Current Perspective on TBI

Traumatic brain injury (TBI) is a major cause of mortality and long-term disability due to cognitive, emotional, and physical impairments. Frequently, individuals with mild traumatic brain injuries (mTBI) do not present with clinically apparent neurologic and morphologic brain lesions. These patients are often not able to get adequate treatment and care, and as a result, may suffer lasting disabilities, which significantly reduce their quality of life[1].

Traumatic Brain Injury Characteristics

There is no single profile which characterises the presentation of TBI, an epidemic of great magnitude matched only by the sheer complexity of the cerebral pathophysiology involved.

The patient's profile is the result of the location, depth, and volume of focal lesions and the extent of diffuse axonal injury (DAI). Additionally, age, previous injury, use of alcohol, and co-morbid conditions, such as hypoxia or hypertension, further contributes to a specific collection of observed deficits, all contributing to producing unique brain pathologies[2,3].

TBI is a result of dysfunction in neuronal metabolism and the microscopic anatomy of the brain that occurs in two distinct phases. DAI occurs during the initial phase of injury as the direct result of the traumatic force. A secondary delayed phase of brain injury includes inflammatory cascade activation, edema, ischemia, release of free radicals, excitatory amino acids, metal ion discharged, and programmed cell death, eventually leading to neurological and functional deficits [4]. Impairments include: memory loss, inability to concentrate, speech problems, motor and sensory deficits, and behavioural problems. Some psychiatric disorders, such as post traumatic stress disorder (PTSD), are more likely to be a psychological consequence of secondary neuronal damage induced by the physical trauma or traumatic event.

Because no pharmacological treatment has currently been proven to prevent secondary damage processes, brain injuries, to-date, are essentially untreatable disorders. Neuroprotective strategies intended to halt or mitigate secondary neuronal damage at the early stage of injury (2–3 hours post-injury) offer a potential therapeutic window of opportunity. These may help block or slow down the development of subsequent neurological and neuropsychiatric impairments[5]. Undiagnosed and untreated, mild traumatic brain injuries (mTBI) can produce significant cognitive deficits due to progressive neurodegeneration and neurosomatic damage[6]. mTBI can place an incredible burden on society, both economically and socially, causing an estimated 75% to 90% of traumatic brain injury-related morbidity hospitalisations and emergency room visits[7].

TBI by the Numbers

The frequency of brain injury is currently higher than that of any other disease, including complex diseases such as breast cancer, AIDS, Parkinson's disease, and multiple sclerosis [3].

A TBI occurs every 15 seconds in the United States, generating 1.7 million new head injury victims per year[8]. These events are responsible for 53,000 deaths[9] and today, 5.3 million Americans are living with TBI-related disabilities[2] at a cost of more than US $77 billion on average per year [3]. Falls account for over 500,000 emergency room visits annually and another 60,000 hospitalisations. These figures do not include US military personnel or veterans.

Most Vulnerable Age Groups

Most vulnerable are children aged 0 to 4 years, and adolescents, 15 to 19 years. There are approximately 765,000 emergency department visits annually for youth aged 25 and younger[8]. Adults aged 75 years and older have the highest rates of TBI-related hospitalisation and death[8]. Older adults require more ongoing care once discharged from the hospital, and have poorer outcomes [10]. The potential public health burden of TBI across all age groups over the next two decades will be significant [11]. A growing number of unanswered questions concerning TBI has uncovered the lack of treatment options for a crisis that affects millions[3].

TBI in Youth

Mild traumatic brain injury is a significant pediatric public health concern. A comprehensive understanding of the acute and chronic effects of concussion on central nervous system structure and function remains incomplete, and little research has been conducted specifically on changes in the brain following concussions in youth[10]. Some researchers have hypothesised that immature brains are more plastic and thus better able to recover from concussion, while others have argued that a developing brain is more susceptible to injury[12]. Regions involved in abstract processes, reasoning, judgment, and emotion, including impulsivity, controlled principally by frontal areas, remain less developed through the teenage years and into the early 20s[13].

Impact

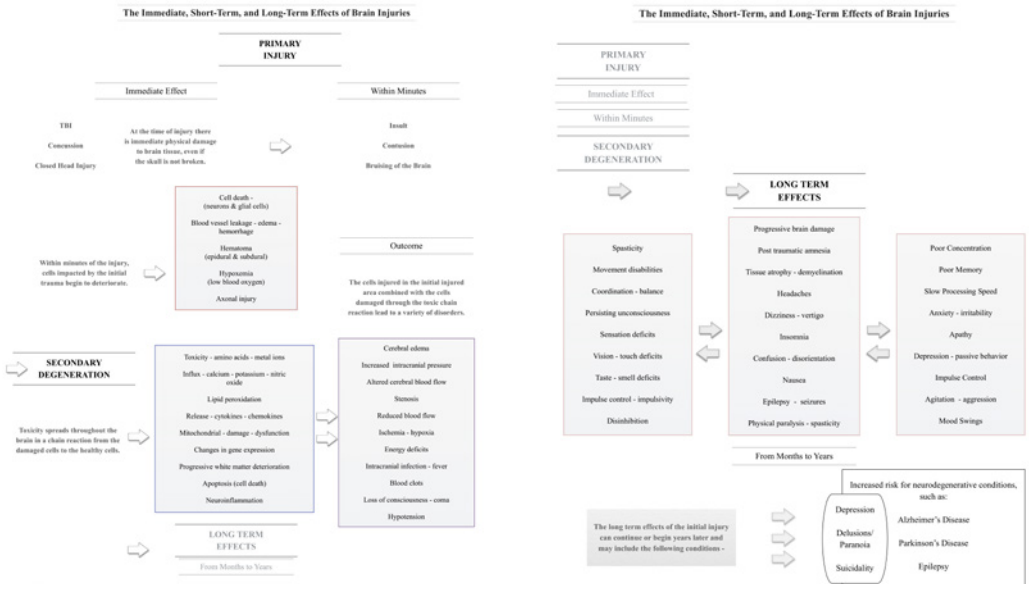
The child and adolescent brain offers a significant challenge in this type of injury and demonstrates the need for specific knowledge and management of their developing central nervous system [14]. Children and teens who sustain a TBI or concussion take longer to recover than adults, and while their symptoms may appear mild, the injury can lead to significant life-long impairment affecting memory, behaviour, learning, and emotions. The main issues that need to be addressed are the ability to diagnose and treat the initial brain changes following injury, measure treatment effectiveness, and provide a predictive and measurable outcome of long-term, post-injury changes[13].

TBI in Athletes

An estimated 1.6-3.8 million sports and recreation-related concussions (mTBI) occur in the United States each year[15]. Many cases remain unreported due to the lack of an immediate and a precise diagnosis; moreover, the long-term effects of the original TBI are not usually monitored.

Research has indicated that even when the symptoms of concussion appear to be spontaneously resolved (usually within 10 days), the injured brain is still experiencing abnormal brain-wave activity. Potentially, this brain-wave activity can last for years after the original head trauma and lead to significant cognitive problems in later life[16].

Falls are the leading cause of TBI[17],



occurring mostly during sports or recreation-related activities where there is physical contact between the players, such as in football, rugby and hockey. Nevertheless, cycling, thought to be a safe physical activity, is at the top of the list of TBI causes. A growing body of sports injury research indicates that the cumulative impact of blows to the head over a period of years leads to a greater risk of dementia and other neurodegenerative diseases in later life. Despite attempts to prevent brain injury by mandating helmets and other preventive actions, the number of sports injuries is gradually rising each year, especially in youth, a group increasingly at risk of suffering repeated brain injury. The pathological consequences of TBI have received increasing media attention following reports of progressive neurological dysfunction in athletes who have been exposed to repetitive concussions in high-impact sports[18]. Athletes with history of concussion have a 5.8-times greater risk of a subsequent concussion and it is suggested that there is a dose–response relationship between the number of previously sustained concussions and future concussion risk[12]. Pathological evidence of chronic traumatic encephalopathy (CTE) has also been found in a variety of contact sports and other activities in which head trauma occurs[12].

Military and Blast-Related TBI

Approximately 280,861 US military personnel returning from Iraq and Afghanistan have sustained one or more brain injuries[19]. Throughout recent military conflicts, improvements in body armour, equipment, and medical care have likely led to an increased number of personnel surviving previously fatal injuries, particularly blast injuries, and subsequent development of TBI[20]. An increasing number of combat veterans presenting with blast-related TBI[18] may also have associated mental health issues compared with other causes of TBI[21, 22]. Although both exposures involve psychological trauma, a blast injury may result in cognitive processing difficulties and an inability to inhibit the experience of the episode resulting in the association between the blast incident and the development of post traumatic stress disorder (PTSD).

"Blast" is most frequently defined as an explosion in the atmosphere characterised by the release of energy in such a short period of time and within such a small volume that it results in the creation of a non-linear shock and pressure wave of finite amplitude, spreading from the source of the explosion. The energy radiating from a conventional blast can be chemical, electrical, thermal, and kinetic or pressure energy[23]. The pressure waves from explosions cause more complex and multiple forms of extensive damage to the body compared to any other wounding agents. Most of the secondary damage following a blast event does not typically occur at the time of initial injur[y24]. Military veterans who have been exposed to repeated blast injury by firing heavy weapons or exposure to other types of explosions are at high risk for developing CTE or post concussion syndrome (PCS), which has been pathologically confirmed in soldiers who have experienced multiple blast injuries[12].

In 2011, more than 69,000 veterans began receiving Veterans Affairs (VA) disability compensation for neurological conditions, reflecting a general increase in TBI cases over the past five years. The Department of Defense (DoD) Disability Evaluation System (DES) demonstrates that neurological conditions are among the top three most prevalent conditions evaluated for disability, with TBI the most common neurological condition among soldiers and marines[25]. The wars in Iraq and Afghanistan have produced a considerable number of advances in battlefield medicine that are being translated into civilian practice[26]. Despite a substantial investment of time, money and effort, clinically effective neuroprotection and neuro-rescue therapies remain elusive [27]. Even when no overt damage is observed in neuroimaging, memory, affective and executive dysfunction emerge and may cause substantial disability and life disruption.

Current TBI Treatments

Over the past 30 years, tremendous efforts and resources have been devoted to studying TBI in search of effective treatments. Because the cerebral physiology is disturbed after mild brain trauma, repeated blows to the head are especially detrimental, making the brain more susceptible to even further injury[24], and has been the focus of various pharmacological therapies[28]. Radosevich *et al.*[28] concluded in the most recent review of current scientific literature that there are few emerging pharmacological therapies for TBI that have been shown to improve survival. The review also concluded there was insufficient data regarding optimal dosing strategies (i.e. dose, duration and timing), for almost all of the agents described in the review. To date, a majority of intervention trials targeting various injury mechanisms during the acute phase of TBI failed to show treatment effectiveness. Additionally, large Phase III pharmacological drug trials have not demonstrated convincing treatment efficacy among selected TBI populations[9].

Research and Meeting an Unmet Public Need

The relationship between early head injury and increased incidence of neurodegenerative disease is a key area for investigation. The extent of neurological recovery depends on the contribution of post traumatic secondary insults in TBI patients[29]. A vital area of brain injury research involves the clarification of secondary injury processes, which may be targeted for intensive care management or pharmacotherapy. Researchers acknowledge that while the relationship between CTE and exposure to concussions and sub-concussions is incompletely understood, it is crucially important to understand in order to develop effective therapies[12]. Significant efforts are needed to improve prevention, diagnosis, and treatment of these conditions, as well as the testing of combination therapies targeting multiple pathomechanisms[29].

Potential Treatment Option

Previous attempts at treating the multi-phasic brain injury process by focusing on a single biochemical mechanism have failed. Since the development of the secondary brain injury stems from simultaneous and consequent activation of several pathways, an intervention that simultaneously targets multiple factors contributing to the progress of neurodegradation could be more effective in halting secondary degradation. Blood-brain-barrier (BBB) breakdown, a major hallmark of TBI, is the focus of many researchers who develop their therapies assuming that once the BBB is damaged, any drug, even a drug with poor BBB-penetration abilities, may cross it and enter the brain parenchyma. A more effective TBI therapeutic agent must exhibit strong BBB permeability, vital for those regions of the brain where the BBB was not compromised; yet, the brain's parenchyma suffers from secondary injury.

An Innovative Approach

To ensure effectiveness, new treatment options must be multifaceted and include neuroprotective, neurorestorative and anti-inflammatory agents. One such multifunctional drug should have at least three different mechanisms of action that simultaneously intervene in different biochemical and physiological pathways. Each of these drug agents must address multiple pathophysiologic mechanisms involved in the degenerative process associated with TBI, and would include ion metal binding capacity, thereby preventing excess release of free radicals and a series of protein degradation cascades and oxidation that could lead to widespread molecular damage and neuronal cell death. Additionally, these drugs would exhibit further anti-inflammatory, and/or anti-bacterial neuroprotective functions. This synergistic approach is expected to prevent the cascade of events leading to brain degeneration. Since multiple, interdependent cascades of biological reactions cause neurodegeneration, intervention must address several pathways simultaneously to be effective. Single pathway agents have a high probability of missing the opportunity window in which their target is valid, thus remaining ineffective. Cell death cascade occurs over a few days; therapeutic agents containing these mechanisms of action would be administered as close as possible to the injury event and for a few weeks following the injury to slow down the deterioration and allow for optimal rehabilitation. Soon the day may come when the brain injuries of children, seniors, athletes, service personnel, and others, will be treated by a medication that inhibits the spread of brain damage and prevents further deterioration, in much the same way injuries in other parts of the body are currently being treated. This combined approach of using a drug that could cross the blood-brain-barrier, capable of metal ion removal, and possess anti-oxidation, anti-inflammatory, and/or anti-bacterial activities may be the best overall strategy for treating individuals with TBI.

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