Serum biomarkers for predicting outcome after TBI
TBI – biomarkers

A biomarker, or biological marker, is in general a substance used as an indicator of a biological state. It is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. It is used in many scientific fields.

Biomarkers of recovery after brain injury:

In recent decades, researchers and clinicians have focused on specific markers of cellular brain injury to improve the diagnosis and the evaluation of outcome. Many proteins synthesized in the astroglia cells or in the neurons, such as neuron-specific enolase, S100 calcium binding protein B, myelin basic protein (MBP), creatine kinase brain isoenzyme, glial fibrillary acidic protein (GPAP), plasma desoxyribonucleic acid, brain-derived neurotrophic factor, ubiquitin carboxy-terminal hydrolase-L1, ectoenzyme CD 38 (cluster of differentiation 38) and neuron specific endolase (NSE), have been proposed as potential markers for cell damage in central nervous system.
Biomarkers of recovery after brain injury:

- fMRI
- PET
- genetic markers of ApoE Gene
- ectoenzyme CD 38 (*cluster of differentiation* 38)
- serum S100B
- myelin basic protein (MBP)
- neuron specific endolase (NSE)
- glial fibrillary acidic protein (GPAP)
Predictors of recovery after TBI

- The clinical condition
- Neuroimaging
- Laboratory
- Biomarkers
- Predictors of improvement of motor function
- Predictors of cognitive improvement
Predictors of recovery after TBI

- **Clinical condition**
  1. Age of the patient
  2. Loss of consciousness
  3. Initial neurological deficit
  4. Post-traumatic amnesia

- **Neuroimaging**
  - CT
  - MRI
  - PET
Predictors of recovery after TBI

- Serum biomarkers
  - glial markers
  - neuronal markers
- Coagulation factors
- Inflammatory markers and other
- Predictors of improvement of motor functions
- Predictors of improvement of cognitive functions
Biomarker – what is that?

- A **biomarker** is a characteristic feature of bioavailability, which can be objectively measure and is an indicator of normal biological and pathological processes or answers for pharmacological therapeutic intervention.

TBI – biomarkers

Biomarkers of recovery after TBI:

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The clinical significance of serum S-100 protein, a protein released by damaged brain tissue, was assessed in patients with acute ischaemic or haemorrhagic stroke and matched controls. Serum S-100 protein concentration was significantly elevated in patients with ischaemic stroke [median (SQR): 0.27 (0.90) microgram/L, n = 68] and haemorrhagic stroke [0.43 (0.23 microgram/L, n = 13] compared to controls [0.11 (0.03) microgram/L, n = 51, P < 0.0001].

Although patients with haemorrhagic stroke had higher serum S-100 concentrations compared to patients with ischaemic stroke, this was not quite statistically significant. Serum S-100 concentrations were related to infarct size, large (total anterior circulation) infarcts concentrations having the highest [0.40 (0.22) microgram/L], and small vessel ('lacunar') infarcts concentrations having the lowest [0.20 (0.60) microgram/L, \( P < 0.0005 \)] concentrations.
S-100 protein concentration was also significantly related to clinical outcome at three months measured using three disability and handicap scales (n = 81): modified Barthel index (rs = -0.285, P = 0.01), modified Rankin score (rs = 0.313, P = 0.004) and Lindley score (rs = 0.262, P = 0.018) with high values associated with poor clinical outcome. Similarly high values of serum S-100 protein were observed in patients who died or were discharged to an institution [median (SQR): 0.63 (0.29) microgram/L and 0.37 (0.13) microgram/L, respectively compared to those who were discharged home [0.26 (0.11) microgram/L, P = 0.13].
Serum S-100 protein, relationship to clinical outcome in acute stroke. cont.

This study suggests that measurement of serum S-100 protein could be a useful prognostic marker of clinical outcome in acute stroke. Whether S-100 concentrations can be altered by therapeutic intervention in acute stroke remains to be elucidated.

Neuron-Specific Enolase (NSE)

Anand N., Stead L.G. Neuron-Specific Enolase as a Marker for Acute Ischemic Stroke: A Systematic Review.

Twelve studies (including 597 patients) satisfied the entry criteria for this qualitative analysis. Results: In 4 studies, time of onset of stroke symptoms was compared with time of first detectable NSE levels, which ranged from 4 to 8 h after stroke onset. In 7 studies, NSE levels increased with increased size of stroke, but in 2 studies there was no correlation. In the 2 studies that compared stroke severity with NSE levels, high NSE levels generally indicated worse outcome, but at low NSE levels the results were equivocal. In 7 studies, functional outcome at hospital dismissal and follow-up was compared with NSE levels; in 4, there was no correlation.

Anand N., Stead LG. Cerebrovasc Dis 2005;20:213-219
Neuron-Specific Enolase (NSE)

- Anand N., Stead L.G. Neuron-Specific Enolase as a Marker for Acute Ischemic Stroke: A Systematic Review.

- Conclusions: The serum level of NSE does seem to be higher in stroke patients than in controls, and it does appear to correlate with volume of infarcted tissue. However, it does not appear to correlate with functional outcome, and its relationship to stroke severity is unclear. This may be explained at least in part by the disparity in sampling times because the NSE level has been shown to peak after 24 h in most studies. Hence, the more delayed the sampling, the greater the correlation with stroke severity.
Neuron-Specific Enolase (NSE)

- Selakovic V. et al. The increase of neuron-specific enolase in cerebrospinal fluid and plasma as a marker of neuronal damage in patients with acute brain infarction.

- The results showed a significant increase of NSE concentration within the first seven days in patients compared to the controls (2.838 ± 0.504 ng/ml CSF and 4.479 ± 0.893 ng/ml plasma). A significant correlation was found between NSE concentration and infarction volume and the degree of neurological and functional deficit both in the CSF (r = 0.828, r = 0.735, r = 0.796; p < 0.001) and in plasma (r = 0.810, r = 0.681, r = 0.783; p < 0.001). The results suggest that an early determination of this marker in CSF and plasma in patients with BI could be a valuable diagnostic factor.

Glial fibrillary acidic protein (GFAP)

- is a biomarker candidate indicative of intracerebral hemorrhage (ICH) in patients with symptoms of acute stroke. GFAP is released rapidly in the presence of expanding intracerebral bleeding, whereas a more gradual release occurs in ischemic stroke.

Plasma GFAP analysis performed within 4.5 h of symptom onset can differentiate ICH and ischemic stroke. Studies are needed to evaluate a GFAP point-of-care system that may help optimize the prehospital triage and management of patients with symptoms of acute stroke.

IL-1 beta

- a cytokine with pro-inflammatory and thrombostic, produced by endothelial cells, macrophages, microglia, keratinocytes, chondrocytes, Langerhans cells, glia cells, mesangial cells and neurons.
IL-1 beta

- IL-1beta
- In the blood and CSF of patients with acute ischemic stroke were observed elevated levels of IL-1.
- Increased levels of cytokines in the serum and CSF do not correlate with brain infarct volume, but is correlated with the severity of neurological symptoms.

Biomarkers specific for TBI

- Glial markers:
  - protein S 100B
  - Coenzyme CD 38
    (cluster of differentiation 38)
  - GFAP
  - UCH-L1
  - SBDP145
Biomarkers specific for TBI

1. **Serum S 100B**

100 patients with a similar severity of brain injury, S100B protein levels measured in 24-hour time point after injury is significantly associated with results of treatment, but below the level 0.53μgL⁻¹ there are no good prognostic features.

Biomarkers specific for TBI

2. Coenzyme CD 38 (cluster of differentiation 38)

Coenzyme CD38 was given to mice with TBI and assessed its impact on cognitive and neurobehavioral using the Neurological Severity Score (NSS) and object recognition test. It was found that CD38 plays a beneficial role in recovery of mice after TBI and that this effect is partially microglial response.

Biomarkers specific for TBI cont.

3. **GFAP** - Glial Fibrillary Acidic Protein
4. **UCH-L1** – final result of ubiquitin C hydrolase
5. **SBDP145 αII** – product of alfa II decay of spectrin

Biomarkers specific for TBI


Biomarkers specific for TBI

- **Calcagnile O.** et al. S100B levels are affected by older age but not by alcohol intoxication following mild traumatic brain injury. Scand J Trauma Resusc Emerg Med. 2013 Jul 6;21(1):52. [Epub ahead of print]


Biomarkers

◆ Janus