluid creatine kinase-bb isoenzyme activity and outcome after subarachnoid hemorrhage. arch neuro 1999; 56: 1348-1352 [pmid: 10556654 doi: 10.1001/archneur.56.11.1348]
Bell RD, Khan M. Cerebrospinal fluid creatine-kinase-BB activity: a perspective. Arch Neurol 1999; 56: 1327-1328 [PMID: 10555649 DOI: 10.1001/archneur.56.11.1327]

Johnsson P. Markers of cerebral ischemia after cardiac surgery. J Cardiothorac Surg 2006; 11: 120-126 [PMID: 16343770 DOI: 10.1186/s11610-006-0081-x]

Bakay RA, Sweeney KM, Wood JH. Pathophysiology of cerebrospinal fluid in head injury: Part 1. Pathological changes in cerebrospinal fluid solute composition after traumatic injury. Neurosurgery 1986; 18: 234-243 [DOI: 10.1093/014270789002003]

Noseworthy TW, Anderson BJ, Noseworthy AF, Shustack A, Johnston BG, Petruk GA, McPherson T.A. Cerebrospinal fluid myelin basic protein as a prognostic marker in patients with head injury. Crit Care Med 1985; 13: 743-746 [PMID: 8008433 DOI: 10.1097/00003495-198510000-00010]

Thomas DG, Palfreyman JW, Ratcliffe JG. Serum-myelin-basic-protein assay in diagnosis and prognosis of patients with head injury. Lancet 1978; I: 113-115 [PMID: 875490 DOI: 10.1016/S0140-6736(89)90415-4]

Thomas DG, Babow L, Teasdale G. Serum myelin basic protein, clinical responsiveness, and outcome of severe head injury. Acta Neurochir Suppl (Wien) 1979; 28: 93-95 [PMID: 90450 DOI: 10.1007/978-3-7091-0888-8_20]

Alling C, Karlsson B, Vällfors B. Increase in myelin basic protein in CSF after brain surgery. J Neurosurg 1980; 223: 225-230 [PMID: 6157784 DOI: 10.1093/jn/223.2.225]

Zemlan FP, Rosenberg WS, Luebbe PA, Campbell TA, Dean GE, Weiner NE, Cohen JA, Radick RA, Wood D. Quantitation of axonal damage in traumatic brain injury: affinity purification and characterization of cerebrospinal fluid tau proteins. J Neurochem 1999; 72: 741-750 [PMID: 9930748 DOI: 10.1006/jnch.1997.3038] [https://doi.org/10.1016/S0022-3042(99)00020-7]

Bazarian JJ, Zemlan FP, Mookerjee S, Stigbrand T. Serum S100B and cleaved-tau are poor predictors of long-term outcome after mild traumatic brain injury. J Neurotrauma 2004; 21: R156 [PMID: 17207985 DOI: 10.1168/cc10286]

Vos PE, Lamers KJ, Hendriks JC, van Haaren M, Beems T, Zimmerman C, van Geel W, de Reus H, Biert J, Verbeek MM. Glial and neuronal proteins in serum predict outcome after severe traumatic brain injury. Neurology 2004; 62: 1303-1310 [PMID: 15111666 DOI: 10.1212/01.wnl.0000120550.00643.d7]

Pelinka LE, Kroepfl A, Leixnering M, Buchinger W, Raabe A, Redl H. GFAP versus S100B in serum after traumatic brain injury: relationship to brain damage and outcome. J Neurotrauma 2004; 21: 1553-1561 [PMID: 15684648 DOI: 10.1088/nuco.2004.21.1553]

Papa L, Lewis LM, Falk JL, Zhang Z, Silvestri S, Giordano P, Brophy GM, Demery JA, Dixin NK, Ferguson I, Liu MC, Mo J, Akinyi L, Schmid K, Mondello S, Robertson CS, Tortella FC, Hayes RL, Wang WK. Elevated levels of serum glial fibrillary acidic protein breakdown products in mild and moderate traumatic brain injury are associated with intracranial lesions and neurosurgical intervention. Ann Emerg Med 2012; 59: 471-483 [PMID: 22071014 DOI: 10.1016/j.annemergmed.2011.08.021]

Metting Z, Wielczak N, Rodiger LA, Schaaf JM, van der Naalt J. GFAP and S100B in the acute phase of mild traumatic brain injury. Neurology 2012; 78: 1428-1433 [PMID: 22517109 DOI: 10.1212/01.wnl.0000413825.57278.37]

Lincoln S, Vaughan J, Wood N, Baker M, Adamson J, Gwinn-Hardy K, Lynch T, Hardy J, Farrer M. Low frequency of pathogenic mutations in the ubiquitin carboxy-terminal hydrolase gene in familial Parkinson’s disease. Neuroreport 1999; 10: 427-429 [PMID: 10203348 DOI: 10.1016/S1052-3027(99)00040-0]

Larsen CN, Price JS, Wilkinson KD. Substrate binding and catalysis by ubiquitin C-terminal hydrolases: identification of two active site residues. Biochemistry 1996; 35: 6735-6744 [PMID: 8639624 DOI: 10.1021/bi9600909]

Koheissy FH, Ottens AK, Zhang Z, Liu MC, Denslow NS, Dave JR, Tortella FC, Hayes RL, Wang KK. Novel differential neuroproteomics analysis of traumatic brain injury in rats. Mol Cell Proteomics 2006; 5: 1887-1898 [PMID: 16801361 DOI: 10.1074/mcp.M600157-MCP200]

Papa L, Lewis LM, Silvestri S, Falk JL, Giordano P, Brophy GM, Demery JA, Liu MC, Mo J, Akinyi L, Mondello S, Schmid K, Robertson CS, Tortella FC, Hayes RL, Wang WK. Serum levels of ubiquitin C-terminal hydrolase distinguish mild traumatic brain injury from trauma controls and are elevated in mild and moderate traumatic brain injury patients with intracranial lesions and neurosurgical intervention. J Trauma Acute Care Surg 2012; 72: 1335-1344 [PMID: 22673263 DOI: 10.1097/TA.0b013e318249e13d]

Mondello S, Jeromin A, Buki A, Bullock R, Czeiter E, Kovacs N, Barzo P, Schmid K, Tortella F, Wang KK, Hayes RL. Glial neuronal ratio: a novel index for differentiating injury type in patients with severe traumatic brain injury. J Neurotrauma 2012; 29: 1096-1104 [PMID: 22165978 DOI: 10.1088/nuco.2012.2092]

Manley GT, Diaz-Arrastia R, Brophy M, Engel D, Goodman C, Gwinn K, Veenastra TD, Ling G, Ottens AK, Tortella F, Hayes RL. Common data elements for traumatic brain injury: recommendations from the biospecimens and biomarkers working group. Arch Phys Med Rehabil 2010; 91: 1667-1672 [PMID: 21044710 DOI: 10.1016/j.apmr.2010.05.018]

Tennissen CE, Petzold A, Bennett JL, Berven FS, Brandlin L, Comabella M, Franciotti D, Frederiksen JL, Fleming JO, Fuelan R, Hintzen RQ, Hughes SG, Johnson MH, Krasulova E, Kuhle J, Magnone MC, Rajda C, Rejak D, Schmidt HK, van Pesch V, Waubant E, Wolf C, Giovannoni G, Hemmer B, Tumani H, Deisenhammer F. A consensus protocol for the standardization of cerebrospinal fluid collection and biobanking. Neurology 2009; 73: 1914-1922 [PMID: 19949037 DOI: 10.1212/WNL.0b013e3181c7e4c2]
Lanksch WR, Unterberg AW. Bedside microdialysis: a tool to monitor cerebral metabolism in subarachnoid hemorrhage patients? Crit Care Med 2002; 30: 1062-1070 [PMID: 12006804 DOI: 10.1097/00003246-200205000-00018]

Skjeth-Rasmussen J, Schulz M, Kristensen SR, Bjørre P. Delayed neurological deficits detected by an ischemic pattern in the extracellular cerebral metabolites in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 2004; 100: 8-15 [PMID: 14743906 DOI: 10.3171/jns.2004.100.1.0008]

Sarfazadeh A, Haux D, Küchler I, Lanksch WR, Unterberg AW. Poor-grade aneurysmal subarachnoid hemorrhage: relationship of cerebral metabolism to outcome. J Neurosurg 2004; 100: 400-406 [PMID: 15035274 DOI: 10.3171/jns.2004.100.3.0400]

Schmidt JM, Ko SB, Helbok R, Kurtz P, Stuart RM, Presciutti M, Fernandez I, Lee K, Badjatia N, Connolly ES, Claassen J, Mayer Schmidt JM. Baseline levels of glucose metabolites, glutamate and glycerol metabolism in stroke patients: a microdialysis study. Acta Neurochir (Wien) 2002; 144: 679-683 [PMID: 12181701 DOI: 10.1007/s00701-002-0946-1]

Berger C, Annecke A, Aschoff A, Spranger M, Schwab S. Effects of hypothermia on excitatory amino acids and metabolic crisis after poor-grade subarachnoid hemorrhage. Acta Neurochir (Wien) 1992; 114: 8-11 [PMID: 1561943 DOI: 10.1007/BF01401106]

Bergenheim AT, Roslin M, Ungerstedt U, Wahlström A, Henriksson R, Ronquist G. Metabolic manipulation of glioblastoma in vivo by retrograde microdialysis of L-2, 4 diaminobutyric acid (DAB). J Neurooncol 2006; 80: 285-293 [PMID: 16773220 DOI: 10.1007/s11060-006-9186-1]

Ronne-Engström E, Hillered L, Flink R, Spännare B, Ungerstedt U, Carlson H. Intracerebral microdialysis of extracellular amino acids in the human epileptic focus. J Cereb Blood Flow Metab 1992; 12: 873-876 [PMID: 1506452 DOI: 10.1038/jcbfm.1992.119]

Ottens AK, Hulshof M, Spanjaard L, Sahu S, Patzschke K, Baumann S, Plattner R, B善良ke K. Blood-based diagnostics of traumatic brain injuries. Expert Rev Mol Diagn 2011; 11: 65-78 [PMID: 21171922 DOI: 10.1586/er.10.104]

Blakeley J, Portnow J. Microdialysis for assessing intratumoral drug disposition in brain cancers: a tool for rational drug development. Expert Opin Drug Metab Toxicol 2010; 6: 1477-1491 [PMID: 20969450 DOI: 10.1517/17425255.2010.523420]

Ronquist G, Hugosson R, Sjölander U, Ungerstedt U. Treatment of malignant glioma by a new therapeutic principle. Acta Neurochir (Wien) 1992; 114: 8-11 [PMID: 1561943 DOI: 10.1007/BF01401106]

