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EDITORIAL

Biochemical changes in the injured brain

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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 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 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 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

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.

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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].

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 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 $t_{1/2}$ 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 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 it 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 neural 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

brain[29]. An experimental TBI model in rats clearly demonstrated that CSF NSE is a more accurate motor of ongoing neuronal damage than serum NSE levels[50].

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[33,37,39,40,51-54]. 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[51].

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[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 with serum NSE levels, NSE has been found to have a positive correlation with infarct size and volume[61-66]. In a study by Cunningham *et al*[67], 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[68-71]. 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[48]. 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[72-78].

MBP

MBP 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 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[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

As a major component of astroglia, glial fibrillary acidic protein (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 or 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 a more sensitive marker of neural injury. It also had higher value for predicting return to work *via-a-vis* S-100 β especially in patients with severe head injury[99].

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[100-102]. There is 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[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 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

Table 1 Serum and cerebrospinal fluid biomarkers of cerebral injury

	Structure effected	Findings in brain injury	
		Cerebro spinal fluid	Blood/serum
Tau protein	Axon	Levels peak 4-8 d after injury[111,112]	Elevated levels in hypoxic injury[113,114]
Myelin basic protein	Axon	Precise measurement difficult[115]	Elevated levels in brain injury[116]
γ-enolase	Neuron	Confounded by blood contaminated CSF[117]	Serum levels are very sensitive to lysis of RBC in blood contaminated CSF[117], elevated levels in brain injury[116]
S-100 β	Astrolglial cells	Elevated levels but less sensitive[108]	Confounded by release from extracerebral tissue[118]
GFAP	Astroglial cells	Elevated levels but less sensitive[107,108]	Serum levels correlate with changes in brain imaging[119], no extracerebral sources detected[120]
UCH-L1	Neuron	NA	Only one pilot study[98]

GFAP: Glial fibrillary acidic protein; UCH-L1: Ubiquitin c terminal hydrolase; NA: Not available; CSF: Cerebrospinal fluid; RBC: Red blood cell.

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[121-123]
Pyruvate	166 ± 47 μmol/L	Decreased levels seen in ischemia and hypoxic conditions[124,125]
L/P ratio	Normal value-20	Value > 25 - metabolic crisis[124]
		Type 1-lactate increased, pyruvate decreased, signifying ischemia
		Type 2-raised LPR due to primarily decreased pyruvate level, seen in glycolysis failure or shunting of glucose to alternative metabolic pathways[125]
Glycerol	82 ± 4 μmol/L	One of the constituents of the cell membranes
		An increase in levels signifies cell damage[124]
Glutamate	16 ± 16 μmol/L	Marker of excitotoxicity[124]
Glucose	1.7 ± 0.9 mmol/L	Changes in blood flow or metabolism cause disproportionate changes in brain glucose
		Affected by ischaemia, hyperaemia, hyperglycaemia, hypermetabolism and hypometabolism[124]

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 have been attempts to isolate the aforementioned biomarkers from urine and saliva of patients to preclude non-invasiveness and ease collection[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 as 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 in 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 bio-chemistry. 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*[108] with subsequent modifications and popularization by Ludvig *et al*[109] and Ungerstedt *et al*[110]. 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[111-120]. Table 2 summarizes components monitored by cerebral microdialysis and their clinical implications[121-125].

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[126-151].

Proteomic analysis of potential new CSF biomarkers for TBI has not yet identified any such markers that can be used in clinically useful tests[152]. A number of proteomic 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

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
	Helpful in indivisualising management on the basis of cerebral perfusion pressure targets and assessment of response to medical and surgical interventions[126,127]
	Predictor of severity, neurological outcome and long-term anatomical aberrations in the injured brain[128-130]
	Detection and management of glycemic perturbations of the injured brain[131,132]
	Predicting long-term anatomical alteration[133]
Subarachnoid haemorrhage	Detection of ischemic changes during aneurysm clipping[134]
	Specific for the detection of delayed ischaemic neurological deficit[135-138]
	Prognostication of SAH patients[139,140]
Acute ischaemic stroke	Detecting development of oedema of the infarcted tissue[141]
	Monitoring effects of decompression hemicraniectomy and hypothermia in stroke patients[142,143]
Brain tumours	Neuro-biochemistry of brain tumours[144,145]
	Biochemical changes during treatment
	Drug pharmacokinetics study[146]
	Monitoring of drug effect
	Development of tumor drug delivery systems[147,148]
Epilepsy	Study of biochemical milieu of epileptic focus[149]
Other applications	Study of the perihaemorrhagic zone in intracranial hemorrhage[150,151]
	Study of biochemical changes and novel therapeutic options in neurodegenerative diseases such as Parkinson's and Alzheimer's disease

CMD: Cerebral microdialysis; SAH: Subarachnoid hemorrhage; ICU: Intensive care unit.

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[153]. 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[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.

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 **Allsopp G**, 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 IA, 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**, Potschka 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.bbabio.2010.08.009]

10 **Marieb EN**, Hoehn K. Human Anatomy & Physiology, 8th ed. San Francisco, CA: Benjamin Cummings, 2010: 385-428

11 **Murai 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/S1566-2772(00)00005-0]

12 **Hajjawi OS.** Human Brain Biochemistry. *Ame J BioS* 2014; **2**: 122-134 [DOI: 10.11648/j.ajbio.20140204.13]

13 **Sherwood L**. Human Physiology from Cells to Systems. 8th ed. Stamford, 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,

1994: 81-90
16 **Kass IS**, Cottrell JE, Lei B. Brain metabolism, the pathophysiology of brain injury, and potential beneficial agents and techniques. In: Cottrell JE, Young WL. Cottrell and Young's Neuroanesthesia. Philadelphia: Elsevier, 2010: 1-16
17 **Rothman SM**, Olney JW. Glutamate and the pathophysiology of hypoxic--ischemic brain damage. *Ann Neurol* 1986; **19**: 105-111 [PMID: 2421636 DOI: 10.1002/ana.410190202]
18 **Choi DW**. Excitotoxic cell death. *J Neurobiol* 1992; **23**: 1261-1276 [PMID: 1361523 DOI: 10.1002/neu.480230915]
19 **Zola-Morgan S**, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *J Neurosci* 1986; **6**: 2950-2967 [PMID: 3760943]
20 **Wang J**, Lei B, Popp S, Meng F, Cottrell JE, Kass IS. Sevoflurane immediate preconditioning alters hypoxic membrane potential changes in rat hippocampal slices and improves recovery of CA1 pyramidal cells after hypoxia and global cerebral ischemia. *Neuroscience* 2007; **145**: 1097-1107 [PMID: 17291693 DOI: 10.1016/j.neuroscience.2006.12.047]
21 **Lawrence T**, Helmy A, Bouamra O, Woodford M, Lecky F, Hutchinson PJ. Traumatic brain injury in England and Wales: prospective audit of epidemiology, complications and standardised mortality. *BMJ Open* 2016; **6**: e012197 [PMID: 27884843 DOI: 10.1016/S0733-8627(05)70319-9]
22 **Prough DS**. Management of head trauma. 1997 Annual Refresher Course Lectures. *Ame Soc Anest* 1997: **253**: 1-7
23 **Hacke W**, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 2005; **36**: 66-73 [PMID: 15569863 DOI: 10.1161/01.STR.0000149938.08731.2c]
24 **Hacke W**, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, Kaste M, Lipka LJ, Pedraza S, Ringleb PA, Rowley HA, Schneider D, Schwamm LH, Leal JS, Söhngen M, Teal PA, Wilhelm-Ogunbiyi K, Wintermark M, Warach S. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol* 2009; **8**: 141-150 [PMID: 19097942 DOI: 10.1016/S1474-4422(08)70267-9]
25 **Bakay RA**, Sweeney KM, Wood JH. Pathophysiology of cerebrospinal fluid in head injury: Part 2. Biochemical markers for central nervous system trauma. *Neurosurgery* 1986; **18**: 376-382 [PMID: 3010171 DOI: 10.1227/00006123-198603000-00026]
26 **Ingebrigtsen T**, Waterloo K, Jacobsen EA, Langbakk B, Romner B. Traumatic brain damage in minor head injury: relation of serum S-100 protein measurements to magnetic resonance imaging and neurobehavioral outcome. *Neurosurgery* 1999; **45**: 468-475; discussion 475-476 [PMID: 10493368 DOI: 10.1097/00006123-199909000-00010]
27 **Nygaard O**, Langbakk B, Romner B. Age- and sex-related changes of S-100 protein concentrations in cerebrospinal fluid and serum in patients with no previous history of neurological disorder. *Clin Chem* 1997; **43**: 541-543 [PMID: 9068602 DOI: 10.1016/s0303-8467(97)81581-8]
28 **Wiesmann M**, Missler U, Hagenström H, Gottmann D. S-100 protein plasma levels after aneurysmal subarachnoid haemorrhage. *Acta Neurochir* (Wien) 1997; **139**: 1155-1160 [PMID: 9479422 DOI: 10.1007/BF01410976]
29 **Hårdemark HG**, Ericsson N, Kotwica Z, Rundström G, Mendel-Hartvig I, Olsson Y, Påhlman S, Persson L. S-100 protein and neuron-specific enolase in CSF after experimental traumatic or focal ischemic brain damage. *J Neurosurg* 1989; **71**: 727-731 [PMID: 2809727 DOI: 10.3171/jns.1989.71.5.0727]
30 **Ingebrigtsen T**, Romner B, Kongstad P, Langbakk B. Increased serum concentrations of protein S-100 after minor head injury: a biochemical serum marker with prognostic value? *J Neurol Neurosurg Psychiatry* 1995; **59**: 103-104 [PMID: 7608699 DOI: 10.1136/jnnp.59.1.103-a]
31 **Ingebrigtsen T**, Romner B. Serial S-100 protein serum measurements related to early magnetic resonance imaging after minor head injury. Case report. *J Neurosurg* 1996; **85**: 945-948 [PMID: 8893737 DOI: 10.3171/jns.1996.85.5.0945]
32 **Ingebrigtsen T**, Romner B, Trumpy JH. Management of minor head injury: the value of early computed tomography and serum protein S-100 measurements. *J Clin Neurosci* 1997; **4**: 29-33 [PMID: 18638920 DOI: 10.1016/S0967-5868(97)90007-2]
33 **Raabe A**, Grolms C, Keller M, Döhnert J, Sorge O, Seifert V. Correlation of computed tomography findings and serum brain damage markers following severe head injury. *Acta Neurochir* (Wien) 1998; **140**: 787-791; discussion 791-792 [PMID: 9810445 DOI: 10.1007/s007010050180]
34 **Raabe A**, Menon DK, Gupta S, Czosnyka M, Pickard JD. Jugular venous and arterial concentrations of serum S-100B protein in patients with severe head injury: a pilot study. *J Neurol Neurosurg Psychiatry* 1998; **65**: 930-932 [PMID: 9854976 DOI: 10.1136/jnnp.65.6.930]
35 **Raabe A**, Grolms C, Sorge O, Zimmermann M, Seifert V. Serum S-100B protein in severe head injury. *Neurosurgery* 1999; **45**: 477-483 [PMID: 10493369 DOI: 10.1097/00006123-199909000-00012]
36 **Raabe A**, Seifert V. Fatal secondary increase in serum S-100B protein after severe head injury. Report of three cases. *J Neurosurg* 1999; **91**: 875-877 [PMID: 10541249 DOI: 10.3171/jns.1999.91.5.0875]
37 **Waterloo K**, Ingebrigtsen T, Romner B. Neuropsychological function in patients with increased serum levels of protein S-100 after minor head injury. *Acta Neurochir* (Wien) 1997; **139**: 26-31; discussion 31-32 [PMID: 9059708 DOI: 10.1007/BF01850864]
38 **Woertgen C**, Rothoerl RD, Holzschuh M, Metz C, Brawanski A. Comparison of serial S-100 and NSE serum measurements after severe head injury. *Acta Neurochir* (Wien) 1997; **139**: 1161-1164; discussion 1165 [PMID: 9479423 DOI: 10.1007/BF01410977]
39 **Rothoerl RD**, Woertgen C, Holzschuh M, Metz C, Brawanski A. S-100 serum levels after minor and major head injury. *J Trauma* 1998; **45**: 765-767 [PMID: 9783618 DOI: 10.1097/00005373-199810000-00025]
40 **Herrmann M**, Curio N, Jost S, Wunderlich MT, Synowitz H, Wallesch CW. Protein S-100B and neuron specific enolase as early neurobiochemical markers of the severity of traumatic brain injury. *Restor Neurol Neurosci* 1999; **14**: 109-114 [PMID: 12671254]
41 **Herrmann M**, Jost S, Kutz S, Ebert AD, Kratz T, Wunderlich MT, Synowitz H. Temporal profile of release of neurobiochemical markers of brain damage after traumatic brain injury is associated with intracranial pathology as demonstrated in cranial computerized tomography. *J Neurotrauma* 2000; **17**: 113-122 [PMID: 10709869 DOI: 10.1089/neu.2000.17.113]
42 **Raabe A**, Grolms C, Seifert V. Serum markers of brain damage and outcome prediction in patients after severe head injury. *Br J Neurosurg* 1999; **13**: 56-59 [PMID: 10492686 DOI: 10.1080/02688699944195]
43 **Persson L**, Hårdemark H, Edner G, Ronne E, Mendel-Hartvig I, Påhlman S. S-100 protein in cerebrospinal fluid of patients with subarachnoid haemorrhage: a potential marker of brain damage. *Acta Neurochir* (Wien) 1988; **93**: 116-122 [PMID: 3177026 DOI: 10.1007/BF01402892]
44 **Hårdemark HG**, Almqvist O, Johansson T, Påhlman S, Persson L. S-100 protein in cerebrospinal fluid after aneurysmal subarachnoid haemorrhage: relation to functional outcome, late CT and SPECT changes, and signs of higher cortical dysfunction. *Acta Neurochir* (Wien) 1989; **99**: 135-144 [PMID: 2788973 DOI: 10.1007/BF01402322]
45 **Takayasu M**, Shibuya M, Kanamori M, Suzuki Y, Ogura K, Kageyama N, Umekawa H, Hidaka H. S-100 protein and calmodulin levels in cerebrospinal fluid after subarachnoid hemorrhage. *J Neurosurg* 1985; **63**: 417-420 [PMID: 4020469 DOI: 10.3171/jns.1985.63.3.0417]
46 **Satoh H**, Ikeda Y, Ohashi K. Measurement of S-100b in cerebrospinal fluid among SAH cases: prediction of outcome. 29th

Annual Meeting of Japanese Society of Surgery for Stroke, 2000
47 **Schoerkhuber W**, Kittler H, Sterz F, Behringer W, Holzer M, Frossard M, Spitzauer S, Laggner AN. Time course of serum neuron-specific enolase. A predictor of neurological outcome in patients resuscitated from cardiac arrest. *Stroke* 1999; **30**: 1598-1603 [PMID: 10436107 DOI: 10.1161/01.STR.30.8.1598]
48 **Ikeda Y**, Mochizuki Y, Nakamura Y, Dohi K, Matsumoto H, Jimbo H, Hayashi M, Matsumoto K, Yoshikawa T, Murase H, Sato K. Protective effect of a novel vitamin E derivative on experimental traumatic brain edema in rats--preliminary study. *Acta Neurochir Suppl* 2000; **76**: 343-345 [PMID: 11450040]
49 **Marangos PJ**, Schmechel DE. Neuron specific enolase, a clinically useful marker for neurons and neuroendocrine cells. *Annu Rev Neurosci* 1987; **10**: 269-295 [PMID: 3551759 DOI: 10.1146/annurev.ne.10.030187.001413]
50 **Uzan M**, Hanci M, Güzel O, Sarioğlu AC, Kuday C, Ozlen F, Kaynar MY. The significance of neuron specific enolase levels in cerebrospinal fluid and serum after experimental traumatic brain damage. *Acta Neurochir* (Wien) 1995; **135**: 141-143 [PMID: 8748804 DOI: 10.1007/BF02187758]
51 **Kuroiwa T**, Tanabe H, Takatsuka H, Arai M, Nagasawa S, Ohta T. [Significance of serum neuron-specific enolase levels after head injury]. *No Shinkei Geka* 1993; **21**: 1021-1024 [PMID: 8255376]
52 **Yamazaki Y**, Yada K, Morii S, Kitahara T, Ohwada T. Diagnostic significance of serum neuron-specific enolase and myelin basic protein assay in patients with acute head injury. *Surg Neurol* 1995; **43**: 267-270; discussion 270-271 [PMID: 7540773 DOI: 10.1016/0090-3019(95)80012-6]
53 **Ross SA**, Cunningham RT, Johnston CF, Rowlands BJ. Neuron-specific enolase as an aid to outcome prediction in head injury. *Br J Neurosurg* 1996; **10**: 471-476 [PMID: 8922706 DOI: 10.1080/02688699647104]
54 **Ergün R**, Bostanci U, Akdemir G, Beşkonakli E, Kaptanoğlu E, Gürsoy F, Taşkin Y. Prognostic value of serum neuron-specific enolase levels after head injury. *Neurol Res* 1998; **20**: 418-420 [PMID: 9664588 DOI: 10.1080/01616412.1998.11740541]
55 **Kacira T**, Kemerdere R, Atukeren P, Hanimoglu H, Sanus GZ, Kucur M, Tanriverdi T, Gumustas K, Kaynar MY. Detection of caspase-3, neuron specific enolase, and high-sensitivity C-reactive protein levels in both cerebrospinal fluid and serum of patients after aneurysmal subarachnoid hemorrhage. *Neurosurgery* 2007; **60**: 674-679; discussion 679-680 [PMID: 17415204 DOI: 10.1227/01.NEU.0000255394.77538.BB]
56 **Kuroiwa T**, Tanabe H, Arai M, Ohta T. [Measurement of serum neuron-specific enolase levels after subarachnoid hemorrhage and intracerebral hemorrhage]. *No Shinkei Geka* 1994; **22**: 531-535 [PMID: 8015673]
57 **Hårdemark HG**, Persson L, Bolander HG, Hillered L, Olsson Y, Påhlman S. Neuron-specific enolase is a marker of cerebral ischemia and infarct size in rat cerebrospinal fluid. *Stroke* 1988; **19**: 1140-1144 [PMID: 3413812 DOI: 10.1161/01.STR.19.9.1140]
58 **Horn M**, Seger F, Schlote W. Neuron-specific enolase in gerbil brain and serum after transient cerebral ischemia. *Stroke* 1995; **26**: 290-296; discussion 296-297 [PMID: 7831703 DOI: 10.1161/01.STR.26.2.290]
59 **Barone FC**, Clark RK, Price WJ, White RF, Feuerstein GZ, Storer BL, Ohlstein EH. Neuron-specific enolase increases in cerebral and systemic circulation following focal ischemia. *Brain Res* 1993; **623**: 77-82 [PMID: 8221097 DOI: 10.1016/0006-8993(93)90012-C]
60 **Steinberg R**, Gueniau C, Scarna H, Keller A, Worcel M, Pujol JF. Experimental brain ischemia: neuron-specific enolase level in cerebrospinal fluid as an index of neuronal damage. *J Neurochem* 1984; **43**: 19-24 [PMID: 6726246 DOI: 10.1111/j.1471-4159.1984.tb06673.x]
61 **Royds JA**, Davies-Jones GA, Lewtas NA, Timperley WR, Taylor CB. Enolase isoenzymes in the cerebrospinal fluid of patients with diseases of the nervous system. *J Neurol Neurosurg Psychiatry* 1983; **46**: 1031-1036 [PMID: 6317805 DOI: 10.1136/jnnp.46.11.1031]
62 **Hay E**, Royds JA, Davies-Jones GA, Lewtas NA, Timperley WR, Taylor CB. Cerebrospinal fluid enolase in stroke. *J Neurol Neurosurg Psychiatry* 1984; **47**: 724-729 [PMID: 6747647 DOI: 10.1136/jnnp.47.7.724]
63 **Jacobi C**, Reiber H. Clinical relevance of increased neuron-specific enolase concentration in cerebrospinal fluid. *Clin Chim Acta* 1988; **177**: 49-54 [PMID: 3052937 DOI: 10.1016/0009-8981(88)90306-3]
64 **Kawasaki H**, Wakayama Y, Okayasu H, Takahashi1 H, Shibuya S. Levels of serum and cerebrospinal fluid enolase in patients with cerebral vascular disease and other neurological diseases. *Stroke* 1988; **10**: 313-318 [DOI: 10.3995/jstroke.10.313]
65 **Vermuyten K**, Lowenthal A, Karcher D. Detection of neuron specific enolase concentrations in cerebrospinal fluid from patients with neurological disorders by means of a sensitive enzyme immunoassay. *Clin Chim Acta* 1990; **187**: 69-78 [PMID: 2317937 DOI: 10.1016/0009-8981(90)90332-M]
66 **Mokuno K**, Kato K, Kawai K, Matsuoka Y, Yanagi T, Sobue I. Neuron-specific enolase and S-100 protein levels in cerebrospinal fluid of patients with various neurological diseases. *J Neurol Sci* 1983; **60**: 443-451 [PMID: 6355398 DOI: 10.1016/0022-510X(83)90155-7]
67 **Cunningham RT**, Watt M, Winder J, McKinstry S, Lawson JT, Johnston CF, Hawkins SA, Buchanan KD. Serum neurone-specific enolase as an indicator of stroke volume. *Eur J Clin Invest* 1996; **26**: 298-303 [PMID: 8732487 DOI: 10.1046/j.1365-2362.1996.129282.x]
68 **Dauberschmidt R**, Zinsmeyer J, Mrochen H, Meyer M. Changes of neuron-specific enolase concentration in plasma after cardiac arrest and resuscitation. *Mol Chem Neuropathol* 1991; **14**: 237-245 [PMID: 1958265 DOI: 10.1007/BF03159939]
69 **Stelzl T**, von Bose MJ, Hogl B, Fuchs HH, Flugel KA. A comparison of the prognostic value of neuron-specific enolase serum levels and somatosensory evoked potentials in 13 reanimated patients. *Eur J Emerg Med* 1995; **2**: 24-27 [PMID: 9422176 DOI: 10.1097/00063110-199503000-00006]
70 **Martens P**, Raabe A, Johnsson P. Serum S-100 and neuron-specific enolase for prediction of regaining consciousness after global cerebral ischemia. *Stroke* 1998; **29**: 2363-2366 [PMID: 9804649 DOI: 10.1161/01.STR.29.11.2363]
71 **Fogel W**, Krieger D, Veith M, Adams HP, Hund E, Storch-Hagenlocher B, Buggle F, Mathias D, Hacke W. Serum neuron-specific enolase as early predictor of outcome after cardiac arrest. *Crit Care Med* 1997; **25**: 1133-1138 [PMID: 9233737 DOI: 10.1097/00003246-199707000-00012]
72 **Tirschwell DL**, Longstreth WT, Rauch-Matthews ME, Chandler 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/WNL.48.2.352]
73 **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.1983.04050030063012]
74 **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: 2441305 DOI: 10.2176/nmc.27.90]
75 **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: 10.1227/00006123-198305000-00010]
76 **Skogseid IM**, Nordby HK, Urdal P, Paus E, Lilleaas F. Increased serum creatine kinase BB and neuron specific enolase following head injury indicates brain damage. *Acta Neurochir* (Wien) 1992; **115**: 106-111 [PMID: 1605077 DOI: 10.1007/BF01406367]
77 **Coplin WM**, Longstreth WT, Lam AM, Chandler WL, Mayberg TS, Fine JS, Winn HR. Cerebrospinal fluid creatine kinase-BB isoenzyme activity and outcome after subarachnoid hemorrhage. *Arch Neurol* 1999; **56**: 1348-1352 [PMID: 10555654 DOI: 10.1001/archneur.56.11.1348]

78 **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]

79 **Johnsson P**. Markers of cerebral ischemia after cardiac surgery. *J Cardiothorac Vasc Anesth* 1996; **10**: 120-126 [PMID: 8634377 DOI: 10.1016/S1053-0770(96)80187-X]

80 **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 [PMID: 2421195 DOI: 10.1227/00006123-198602000-00023]

81 **Noseworthy TW**, Anderson BJ, Noseworthy AF, Shustack A, Johnston RG, Petruk KC, McPherson TA. Cerebrospinal fluid myelin basic protein as a prognostic marker in patients with head injury. *Crit Care Med* 1985; **13**: 743-746 [PMID: 4028768 DOI: 10.1097/00003246-198509000-00010]

82 **Thomas DG**, Palfreyman JW, Ratcliffe JG. Serum-myelin-basic-protein assay in diagnosis and prognosis of patients with head injury. *Lancet* 1978; **1**: 113-115 [PMID: 87549 DOI: 10.1016/S0140-6736(78)90415-4]

83 **Thomas DG**, Rabow 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: 10.1007/978-3-7091-4088-8_20]

84 **Alling C**, Karlsson B, Vällfors B. Increase in myelin basic protein in CSF after brain surgery. *J Neurol* 1980; **223**: 225-230 [PMID: 6157784 DOI: 10.1007/BF00313336]

85 **Zemlan FP**, Rosenberg WS, Luebbe PA, Campbell TA, Dean GE, Weiner NE, Cohen JA, Rudick RA, Woo D. Quantification 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: 10.1046/j.1471-4159.1999.0720741.x]

86 **Zemlan FP**, Jauch EC, Mulchahey JJ, Gabbita SP, Rosenberg WS, Speciale SG, Zuccarello M. C-tau biomarker of neuronal damage in severe brain injured patients: association with elevated intracranial pressure and clinical outcome. *Brain Res* 2002; **947**: 131-139 [PMID: 12144861 DOI: 10.1016/S0006-8993(02)02920-7]

87 **Bazarian JJ**, Zemlan FP, Mookerjee S, Stigbrand T. Serum S-100B and cleaved-tau are poor predictors of long-term outcome after mild traumatic brain injury. *Brain Inj* 2006; **20**: 759-765 [PMID: 16809208 DOI: 10.1080/02699050500488207]

88 **Bulut M**, Koksal O, Dogan S, Bolca N, Ozguc H, Korfali E, Ilcol YO, Parklak M. Tau protein as a serum marker of brain damage in mild traumatic brain injury: preliminary results. *Adv Ther* 2006; **23**: 12-22 [PMID: 16644603 DOI: 10.1007/BF02850342]

89 **Ma M**, Lindsell CJ, Rosenberry CM, Shaw GJ, Zemlan FP. Serum cleaved tau does not predict postconcussion syndrome after mild traumatic brain injury. *Am J Emerg Med* 2008; **26**: 763-768 [PMID: 18774039 DOI: 10.1016/j.ajem.2007.10.029]

90 **Kavalci C**, Pekdemir M, Durukan P, Ilhan N, Yildiz M, Serhatlioglu S, Seckin D. The value of serum tau protein for the diagnosis of intracranial injury in minor head trauma. *Am J Emerg Med* 2007; **25**: 391-395 [PMID: 17499655 DOI: 10.1016/j.ajem.2006.10.008]

91 **Eng LF**, Vanderhaeghen JJ, Bignami A, Gerstl B. An acidic protein isolated from fibrous astrocytes. *Brain Res* 1971; **28**: 351-354 [PMID: 5113526 DOI: 10.1016/0006-8993(71)90668-8]

92 **Missler U**, Wiesmann M, Wittmann G, Magerkurth O, Hagenström H. Measurement of glial fibrillary acidic protein in human blood: analytical method and preliminary clinical results. *Clin Chem* 1999; **45**: 138-141 [PMID: 9895354]

93 **Webster MJ**, Knable MB, Johnston-Wilson N, Nagata K, Inagaki M, Yolken RH. Immunohistochemical localization of phosphorylated glial fibrillary acidic protein in the prefrontal cortex and hippocampus from patients with schizophrenia, bipolar disorder, and depression. *Brain Behav Immun* 2001; **15**: 388-400 [PMID: 11782105 DOI: 10.1006/brbi.2001.0646]

94 **Vos PE**, Jacobs B, Andriessen TM, Lamers KJ, Borm GF, Beems T, Edwards M, Rosmalen CF, Vissers JL. GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. *Neurology* 2010; **75**: 1786-1793 [PMID: 21079180 DOI: 10.1212/WNL.0b013e3181fd62d2]

95 **Mondello S**, Papa L, Buki A, Bullock MR, Czeiter E, Tortella FC, Wang KK, Hayes RL. Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: a case control study. *Crit Care* 2011; **15**: R156 [PMID: 21702960 DOI: 10.1186/cc10286]

96 **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.DC]

97 **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: 10.1089/neu.2004.21.1553]

98 **Papa L**, Lewis LM, Falk JL, Zhang Z, Silvestri S, Giordano P, Brophy GM, Demery JA, Dixit NK, Ferguson I, Liu MC, Mo J, Akinyi L, Schmid K, Mondello S, Robertson CS, Tortella FC, Hayes RL, Wang KK. 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]

99 **Metting Z**, Wilczak 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/WNL.0b013e318253d5c7]

100 **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: 10.1097/00001756-199902050-00040]

101 **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/bi960099f]

102 **Kobeissy FH**, Ottens AK, Zhang Z, Liu MC, Denslow ND, 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]

103 **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 KK. 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.0b013e3182491e3d]

104 **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: 10.1089/neu.2011.2092]

105 **Manley GT**, Diaz-Arrastia R, Brophy M, Engel D, Goodman C, Gwinn K, Veenstra 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]

106 **Teunissen CE**, Petzold A, Bennett JL, Berven FS, Brundin L, Comabella M, Franciotta D, Frederiksen JL, Fleming JO, Furlan R, Hintzen RQ, Hughes SG, Johnson MH, Krasulova E, Kuhle J, Magnone MC, Rajda C, Rejdak K, 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.0b013e3181c47cc2]

107 **Hallén M**, Karlsson M, Carlhed R, Hallgren T, Bergenheim M. S-100B in serum and urine after traumatic head injury in children. *J Trauma* 2010; **69**: 284-289 [PMID: 20734463 DOI: 10.1097/TA.0b013e3181ca060b]

108 **Delgado JM**, DeFeudis FV, Roth RH, Ryugo DK, Mitruka BM. Dialytrode for long term intracerebral perfusion in awake monkeys. *Arch Int Pharmacodyn Ther* 1972; **198**: 9-21 [PMID: 4626478]

109 **Ludvig N**, Potter PE, Fox SE. Simultaneous single-cell recording and microdialysis within the same brain site in freely behaving rats: a novel neurobiological method. *J Neurosci Methods* 1994; **55**: 31-40 [PMID: 7891459 DOI: 10.1016/B978-0-444-81194-3.50006-X]

110 **Ungerstedt U**. Measurement of neurotransmitter release by intracranial dialysis. In: Marsden CA, ed. Measurement of Neurotransmitter Release In Vivo. IBRO Handbook Series: Methods in the Neurosciences. New York: John Wiley & Sons Ltd, 1984: 81-105

111 **Zetterberg H**, Hietala MA, Jonsson M, Andreasen N, Styrud E, Karlsson I, Edman A, Popa C, Rasulzada A, Wahlund LO, Mehta PD, Rosengren L, Blennow K, Wallin A. Neurochemical aftermath of amateur boxing. *Arch Neurol* 2006; **63**: 1277-1280 [PMID: 16966505 DOI: 10.1001/archneur.63.9.1277]

112 **Neselius S**, Brisby H, Theodorsson A, Blennow K, Zetterberg H, Marcusson J. CSF-biomarkers in Olympic boxing: diagnosis and effects of repetitive head trauma. *PLoS One* 2012; **7**: e33606 [PMID: 22496755 DOI: 10.1371/journal.pone.0033606]

113 **Mörtberg E**, Zetterberg H, Nordmark J, Blennow K, Catry C, Decraemer H, Vanmechelen E, Rubertsson S. Plasma tau protein in comatose patients after cardiac arrest treated with therapeutic hypothermia. *Acta Anaesthesiol Scand* 2011; **55**: 1132-1138 [PMID: 22092212 DOI: 10.1111/j.1399-6576.2011.02505.x]

114 **Randall J**, Mörtberg E, Provuncher GK, Fournier DR, Duffy DC, Rubertsson S, Blennow K, Zetterberg H, Wilson DH. Tau proteins in serum predict neurological outcome after hypoxic brain injury from cardiac arrest: results of a pilot study. *Resuscitation* 2013; **84**: 351-356 [PMID: 22885094 DOI: 10.1016/j.resuscitation.2012.07.027]

115 **Gupta MK**. Myelin basic protein and demyelinating diseases. *Crit Rev Clin Lab Sci* 1987; **24**: 287-314 [PMID: 2436854]

116 **Borg K**, Bonomo J, Jauch EC, Kupchak P, Stanton EB, Sawadsky B. Serum Levels of Biochemical Markers of Traumatic Brain Injury. *ISRN Emergency Medicine* 2012; 2012 [DOI:10.5402/2012/417313]

117 **Ramont L**, Thoannes H, Volondat A, Chastang F, Millet MC, Maquart FX. Effects of hemolysis and storage condition on neuron-specific enolase (NSE) in cerebrospinal fluid and serum: implications in clinical practice. *Clin Chem Lab Med* 2005; **43**: 1215-1217 [PMID: 16232088 DOI: 10.1515/CCLM.2005.210]

118 **Fazio V**, Bhudia SK, Marchi N, Aumayr B, Janigro D. Peripheral detection of S100beta during cardiothoracic surgery: what are we really measuring? *Ann Thorac Surg* 2004; **78**: 46-53 [DOI: 10.1016/j.athoracsur.2003.11.042]

119 **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 Neurotr* 2004; **21**: 1553-1561 [PMID: 15684648 DOI:10.1089/neu.2004.21.1553]

120 **Mayer CA**, Brunkhorst R, Niessner M, Pfeilschifter W, Steinmetz H, Foerch C. Blood Levels of Glial Fibrillary Acidic Protein (GFAP) in Patients with Neurological Diseases. Kleinschnitz C, ed. *PLoS ONE* 2013; **8**: e62101 [DOI:10.1371/journal.pone.0062101]

121 **Bergsneider M**, Hovda DA, Shalmon E, Kelly DF, Vespa PM, Martin NA, Phelps ME, McArthur DL, Caron MJ, Kraus JF, Becker DP. Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. *J Neurosurg* 1997; **86**: 241-251 [PMID: 9010426 DOI: 10.3171/jns.1997.86.2.0241]

122 **Reinstrup P**, Ståhl N, Mellergård P, Uski T, Ungerstedt U, Nordström CH. Intracerebral microdialysis in clinical practice: baseline values for chemical markers during wakefulness, anesthesia, and neurosurgery. *Neurosurgery* 2000; **47**: 701-709; discussion 709-710 [PMID: 10981758 DOI: 10.1227/00006123-200009000-00035]

123 **Tisdall MM**, Smith M. Cerebral microdialysis: research technique or clinical tool. *Br J Anaesth* 2006; **97**: 18-25 [PMID: 16698861 DOI: 10.1093/bja/ael109]

124 **Ungerstedt U**, Rostami E. Microdialysis in neurointensive care. *Curr Pharm Des* 2004; **10**: 2145-2152 [PMID: 15281890 DOI: 10.2174/1381612043384105]

125 **Hillered L**, Persson L, Nilsson P, Ronne-Engstrom E, Enblad P. Continuous monitoring of cerebral metabolism in traumatic brain injury: a focus on cerebral microdialysis. *Curr Opin Crit Care* 2006; **12**: 112-118 [PMID: 16543785 DOI: 10.1097/01.ccx.0000216576.11439.df]

126 **Timofeev I**, Czosnyka M, Carpenter KL, Nortje J, Kirkpatrick PJ, Al-Rawi PG, Menon DK, Pickard JD, Gupta AK, Hutchinson PJ. Interaction between brain chemistry and physiology after traumatic brain injury: impact of autoregulation and microdialysis catheter location. *J Neurotrauma* 2011; **28**: 849-860 [PMID: 21488707 DOI: 10.1089/neu.2010.1656]

127 **Timofeev I**, Carpenter KL, Nortje J, Al-Rawi PG, O'Connell MT, Czosnyka M, Smielewski P, Pickard JD, Menon DK, Kirkpatrick PJ, Gupta AK, Hutchinson PJ. Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients. *Brain* 2011; **134**: 484-494 [PMID: 21247930 DOI: 10.1093/brain/awq353]

128 **Sala N**, Suys T, Zerlauth JB, Bouzat P, Messerer M, Bloch J, Levivier M, Magistretti PJ, Meuli R, Oddo M. Cerebral extracellular lactate increase is predominantly nonischemic in patients with severe traumatic brain injury. *J Cereb Blood Flow Metab* 2013; **33**: 1815-1822 [PMID: 23963367 DOI: 10.1038/jcbfm.2013.142]

129 **Sahuquillo J**, Merino MA, Sánchez-Guerrero A, Arikan F, Vidal-Jorge M, Martínez-Valverde T, Rey A, Riveiro M, Poca MA. Lactate and the lactate-to-pyruvate molar ratio cannot be used as independent biomarkers for monitoring brain energetic metabolism: a microdialysis study in patients with traumatic brain injuries. *PLoS One* 2014; **9**: e102540 [PMID: 25025772 DOI: 10.1371/journal.pone.0102540]

130 **Bullock R**, Zauner A, Woodward JJ, Myseros J, Choi SC, Ward JD, Marmarou A, Young HF. Factors affecting excitatory amino acid release following severe human head injury. *J Neurosurg* 1998; **89**: 507-518 [PMID: 9761042 DOI: 10.3171/jns.1998.89.4.0507]

131 **Rostami E**. Glucose and the injured brain-monitored in the neurointensive care unit. *Front Neurol* 2014; **5**: 91 [PMID: 24936196 DOI: 10.3389/fneur.2014.00091]

132 **Oddo M**, Schmidt JM, Carrera E, Badjatia N, Connolly ES, Presciutti M, Ostapkovich ND, Levine JM, Le Roux P, Mayer SA. Impact of tight glycemic control on cerebral glucose metabolism after severe brain injury: a microdialysis study. *Crit Care Med* 2008; **36**: 3233-3238 [PMID: 18936695 DOI: 10.1097/CCM.0b013e31818f4026]

133 **Marcoux J**, McArthur DA, Miller C, Glenn TC, Villablanca P, Martin NA, Hovda DA, Alger JR, Vespa PM. Persistent metabolic crisis as measured by elevated cerebral microdialysis lactate-pyruvate ratio predicts chronic frontal lobe brain atrophy after traumatic brain injury. *Crit Care Med* 2008; **36**: 2871-2877 [PMID: 18766106 DOI: 10.1097/CCM.0b013e318186a4a0]

134 **Bhatia R**, Hashemi P, Razzaq A, Parkin MC, Hopwood SE, Boutelle MG, Strong AJ. Application of rapid-sampling, online microdialysis to the monitoring of brain metabolism during aneurysm surgery. *Neurosurgery* 2006; **58**: ONS-313-ONS-20; discussion ONS-321 [PMID: 16582655 DOI: 10.1227/01.NEU.0000208963.42378.83]

135 **Unterberg AW**, Sakowitz OW, Sarrafzadeh AS, Benndorf G, Lanksch WR. Role of bedside microdialysis in the diagnosis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg* 2001; **94**: 740-749 [PMID: 11354405 DOI: 10.3171/jns.2001.94.5.0740]

136 **Ulrich CT**, Fung C, Vatter H, Setzer M, Gueresir E, Seifert V, Beck J, Raabe A. Occurrence of vasospasm and infarction in relation to a focal monitoring sensor in patients after SAH: placing a bet when placing a probe? *PLoS One* 2013; **8**: e62754 [PMID: 23658768 DOI: 10.1371/journal.pone.0062754]

137 **Sarrafzadeh AS**, Sakowitz OW, Kiening KL, Benndorf G,

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]

138 **Skjøth-Rasmussen J**, Schulz M, Kristensen SR, Bjerre 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]

139 **Sarrafzadeh 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]

140 **Schmidt JM**, Ko SB, Helbok R, Kurtz P, Stuart RM, Presciutti M, Fernandez L, Lee K, Badjatia N, Connolly ES, Claassen J, Mayer SA. Cerebral perfusion pressure thresholds for brain tissue hypoxia and metabolic crisis after poor-grade subarachnoid hemorrhage. *Stroke* 2011; **42**: 1351-1356 [PMID: 21441155 DOI: 10.1161/STROKEAHA.110.596874]

141 **Berger C**, Annecke A, Aschoff A, Spranger M, Schwab S. Neurochemical monitoring of fatal middle cerebral artery infarction. *Stroke* 1999; **30**: 460-463 [PMID: 9933288 DOI: 10.1161/01.STR.30.2.460]

142 **Berger C**, Kiening K, Schwab S. Neurochemical monitoring of therapeutic effects in large human MCA infarction. *Neurocrit Care* 2008; **9**: 352-356 [PMID: 18415031 DOI: 10.1007/s12028-008-9093-8]

143 **Berger C**, Schäbitz WR, Georgiadis D, Steiner T, Aschoff A, Schwab S. Effects of hypothermia on excitatory amino acids and metabolism in stroke patients: a microdialysis study. *Stroke* 2002; **33**: 519-524 [PMID: 11823663 DOI: 10.1161/hs0102.100878]

144 **Roslin M**, Henriksson R, Bergström P, Ungerstedt U, Bergenheim AT. Baseline levels of glucose metabolites, glutamate and glycerol in malignant glioma assessed by stereotactic microdialysis. *J Neurooncol* 2003; **61**: 151-160 [PMID: 12622454 DOI: 10.1023/A:1022106910017]

145 **Xu W**, Mellergård P, Ungerstedt U, Nordström CH. Local changes in cerebral energy metabolism due to brain retraction during routine neurosurgical procedures. *Acta Neurochir* (Wien) 2002; **144**: 679-683 [PMID: 12181701 DOI: 10.1007/s00701-002-0946-1]

146 **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]

147 **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]

148 **Bergenheim AT**, Roslin M, Ungerstedt U, Waldenström 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]

149 **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]

150 **Qureshi AI**, Ali Z, Suri MF, Shuaib A, Baker G, Todd K, Guterman LR, Hopkins LN. Extracellular glutamate and other amino acids in experimental intracerebral hemorrhage: an in vivo microdialysis study. *Crit Care Med* 2003; **31**: 1482-1489 [PMID: 12771622 DOI: 10.1097/01.CCM.0000063047.63862.99]

151 **Orakcioglu B**, Kentar MM, Schiebel P, Uozumi Y, Unterberg A, Sakowitz OW. Perihemorrhagic ischemia occurs in a volume-dependent manner as assessed by multimodal cerebral monitoring in a porcine model of intracerebral hemorrhage. *Neurocrit Care* 2015; **22**: 133-139 [PMID: 25052158 DOI: 10.1007/s12028-014-0027-3]

152 **Ottens AK**, Kobeissy FH, Golden EC, Zhang Z, Haskins WE, Chen SS, Hayes RL, Wang KK, Denslow ND. Neuroproteomics in neurotrauma. *Mass Spectrom Rev* 2006; **25**: 380-408 [PMID: 16498609 DOI: 10.1002/mas.20073]

153 **Mondello S**, Muller U, Jeromin A, Streeter J, Hayes RL, Wang KK. Blood-based diagnostics of traumatic brain injuries. *Expert Rev Mol Diagn* 2011; **11**: 65-78 [PMID: 21171922 DOI: 10.1586/erm.10.104]

154 **Pasinetti GM**, Ho L, Dooley C, Abbi B, Lange G. Select non-coding RNA in blood components provide novel clinically accessible biological surrogates for improved identification of traumatic brain injury in OEF/OIF Veterans. *Am J Neurodegener Dis* 2012; **1**: 88-98 [PMID: 22737634]

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