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Biomarkers in acute brain trauma: A narrative review

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ABSTRACT

Biomarkers have been used to diagnose, prognose, evaluate, and identify the severity and outcomes in traumatic brain injury (TBI) patients. This study explored if it is possible to predict the outcome of TBI patients by estimating the biomarkers in cerebrospinal fluid and serum. We searched data bases and literature about biomarkers, and found forty epidemiologic studies from 92 potentially relevant articles. However, limited data are available about postanoxic encephalopathy. It showed that presently, neurofilament, S100B, glial fibrillary acidic protein, and ubiquitin carboxyl terminal hydrolase-L1 seemed to have the best potential as diagnostic biomarkers for distinguishing focal and diffuse injury, whereas C-Tau, neuron-specific enolase, S100B, glial fibrillary acidic protein, and spectrin breakdown products appear to be candidates for reflective biomarkers of TBI. Point-of-care biomarkers are needed in TBI which is one of the most important additional risk factors in road traffic injuries. In a holistic approach, more researches about biomarkers of TBI are required. These biomarkers are very useful for treatment of patients with TBI.

1. Introduction

Technical advancements and multipronged researches about biomarker molecules in the last century are helpful for the early diagnosis and prognosis of morbidity, mortality and disability. A large population including athletic and military staffs are at higher risk of repetitive injury resulting in second impact syndrome or chronic traumatic encephalopathy[1,2]. Neurotrauma particularly

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traumatic brain injury (TBI) is a worldwide public health problem and a major cause of death especially in rural areas in low- and middle-income countries. U.S. Food and Drugs Administration has only approved two biomarkers for clinical use of TBI, but there is still a lot of biomarkers that could be helpful for the medical practice especially in setting with poor resource[3-8]. TBI has been labelled as a "silent epidemic" affecting both the developed and the developing nations[9]. The objective of this study is to make a narrative review of some biomarkers and to explore their correlation with TBI in clinical practice.

2. Methods

We attempted a comprehensive, annotated assembly of survey results by exploring various resources, including published surveys, field studies, meeting presentations, personal communications, *etc*. The search terms were selected based on combinations of MeSH terms and empirical taxonomies about biomarkers of TBI. Firstly, reports of biomarkers in TBIs among literature sources were sourced; Secondly, reports containing 'biomarkers' impacting diagnosis and prognosis of TBIs were identified and collated; Thirdly, globally published information from apex bodies *e.g.* WHO, Centre for Disease Control and Prevention, Atlanta USA and others were given due weightage for their multi-authored multi-disciplinary authenticity. Finally, we identified 40 research publications from 92 potentially relevant articles.

3. Discussion

TBI is a traumatically-induced brain injury known as a spectrum disorder due to traumatic events and a range of physical external forces (*i.e.* explosive blast shock wave, head and neck injuries occurred during falls, traffic road accidents violence, and even by head blows and concussions in contact sports), which produce structural brain injury with physiological disruption[3,9]. Even in 2018 despite the advances in medical and surgical treatment, TBI is still a critical global public health problem especially in rural areas of low and middle -income countries. WHO considers TBI as one of the major causes of death and disability by 2020[7,8,10-14]. TBI is one of the leading global causes of death and long-term disability with an estimated incidence of 54 to 60 million persons per year[5,6,15]. The TBI is classified as mild TBI (mTBI) (synonym of concussion, that is a non-penetrating injury), moderate TBI, and severe TBI (sTBI) (that could be a penetrating injury). Each one represents a special medical challenge considering the management and its respective complications and sequelae[3,16,17].

The biomarkers are biomolecules which are found and measured in biofluids and tissues. Biomarkers have many characteristics, one of them is to be present in the biofluids (sensitivity) but never be present in absence of the pathological damage process (specificity). As mentioned before, biomarkers provide information about the basal status, the prognosis of complications and outcomes possibilities[16,18]. The ideal biomarkers should be cost-effective with a high sensitivity and specificity. They can be used to stratify the severity of injuries, report injury mechanism and progression, and predict outcomes and complications due to the progression monitorization and treatment response[13,18]. The sample must be acquired using a minimally invasive method and could be widely measured. They play important roles in neuroimaging referrals, identification of various types of parenchymal and blood-brain barrier injuries, *etc*[13,18].

A lot of different biomarkers that are measured in fluids like serum have been approved and used during pathological processes of many diseases, but for TBI the FDA have only approved two biomarkers ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1) biomarker along with glial fibrillary acidic protein (GFAP) for clinical use. An ALERT-TBI study selected 1 288 patients with TBI, draw blood-samples 2 or 3 h after the injury, and measured the samples by combined test with UCHL-1 and GFAP (327 and 22 pg/mL, respectively as a standard prespecified cut-off). The result demonstrated high concentration in draw[4,19,20]. The biomarkers of TBI may be classified in two types, one demonstrating astroglia injury like GFAP and S100 calcium-binding protein B (S100B), and the other one showing if there is a neuronal injury like UCH-L1, neuron specific enolase (NSE) and proteins (Tau). These biomarkers are elevated during acute phase of TBI. These biomarkers may be affected sometimes, and demonstrate false positive results when the biomarker is measured in serum but is also expressed in other tissues and organs, which present injurys such as polytrauma or a pre-existing disease (heart, liver, demyelinating and kidney disease)[3,13,20].

Biomarkers of TBI including UCH-L1, GFAP, S100B, Tau, NSE, C-reactive protein (CRP), creatine-kinase brain isoenzyme (CK-BB) and matrix metalloproteinase-2 (MMP-2) can be measured in cerebrospinal fluid (CSF). The blood brain barrier can block the proteins flux, but when this barrier suffers from damage these proteins may be found in plasma in low levels. It is reported that S100B and GFAP have potential as differentiation indicators of mTBI and sTBI and as peripheral markers with predictive value[20]. Alpha-II-spectrin breakdown products in CSF from adults with sTBI have shown significant relationship with severity of TBI and clinical outcome[21-23].

3.1. UCH–L1

UCH-L1 is a neuronal cytoplasmic enzyme. It has an especial role in the ATP-dependent proteasome pathway for the elimination and the ubiquitination of proteins destined for this pathway, and can removes the oxidized and misfolded proteins glut[24]. The UCH-L1 can be used for neuronal injury. However, it is not a central

nervous system specific protein because it is also expressed in endocrine cells, endothelial cells, aortic endothelium, muscle, and a few tumours cells. Despite its presence in other tissues, UCH-L1 is highly expressed in CSF and serum[24,25]. Due to the abundance of this biomarker in neuronal tissue and CSF it was used as histological neuron marker to discriminate patients with head injury from patients without head injury due to trauma. It is reported that patients who suffer from head injuries with a consequent intracranial lesion had higher levels within the first 4 h (if it is detectable in the first hour), and the levels are higher in patients who required surgical management. It demonstrated the UCH-L1 has association with injury severity and in-hospital prognosis of mortality and clinical outcomes[25-27]. Before the ALERT study, it was considered that because the increased levels related to the acute phase of the TBI, combination with serum GFAP can improve its correlation with TBI injury severity and predictive value[28]. It is a good biomarker for diagnosing of TBI and intracranial lesions, and can differentiate injured TBI from non-injured TBI when GCS is altered by any substance due to unclear cause[3,4,9,16,29].

3.2. GFAP

GFAP is a monomeric intermediate filament protein that is mainly expressed in astrocytes because of its association with the astroglia cytoskeleton[30]. Its increased level in response of mTBI indicates astroglia injury. In 1999, it was measured for the first time in human blood-samples. It is also detectable in CSF, and more sensitive than S100B as identifying intracranial lesions. It has been found to be related to lesions detected by CT-scans for mTBI and moderate TBI[31,32]. It is also reported that even in minor head injury, GFAP and S100B still show a minimum increased level in CSF[30-32]. Increased concentration level of GFAP is associated with bad prognosis outcome, such as vegetative and other severe disability states even 6 months after sTBI[1,2,4,9,10,16-18,29,30,33].

3.3. S100B

S100B is the most studied biomarker of all TBI types (more than 300 hundred studies), and it is potential biomarker of silent TBI. It is an intracellular calcium binding protein and is abundant in neurons and astroglia produced by astrocytes. However, it is not a specific biomarker because it might be increased in response to other type of traumas without any TBI (*i.e.* muscle injury and polytrauma) and can be found in other cells like chondrocytes, Schwann cells, exocrine cells, melanoma cells, and adipocytes cells[34-36]. Because of this characteristic, it is not used to differentiate the cause of mTBI. For this reason, its biomarker specificity is still unclear[2,16,37,38]. The normal levels of S100B are approximately 5 ng/mL and has two increased peaks. As mentioned above, the increased serum level is associated with bad outcomes, poor prognosis and high mortality[3,18]. The second peak suggests that there is an on-going damage in the astroglia caused by excitotoxicity and inflammation, in the other way, low initial levels without a second peak is related with good prognosis and outcome[3,18]. Increased initial level of S100B is associated with higher incidence of some adverse events like the transient impairment of cognition or the post-concussion syndrome after TBI. Due to this reason, its use is limited as a marker of disease progress, but it is associated with neurologic and psychological disturbance caused by mTBI[3,9,29,33].

3.4. NSE

It has been reported that the use of NSE is promising as a TBI biomarker, as it is considered as a potential neuronal injury biomarker[39-42]. High level of NSE is associated with higher mortality and poor outcomes and sequelae even 6 months after the injury[39]. Patients with sTBI have higher levels of NSE. The CSF concentration is proportional to the severity, and these levels can be increased up to 72 h post injury, which is associated with poor outcome prognosis[9,18,39,42,43].

3.5. Tau

Tau protein is an intracellular protein which is highly concentrated in thin non-myelinated axons in cortical interneurons and has an especial role in the axoplasmic anterograde transport and microtubule bundles[44,45]. Tau protein concentration in serum and CSF is increased as a consequence of TBI, and this increase is related with gray matter injury (axonal damage). Early elevated CSF Tau level in sTBI patients has been utilized to predict elevations in intracranial pressure and it is found that the elevated level is associated with poor clinical outcome[44,45]. As an amyloid and gray substance damage related protein, the elevated concentrations of Tau might be used to differentiate patients with intracranial injury from those who do not suffer any injury. Even 90 d after the traumatic event, the Tau protein still could be elevated[44-47].

3.6. Cleaved–tau

Cleaved-tau is a potential biomarker of silent TBI, and can lead to the proteolytic cleavage of tau protein[48,49]. It is reported that in both mTBI and sTBI, cleaved tau protein levels in serum were significantly higher as compared to the controls in prospective study[49]. More studies are required to identify its role as a diagnostic and prognostic marker with multicentric larger sample[48,50,51].

3.7. CRP

CRP is a sensitive biomarker but with a low specificity, and plays an important role in systemic pathologies, prediction, prognosis, and diagnosis of trauma, burns, infections, cancer, heart diseases, and some other inflammatory processes[52,53]. In TBI patients, increased

level of CRP is related to the severity, secondary pathologies and sequelae, and the post-TBI physiologic and cognitive dysfunction[38-40,54-56].

3.8. Creatine–kinase brain isoenzyme (CK–BB)

CK-BB is a CK brain isoenzyme, which is an isoform of CK in astrocytes. It plays an important role in transferring energy in organs with a large energy demand like the brain and neural tissue by catalyzing the ATP phosphate groups in CK. It also has been found in large intestine and prostate tissue in lower concentrations[57-59]. CK-BB is released in response to acute TBI especially as consequence of blast-induced trauma, and brain tissue injury due to cardiac arrest, strokes, intracranial hemorrhage, *etc*, but it returns to normal levels in a short time period[38,41-43].

3.9. Myelin basic protein (MBP)

MBP is part of oligodendrocytes extrinsic membrane found abundantly in CNS and Schwann cells in the peripheral nervous system. MBP concentration rise in CSF and serum of patients who suffer from TBI or have demyelinating disorders. MPB has been measured in patients with acute TBI and its increased level is related to TBI severity. However, its expression in peripheral nerves is not specific and does not have predictive or prognostic value due to the compromise of the peripheral nerves in DAI resulting from TBI and other demyelinating pathologies like multiple sclerosis[2,3,60,61].

3.10. MMP–2

MMP-2 is a zinc-dependent protease and a type IV collagenase. It is highly expressed in brain tissue along with MMP-9, and it is the result of the secretion and production of the infiltration of neural, endothelial and inflammatory cells[62]. It is related to focal cerebral ischemia because of macrophages phagocytosis and apoptosis secondary to the inflammatory response[38,63,64].

3.11. Surrogate biomarkers

Relatively few studies have reported the relation between laboratory parameters on admission and outcome[65-68]. However, among the routine laboratory work, blood sugar estimation is important for outcome of TBI[65]. Yet, there is no consensus on optimal and safe glycaemic target during intervention of TBI patients. It varies among individuals at different time points during the clinical course. As resource utilization becomes been increasingly scrutinized, whether any laboratory test battery should be recommended as a “routine protocol” across the entire spectrum of trauma patients remains questionable[65].

4. Conclusion

User-friendly biomarkers are required in daily medical practice for treatment of patients with TBI. S100B is one of the most studied biomarkers but its clinical utility is still need to be explored. For best possible benefits for the diagnosis and prognosis of TBI victims at the primary health care levels, we have to improve the simplicity of use and speed of identification of these biomarkers as a point-of-care tool. To sum up, the most common biomarkers of TBI are NSE and S100B, which are commonly released into the CSF and then into the systemic circulation after different types of neuronal damage.

Conflict of interest statement

The authors declare that we have no conflict of interest.

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