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NOVEL THERAPEUTIC APPROACH FOR EVALUATION ON TRAUMATIC BRAIN INJURY

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Abstract:
Traumatic brain injury (TBI) can manifest in a variety of ways, from slight changes in consciousness to a fully unconscious, lifeless state and even death. Diffuse type damage and edema involve the entire brain in the most severe kind of traumatic brain injury. Depending on how severe the injury is, there are many different treatment options available, ranging from drastic surgery like bilateral decompressivecraniectomy to daily cognitive therapy sessions. There are established guidelines for the best treatment of traumatic brain injury (TBI), but they must be used situation-specifically and should not be applied blindly. Also some of the treatment can cause side effect so more of the new strategies are required which may include therapeutic targets. Therapeutic targets are biological molecules, biological pathways, or physiological responses linked to specific disease processes that can be positively or negatively altered by therapy to alter the disease's course. In this overview, Nrf2, IL-1, Glutamate, Mitogen-activated protein kinase, C-C chemokine receptor 5 are briefly reviewed. Making change in these therapeutic targets can help in treating TBI

Keywords— Traumatic Brain Injury; Treatment strategies, Therapeutic Targets, Nrf2, Glutamate.

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I. INTRODUCTION

Traumatic brain injury (TBI) can be caused by anything from a minor head injury to a severe brain injury. About 1.7 million people in the US experience TBI, with older adults (65 years and older) and adolescents (ages 15 to 19) having the highest rate of TBI. The frontal and temporal regions of the brain are the primary brain regions affected. Initially thought to be a benign event, mild traumatic brain injury (MTBI), sometimes referred to as brain concussion, has drawn a lot of attention due to some of its unfavourable neuropsychological effects in both military and civilian populations, such as athletes who plays contact sports. One of the main causes of injury-induced death and disability is moderate to severe traumatic brain damage. Its annual incidence in the United States is roughly 500 per 100,000. However, moderate headtraumas account for about 80% of all TBI cases [1, 2]

Etiology: When the head is struck by an item, like a bat or a fist during a fight, or when the head is damaged by a nearby blast or explosion, mild traumatic brain injury, also known as a brain concussion, typically develops from closed brain injuries. Such wounds have been demonstrated to impact the neurons' structural integrity.

Epidemiology: The ratio of men to women is 2:1. Traumatic brain injury (TBI) was found to be a high-risk factor for various psychiatric diseases, including post-traumatic stress disorder (PTSD), according to a private study involving 1084 patients with TBI. According to statistical estimates from the Centres for Disease Control and Prevention (CDC), roughly 1.5 million Americans per year escape a traumatic brain injury (TBI). Of these, almost 230,000 are admitted to hospitals. 10,958 TBIs were diagnosed in 2000. This figure increased to

344,030 in 2015. While morbidity is harder to determine, mortality is roughly 3% across all TBI severities. [3]

Pathophysiology:According to the Monro-Kellie hypothesis, because the cranium is a rigid, non-expandable container, the total intracranial volume which is made up of brain tissue, cerebrospinal fluid, venous blood, and arterial blood should always be constant. To avoid intracranial pressure, a compensatory reduction in another compartment must occur when a new compartment is introduced (such as a hematoma). Mean artery pressure (MAP) minus intracranial pressure (ICP) is the definition of cerebral perfusion pressure (CPP). The CPP will decrease as the ICP rises, which may result in secondary cerebral ischemia and stroke. Prevention of this secondary insult is the aim of TBI management**.** [4]

The Many TBI Varieties That Are Frequently Encountered Are Listed Below: [5]

1. **Diffuse Axonal Injury (DAI) :**

This may be the cause of any shearing, stretching, or twisting lesions to the neuronal axons and can accompany mild to moderate traumatic brain injury. This behaviour is primarily observed where neuronal axons are entering a more dense, fatty (myelinated), and less fluid-filled white matter at the intersection of the grey and white matter. Stretching of the neural axon due to shearing pressures can result in cytoskeleton damage, which can then induce axonal swelling, increased permeability, calcium influx, separation, and axonal death. Usually, diffuse laminar necrosis is observed during an autopsy. [6]

2. **Extra-axial Hematoma:**

Subdural hematomas (SDH) and epidural hematomas (EDH) are two types of extra-axial hematomas. EDH is typically acute and is caused by bleeding from a fracture or the main meningeal artery and its branches. SDH can be either acute or chronic and arise from bleeding from a bridging vein. [7]

3. **Traumatic Subarachnoid Hemorrhage (SAH)**

Trauma is the most common cause of subarachnoid haemorrhage, which happens when tiny capillaries are torn and blood leaks into the subarachnoid region. While SAH due to aneurysmal rupture happens in the basal cisterns, it typically occurs over the convexity.

4. **Contusion**

Brain bruises known as contusions can be either coup or contrecoup in nature. Contrary to contrecoup injuries, which usually occur on the opposite side of impact, primarily the anterior temporal lobe and basi-frontal lobe, coup contusions happen at the site of impact.

5. **Concussion**

This usually results from a non-penetrating TBI and is a moderate TBI with no obvious structural damage. It frequently happens as a result of forces that accelerate or decelerate after a direct hit to the head. It results in a momentary altered mental state that might vary from disorientation to unconsciousness. A standard magnetic resonance imaging (MRI) scan or computed tomography (CT) scan cannot diagnose this. Diffusion tensor imaging and functional MRI are examples of special sequence MRI that may lead to an earlier concussion diagnosis.

Second impact syndrome: The first injury is usually a concussion, but if the patient—who is frequently an athlete—continues to play before fully recovering from this and suffers another accident, malignant cerebral edema may quickly progress and develop over a few period of time.

Chronic Traumatic Encephalopathy (CTE): Repeated mild traumatic brain injury typically manifests as chronic traumatic encephalopathy (CTE), a delayed condition. This is frequent in athletes and can result in attention deficiencies, memory and executive function disorders, mental issues, and suicidal conduct.

MECHANISM OF INJURY

Blunt head trauma causes multifactorial brain damage because the first insult causes widespread depolarization as well as mechanically deforms tissue components, particularly axons and micro vessels, through temporary sheer forces. Furthermore, areas of focal ischemia may arise via subsequent tissue edema and micro vascular perfusion shunting, even though there is minimal evidence for early energy depletion. These occurrences culminate in a common mechanism of neuronal death that includes the generation of harmful free radicals, tissue acidosis, and loss of cellular calcium homeostasis [8]

The features and severity of traumatic brain injury (TBI) are influenced by the kind, direction, magnitude, and duration of forces. Shear, translational, rotational, and angular forces are some of the forces that can cause traumatic brain injury.

Significant head acceleration or deceleration can result in traumatic brain injury (TBI) even in the absence of an impact; nevertheless, most of the time, both an impact and acceleration are likely to be at fault. Most focal injuries are caused by forces involving the head striking or being struck by something; these forces are referred to as contact or impact loading. Diffuse injuries are typically caused by movement of the brain within the skull, which is referred to as noncontact or inertial loading.

EXPLOSIVE BLASTS AND OTHER COMBAT INJURIES

Active-duty military members frequently sustain traumatic brain injuries as a result of explosive incidents. While the exact mechanism of the harm is still unknown, many scientists think that the pressure pulse that travels through the brain seriously impairs brain activity. Penetrating wounds, severe strikes to the head with shrapnel or debris, falls, or physical impacts with objects after a blast can also cause traumatic brain damage. [9]

CLASSIFICATION OF TRAUMATIC BRAIN INJURY

Traumatic brain injury is categorized using a number of different classification determinants. The specifics of the injury—which frequently coexist with other forms of traumatic brain injury—determine the clinical appearance and prognosis. Regarding acute management, prognosis, and treatment, as well as the needs for Neuro-rehabilitation, the classification is crucial. [9]

Primary v secondary injuries

1. **Primary Injury:**

- Occurs at the time of injury and is decreased by mechanical forces. Two main mechanisms that can cause primary injury:

A. Contact i.e. , an object striking the head or the brain striking the inside of the skull
B. Accerlation- Declaration

- The primary injury because of acceleration-declaration results from unrestricted movement of the head and leads to shear, tensile and compressive strains. These force scan cause intracranial hematoma, diffuse vascular injury, and injury to cranial nerves and the pituitary stalk.

2. **Second Injury:**

- A Secondary injury is not mechanically increased. It may be delayed from the moment of impact, and it may superimpose injury on a brain already affected by a mechanical injury
- The secondary damage is caused by care, acade of process impacting “cerebral blood flow (hyper or hypoperfusion), Impaired cerebrovascular auto regulation, cerebral metabolic dysfunction and impariedcerebral oxygenation.

Focal v diffuse injuries

1. **Focal Injuries:**

- Usually due to contact and causing scalp injury, it might present as skull, fracture, contusions and/or intracranial hemorrhage. Those injuries are detectable by CT, MRI or PET scans.
- This mechanism is relayed to the moving of intracranial content in the skull and

impinging on the internal surface of the skull. Commonly observed injury is coup-contrecoup injury presenting with a contusion on opposite sides of the brain.

2. **Diffuse Injury:**

- Usually due to acceleration/deceleration injury (DAI) and brain swelling
- A diffuse axonal injury might be accompanied by some focal lesions, but again only diagnosable microscopically. The tearing of the nerve tissue disrupts the brain's regular communication metabolic process**.**

Opened v closed injuries

1. **Open/Penetrating Injury:**
   Permeable/Open When a bullet, knife, or other sharp item penetrates the dura mater and pushes hair, skin, bone, and other particles into the brain, injury results.

2. **Closed/Non-Penetrating Injury:**
   A closed injury is one that affects the brain without penetrating the skull and is brought on by an external force. The most dangerous consequence is brain edema within the skull's limited space, which compresses cranial nerves and brain structures and causes intracranial pressure.

RISK FACTORS

Inside your skull, your brain is well protected. For instance, the fluid that envelops your brain prevents it from ever coming into contact with the rigid interior of your skull. After all, your brain may move in response to a shocking blow to your body or head, increasing the possibility of a catastrophic brain-skull collision. Though anyone can sustain a brain injury, there are some risk factors you should be aware of.

The Risk factor includes:

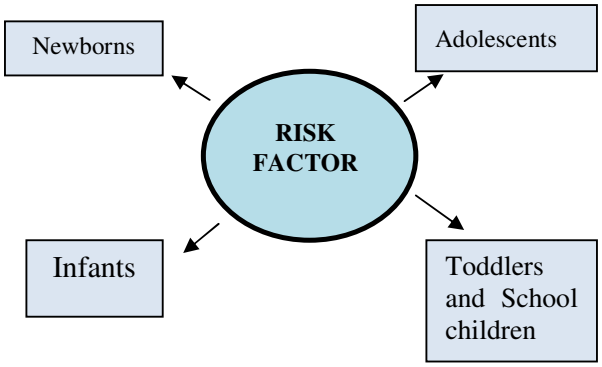

Fig1:The Risk factor.

1. Newborns:

Delivery head injury Intracranial hemorrhages Cephalic hematoma Subgaleal hematoma: caused by traction via the birth canal (vaginal delivery) and compression of the head with obstetric equipment. Hypoxia and a low birth mass are associated with an increased risk of cerebral bleeding.

2. Infants :

Accidental head injury Abusive Head Trauma: caused by improper methods of child care. It is necessary to give serious thought to the diagnosis of child abuse if the mechanism of injury is unclear. The most common reason for hospitalization and death from TBI is AHT.

3. Toddlers and School children:

Accidental head injury: As children's motor abilities develop, so do the causes of accidents. The severity of injuries and the number of fatalities have decreased as kid safety seats are used more frequently. This age group also sees an increase in pedestrian injuries.

4. Adolescents :

Bicycle and motorcycle-related accidents Sports-related head injuries: Prevention needs to be made more widely known. Concussion education is necessary for coaches and athletes involved in contact sports including American football, rugby, and judo. [9]

COMPLICATIONS:

People with moderate to severe traumatic brain injuries may experience long-lasting or irreversible changes in their level of awareness, consciousness, or response. Various awareness states consist of: [9]

- Altered Consciousness

1. Coma
2. Vegetative state
3. Minimally Conscious State
4. Brain death

- Physical Complications

1. Fluid build-up in brain
2. Headache
3. Infections
4. Blood vessel damage

THERAPEUTIC TARGETS IN TRAUMATIC BRAIN INJURY:

There are many available treatments for Traumatic brain injury. But this may have some side effect. To overcome this new techniques are used. This also includes Therapeutic targets by making slight change in it. Some of the therapeutic targets are as follow:

1) Nrf2
2) IL-1
3) Glutamate
4) Mitogen-activated protein kinase
5) C-C chemokine receptor 5
6) BDNF

1) Nrf2 as a Potential Therapeutic Target for TBI:

A fundamental leucine-zipper transcription factor, Nrf2 is a key regulator of the antioxidant and anti-inflammatory defensive systems found in cells. It is a member of the Cap'N'collar protein family. It is essential for regulating the cells' reactions to various forms of stress because it triggers the transcription of numerous genes that code for antioxidants, detoxifying enzymes, and other proteins that protect cells. [10] Nrf2 plays a significant role in reducing inflammation and cytotoxicity, which are frequently linked to chronic and degenerative diseases caused by oxidative stress. Kelch-like ECH-Keap1 (Keap1), an adaptor protein, tightly regulates the Nrf2 protein in the cytoplasm of most cells, including neurons, astrocytes, and endothelial cells. Under physiologically normal conditions, Nrf2 binds to Keap1 and is subsequently degraded by proteasome-mediated degradation and ubiquitination. When the Nrf2-Keap1 connection is disrupted by free radicals, Nrf2 splits and is released into the nucleus. By attaching to the ARE region of antioxidant genes in the nucleus, Nrf2 binds to Maf proteins to control gene expression [11] As a result, natural scavenging enzymes are upregulated. Hemeoxygenase 1 (HO-1), catalase, superoxide dismutase (SOD), glutathione modulators, and oxidoreductases such nicotinamide adenine dinucleotide phosphate (NADPH) are examples of these cellular antioxidants: oxidoreductase 1 of Quinone. Recent research has demonstrated that Nrf2 expression, both in its phosphorylated form and its unphosphorylated form, protects the brain against oxidative stress, neuroinflammation, and apoptotic cell death [12]. Oxidative stress has been linked to Nrf2 dysfunction in a number of additional CNS pathophysiological consequences, including ischemia, bleeding, and other neurodegenerative diseases. Activating Nrf2 would be the ideal strategy to lessen the pathogenesis of these conditions. Because of this, Nrf2 may lead to the development of a novel therapeutic approach that lessens brain damage brought on by CNS injury.

Mechanisms of Nrf2 activation: In a healthy state, Nrf2 is expressed in the cytoplasm, and Keap1 controls this expression. Through either ubiquitination or proteasomal degradation, Nrf2 is broken down as a result of its connection or association with Keap1. On the other hand, oxidative stress converts Nrf2 into its phosphorylated form and releases it into the nucleus, activating Nrf2 and breaking the Nrf2-Keap1 connection. Nrf2 attaches itself to Maf in the nucleus to create a dimer. The transcription of the antioxidant gene promoter is started by this Nrf2-Maf dimer binding to the ARE region of the promoter. Antioxidant gene activation decreases TBI-induced oxidative stress, BBB disruption,

TGF-β1 and MMPs activation, neuroinflammation, and neurodegeneration. [13]

2) IL-1:

Damage to the tissue causes damage-associated molecular pattern (DAMPs) to be released from dying cells and a breached blood-brain barrier to allow inflammatory mediators like complement to seep in. The binding of DAMPs to pattern recognition receptor (PRRs) triggers innate CNS immune responses. Microglia is a central, specifically CNS-related immune cell throughout these processes. Different PRRs trigger distinct immunological reactions. A priming and activation stimulus, which is usually required to activate the inflammasome within microglia, is shown in the inset. As a result, pro-IL1β cleaves to produce its active version. Pyroptosis, which is another effect of inflammatory mediator activation, is anticipated to release additional IL-1β into the extracellular space. In this case, IL-1β triggers a variety of biological processes that might be advantageous or detrimental to the damaged central nervous system. i.e. IL-1 synthesis causes downstream effects of traumatic brain injury. [14]

3) Glutamate:

A key part of the immediate pathophysiology of traumatic brain injury (TBI) is played by glutamate signalling in the central nervous system (CNS). The blood-brain barrier and cellular membranes may be compromised by the primary mechanical forces of the initial lesion, which would increase glutamate release into the extracellular area. Following an injury, the redistribution of ions can further depolarize neurons and increase glutamate release. Over-activation of glutamate receptors can lead to secondary injury cascades that cause cellular damage by upsetting the cell's ionic balance, triggering calcium-dependent proteases and phospholipases, disconnecting mitochondrial ATP synthesis, encouraging oxidative stress, generating reactive oxygen species, lowering glutathione levels, and raising the energy requirement of the cell. Moreover, elevations in extracellular glutamate have been seen in clinical studies up to 4 days following injury, and these have been linked to worse outcomes and elevated intracranial pressure. The ramifications of CNS glutamate dysregulation are highlighted in this earlier research, as is the necessity of looking into alterations in glutamate signaling that take place during the post-traumatic phase following traumatic brain injury (TBI). These changes may be the cause of aberrant neuronal signaling and lead to neurological impairments. [15]

4) Mitogen-activated protein kinase:

The pathogenesis of traumatic brain injury involves signal-transduction pathways including mitogen-activated protein kinase (MAPK). The extracellular signal-regulated kinase (ERK) and p38 kinase were rapidly and selectively phosphorylated in primary rat cortical cultures in response to mechanical stress, whereas the c-jun N-terminal kinase (JNK) pathway remained unaltered. In vitro cell survival was markedly enhanced by treatment with PD98059, which suppresses MAPK/ERK 1/2, the upstream activator of ERK. SB203580, a JNK and p38 kinase inhibitor demonstrated no protective effect. A controlled cortical impact model of traumatic brain damage in mice produced comparable in vivo outcomes. JNK showed no discernible alterations, however the ERK and p38 pathways experienced rapid and specific overexpression. Confocal immunohistochemistry revealed that phospho-ERK colocalized with the marker for neuronal nuclei but not with the glial fibrillary acidic protein astrocytic marker. Seven days after trauma, there was a significant decrease in cortical lesion volumes when PD98059 was used to inhibit the ERK pathway. The JNK and p38 kinase inhibitor SB203580 demonstrated no discernible positive effects. These findings imply that ERK is a novel therapeutic target in traumatic brain injury and further reveal that key alterations in MAPK pathways mediate cerebral damage following acute injury [16]

5) C-C chemokine receptor 5:

The two main conditions that lead to adult impairment because of restricted neurological recovery are stroke and traumatic brain injury (TBI). After a stroke, between 50 and 60 percent of individuals still have movement deficits. Long-term impairment affects 43% of TBI patients who are

admitted to hospitals. Learning and memory systems and brain injury recovery are related through molecular, cellular, and neuropsychological concepts. These parallels suggest that therapies that improve synaptic plasticity may hasten the recovery of function following a stroke or traumatic brain injury. Recent research has demonstrated that improving C-C chemokine receptor 5 (CCR5) signalling improves hippocampus and cortical circuit functions related to learning, memory, and plasticity. We shut down CCR5 in motor to pre-motor cortex in neurons well after the initial stroke, during the period of limited repair and recovery, in order to better understand the role of CCR5 and the processes by which it impacts stroke recovery. We demonstrate that early motor recovery is supported by CCR5 neuronal knockdown. Increased plasticity in the pre-motor cortex leads to motor recovery following CCR5 knockdown (kd). This recovery is linked to the stabilization of dendritic spines in the pre-motor cortex near the stroke site, the up-regulation of CREB and dual leucine zipper kinase (DLK) signalling in CCR5 kd neurons, and the creation of new connections in the contralateral pre-motor cortex. Our findings demonstrate how an FDA-approved CCR5 antagonist used in clinical settings for AIDS therapy aids in stroke and traumatic brain injury recovery. Lastly, we demonstrate that patients with a naturally occurring CCR5Δ32 loss-of-function mutation have improved motor recovery and decreased cognitive sequelae months after the stroke in a large human stroke epidemiology investigation. All of our findings point to CCR5 as a legitimate target for the recovery from stroke and traumatic brain injury. [17]

6) BDNF:

Significant impacts are seen in the regulation of cell survival and other biological processes by the BDNF and TrkB pathway. BDNF is necessary for the survival and development of dopaminergic, GABAergic, serotonergic, and cholinergic neurons. It also plays a role in neurite and axonal growth.

It is not surprising that BDNF is crucial for neuronal survival, differentiation, and plasticity after traumatic brain injury. The mRNA expression level of BDNF is temporarily and dramatically elevated in response to TBI. Research findings indicate that BDNF mRNA expression is markedly elevated in the injured cortex and hippocampus within hours of the lesion. Within 24 hours of the injury, the level of BDNF starts to decrease, and by 36 hours, it is no longer relevant. After damage, the dentate gyrus and hippocampal regions also temporarily exhibit elevated TrkB receptor mRNA expression levels. Following a traumatic brain injury, there appears to be a brief increase in both BDNF and its receptor, indicating that BDNF functions as an endogenous neuroprotective response aimed at reducing subsequent cell damage. Many researches have looked into the therapeutic potential of BDNF/TrkB for a variety of neurological illnesses, including traumatic brain injury (TBI), as a result of the significance of the BDNF/TrkBsignaling system in controlling CNS function. Because of its enormous size (27 kDa) and short half-life (less than 10 minutes), BDNF has limited therapeutic potential. It also cannot pass the blood-brain barrier (BBB). After a weight-drop injury in mice, greater levels of BDNF were discovered in the brain after intravenous injection of nanoparticle-bounded BDNF, and the animals' neurological and cognitive skills improved. [18]

Conclusion

These days, a significant percentage of people may suffer from TBI. Although there are already some treatments for traumatic brain injury (TBI), some of the drugs used to treat it have very harmful side effects. Novel therapeutic techniques are desperately needed to slow or stop the disease's course. Our present literature search explored a number of approaches to address the pathophysiology of TBI, including C-C chemokine receptor 5, Nrf2, IL-1, glutamate, and mitogen-activated protein kinase. Before proceeding with clinical trial phases, it is crucial to look into any potential safety problems with relation to these targets, as many of the new techniques are still being explored and evaluated on animal models.

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