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THE EVOLVING MANAGEMENT OF TRAUMATIC BRAIN INJURY WITH NEURONAL BIOMARKERS OVER THE LAST DECADE.

Medical Science

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KEYWORDS

INTRODUCTION AND BACKGROUND:

Traumatic Brain Injury (TBI) is a fatal injury and often these patients would require attention and treatment in the intensive care unit (1). Diagnosis of TBI depends on clinical findings and relies on imaging modalities like CT and MRI (2). These may have some limitations particular to time sensitivity, capable of detecting extent of injury and intracranial hypertension. This leads to delay in treatment or surgical intervention. Hence, An ideal biomarker in ICU setup enables sensitivity and allows for clinical applications in the diagnosis, staging, prognosis, and treatment of disease (3). Some of the brain biomarkers which are studied include neurofilaments, tau protein, microtubule-associated protein 2, myelin basic protein, neuron-specific enolase, S-100β, glial fibrillary acidic protein, ubiquitin c-terminal hydrolase-L1, alpha-II spectrin breakdown product, and microRNA. Unfortunately, the use of biomarkers in current clinical practice is limited.

Biomarker assessment: Evaluation of biomarkers helps in diagnosing the progression of disease in less time compared to neuroimaging. However, faster analysis of biomarkers is required in especially ICU patients where every second counts the life of the patient. Keeping this in mind, some companies have developed point of care devices for some biomarkers where the analysis can be done bedside within a few minutes which would help the patients treatment and economically also. Hence, developing point of care devices for biomarkers of TBI are a major necessity. With the exponential growth in biomarker research, our expanding knowledge will translate into improved decision-making and outcomes.

Choosing the right biomarker at the right time: TBI is a devastating injury, and it progresses from primary injury to secondary injury within a few minutes to days. There are many biomarkers available in literature depending on the time of release after trauma, area of damage, biomarkers released long term (post trauma) etc., Hence, choosing a biomarker at the appropriate time point is very crucial, and it will help in treating the patient precisely.

Biomarkers of Neurotrauma:

Neuronal biomarkers:

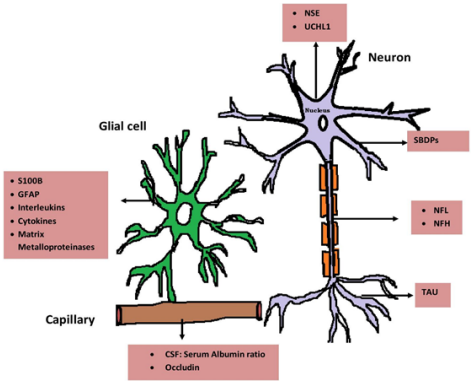
Ubiquitin carboxy terminal hydroxylase L-1 (UCHL-1): UCHL1 is an enzyme with protease activity and specifically present in neurons. It has a half life of 7-9 hours after severe TBI and can be detected in the CSF and serum of TBI patients. Rapid detection method of UCHL-1 was developed and proved 100% sensitivity and 100 % specificity (4). The levels of UCHL1 helps to differentiate between injured and non-head injured patients and higher levels indicate the need for neurosurgical intervention (5).

Neuron specific enolase (NSE): NSE is an enzyme predominantly found in the cytoplasm of neurons. It does not secrete in normal conditions unless there is damage to the axons, NSE is upregulated to maintain homeostasis (6). It has a half life of 24 hours in serum (7). A study in 2015 has shown that NSE levels were elevated in TBI patients hence it can be used as a screening tool (8). A meta-analysis by Cheng et al. in 2014 has shown that there is a significant rise in serum levels of NSE in adult patients with moderate to severe traumatic injuries (6) whereas in other meta-analysis done in 2017 in children has reported the performance of NSE level in prediction of unfavorable outcome in children with TBI is in a moderate level (9). The POC immunosensor shows excellent performance for NSE detection with a remarkable detection limit, good stability, and wide linear range, and exhibits a good correlation with enzyme-linked immunosorbent assay (10). Therefore, using this marker may be an accurate and sensitive tool for assessing brain injury on a molecular level before occurrence of extensive injuries.

Astrocyte biomarkers:

Glial fibrillary acidic protein (GFAP): GFAP is a filament protein concentrated in the astroglial cytoskeleton. GFAP is specific to brain tissue and is released after astrocyte death, making it an ideal candidate marker for brain injury patients (11). It has a half life of 48 hours after injury(12). A study has reported that Elevated serum GFAP on admission and over a range of days post injury was a strong predictor for death and unfavorable outcome at 6 months (13). Increased levels of GFAP was observed in abnormal CT compared to normal CT after mTBI and can also predict patients who required neurosurgical intervention (14). GFAP can also distinguish between head injured and non head injured trauma patients with a rise in levels within 1 hour after trauma (15). GFAP, measured on a POC platform prototype assay, is a sensitive blood-based biomarker with high discriminative ability to predict intracranial injuries on CT scan in patients with TBI (16).

S100 calcium-binding protein B (S100b): S100β is a calcium-binding protein highly abundant in the astroglia cells of the brain. It has a half life of 60-120 min (17). S100b can detect CT abnormalities with increased levels in blood (18), (19), (20). The values of s100b were decreased when the samples were collected more than 6 hours post injury (21). These studies have shown that s100b is a promising biomarker of TBI. But it has some limitations due to its extracerebral sources. It has poor sensitivity (61%) and specificity (77%) as it is elevated in patients with fractures and other extracranial injuries (22), (23).



Axonal biomarkers:

Tau protein: Tau protein is localized specifically in neuronal axons (24). Tau increases within an hour and has a half-life of around 10 h in plasma (25). Tau proteins were found to be accumulated in the brain and CSF of patients who had a single head trauma decades earlier. This can be a diagnostic tool for neurodegenerative diseases like Alzheimer's (26). Serum levels of Tau increase with increase in severity, hence DAI patients have higher levels compared to mTBI (27) and can be useful in differentiating patients at high risk for mTBI (28). The levels of cleaved tau protein is elevated in CSF compared to serum which correlates with traumatic lesions on CT. This is likely to limit its usefulness in the diagnosis of mTBI in the ED (29).

Spectrin breakdown product (SBDP): α-II-spectrin may be a cytoskeletal protein that's a substrate for the calcium-activated cysteine proteases calpain and caspase-3. Calpain and caspase-3 cleave α-II-spectrin to generate α-II-spectrin breakdown products (SBDPs) (30). SBDPs peak at 6 hours and keep elevated at 24-72 hours post injury (31). Cerebrospinal fluid (CSF) and blood SBDPs are being evaluated as novel biomarkers for TBI (32). A study proposed the existence of calcium dyshomeostasis and its consequent activation of calpain and caspases in aging cells/brain and age-related neurodegenerative diseases including Alzeimers, Parkinson's Disease. Hence, SBDPs may serve as novel biomarkers for chronic neurodegenerative diseases (33).

Neurofilament: Neurofilaments are intermediate filaments present in the cytoplasm of neurons. The elevated l;evels of NFL was observed immediately after injury for 12 days (34). mTBI patients exhibited a significant increase in the serum levels of hyperphosphorylated neurofilaments H (p-NfH) on days 1 and 3 (35), however, a 6-hour lag between the onset of injury and the rise in blood levels of p-NfH may limit the usefulness of this biomarker as an aid to diagnosis in the acute setting (36). NfL protein levels have been increased in TBI patients compared to non TBI (37). NF-L could separate survivors from non-survivors, and the initial levels were predictive of 12 months of adverse clinical outcomes (38).

The exponential growth in biomarker research, development of POC assay methods will translate into improved decision-making and outcomes, has the potential to improve ICU patient care. The future development of POC devices for the biomarkers of TBI has potential to minimize variability and maximize benefit. Through thoughtful study design and collaboration, it will surely transform and shape the future of medicine.

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