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**Biochemical changes in the injured brain**

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

**Seelora Sahu, Deb Sanjay Nag, Amlan Swain, Devi Prasad Samaddar**, Department of Anaesthesia and Critical Care, Tata Main Hospital, Jamshedpur 831001, India

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**Correspondence to: Dr. Deb Sanjay Nag,** Department of Anaesthesia and Critical Care, Tata Main Hospital, C Road West, Northern Town, Bistupur, Jamshedpur 831011, India. debsanjay@gmail.com

**Telephone:** +91-943-1166582

**Fax:** +91-657-2224559

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**Abstract**

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 intra cranial 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 biomarker 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 are of value in predicting long term complications and prognosis in such patients. In recent times Cerebral microdialysis has established itself as a novel way of monitoring brain tissue biochemical metabolites such as glucose, lactate, pyruvate, glutamate and glycerol while expression of 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

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**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 biomarker 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 expression of small non coding RNAs have presented themselves as potential markers of brain injury for future research.

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**INTRODUCTION**

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 has 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% to 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 exhibits various peculiarities with ramifications in brain injury. First is the presence of a blood brain barrier formed by endothelial cells 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 GABA as well as the activation of various ion channels. Sodium and potassium are the major ions involved in the generation of action potentials, especially 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 between 1000 to 20000 synapses, there are around 90 billion neurons in an adult human brain[15]. Brain injured states such as stroke, head injury etc 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 leads 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 the activating of AMPA, NMDA and metabolic receptors. Calcium as well as 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 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 roles in traumatic brain injury and calcium is an important ion implicated in traumatic brain injury at the cellular level[21,22].

***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 excitotoxicoty 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 should 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, subarachnoid hemorrhage, and intra cranial space occupying lesions. The use of such markers in brain *via* a vis their use in 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 neuro pathological 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**

It 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 t1/2 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 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 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 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 subarachnoid hemorrhage:** Plasma concentration of S-100 β in patients with subarachnoid hemorrhage (SAH) has shown 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 S-100 β concentrations. There is significant evidence to suggest that S-100 β in cerebrospinal fluid may show superior correlation with CT and SPECT findings in addition to being predictive for outcome in patients with cerebral aneurysm[43-46].

***Neuron specific enolase***

As an isoenzyme of enolase enzyme involved in glycolysis NSE was thought to be 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 it specificity for neural tissues is doubtful[48]. Serum levels are in the range of 5-12 ng/mL and cerebrospinal fluid (CSF) levels normally assess less them 2 ng/mL[49].

**NSE in TBI:** In experimental model studies on cortical contusion, 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 neural and glial tissue. A secondary peak in the NSE levels were observed at around 1.5 d and in all probability reflect secondary ischemic damage to the contused brain[29]. An experimental TBI model in rats clearly demonstrated that cerebrospinal fluid NSE is a more accurate motor of ongoing neuronal damage than serum NSE levels[50].

 There have been a plethora of studies in the correlation of serum and cerebrospinal fluid NSE levels with head injury as well as its prediction of long term outcome[33,37,39,40,51-54]. Serum NSE levels showed a significant correlation with a identifiable contusion on CT scan and also predicted the incidence is long term mortality and persistent vegetative state in patients with TBI[51].

***NSE in subarachnoid hemorrhage***

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 and the clinical grade of SAH patients at the time of admission is a contentious issues with various studies giving different levels[55-57].

***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[58-60]. In human studies examining the correlation of CSF and serum NSE levels, NSE has been found to have a positive correlating with infarct size and volume[61-66]. In a study by Cunningham et al. serum NSE levels in patients with ischemic stroke was higher when compared with hemorrhagic stroke and highest levels in ischemia was observed at 48 to 96 h[67]. NSE had also been found to correlate with and help in differentiation between reversible and irreversible brain damage in survivors of cardiac arrest[68-71]. In such patients, post resuscitation care serum NSE levels are reliable predictor of neurologic outcome and they also aid in prognostication of such patients.

**CREATININE PHOSPHO KINASE BB (CPK-BB)**

Of the three isoenzymic forms of creatinine phospho kinase, the CPK-BB isoform is found in the brain and in presence of intact BBB is confined within it [48]. CPK-BB levels in the various pathological entities of brain injury such as about stroke, TBI, post cardiac arrest and SAH has shown correlation to the extent of injury and have also shown to predict outcome[72-78].

**MYELIN BASIC PROTEIN (MBP)**

Myelin basic protein originates from oligodendroglial cells and binds with myelin[79]. In TBI it is released into CSF and serves as a useful marker predicting the clinical course and outcome[52,80-84].

In addition there are various other proteins which are less established *via* a vis their role in prognosis of 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 studies in TBI states[85,86]. 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[87-90].

**GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP**)

As a major component of the astroglia GFAP offers the promise of exclusivity to the central nervous system[91-93]. There have been numerous studies in TBI sub-population such as severe as moderate TBI wherein GFAP concentration has shown a positive correlation with severity of injury, outcomes as well as CT and MRI findings[94-98]. In a study comparing GFAP and S-100 β, GFAP exhibited characteristics of being more sensitive marker of neural injury. It also had higher predictive value for predicting return to work *via* a vis S-100 β especially in patients with severe head injury[99].

**UBIQUITIN C TERMINAL HYDROLASE (UCH-L1)**

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[100-102]. There is a release of UCH-L1 into CSF and blood in brain injury and elevated levels have exhibited correlation with severity and outcome in TBI populations[103].

**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[101,104]. S-100, GFAP and UCH-L1 are early biomarker 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[105,106]. Recently there has been attempts to isolate the aforementioned biomarkers from urine and saliva of patients thus precluding to non- invasiveness and ease of collecting[107].

**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 add non standardization of techniques in collection, handling and assay of such biomarkers. To summarize, the data till date on biomarkers of the injured brain can be described as a work in progress. There is a need for robust multicentric studies which will go a long way in the determination of reference points for guidance of care on patients presenting with neurological injury.

**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 then push-pull cannula technique and was invented by Delgado *et al*[108] with subsequent modification and popularization by Ungerstedt *et al*[110,111]. 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 While Table 1 (Table 1: Serum and CSF biomarkers of cerebral injury) summarizes all the commonly used serum and CSF biomarkers of cerebral injury with their clinical implications, Table 2 (Table 2: The components monitored by cerebral microdialysis and their clinical implications) summarizes components monitored by cerebral microdialysis and their clinical implications.

CMD is being increasingly used as a research tool and as a component of multi-modality monitoring in the brain injured states such as TBI, SAH, Brain tumors, Stroke and epilepsy. Table 3 illustrates the clinical implications of cerebral microdialysis in various scenarios (Table 3: Cerebral microdialysis implications in clinical scenarios).

Proteomic analysis of potential new CSF biomarkers for TBI has not yet identified any such markers that can be used in clinically useful tests[153]. A number of proteomics studies on potential biomarkers of TBI in peripheral blood have been published. These studies have replicated the findings from targeted analyses of specific candidate biomarkers, but as yet none of 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[154]. Exciting preliminary data on the expression profiles of small noncoding 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[154].

**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.

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**Table 1 Serum and cerebrospinal fluid biomarkers of cerebral injury**

|  |  |  |
| --- | --- | --- |
|  | Structure effected | Findings in brain injuryCerebro spinal fluid Blood/Serum |
| Tau protein | Axon | Levels peak 4-8 d after injury[115,116] | Elevated levels in hypoxic injury[117,118] |
| Myelin Basic Protein | Axon | NA | Detection methods are not very sensitive[119] |
| γ-Enolase | Neuron | Confounded by Blood contaminated CSF[120] | Serum levels are very sensitive to lysis of RBC in blood contaminated CSF[112] |
| S-100 β | Astrolglial cells | Elevated levels but less sensitive[108] | Confounded by release from extracerebral tissue[121] |
| GFAP | Astroglial cells | Elevated levels but less sensitive[107,108] | Serum levels correlate with changes in brain imaging[[122] no extracerebral sources detected[123] |
| UCH-L1 | Neuron  | NA | Only one pilot study[124] |

**Table 2 The components monitored by cerebral microdialysis and their clinical implications**

|  |  |  |
| --- | --- | --- |
| Variable | Normal levels (at a flow rate of 0.3 μL/min) | Clinical implications |
| Lactate | 2.9 ± 0.9 mmol/L | Increased levels seen in ischemia and hyperglycolysis[125-127] |
| Pyruvate | 166 ± 47 μmol/L | Decreased levels seen in ischemia and hypoxic conditions[118,119] |
| L/P ratio | Normal value -20 | Value > 25 -metabolic crisis[128]Type 1-lactate increased, pyruvate decreased signifies ischemiaType 2-raised LPR due to primarily decreased pyruvate level, seen in glycolysis failure or shunting of glucose to alternative metabolic pathways[129] |
| Glycerol | 82 ± 4 μmol/L | One of the constituents of the cell membranesAn increase in levels signifies cell damage[118] |
| Glutamate | 16 ± 16 μmol/L | Marker of excitotoxicity[118] |
| Glucose | 1.7 ± 0.9 mmol/L | Changes in blood flow or metabolism cause disproportionate changes in brain glucoseAffected by ischaemia,hyperaemia, hyperglycaemia, hypermetabolism and hypometabolism[118] |

**Table 3 Cerebral microdialysis implications in clinical scenarios**

|  |  |
| --- | --- |
| Clinical condition  | CMD implications |
| Traumatic brain injury | -helpful in optimising therapy in Neuro ICUs as a component of Multi-modality Monitoring-helps in indivisualising management on the basis of Cerebral Perfusion Pressure targets and assessment of response to medical and surgical interventions[127,129]-predictor of severity, neurological outcome and long term anatomical aberrations in the injured brain[132-134]-detection and management of glycemic perturbations of the injured brain[132,133]-predict long-term anatomical alteration[134] |
| Subarachnoid haemorrhage | -detection of ischemic changes during aneurysm clipping[135]-specific for the detection of delayed ischaemic neurological deficit (DIND) [136-139]-prognostication of SAH patients[140,141] |
| Acute ischaemic stroke | -detect development of oedema of the infarcted tissue[142]-monitoring effects of decompression hemicraniectomy and hypothermia in stroke patients[143,144] |
| Brain tumours | -neuro‑biochemistry of brain tumours [145,146]- biochemical changes during treatment-drug pharmacokinetics study[147]-monitoring of drug effect-development of tumor drug delivery systems[148,149] |
| Epilepsy | -study of biochemical milieu of epileptic focus[150] |
| Other applications | -study the perihaemorrhagic zone in intra cranial hemorrhage[151,152]- study of biochemical changes and novel therapeutic options in Neurodegenerative diseases such as Parkinson and Alzheimer’s disease  |