Clinical Case Reports International

Research Article
Published: 11 Nov, 2022

Pathological Aspects of Traumatic Brain Injury: Role of Biomarkers and Current Drug Therapy

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Abstract

Traumatic Brain Injury (TBI) is the most common cause of illness and mortality worldwide, affecting millions of people. It is brought on by car accidents, falls, and assault. The primary insult of TBI occurs at impact, which leads to subsequent damage and a cascade of cellular processes. Other variables that contribute to subsequent TBI insult include excitotoxicity, neuroinflammation, apoptosis, necrosis, mitochondrial malfunction, and lipid peroxidation. Secondary damage during TBI must be treated in order to avoid its development and additional neurodegeneration. However, no specific drug is available to prevent secondary insult in TBI, but alternative medications such as anti-inflammatory, diuretic, and corticosteroids are preferred. There are various diagnostic markers used to confirm the injury stage and its progressions such as HMGB1, Tenascin-c, S100B proteins, ghrelin, UCHL-1, and others. We investigated the causes of TBI, the prognostic relevance of biomarkers, and the current treatment strategies in this review.

Keywords: Traumatic brain injury; Biomarkers; HMGB1; UCHL-1; Diagnostic techniques

Abbreviations

TBI: Traumatic Brain Injury; HMGB1: High Mobility Group Box-1; S100B: Calcium Binding Protein Tenascin-c Ghrelin; UCHL-1: Ubiquitin C terminal Hydroxylase; NLRP1: Nucleotide-Binding Oligomerization Domain; GCS: Glasgow Coma Scale; ROS: Reactive Oxygen Species

Introduction

Traumatic Brain Injury (TBI) is a significant health problem that affects millions of people worldwide. In India, the bulk of TBI cases (60%) are caused by car accidents, falls (20% to 30%), and violence (10%), among other things [1]. According to the Centers for Disease Control and Prevention (CDC), 1.7 million individuals in the United States suffer from TBI each year, with an additional 5.3 million living with TBI-related disability [2]. It is one of the most common causes of morbidity, death, and medical complications in modern countries; around 70% to 90% of TBI are moderate, and only a tiny fraction of individuals are sent to the hospital as a result, The National Institute of Health (NIH) declared in 1999 that mild TBI is a major health problem because majority of peoples suffers from post- traumatic related disabilities such as retrograde amnesia, migraine, behavioral changes, lack of attention, and neurological problems such as Alzheimer's disease and Parkinson's disease, the probability of PD occurrence after TBI has been increased [2]. The process behind TBI is the transmission of external stresses to brain tissue, which can induce brain damage. The main damage is produced by an impact and contusion, laceration, and diffuse axonal injury as a result of shearing, tearing, or stretching. The severity of injury is determined by the originating forces as well as the location, direction, and amount of the force [3].

According on the location of the damage, it can be either diffuse or focal. Focal brain injuries affect a specific part of the brain, but diffuse brain injuries can penetrate deep and impact various parts of the brain depending on the severity. Because they are caused by penetrating foreign bodies that can occasionally be left there and seriously impact the brain, skull, and cranial cavity, focal brain injuries can be acute or blunt. Similarly, diffuse brain injury is classified into two types: Cerebral contusion and diffuse axonal injury [4]. Diffuse axonal injury will penetrate inside the skull, causing the foreign body to remain inside the brain; this is also known as penetrating injury, and it can cause further damage inside the brain and ultimately cause death [5]. Whereas in the case of blunt focal injury, external forces play an important role, when a high acceleration force strikes the head, the brain is accelerated further, moving inside the cranial cavity and impacting on the opposite side of the skull, causing further injury on the opposite side of the skull [6]. Blunt damage to the rear of the

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Received Date: *04 Oct 2022*
Accepted Date: *07 Nov 2022*
Published Date: *11 Nov 2022*

Citation:
Kaushik A, Singh S. Pathological Aspects of Traumatic Brain Injury: Role of Biomarkers and Current Drug Therapy. Clin Case Rep Int. 2022; 6: 1420.

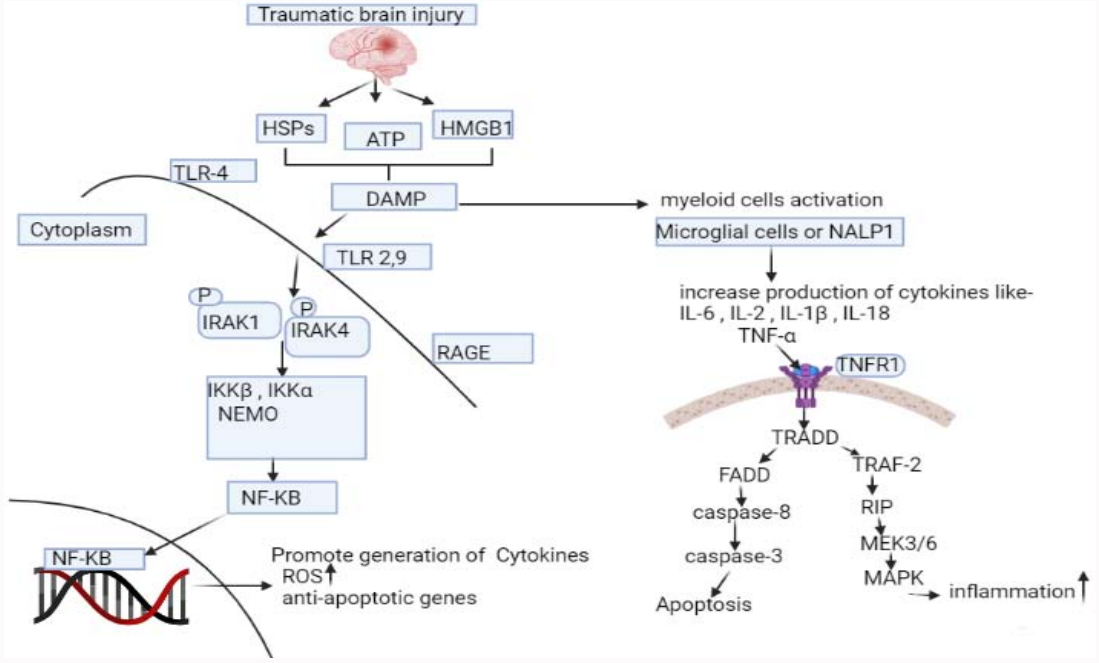

Figure 1: Role of inflammation and various cellular events occurs in primary injury.

head, speeding the brain and smashing within the foot's skull. Whereas diffuse brain damage is further classified into two types: Cerebral contusion and diffuse axonal injury. In the case of cerebral contusion, cerebral refers to the brain, and contusion refers to a bruise. When any tissue is damaged, the small blood vessels are disrupted, causing blood to leak out into the tissue spaces, so a contusion or a bruise is simply bleeding from small blood vessels, resulting in blood in the tissue spaces [7]. However, in the event of diffuse axonal injuries, when an external force is applied to the head, the brain suffers from acceleration and deceleration, causing the brain's top section to move in both directions, but the brain stem part remains constant or fixed in the same position and due to the movement of the upper portion axons present in the brain stem are damaged because these axons are very sensitive to shearing, they got injured that means consciousness might still be generated because consciousness is generated from the brain stem, but when axons are injured TBI injured patient suffered from impaired consciousness and became confused [8].

TBI's pathogenic process comprises both primary and secondary brain damage. The Primary brain injury is also called phase 1 injury occur within minutes of primary insult which damage meninges, glial-limitans, and parenchyma cells of the brain such as ATP (Adenosine Triphosphate), HMGB-1. These signals binds with the PAMP (Pathogen-Associated Molecular Pattern) or DAMP (Damage-Associated Molecular Pattern), Inflammation is initiated by PAMP or DAMP [9]. They induce inflammation to eliminate infection or for healing wounds. An example of DAMP or PAMP is TLR (Toll-Like Receptor) and Purinergic receptor that induce immediate activation of resident myeloid cells like (Microglial cells and NALP1) that promote the generation of IL-1β and IL-18. NF-κB (Nuclear Factor Kappa B) is also activated which further induce immunological response and translocate to the nuclei of cells and persuade immunological program involving cellular proliferation and release inflammatory marker such as chemokines, cytokines, NO (Nitric Oxide) and ROS (Reactive Oxygen Species) [10]. NF-κB play important role as anti-apoptotic agent, inhibit the apoptosis in TNF pathway. when TNF-α molecule bind to its TNFR1 receptor and initiate the apoptosis process by increasing the activity of SODD (Silencing of Death Domain), but if SODD is not activated or TNF-α unable to bind with its receptor then TRAF-2 (TNF Receptor-Associated Factor) is recruited on the SODD site due to which apoptosis process is skipped and we will move towards the NF-κB pathway, TRAF (TNF-Receptor Apoptosis Factor) complex further recruits IAP protein (Inhibitor of Apoptosis Protein) and binds with the TRAF, further TRAF also recruits rip protein(receptor-interacting protein kinases), this IKK (Inhibitor of nuclear factor Kappa-B subunit alpha) protein has kinase activity. This IKK molecule phosphorylate Inhibitor of Kappa B (IK-BA) due to which NF-κB dislocated from IKBA and NF-κB molecule become free and able to enter inside the nucleus, drives the expression of pro-inflammatory genes and anti-apoptotic genes and cytokines production (Figure 1) [11].

As we detect secondary brain damage, it frequently progresses from hours to months or years. It refers to the full set of phases or stages of cellular, tissue, chemical, or blood vascular alterations in the brain that may exacerbate brain tissue damage. Variables such as excitotoxicity, mitochondrial dysfunction, oxidative stress, neuroinflammation, axon degeneration, apoptotic cell death, and lipid peroxidation will all contribute to the secondary insult [12]. It has been shown that glutamate and aspartate assist to generate cellular alterations during secondary damage. Excess glutamate after TBI is caused by a lack of glutamate re-uptake owing to glutamate transporter malfunction. Furthermore, some studies show a 40% reduction in the expression of astrocytic sodium-dependent glutamate transporters GLAST and GLT-1 within 24 h of TBI, resulting in a considerable decrease in glutamate resorption. These are excitatory amino acids that play a crucial role in the activation of both ionotropic Glutamate Receptors (iGluRs) and metabotropic Glutamate Receptors (mGluRs) [13]. The N-Methyl-D-Aspartate (NMDA) receptor and -Amino-3-hydroxy-5-Methyl-4-isoxazole Propionate (AMPA) receptors are examples of

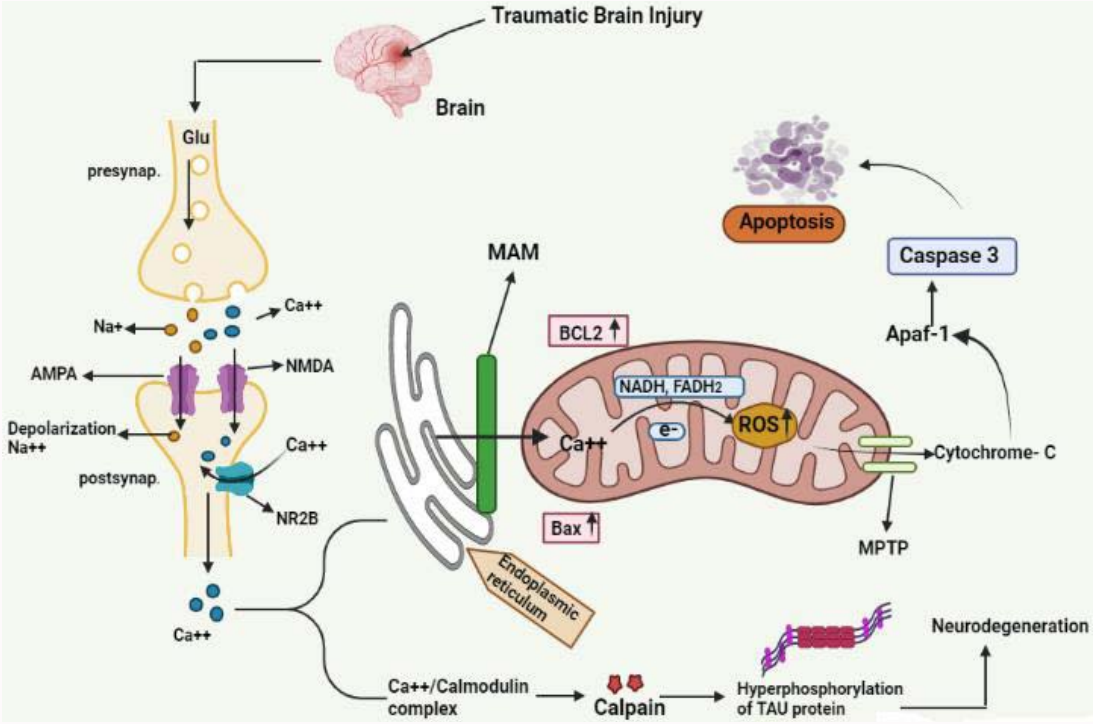

Figure 2: Role of glutamate in TBI and its role in apoptosis and neurodegeneration.

(iGluRs), which are ligand-gated ion channel receptors that enable the inflow of Na+, k+, and Ca2+ upon binding to glutamate, causing membrane depolarization in neurons. Excess glutamate activates both AMPA and NMDA receptors, affecting ion homeostasis in postsynaptic neurons by increasing calcium and sodium ion influx. Glutamate activation of NMDA receptors increases the formation of Reactive Oxygen Species (ROS) and Nitric Oxide (NO), which can trigger secondary brain damage [14] (Figure 2).

Accumulation of Ca2+ and ROS impairs mitochondrial function, which is one of the defining events of TBI because it causes severe metabolic and physiologic abnormalities, ultimately leading to cell death. Excess calcium and iron influx into the mitochondria cause the formation of ROS, inhibit the synthesis of ATP, and depolarize the mitochondrial membrane, resulting in the breakdown of the electron transport chain and disruption of the oxidative phosphorylation process, affecting the restoration of metabolic reactions for cell survival and calcium cycle regulation [15]. When the inner membrane protein Adenine Nucleotide Translocator (ANT) interacts to cyclophilin D, the conformational shift causes the mPTP to open, increasing the inner membrane permeability [16]. TBI contains particular proteins that target mitochondrial activity, causing mitochondria to enlarge by spilling apoptotic effectors over the mitochondrial membrane. These proteins are tiny mitochondria-derived activator caspases that are released into the cytosol and attach to the inhibitor of apoptosis protein, preventing apoptosis inhibition. Furthermore, cytochrome C is released from the mitochondria, where it binds to APAF-1 and ATP to form apoptosomes. These apoptosomes then cleave pro-caspase into caspase 3, resulting in cell death [17].

Preclinical TBI Biomarkers

Biomarkers are biological substances present in the blood and other bodily fluids that can play an essential role in providing objective and quantitative information regarding the process behind neurological impairments and the degree of the damage. In the case of TBI, biomarkers such as HMGB1, S100B protein, MMP (Matrix Metalloproteins), TIMP, LGALS3, ghrelin, UCHL-1, Tenascin-C, and HSP proteins are utilized to aid in the diagnosis and prognosis of the condition.

Role of HMGB1 protein in TBI

HMGB1 (High Mobility Group Box-1) is a ubiquitous nuclear protein that is an architectural chromatin-binding factor that can be involved in the maintenance of nucleosomes as well as the regulation of gene transcription [18]. It has two DNA binding domains known as the A and B box domains. A box has a binding site for the HMGB1 receptor, but the B box has been identified as a pro-inflammatory domain, suggesting that it might be a functional biomarker of TBI [19]. During the primary insult, BOX protein is produced in the form of alarmin signals from the injured meninges and parenchyma cells; these signals then bind to the DAMP (Damage-Associated Molecular Pattern) or PAMP (Paracrine-Associated Molecular Pattern) (Pathogen-Associated Molecular Pattern) TLR (Toll-Like Receptor) is an example of a DAMP. These receptors also trigger or activate microglial cells and NLRP1 (Nucleotide-Binding Oligomerization Domain), which can accelerate the creation of an inflammasome, which initiates pro-inflammatory cytokine production and causes an inflammatory response. HMGB1 has been shown to disrupt the Blood-Brain Barrier (BBB), resulting in cognitive impairment [20]. It has been observed that TBI is related with neuroinflammation and cognitive abnormalities [21], and HMGB1 has been shown to increase or begin neuroinflammation. In experimental models of TBI, treatment with an HMGB1 antagonist had a positive impact [22]. BOX protein is released after 30 min of damage and its expression decreases between one and six hours after TBI [23]. BOX protein has been linked to increased intracranial pressure in patients and the

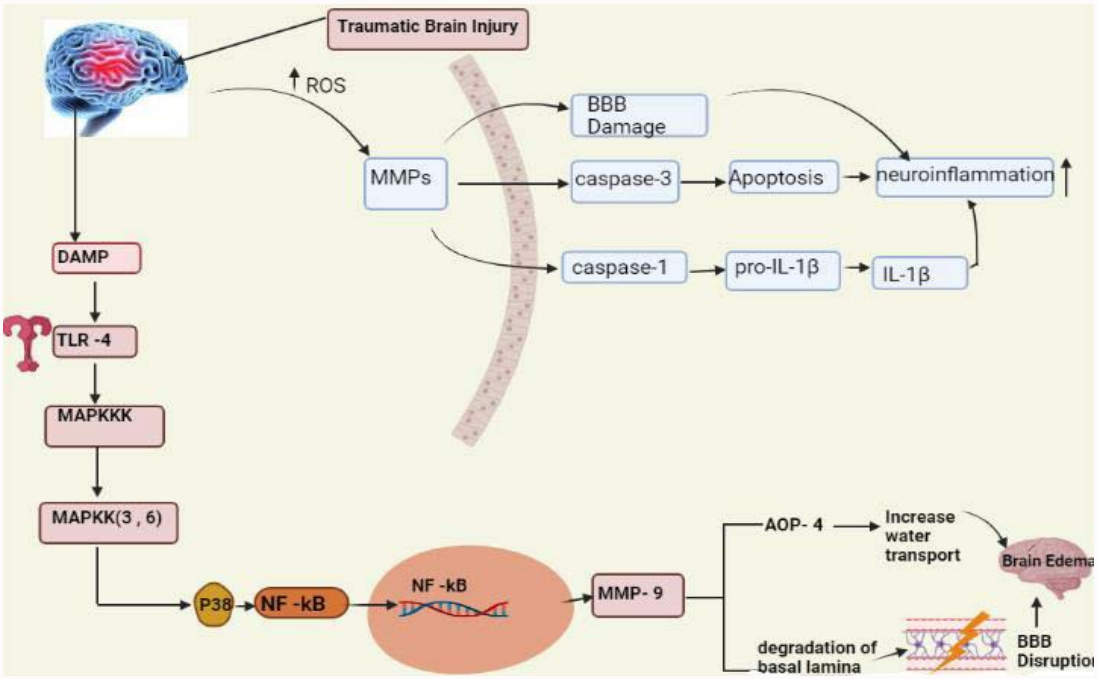

Figure 3: Role of matrix metalloproteinases in Traumatic brain injury.

promotion of cerebral edema following injury, with the hazardous impact of box protein aided by microglial activation. When compared to a normal control, the amount of HMGB1 following trauma increases up to thirty-fold within the first hour of damage [22].

Role of Heat Shock Protein (HSPs) in TBI

HSPs are basically chaperones that allow proteins to fold and accelerate the refolding of denatured proteins. They are increased inside cells when they are subjected to extreme stress, such as heat, cold, UV radiation, or damage. In the event that a protein is substantially misfolded, HSP has the capacity to destroy it [24]. Stress on the cells occurs during TBI as a result of a blow to the head and trauma, and at the time of the primary insult, [25] these proteins are released in the form of alarmin signals and bind with the DAMP proteins, inducing a cascade of events and allowing the production of pro-inflammatory cytokines [26]. HSPs are classified based on their molecular mass, and each one performs a unique set of functions. For example, HSP40 is involved in the breakdown of damaged proteins, whereas HSP70 has been shown to enhance neurological outcomes [27]. It has been observed that HSP70 protects brain cells from experimental brain damage during TBI, but HSP70 downregulation has different results, and HSP70 activation reduces protein aggregation. HSP induction is mediated by the Heat Shock Factor (HSF), which binds to all HSP genes. HSF is essentially a transcriptional factor [28]. Under normal settings, HSPs are found intracellularly and coupled with HSF1, but when cells are subjected to stress, such as injury or trauma, this causes protein dissociation from HSF, causing these HSPs to link to the denatured proteins [29]. HSP70 overexpression decreased the degree of brain bleeding and Blood-Brain Barrier (BBB) disruption, which will lessen BBB damage in TBI and suppress MMP production, improving neurological outcomes [30]. HSP70 also plays an important role in apoptosis, influencing the recruitment of procaspase 9 and Apoptosis protease factor 1 (Apaf-1) and so inhibiting the intrinsic apoptotic pathway [31]. It has also been discovered that HSP70 suppresses NF-κB activation, which affects the generation of pro-inflammatory cytokines [32].

Role of MMP (Matrix Metalloproteinases) and TIMP (Tissue Inhibitor of Metalloproteinase) in TBI

MMPs are extracellular enzymes that can play a significant role in the destruction of extracellular matrix proteins, [33] they have been found in the Cerebrospinal Fluid (CSF) of TBI patients in several investigations. MMPs have a role in proper growth, wound healing, and development; they are generally released as latent enzymes [34]. In the event of TBI, inflammation develops, which increases BBB permeability and, as a result, the number of MMPs greatly increases [35]. MMP-9 (Gelatinase-B) and MMP-2 (Gelatinase-A) levels rise during injury, which can lead to BBB breakdown, while MMP-3 (stromelysin-1) contributes to the degradation of BBB basal lamina and tight junction proteins [36]. However, a larger concentration of MMP-9 has been found in the CSF of TBI patients, indicating the severity of the damage; they are an essential CSF biomarker for predicting the clinical fate of TBI patient [37]. As a result, while a rise in MMP concentration after TBI may be advantageous, a larger concentration might have negative consequences. It has also been claimed that MMPs are implicated in subsequent brain damage. MMP-9 levels are increased in neurological disorders, and its activation causes excitotoxicity, mitochondrial malfunction, and apoptosis [38]. The level of MMP-9 increases on the first day of the primary injury and is increased for seven days following the insult. Its concentration is greater in the TBI patient's cerebral cortex and hippocampus [39], and it has also been observed in blood plasma. It has been suggested that a high level of MMPs leads to the development of Post-Traumatic Epilepsy (PTE), and that inhibiting MMP-9 may be beneficial in guarding against PTE [40]. The molecular mechanism of MMP and its function in TBI are (Figure 3). MMPs contribute to apoptosis, they activate the TNF-α which further activate TRADD and FADD, results in caspase-3 activation which induce apoptosis [41].

Tissue Inhibitors of Metalloproteinase (TIMPs) are balancing

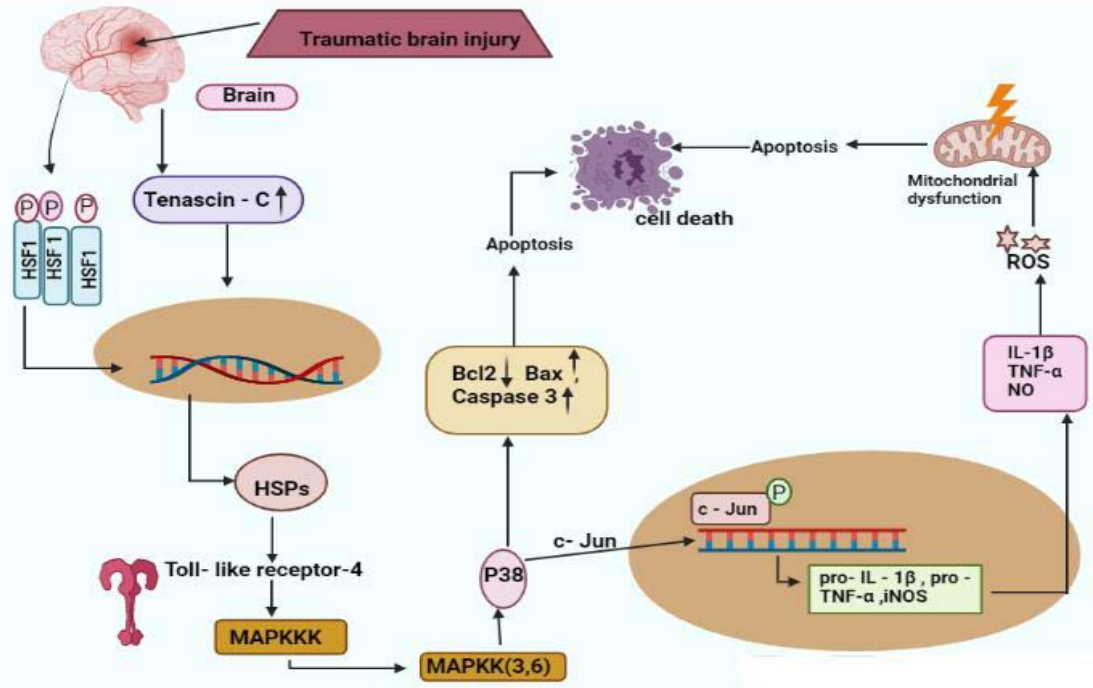

Figure 4: Role of tenascin-c in Traumatic brain injury.

proteins that modulate the activity of MMPs. TIMPs are classified into four kinds (1, 2, 3, 4). They all have diverse mechanisms of action and operate on different MMPs to modulate their activities, such as TIMP-1 controlling MMP-9 or MMP-3 activity and TIMP-2 inhibiting MMP-2 activity [42]. TIMPs are dimers composed of an N-terminal domain and a smaller C-terminal domain that are stabilized by three disulfide bonds. The n-terminal domain of TIMP non-covalently binds to MMPs substrate unit at the zinc-binding site, which can be useful in inhibiting MMP activity [43]. TIMP-1 is an inducible form whose upregulation is dependent on factors such as TGF, IL-1, IL-6, epithelial growth factor and leukemia inhibitory factor, oncostatin, retinoids, etc. TIMP-1 is known to induce neuroprotective effects in the CNS by maintaining the BBB, suppressing apoptosis, and inhibiting excitotoxic cell death of neurons, whereas TIMP-2 and TIMP-3 are soluble non-glycosylated proteins that are expressed constitutively, and TIMP-3 is an insoluble protein that will bind to ECM components, and it is the only MMP that will inhibit TNF-α [44].

Role of ghrelin in TBI

Ghrelin is a peptide that is released inside the stomach. Its main function is to control food and metabolism, and it also has some neuroprotective properties. It also stimulates the production of growth hormone [45]. Ghrelin Receptors (GHS-R1a) are situated inside the brain and trigger growth hormone release. It also has certain extra-hypothalamic neuronal activities such as learning, memory, stress, and motivation [46]. Ghrelin has the ability to cross the BBB and has significant beneficial effects in TBI, particularly reducing the poor results of subsequent brain injury [47]. Following a first injury, numerous proteins are produced, which may contribute to later brain damage such as increased apoptosis and neuronal inflammation [48]. However, it has been reported that ghrelin has anti-apoptotic activity, and the mechanism behind this is that during the primary insult, proapoptotic BAX protein is stimulated and anti-apoptotic BCL-2 protein is suppressed, causing cytochrome-C to be released from the mitochondria due to the opening of the MPTP and interacting with APAF-1 protein [49]. This will then interact with procaspase-9, resulting in the activation of the procaspase-9 molecule, which will then activate caspase-3, and apoptosis will begin; however, ghrelin also inhibits the activation of the BAX protein, which plays a crucial role in apoptosis. It will also activate ERK1/2, the protein kinase C pathway, and the protein kinase-A pathway, as well as enhance the production of mitochondrial Uncoupling Protein (UCP-2). Long-term inflammation is also a key source of secondary damage after TBI, although ghrelin will have a favorable impact by regulating inflammation and decreasing the production of TNF- or IL-1, making it appears to be advantageous in TBI [51].

Role of galectin-3 in TBI

Galectins are a protein family with 15 members, each with a unique function. Galectin-3 is one of the proteins present inside the nucleus or cytoplasm, and it will become the master regulator of inflammatory response in neurodegenerative illness [52]. In general, active microglial cells produce galectin-3; moreover, it is required for resident microglial activation and proliferation in response to damage [53]. Galectin-3 levels in plasma are linked to the severity and prognosis of severe TBI; it is involved in cell adhesion, proliferation, migration, activation, apoptosis, and phagocytosis [54]. Galectin-3 plays an important role in the regulation of brain inflammation and neurodegeneration; its level in the CSF is significantly increased within 24 h of injury; microglial cells express this protein in the presence of brain trauma [55]; and it has been observed that during the time of primary insult, the BBB is immediately disrupted, resulting in substantial leakage of Galectin-3 from the parenchyma cell into the CSF [56]. It will bind to the Toll-Like Receptors (TLR), which are DAMP (Damage-Associated Molecular Pattern) that will induce activation of microglial cells, resulting in the release of proinflammatory cytokines such as IL-1, TNF-, and NF-κB, which

can further promote neurodegeneration, so neutralizing antibodies against Galentin-3 provide a beneficial effect, inhibiting the activation of microglial cells and the formation of inflammatory cytokines and promotes neuroprotection in head injury. TLR receptor inhibition has also been shown to be advantageous. According to research, Galactin-3 acts as an alarmin signal in TBI, and a high quantity of Galectin-3 in the CSF suggests a significant degree of damage [57].

Role of S100B protein in TBI

S100B protein is a calcium-binding protein present in the cytoplasm that is involved in a variety of activities such as cell differentiation and cell cycle progression [58]. It is an essential blood biomarker protein that plays a key role in TBI after the primary insult, these proteins are quickly released from the injured glial cell into the circulatory system, and it is an important tool that may be utilized as a proxy of imaging in TBI in contrast to MRI.

The mechanism underlying S100B in TBI is that during the primary insult, the BBB is damaged, causing S100B to be immediately released from the damaged glial cells. Following this, microglial cells are activated, and ROS production begins, which increases the production of proinflammatory cytokines and may lead to cell death and neuronal dysfunction [59]. It also increases RAGE signaling activation in neurons, which can lead to neuronal death. Changes in the expression of this marker have been linked to the severity of the injury and neurological consequences. It has been observed that in patients with severe damage, the concentration of S100B in blood is greater than 1.13 ng/ml, which is associated with an increase in mortality and morbidity [60].

Role of UCHL-1 in TBI

Ubiquitin C-terminal hydroxylase is a blood biomarker protein that is present mostly in neurons throughout the brain after TBI [61]. It can be used to detect the severity of injury because it is a promising TBI biomarker that belongs to the family of deubiquitinating enzymes that recycle ubiquitin monomers and has the ability to promote the aggregation of α-synuclein, during the time of injury neurons are injured and then UCHL-1 are released into the CSF, it can also be detected in the systemic circulation [62]. UCHL-1 shows some favorable effects, such as mending the axons or neurons after injury by eliminating the aberrant protein *via* ubiquitin-proteasome pathway, which can keep the axons intact [63]. During the time of brain injury, various unpleasant lipid proteins are released, such as cyclopentenone and prostaglandin, which interact with the UCHL-1 and hinder its activity. It has been shown that after moderate TBI, only a temporary increase in the level of UCHL-1 has been seen [62], however in severe TBI, the level of UCHL-1 in CSF is too high, and the level of this protein in the CSF or serum may be measured within 7 h to 9 h after severe TBI. It can be identified by using the sandwich ELISA technique, and it is an essential biomarker that may be used to distinguish between minor and severe TBI. The half-life time (t1/2) of UCHL-1 in mTBI is around 7 h, but that of severe TBI is approximately 10 h [64].

Role of Tenascin-C in TBI

TNCs are matricellular proteins that are important inducers of inflammatory cascades in response to various stimuli and tissue injury [65]. TNCs, which are MCPs (Multicellular Proteins), are significantly expressed throughout embryonic development. They are triggered by glial cells and astrocytes and play a vital part in brain development [66], performing a range of activities including as neuronal progenitor cell maturation, cell proliferation, proper CNS development, and maintaining synaptic plasticity, among others.

TNC levels have been significantly increased in brain parenchyma cells such as neurons and astrocytes during TBI, indicating multiple deleterious events such as BBB disruption, apoptosis, activation of the MAPK pathway, and NF-κB pathway activation [67], which can further increase the severity of the injury. It will also raise the likelihood of first injury, which may increase the likelihood of subsequent damage. TNC will activate the TLR-4 receptor, which is basically a DAMP signal, which will further induce the activation of the microglial cells and inflammasomes, which will promote the generation of proinflammatory cytokines like IL-1 and NF-KB, which can promote the generation of ROS and enhance the inflammation [68]. TNC will also upregulate the production of MMP-9 by activating the MAPK pathway, resulting in secondary brain damage. Excitotoxicity, mitochondrial malfunction, and apoptosis will follow [69]. Patients with TBI had increased TNC levels in their CSF and plasma, indicating severe TBI [70] (Figure 4).

Role of tau protein in TBI

Tau protein is a microtubule-associated protein that is found in the neurons and helps in maintaining the morphology of neurons, they will play important role in signal transduction or vesicular transport [71]. The normal physiological function of tau protein is to promote the formation of microtubules. It will undergo post-translational changes, such as phosphorylation, which is essential for their proper functioning and is controlled by the balance of kinase and phosphatase activity [72]. This will affect the affinity of microtubules binding. Tau proteins become hyperphosphorylated during TBI because the microtubule by which tau protein binds is disintegrated during primary injury, resulting in the formation of neurofibrillary tangles of tau protein, which accumulate inside the brain and increase a cascade of events that show harmful effects such as increased oxidative stress because mitochondria is damaged and ROS formation is increased [73]. Tau proteins will also boost glutamate activation *via* the NMDA receptor, resulting in an increase in calcium influx into the cell, which will exacerbate excitotoxicity and neuronal death [74]. It also activates glial cells, which can boost the production of proinflammatory cytokines such as IL-1 and TNF-α. These cytokines further exacerbate neuroinflammation, which eventually leads to neuronal death. These variables occur because tau protein hyperphosphorylation ameliorates subsequent damage in TBI while eventually worsening the situation [75].

Diagnostic techniques for TBI

Diagnosis of TBI is itself a challenging task because in TBI different signs and symptoms have been seen with respect to time and different diagnostic techniques have been implemented, the mildness of injury is difficult to identify. Patients suffering from TBI report complex neurocognitive, neuropsychological, and physical symptoms these symptoms differ with respect to the severity of injury (e.g., dizziness, motor problem, blurred vision, irritability, sensitivity to noise or light, the problem with memory or concentration, transient neurological abnormalities, sleep disturbance, nausea and behavioral/emotional symptoms (e.g., depression, anxiety, aggression, impulsivity). whereas in case of severe TBI symptoms have been worsened like loss of consciousness, severe headache, short term memory loss, seizures or convulsions, coma, locked-in syndrome, and brain herniation have been seen. Therefore, clinicians have evaluated the severity of the injury and facilitate the diagnostic management for each patient

different diagnostic tool have been employed and practically used for the assessment of TBI [76].

Evaluation of Consciousness

Different tools have been used to check the level of consciousness.

Glasgow coma scale

The Glasgow coma scale is a useful instrument for providing an initial evaluation score by monitoring a person's degree of consciousness following a TBI [77]. GCS evaluates a patient's ability to do the visual movement, motor movement, and verbal test; these three characteristics assist clinicians in determining the severity of the damage [78]. GCS scores range from 1 to 15, if the patient score is 1 to 3, it indicates that the patient's condition is worsening or that the injury is more severe because the patient is completely unconscious [79]. If the patient score is 13 to 15, it indicates that the patient has a mild TBI and is not in danger [80]; with the help of this scoring scale, clinicians can determine the severity of the injury.

Evaluation of Cognitive Function

For assessment of cognitive function different tests have been conducted like-

King-Devick test

King-Devick is a concussion screening test used to assess the patient's cognitive health because after TBI, the hippocampus, also known as the memory store, is disrupted, resulting in post-injury cognitive impairment [81]. If the patient's cognitive function is disrupted, it indicates the severity of the damage because it has been seen that in severe TBI, cognitive or memory function is impaired [82].

The doctor analyses the patient's cognitive performance with the assistance of this KD test, which consists of several cards with numbers printed on them, and the patient reads the number aloud. This test takes less than 2 min to complete, and the clinician scores the patient based on the time required.

Evaluation of Motor Function

Balance Error Scoring System (BESS)

BESS is an important tool for evaluating the patient's postural stability and motor function; in this subject, perform some simple activities such as opening the eyes, falling out of the initial position, movement of the hands, lifting the toes, remaining out of the same position for more than 5 sec, simply walking in a straight line, and so on. Clinicians use these functions to assess the patient's motor function and postural stability [83].

Blood biomarker analysis

These are crucial tools in the diagnosis of a TBI. Using these blood biomarker tests; clinicians may quickly evaluate the degree of the damage and the status of the TBI. Various biomarker analyses, such as levels of S100B, MMPs, HMGB1, TAU protein, and Galentin-3, can be performed. If the level of these protein biomarkers in the bloodstream significantly increases, it indicates the severity of the injury because these protein biomarkers are somehow involved in the injury, some of which are released from the damaged cell and further ameliorate the injury condition, and some of which are involved in worsening the primary injury to secondary injury and at that time [84]. These biomarkers are released into the bloodstream or CSF by blood plasma analysis. These proteins are identified in an excessive amount, indicating the severity of the damage, and are utilized as a diagnostic tool.

Neuroimaging for diagnosis of TBI

Neuroimaging techniques can be used for the diagnosis of brain injury these are of various types and they will provide injury status of the brain [85], and the amount of injury received by the brain generally Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) [86]. CT is a widely used neuroimaging technique for the diagnosis of brain injury because it is a fast and highly accurate process in the detection of skull fracture and hemorrhage, it is generally indicated for moderate and severe TBI where GCS score is less than or equals to 12 (GCS ≤ 12) and for the patient who is suffering from persistent headache, seizures, amnesia, loss of consciousness, etc. CT is able to reflect the size, shape, and distribution of the brain tissue, but there is a limitation with the CT that it is unable to detect all types of brain injury [87].

The second widely used neuroimaging technique is MRI, it can provide detailed information of the concussion, tissue injury, and hemodynamics, by the help of MRI clinician is able to detect the minute bleeding, contusion or it is able to detect changes in the brain function. Nowadays PET imaging technique has increased attention clinically in detecting the condition of the brain after TBI in this radiotracer is used to detect the injury generally, Fluorodeoxyglucose (FDG) is the most widely used radiotracer, by the help of (PET) clinicians are able to analyze a single biomarker like TAU protein level in the brain, amyloid-β level, etc., [88].

Current drug therapy used in TBI

TBI is a serious problem all over the world. Generally, at the time of impact, primary injury occurs, which is unpreventable; however, if the patient remains untreated or undiagnosed, the condition worsens and leads to secondary brain injury, which is the leading cause of death; various factors are involved in secondary injury, which can exacerbate the injury.

Many drugs that can undergo clinical trials and have the ability to reduce the incidence and disastrous effect of secondary injury, many of them inhibit secondary injury and increase the chance of the patient becoming healthy, these are some drugs that can be used in TBI like N-acetyl cysteine, minocycline, phenserine, progesterone, Erythropoietin, Glibenclamide, minocycline, propranolol, Tranexamic acid, Valproic acid, simvastatin, Cyclosporine.

N-acetyl cysteine

N-acetyl cysteine is a key neuroprotective drug that can increase the level of GSH in the brain because GSH possesses (ROS) scavenging characteristics [89]. NAC will also lower Tau proteins and amyloid-deposition in the brain and serve as an anti-inflammatory agent. NAC will enhance cognitive performance and alleviate mild TBI symptoms [90].

Minocycline

Minocycline (MINO) is an antibiotic that will exhibit neuroprotective activity in TBI. In a TBI rat model, (MINO) will treat the neurological deficits caused by TBI [91]. MINO is also known to decrease microglial activation and IL-1 release, both of which can contribute to an inflammatory response and exacerbate damage [92]. It will also diminish TBI-induced locomotor abnormalities, which will enhance long-term results post-TBI. At a dosage of 100 mg BID for 7 days, MINO will drastically lower S100B and NSE levels [93].

Cyclosporine A

Cyclosporine is a commonly used immunosuppressant medicine with a neuroprotective effect because CsA suppresses apoptosis and the mitochondrial permeability transition pore, preventing mitochondrial damage after TBI, [94] CsA's neuroprotective impact is dose-dependent, and its therapeutic window lasts up to 24 h after damage [95]. When CsA is taken early after a severe TBI, it has an excellent activity and safety profile, and it also reduces lesion volume. CsA injection post-injury dramatically reduces brain lesion volume and improves indicators of neurological impairment [96].

Progesterone

Progesterone (anti-oxidant) was given within 24 h of the TBI, and the intervention lasted from three days to six weeks [97]. The effect of progesterone therapy on TBI clinical outcomes was beneficial, with increased recovery from damage, stabilization of edema, enhanced cognitive performance that can be compromised during injury, and decreased TBI sequelae.

Progesterone is able to reduce the proinflammatory cytokine production, the amount of inflammation-related substances, excitotoxicity, and apoptosis by reducing the level of caspase-3, which inhibits secondary damage outcomes and clinically improves the condition of patients [98].

Simvastatin

Simvastatin is an antihyperlipidemic medication that will also exhibit neuroprotective action in a TBI model by inhibiting the apoptotic pathway by downregulating caspase-3 activation and increasing the production of various growth factors that can induce neurogenesis [99]. Simvastatin inhibited the activation of Toll-Like Receptors (TLR) throughout the clinical trial, which are DAMP signals that can further activate proinflammatory cytokines, TLR remain inactivated, however, due to Simvastatin's protective function, and the activation of IL-1, NF-KB, and TNF- is blocked [100].

Simvastatin also reduces the amount of GFAP, which is a powerful TBI blood biomarker that can reflect the severity of the injury [101].

Propranolol

Over-excitation of the sympathetic or adrenergic system has negative consequences after a TBI; to reduce sympathetic excitation, propranolol has a positive impact in TBI [102]. our strategy is to use β-blocker to reduce sympathetic hyperactivity. Propranolol has a beneficial effect by reducing sympathetic storm, it can cross the BBB and help reduce brain edema, increase cerebral perfusion, improve neurological outcomes, and it also inhibits the cascade of inflammatory changes associated with injury [103].

Phenserine

Phenserine is an anti-acetylcholinesterase drug that reduces neuroinflammation by suppressing the synthesis of proinflammatory cytokine like TNF-α and prevents apoptosis by upregulating BCL-2 and BDNF levels [104]. While decreasing the amounts of proapoptotic enzymes like as caspase-3, phenserine has been shown to lower the level of GFAP protein biomarker of TBI and limit the creation of amyloid precursor protein and α-synuclein.

Phenserine reduces the effects of secondary damage by inhibiting excitotoxicity and oxidative stress [105].

Calcium channel blockers

Excitotoxicity is the primary source of subsequent damage following TBI; it arises as a result of a high intracellular calcium concentration, which can over-activate glutamate [106]. Excitotoxicity can be prevented by using one of two types of calcium channel blockers: L-type or N-type calcium channel blockers [107].

The two primary calcium channel blockers that will prevent additional neuronal damage are Nimodipine (L-type) and Ziconotide (N-type). Ziconotide has been demonstrated to increase mitochondrial function and has been shown to improve patient condition [108].

Future outcomes

TBI is a complex dynamic process that initiates a cascade of cellular pathway that will produce a deleterious effect. Pathology of TBI is so wide, it includes a variety of events that will initiates the injury and worsening the condition like excitotoxicity, neuroinflammation, cell death, oxidative stress. Primary injury is unpreventable but our main goal is to prevent the secondary injury, many biomarkers are which can be used for the diagnosis of TBI like HMGB1, MMP, UCHL-1, but there is a greater need to explore specific biomarker of TBI.

Each biomarker of this review could be carefully considered for future application in the research of TBI.

References

1. Venkatesh VT, Pradeep Kumar MV, Jagannatha SR, Radhika RH, Pushpalatha K. Pattern of skeletal injuries in cases of falls from a height. Med Sci Law. 2007;47(4):330-34.
2. Roebuck-Spencer T, Cernich A. Epidemiology and societal impact of traumatic brain injury. Handbook on the Neuropsychology of Traumatic Brain Injury. 2014;3-23.
3. Ommaya A, Goldsmith W, Thibault L. Biomechanics and neuropathology of adult and paediatric head injury. Br J Neurosurg. 2002;16(3):220-42.
4. Ommaya AK, Gennarelli T. Cerebral concussion and traumatic unconsciousness: Correlation of experimental and clinical observations on blunt head injuries. Brain. 1974;97(4):633-54.
5. Young L, Rule GT, Bocchieri RT, Walilko TJ, Burns JM, Ling G. When physics meets biology: Low and high-velocity penetration, blunt impact, and blast injuries to the brain. Front Neurol. 2015;6:89.
6. Bailes JE, Hudson V. Classification of sport-related head trauma: A spectrum of mild to severe injury. J Athl Train. 2001;36(3):236.
7. Adams JH, Graham DI, Murray LS, Scott G. Diffuse axonal injury due to nonmissile head injury in humans: An analysis of 45 cases. Ann Neurol. 1982;12(6):557-63.
8. Xiao-Sheng H, Sheng-Yu Y, Xiang Z, Zhou F, Jian-ning Z. Diffuse axonal injury due to lateral head rotation in a rat model. J Neurosurg. 2000;93(4):626-33.
9. Jassam YN, Izzy S, Whalen M, McGavern DB, El Khoury J. Neuroimmunology of traumatic brain injury: Time for a paradigm shift. Neuron. 2017;95(6):1246-65.
10. Chiarini A, Armato U, Hu P, Prà ID. Danger-sensing/patten recognition receptors and neuroinflammation in Alzheimer's disease. Int J Mol Sci. 2020;21(23):9036.
11. MacEwan DJ. TNF ligands and receptors–a matter of life and death. Br J Pharmacol. 2002;135(4):855.
12. Fehily B, Fitzgerald M. Repeated mild traumatic brain injury: Potential mechanisms of damage. Cell Transplant. 2017;26(7):1131-55.
13. Levenson J, Weeber E, Selcher JC, Kategaya LS, Sweatt JD, Eskin A. Long-term potentiation and contextual fear conditioning increase neuronal glutamate uptake. Nat Neurosci. 2002;5(2):155-61.

14. Kostandy BB. The role of glutamate in neuronal ischemic injury: The role of spark in fire. Neurol Sci. 2012;33(2):223-37.
15. Busija DW, Gaspar T, Domoki F, Katakam PV, Bari F. Mitochondrial-mediated suppression of ROS production upon exposure of neurons to lethal stress: Mitochondrial targeted preconditioning. Adv Drug Deliv Rev. 2008;60(13-14):1471-7.
16. Leung AW, Varanyuwatana P, Halestrap AP. The mitochondrial phosphate carrier interacts with cyclophilin D and may play a key role in the permeability transition. J Biol Chem. 2008;283(39):26312-23.
17. Hiebert JB, Shen Q, Thimmesch AR, Pierce JD. Traumatic brain injury and mitochondrial dysfunction. Am J Med Sci. 2015;350(2):132-8.
18. Musumeci D, Roviello GN, Montesarchio D. An overview on HMGB1 inhibitors as potential therapeutic agents in HMGB1-related pathologies. Pharmacol Ther. 2014;141(3):347-57.
19. Paudel YN, Angelopoulou E, Piperi C, Vinod Balasubramaniam RMT, Othman I, Shaikh MF. Enlightening the role of High Mobility Group Box 1 (HMGB1) in inflammation: Updates on receptor signaling. Eur J Pharmacol. 2019;858:172487.
20. Festoff BW, Sajja RK, van Dreden P, Cucullo L. HMGB1 and thrombin mediate the blood-brain barrier dysfunction acting as biomarkers of neuroinflammation and progression to neurodegeneration in Alzheimer's disease. J Neuroinflammation. 2016;13(1):194.
21. Faden AI, Loane DJ. Chronic neurodegeneration after traumatic brain injury: Alzheimer disease, chronic traumatic encephalopathy, or persistent neuroinflammation? Neurotherapeutics. 2015;12(1):143-50.
22. Paudel YN, Shaikh MF, Chakraborti A, Kumari Y, Aledo-Serrano A, Aleksovska K, et al. HMGB1: A common biomarker and potential target for TBI, neuroinflammation, epilepsy, and cognitive dysfunction. Front Neurosci. 2018;12:628.
23. Gao TL, Yuan XT, Yang D, Dai HL, Wang WJ, Peng X, et al. Expression of HMGB1 and RAGE in rat and human brains after traumatic brain injury. J Trauma Acute Care Surg. 2012;72(3):643-9.
24. Sørensen JG, Kristensen TN, Loeschcke V. The evolutionary and ecological role of heat shock proteins. Ecology Letters. 2003;6(11):1025-37.
25. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Br J Anaesth. 2007;99(1):4-9.
26. Álvarez K, Vasquez G. Damage-associated molecular patterns and their role as initiators of inflammatory and auto-immune signals in systemic lupus erythematosus. Int Rev Immunol. 2017;36(5):259-70.
27. Turturici G, Sconzo G, Geraci F. Hsp70 and its molecular role in nervous system diseases. Biochem Res Int. 2011;2011:618127.
28. Sharp FR, Zhan X, Liu DZ. Heat shock proteins in the brain: role of Hsp70, Hsp 27, and HO-1 (Hsp32) and their therapeutic potential. Transl Stroke Res. 2013;4(6):685-92.
29. Kim JY, Yenari MA. The immune modulating properties of the heat shock proteins after brain injury. Anat Cell Biol. 2013;46(1):1-7.
30. Kim N, Kim JY, Yenari MA. Anti-inflammatory properties and pharmacological induction of Hsp70 after brain injury. Inflammopharmacology. 2012;20(3):177-85.
31. Bratton SB, Salvesen GS. Regulation of the Apaf-1-caspase-9 apoptosome. J Cell Sci. 2010;123(19):3209-14.
32. Somensi N, Brum PO, Vitor de MR, Gasparotto J, Zanotto-Filho A, Rostirolla DC, et al. Extracellular HSP70 activates ERK1/2, NF-kB and pro-inflammatory gene transcription through binding with RAGE in A549 human lung cancer cells. Cell Physiol Biochem. 2017;42(6):2507-22.
33. Bodet C, Chandad F, Grenier D. Inhibition of host extracellular matrix destructive enzyme production and activity by a high-molecular-weight cranberry fraction. J Periodontal Res. 2007;42(2):159-68.
34. Löffek S, Schilling O, Franzke CW. Biological role of matrix metalloproteinases: A critical balance. Eur Respir J. 2011;38(1):191-208.
35. Okuma Y, Liu K, Wake H, Zhang J, Maruo T, Date I, et al. Anti-high mobility group box-1 antibody therapy for traumatic brain injury. Ann Neurol. 2012;72(3):373-84.
36. Rosenberg GA, Yang Y. Vasogenic edema due to tight junction disruption by matrix metalloproteinases in cerebral ischemia. Neurosurg Focus. 2007;22(5):1-9.
37. Berger RP, Ta'asan S, Rand A, Lokshin A, Kochanek P. Multiplex assessment of serum biomarker concentrations in well-appearing children with inflicted traumatic brain injury. Pediatr Res. 2009;65(1):97-102.
38. Hadass O, Tomlinson BN, Gooyit M, Chen S, Purdy JJ, Walker JM, et al. Selective inhibition of matrix metalloproteinase-9 attenuates secondary damage resulting from severe traumatic brain injury. PloS One. 2013;8(10):e76904.
39. Pijet B, Stefaniuk M, Kostrzewska-Ksiezyk A, Photini-Effie T, Tzinia A, Kaczmarek L. Elevation of MMP-9 levels promotes epileptogenesis after traumatic brain injury. Mol Neurobiol. 2018;55(12):9294-306.
40. Sharma R, Leung WL, Zamani A, O'Brien TJ, Casillas Espinosa PM, Semple BD. Neuroinflammation in post-traumatic epilepsy: Pathophysiology and tractable therapeutic targets. Brain Sci. 2019;9(11):318.
41. Moon DO, Mun-Ock K, Sang-Hyuck K, Choi YH, Gi-Young K. Sulforaphane suppresses TNF-α-mediated activation of NF-κB and induces apoptosis through activation of reactive oxygen species-dependent caspase-3. Cancer Lett. 2009;274(1):132-42.
42. Baker AH, Edwards DR, Murphy G. Metalloproteinase inhibitors: Biological actions and therapeutic opportunities. J Cell Sci. 2002;115(19):3719-27.
43. Nagase H. Matrix metalloproteinases. Zinc metalloproteases in health and disease. 1996:173-224.
44. Mosher KLI. Understanding mechanisms of microglia regulation: Neural progenitor cells and molecular changes in the aging systemic environment regulate microglial activity. 2014: Stanford University.
45. Müller TD, Nogueiras R, Andermann ML, Andrews ZB, Anker SD, Argente J, et al. Ghrelin. Mol Metab. 2015;4(6):437-60.
46. Andrews ZB. The extra-hypothalamic actions of ghrelin on neuronal function. Trends Neurosci. 2011;34(1):31-40.
47. Gan ZS, Stein SC, Swanson R, Guan S, Garcia L, Mehta D, et al. Blood biomarkers for traumatic brain injury: A quantitative assessment of diagnostic and prognostic accuracy. Front Neurol. 2019;10:446.
48. Jean WC, Spellman SR, Nussbaum ES, Low WC. Reperfusion injury after focal cerebral ischemia: The role inflammation and the therapeutic horizon. Neurosurgery. 1998;43(6):1382-96.
49. Chung H, Seo S, Moon M, Park S. Phosphatidylinositol-3-kinase/Akt/glycogen synthase kinase-3b and ERK1/2 pathways mediate protective effects of acylated and unacylated ghrelin against oxygen-glucose deprivation-induced apoptosis in primary rat cortical neuronal cells. J Endocrinol. 2008;198(3):511-22.
50. Cheng-Fang T, Wei-Lan Y, Huang SM, Tzu-Wei T, Dah-Yuu L. Wogonin induces reactive oxygen species production and cell apoptosis in human glioma cancer cells. Int J Mol Sci. 2012:13(8):9877-92.
51. Bansal V, Ryu SY, Lopez N, Allexan S, Krzyzaniak M, Eliceiri B, et al. Vagal stimulation modulates inflammation through a ghrelin mediated mechanism in traumatic brain injury. Inflammation. 2012;35(1):214-20.
52. Hernandez ER, Sánchez-Maldonado C, Mayoral Chávez MA, Hernández-Zimbrón LF, Martínez AP, Zenteno E, et al. The therapeutic potential of galectin-1 and galectin-3 in the treatment of neurodegenerative diseases.

Expert Rev Neurother. 2020;20(5):439-48.

53. Lalancette-Hébert M, Swarup V, Beaulieu JM, Bohacek I, Abdelhamid E, Weng YC, et al. Galectin-3 is required for resident microglia activation and proliferation in response to ischemic injury. J Neurosci. 2012;32(30):10383-95.

54. Xin-Jiang Y, Guo-Feng Y, Yuan-Qing J, Xiao-Feng F, Huang Q, Wei-Min D. Role of galectin-3 in plasma as a predictive biomarker of outcome after acute intracerebral hemorrhage. J Neurol Sci. 2016;368:121-7.

55. Yip PK, Carillo-Jimenez A, King P, Vilslta A, Nomura K, Chau CC, et al. Galectin-3 released in response to traumatic brain injury acts as an alarmin orchestrating brain immune response and promoting neurodegeneration. Sci Rep. 2017;7(1):1-13.

56. Nishikawa H, Suzuki H. Possible role of inflammation and galectin-3 in brain injury after subarachnoid hemorrhage. Brain Sci. 2018;8(2):30.

57. Tan Y, Zheng Y, Xu D, Sun Z, Yang H, Yin Q. Galectin-3: A key player in microglia-mediated neuroinflammation and Alzheimer's disease. Cell Biosci. 2021;11(1):78.

58. Schäfer BW, Heizmann CW. The S100 family of EF-hand calcium-binding proteins: Functions and pathology. Trends Biochem Sci. 1996;21(4):134-40.

59. Alam A, Thelin EP, Tajsic T, Khan DZ, Khellaf A, Patani R, et al. Cellular infiltration in traumatic brain injury. J Neuroinflammation. 2020;17(1):328.

60. Dash PK. Zhao J, Hergenroeder G, Moore AN. Biomarkers for the diagnosis, prognosis, and evaluation of treatment efficacy for traumatic brain injury. Neurotherapeutics. 2010;7(1):100-14.

61. Dadas A, Washington J, Diaz-Arrastia R, Janigro D. Biomarkers in Traumatic Brain Injury (TBI): A review. Neuropsychiatr Dis Treat. 2018;14:2989-3000.

62. Mondello S, Linnet A, Buki A, Robicsek S, Gabrielli A, Tepas J, et al. Clinical utility of serum levels of ubiquitin C-terminal hydrolase as a biomarker for severe traumatic brain injury. Neurosurgery. 2012;70(3):666-75.

63. Day IN, Thompson RJ. UCHL1 (PGP 9.5): Neuronal biomarker and ubiquitin system protein. Prog Neurobiol. 2010;90(3):327-62.

64. Brophy GM, Mondello S, Papa L, Robicsek SA, Gabrielli A, Tepas J 3rd, et al. Biokinetic analysis of Ubiquitin C-terminal Hydrolase-L1 (UCH-L1) in severe traumatic brain injury patient biofluids. J Neurotrauma. 2011;28(6):861-70.

65. Okada T, Suzuki H. The role of tenascin-C in tissue injury and repair after stroke. Front Immunol. 2021;11:607587.

66. Bodey B, Siegel SE, Kaiser HE. Molecular markers of brain tumor cells: Implications for diagnosis, prognosis and anti-neoplastic biological therapy. 2004: Springer Science & Business Media.

67. Sochocka M, Diniz BS, Leszek J. Inflammatory response in the CNS: Friend or foe? Mol Neurobiol. 2017;54(10):8071-89.

68. Thomas D, Apovian C. Macrophage functions in lean and obese adipose tissue. Metabolism. 2017;72:120-43.

69. Suzuki H, Kanamaru H, Kawakita F, Asada R, Fujimoto M, Shiba M. Cerebrovascular pathophysiology of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage. Histol Histopathol. 2021;36(2):143-58.

70. Suzuki H, Fujimoto M, Kawakita F, Lie L, Nakatsuka Y, Nakano F, et al. Tenascin-C in brain injuries and edema after subarachnoid hemorrhage: Findings from basic and clinical studies. J Neurosci Res. 2020;98(1):42-56.

71. Wang JZ, Liu F. Microtubule-associated protein tau in development, degeneration and protection of neurons. Prog Neurobiol. 2008;85(2):148-75.

72. Guo T, Noble W, Hanger DP. Roles of tau protein in health and disease. Acta Neuropathol. 2017;133(5):665-704.

73. Aka TD, Rashid MD, Paul SC, Halim A. A review on molecular neuropathology of Alzheimer's disease in association with aging. J Res Pharm. 2019;23(1):1-15.

74. Miyamoto T, Stein L, Thomas R, Djukic B, Taneja P, Knox J, et al. Phosphorylation of tau at Y18, but not tau-fyn binding, is required for tau to modulate NMDA receptor-dependent excitotoxicity in primary neuronal culture. Mol Neurodegener. 2017;12(1):41.

75. Didonna A. Tau at the interface between neurodegeneration and neuroinflammation. Genes Immun. 2020;21(5):288-300.

76. Capó-Aponte JE, Urosevich TG, Temme LA, Tarbett AK, Sanghera NK. Visual dysfunctions and symptoms during the subacute stage of blast-induced mild traumatic brain injury. Mil Med. 2012;177(7):804-13.

77. Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G. The Glasgow Coma Scale at 40 years: St#anding the test of time. Lancet Neurol. 2014;13(8):844-54.

78. Borer-Alafi N, Gil M, Sazbon L, Korn C. Loewenstein communication scale for the minimally responsive patient. Brain Inj. 2002;16(7):593-609.

79. Iverson GL. Complicated vs uncomplicated mild traumatic brain injury: Acute neuropsychological outcome. Brain Inj. 2006;20(13-14):1335-44.

80. Stulemeijer M, Vos PE, Bleijenberg G, Werf SPVD. Cognitive complaints after mild traumatic brain injury: Things are not always what they seem. J Psychosom Res. 2007;63(6):637-45.

81. Lee H, Lee S, Black I, Salado L, Estrada J, Isla K. Long-term impact of mild traumatic brain injuries on multiple functional outcomes and epigenetics: A pilot study with college students. Appl Sci. 2020;10(12):4131.

82. Christodoulou C, DeLuca J, Ricker JH, Madigan NK, Bly BM, Lange G, et al. Functional magnetic resonance imaging of working memory impairment after traumatic brain injury. J Neurol Neurosurg Psychiatry. 2001;71(2):161-8.

83. Valovich McLeod TC, Hale TD. Vestibular and balance issues following sport-related concussion. Brain Inj. 2015;29(2):175-84.

84. Relja B, Land WG. Damage-associated molecular patterns in trauma. Eur J Trauma Emerg Surg. 2020;46(4):751-75.

85. Wintermark M, Sanelli PC, Anzai Y, Tsiouris AJ, Whitlow CT. Imaging evidence and recommendations for traumatic brain injury: Conventional neuroimaging techniques. J Am Coll Radiol. 2015;12(2):e1-e14.

86. Langfitt TW, Obrist WD, Alavi A, Grossman RI, Zimmerman R, Jaggi J, et al. Computerized tomography, magnetic resonance imaging, and positron emission tomography in the study of brain trauma: Preliminary observations. J Neurosurg. 1986;64(5):760-7.

87. Haacke EM, Duhaime AC, Gean AD, Riedy G, Wintermark M, Mukherjee P, et al. Common data elements in radiologic imaging of traumatic brain injury. J Magn Reson Imaging. 2010;32(3):516-43.

88. Fink HA, Linskens EJ, Silverman PC, McCarten JR, Hemmy LS, Ouellette JM, et al. Accuracy of biomarker testing for neuropathologically defined Alzheimer disease in older adults with dementia: A systematic review. Ann Intern Med. 2020;172(10):669-77.

89. Morris G, Anderson G, Dean O, Berk M, Galecki P, Martin-Subero M, et al. The glutathione system: A new drug target in neuroimmune disorders. Mol Neurobiol. 2014;50(3):1059-84.

90. Crupi R, Cordaro M, Cuzzocrea S, Impellizzeri D. Management of traumatic brain injury: From present to future. Antioxidants (Basel). 2020;9(4):297.

91. Zhang L, Xiao H, Yu X, Den Y. Minocycline attenuates neurological impairment and regulates iron metabolism in a rat model of traumatic brain injury. Arch Biochem Biophys. 2020;682:108302.

92. Terrando N, Fidalgo AR, Vizcaychipi M, Cibelli M, Ma D, Monaco C, et al.

The impact of IL-1 modulation on the development of lipopolysaccharide-induced cognitive dysfunction. Crit care. 2010;14(3):R88.

93. Ghiam MK, Patel SD, Hoffer A, Selman WR, Hoffer BJ, Hoffer ME. Drug repurposing in the treatment of traumatic brain injury. Front Neurosci. 2021;15:635483.

94. Sullivan PG, Rabchevsky AG, Waldmeier PC, Springer JE. Mitochondrial permeability transition in CNS trauma: Cause or effect of neuronal cell death? J Neurosci Res. 2005;79(1-2):231-9.

95. Sullivan PG, Sebastian AH, Hall ED. Therapeutic window analysis of the neuroprotective effects of cyclosporine A after traumatic brain injury. J Neurotrauma. 2011;28(2):311-8.

96. Alessandri B, Rice AC, Levasseur J, DeFord M, Hamm RJ, Bullock MR. Cyclosporin A improves brain tissue oxygen consumption and learning/memory performance after lateral fluid percussion injury in rats. J Neurotrauma. 2002;19(7):829-41.

97. Stein DG. Brain damage, sex hormones and recovery: a new role for progesterone and estrogen? Trends Neurosci. 2001;24(7):386-91.

98. Cornelius C, Crupi R, Calabrese V, Graziano A, Milone P, Pennisi G, et al. Traumatic brain injury: Oxidative stress and neuroprotection. Antioxid Redox Signal. 2013;19(8):836-53.

99. Husain I, Khan S, Khan S, Madaan T, Kumar S, Najmi AK. Unfolding the pleiotropic facades of rosuvastatin in therapeutic intervention of myriads of neurodegenerative disorders. Clin Exp Pharmacol Physiol. 2019;46(4):283-91.

100. Alshalmani SK. Comparison of the effects of dietary flavonoids and statins on lipopolysaccharide-induced vascular inflammation. 2011. University of Nottingham.

101. Mountney A, Bramlett HM, Dixon CE, Mondello S, Dietrich WD, Wang KKW, et al. Simvastatin treatment in traumatic brain injury: Operation brain trauma therapy. J Neurotrauma. 2016;33(6):567-80.

102. Fauss GN, Hudson KE, Grau JW. Role of descending serotonergic fibers in the development of pathophysiology after Spinal Cord Injury (SCI): Contribution to chronic pain, spasticity, and autonomic dysreflexia. Biology (Basel). 2022;11(2):234.

103. Jain KK. Neuroprotection in traumatic brain injury. The Handbook of Neuroprotection. 2019:281-336.

104. Akkol EK, Çankaya IT, Karatoprak GS, Carpar E, Sobarzo-Sánchez E, Capasso R. Natural compounds as medical strategies in the prevention and treatment of psychiatric disorders seen in neurological diseases. Front Pharmacol. 2021;12:669638.

105. Tweedie D, Fukui K, Li Y, Yu QS, Barak S, Tamargo IA, et al. Cognitive impairments induced by concussive mild traumatic brain injury in mouse are ameliorated by treatment with phenserine *via* multiple non-cholinergic and cholinergic mechanisms. PLoS One. 2016;11(6):e0156493.

106. Baracaldo-Santamaría D, Ariza-Salamanca DF, Corrales-Hernández MG, Pachón-Londoño MJ, Hernandez-Duarte I, Calderon-Ospina CA. Revisiting excitotoxicity in traumatic brain injury: From bench to bedside. Pharmaceutics. 2022;14(1):152.

107. Nimmrich V, Eckert A. Calcium channel blockers and dementia. Br J Pharmacol. 2013;169(6):1203-10.

108. Berman RF, Verweij BH, Muizelaar JP. Neurobehavioral protection by the neuronal calcium channel blocker ziconotide in a model of traumatic diffuse brain injury in rats. J Neurosurg. 2000;93(5):821-8.