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Traumatic brain injury: a review of characteristics, molecular basis and management

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1. ABSTRACT

Traumatic brain injury (TBI) is a critical cause of hospitalization, disability, and death worldwide. The global increase in the incidence of TBI poses a significant socioeconomic burden. Guidelines for the management of acute TBI mostly pertain to emergency treatment. Comprehensive gene expression analysis is currently available for several animal models of TBI, along with enhanced understanding of the molecular mechanisms activated during injury and subsequent recovery. The current review focuses on the characteristics, molecular basis and management of TBI.

2. INTRODUCTION

Traumatic brain injury (TBI), characterized by long-term consequences and debilitating post-injury disability, is a major health concern, with an incidence of 1.7 million cases per year in the United States alone (1, 2). The incidence of TBI is increasing globally, largely due to an increase in motor vehicle use among people with low or medium incomes in both developing and developed countries.

TBI is additionally a leading cause of death in childhood. The mortality rate in the U.S. is estimated as 21% within 30 days after TBI. In Germany, ~83,000 children younger than 15 years are hospitalized each year due to head trauma. About 80% of these children present with mild trauma and 20% with moderate or major brain trauma (3–6). TBI refers to a spectrum of focal and diffuse cerebral insults resulting from sudden shock, blunt or transmitted force, hypoxia, intoxication, and vascular injury to the brain. The immediate phase of injury arises from direct mechanical injury while the secondary latent phase results from systemic biochemical and physiological changes involving excitotoxicity, energy failure, ischemia, cell death, edema, delayed axonal injury, and inflammation (7, 8).

3. CHARACTERISTICS OF TBI

Generally, the symptoms of brain injury include unconsciousness, headache, dizziness, confusion and disorientation, blurred vision, difficulty in remembering new information, nausea and vomiting, trouble speaking coherently, and inability to recall the cause of injury or events that occurred immediately before or up to 24 h after the incident (9–15). Symptoms are dependent on the type of TBI and the part of the brain affected. Unconsciousness tends to last longer in people with injuries in the left hemisphere than those with injuries in the right hemisphere of the brain. Symptoms additionally depend on the severity of injury (12–15). Three types of TBI have been classified according to severity: mild, moderate, and severe.

4. CLASSIFICATION OF TBI

TBI has been classified based on severity, mechanism (closed or penetrating head injury) or other features (e.g. occurring in a specific location or over a widespread area) (16, 17).

4.1. Severity

TBI is classified as mild, moderate or severe using the Glasgow Coma Scale (GCS) to estimate

the approximate level of consciousness based on motor, verbal, and eye responses (16, 18). The GCS is the most commonly used system for classifying TBI severity to grade consciousness of patients on a scale of 3 to 15. In general, TBI with a GCS of 13 or above is classified as mild, 9 to 12 as moderate, and 8 or below as severe (19–21). Patients with mild TBI may remain conscious or lose consciousness for a few seconds or minutes. With moderate or severe TBI, patients may suffer persistent headache with repeated vomiting or nausea, convulsions, inability to awaken, aphasia, dysarthria, dilation of one or both pupils, slurred speech, weakness or numbness in the limbs, loss of coordination, confusion, restlessness, or agitation. Common long-term symptoms of moderate to severe TBI are changes in appropriate social behavior, deficits in social judgment, cognitive changes, problems with sustained attention, decline in processing speed, and loss of executive functioning. Cognitive and social deficits have long-term consequences on daily life for people with moderate to severe TBI. However, these symptoms can be improved with appropriate rehabilitation. Young children with moderate to severe TBI may suffer from some of these symptoms, which are difficult to diagnose due to poor communication (19–21).

4.2. Principal mechanisms

TBI is divided into closed and penetrating head injury based on mechanism-related classification (17). A closed (also known as nonpenetrating or blunt) brain injury occurs when the wound does not expose the brain. A penetrating or an open-head injury occurs when an object pierces the skull and breaches the dura matter, the outermost membrane surrounding the brain (22, 23). Closed-head injuries are primarily caused by vehicular accidents, falls, acts of violence, and sports injuries. Falls account for 35.2% of brain injuries in the U.S., with the highest rates recorded in children from 0 to 4 years and adults 75 years and older. Closed-head injuries are the leading cause of death in children under 4 years of age and the most common cause of physical disability and cognitive impairment in young people. Overall, closed-head injuries, ranging from mild to debilitating traumatic brain injuries, and other forms of mild traumatic brain injury account for about 75% out of the estimated annual 17 million brain injuries in the U.S. and can lead to severe brain damage or death. Common closed-head injuries involve concussion, intracranial hematoma, cerebral contusion, and diffuse axonal injury (24, 25). On the other hand, penetrating injuries occur as a direct result of wounding from objects, such as bullets, shrapnel, arrows, knives, forks, glass, nails, scissors, ice picks, pool cues, pencils, plastics, and metal, or indirectly from bone fragments secondary to the original penetrating implement (26, 27). Penetrating injuries may occur anywhere, such as at home or the workplace, recreational facilities and urban or rural settings. The injury may be accidental, intentional, homicidal, or suicidal. Although they represent only a small proportion of total traumatic brain injury, open-head injuries lead to approximately 32,000 to 35,000 deaths each year in the U.S. (26, 27).

4.3. Pathological features

TBI has also been classified based on pathological features. Damage in TBI is categorized as focal or diffuse, confined to specific areas or distributed in a more general manner, respectively. Focal injuries often produce symptoms related to the functions of the damaged area (28-31)

Diffuse injury manifests with little apparent damage in neuroimaging studies, but lesions are evident with microscopy techniques post-mortem (32, 33). Diffusion tensor imaging, a novel method of processing MRI images that presents an effective tool to determine the extent of diffuse axonal injury, may show white matter tracts. Diffuse injuries include edema and diffuse axonal injury representing widespread damage to axons, including white matter tracts, cerebral hemispheres and projections to the cortex (34).

5. THE MOLECULAR BASIS OF TBI

Based on the time-course, brain injury can be divided into primary and secondary injury (35). Primary brain injury exclusively results from the initial impact. Adverse physiologic conditions during recovery after head trauma may account for additional brain damage, referred to as secondary brain injury. Primary brain injury occurs at the moment of trauma when tissues and blood vessels are stretched, compressed, and torn (35). Secondary brain injury, including damage to the blood–brain barrier, release of inflammatory factors, overload of free radicals, excessive release of neurotransmitter glutamate, influx of calcium and sodium ions into neurons, and dysfunction of mitochondria, occurs hours or even days after the initial trauma (35). Injured axons in the white matter of brain may separate from their cell bodies, potentially leading to neuronal death. Other factors in secondary injury are changes in blood flow to the brain, ischemia, cerebral hypoxia, cerebral edema, and raised intracranial pressure (ICP, the pressure within the skull) (36). ICP may rise due to swelling or mass effects from lesions, such as hemorrhage, resulting in reduced cerebral perfusion pressure (37). A dramatic increase in the pressure within the skull can cause brain death or herniation, in which parts of the brain are squeezed by structures in the skull.

Cellular responses result in brain dysfunction after TBI, involving an array of neurotransmitters and neurochemical mediators of injury (38, 39). Cellular excitotoxicity is a key component in the pathophysiology of TBI (21). Excitotoxicity occurs when receptors for the excitatory neurotransmitter glutamate, N-methyl-D-aspartic acid (NMDA) receptor and α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPA)

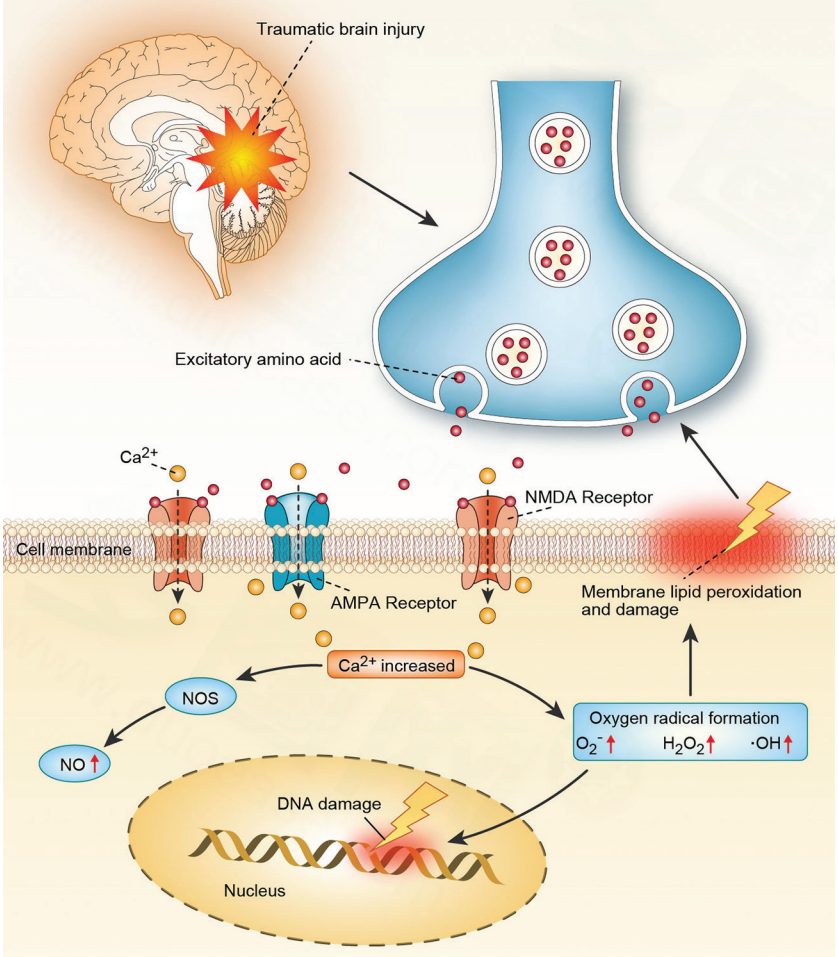

Figure 1. Primary brain injury causes depolarization, leading to the release of excitatory amino acid and activation of NMDA receptors, AMPA receptors and other receptor families. Intracellular calcium is increased in neurons and other brain cells by activated receptors. High levels of intracellular calcium promote oxygen radical reactions. Free radical molecules create an unstable environment in cells that may lead to DNA or cell membrane damage, which in turn triggers increased production and release of excitatory amino acids (e.g. glutamate). Additionally, calcium stimulates the production of NO, which may participate in oxygen radical reactions and lipid peroxidation in neighboring cells, with subsequent release of excitatory amino acids.

receptor (40-42), are overactivated by glutamatergic storm (41, 42). Excitotoxins, such as NMDA and kainic acid that bind to these receptors as well as high levels of glutamate, trigger excitotoxicity by allowing high levels of calcium ions (Ca^{2+}) to enter the cells. Influx of Ca^{2+} into cells activates a number of enzymes, including phospholipases, endonucleases, and proteases, such as calpain, which in turn damage cell structures, such as components of the cytoskeleton, membrane, and DNA (43) (Figure 1). Excitatory neurotransmitter glutamate is rapidly released from injured neurons, thereby activating the NMDA receptor complex, which allows influx of Ca^{2+} into cells unless it is blocked by magnesium. Compounds that block excitatory amino acids like NMDA receptors have been shown to improve neurologic outcomes in animal models of TBI (43).

Along with excitotoxic injury, the other major proposed mechanism for cellular damage after TBI involves oxygen radical reactions. In experimental models of TBI and stroke, oxygen radicals and lipid peroxidation play a significant role in cell dysfunction or death (44, 45). Both depolarization and calcium influx after TBI activate pathways that generate the superoxide radical (O_2), hydroperoxyl radical ($H_2OO\cdot$), and highly reactive hydroxyl radical (·OH) (46). Membrane lipid peroxidation, initiated when an oxygen radical molecule removes a hydrogen atom from unsaturated fatty acid, is the result of damage from oxygen radicals in brain tissues. A chain reaction subsequently leads to loss of a significant proportion of membrane fatty acids. Consequently, the membrane becomes dysfunctional, leading to cell lysis and death (46).

Nitric oxide (NO) is another potential mediator of brain cell damage and death (47, 48). High levels of NO appear to be involved in cell death caused by glutamate excitotoxicity and NMDA receptor activation.

The formation of NO from nitric oxide synthase (NOS) is enhanced by an increase in intracellular calcium. NO also reacts with superoxide to form the peroxynitrite anion that can decay to yield hydroxyl radicals and initiate lipid peroxidation (49).

Additionally, the biologic response to TBI involves apoptosis. Apoptosis is a sequential, energy-dependent process that promotes cell dysfunction via degradation of nuclear DNA. Unlike cell necrosis, apoptosis does not result in a significant inflammatory response, cell membrane destruction or cell swelling (50-52). The primary proteases that lead to degradation of DNA are known as caspases. An important aspect of apoptosis is that caspases acting on neurons must be synthesized after injury. Synthesis of caspases after injury could be postponed via administration of agents that inhibit caspase activity (52).

Extracellular concentrations of many other neurochemicals, including γ–aminobutyric acid, adenosine, acetylcholine, endogenous opioids, bradykinin, and cytokines, are increased immediately after TBI. Animal studies have suggested that blocking the effects or activities of these molecules may have a neuroprotective effect. For example, administration of an opiate antagonist improved cerebral hemodynamics, decreased mortality, and improved neurologic outcome in an animal model of TBI (53, 54).

Recent comprehensive gene expression analyses conducted in TBI animal models revealed that genes associated with inflammation or immune processes and cytokine activity are invariably upregulated while those associated with neurotransmission or plasticity, development and metabolism are preferentially downregulated (55). Interestingly, alterations in glucose metabolism present a hallmark of TBI across experimental models, and have also been observed clinically. Immediately after TBI, adult rat brain shows an indiscriminate efflux of ions and neurotransmitters and a transient increase in local cerebral metabolic rate of glucose (LCMRglc), due to the increased cellular energy required to restore ionic balance and maintain the neuronal membrane potential. A longer period (10–14 days) of glucose metabolic depression follows this transient increase in LCMRglc (56, 57).

6. DIAGNOSIS, MANAGEMENT AND PROGNOSIS OF TBI

As with all acute pathologies, the quality of care and treatment largely depends on the caregiver's determination. Pre-hospital assessment is necessary for patients to determine whether head trauma has occurred, estimate the severity of injury to the brain, detect hypotension and/or hypoxia, and identify risk factors for acute complications of TBI as well as other injuries that may require urgent management (58). Acute complications of TBI require intervention, especially intracranial bleeding. Clinical evidence has indicated three therapeutic strategies of importance to prevent or minimize secondary brain injury, avoid hypoxemia or post-traumatic arterial hypotension and refer traumatized patients to the emergency department (59-61). Transportation of TBI patients for the appropriate treatment is a key step in management. During transportation and inpatient service, the primary concerns are to ensure proper oxygen supply, maintain adequate blood flow to the brain, and control raised ICP, which could deprive the brain of divengent blood flow and cause fatal brain herniation. Additional methods to prevent damage are management of other injuries and prevention of seizures (62).

Diagnosis of TBI often requires physical examination of the head and verbal assessment by a physician. Using either the GCS or Rancho Los Amigos Coma Scale, TBI patients are assessed with regard to their level of consciousness and ability to speak, move and open their eyes. Diagnosis is mainly based on the circumstances of lesions and clinical evidence, predominantly, neurological presentation (63, 64).

Neuroimaging aids in diagnosis and prognosis as well as deciding on potential treatments. The preferred radiologic test in the emergency setting is computed tomography (CT) (65). Follow-up CT scans may be subsequently performed to determine the progression of injuries (66). Magnetic resonance imaging (MRI) is another medical imaging technique employed to further confirm diagnosis. MRI is used in radiology to investigate the anatomy and physiology of the body in both health and disease (67). MRI scanners use strong magnetic fields and radiowaves to generate images of the body (68).

Management of TBI, especially in children, should be optimized to prevent secondary brain injury. Patients with moderate to severe injuries are likely to receive treatments in an intensive care unit with close attention from neurologists (69). Individual treatments depend on the recovery stages of the patients. In the acute stage, the primary aim is to stabilize the patient and prevent further injury, since little can be done to reverse the initial damage caused by trauma (70).

After initial resuscitation and stabilization, the main therapeutic strategy is to control the increasing ICP due to the formation of brain edema, intracerebral hemorrhage or cerebrospinal fluid stasis. Increased ICP presents a major complication after TBI and significantly increases mortality among patients. Elevated ICP may be treated by simply tilting the patient's bed or straightening the head to promote blood flow through the veins at the neck (71, 72). Sedatives, analgesics and paralytic agents are often employed. Hypertonic saline can improve ICP

by reducing the amount of cerebral fluid, but is used with caution to avoid electrolyte imbalance or heart failure. Mannitol, an osmotic diuretic, appears to be equally effective in reducing ICP. Furthermore, a catheter placed into the lateral ventricle may allow continuous drainage of cerebrospinal fluid, thereby providing a direct means to reduce ICP as well as detect intracranial hemorrhage early in some cases, prior to the appearance of neurological symptoms. Surgery can be performed on mass lesions or to eliminate objects that have penetrated the brain. Mass lesions, such as contusions or hematomas that cause a significant mass effect (shift of intracranial structures), are considered emergencies and require immediate surgical removal (73, 74). For intracranial hematomas, collected blood may be removed using suction or forceps or floated off with fluid. Surgeons usually attempt to detect hemorrhaging blood vessels and seek to control bleeding. In penetrated brain injury, damaged tissue is surgically debrided, and craniotomy, involving removal of part of the skull, may be needed to remove pieces of fractured skull or objects embedded in the brain (73, 74).

Once medically stable, patients may be transferred to a subacute rehabilitation unit in a medical center or an independent rehabilitation hospital. Clinical post-TBI recovery takes months or even years. Rehabilitation aims to improve independent function at home and society and aid in adaption to disabilities, and is the major option for the subacute and chronic stages of recovery. International clinical guidelines have been proposed with the aim of guiding decisions in TBI treatment, as defined by an authoritative examination of current evidence (75, 76).

Individuals with behavioral problems following TBI should be referred to specialist behavioral management services. Psychotropic medications used to manage agitation and aggression in people with TBI should be carefully selected according to their side-effect profiles, and patients need to be closely monitored. If no effect is observed within the first six weeks, prescription of the drug should be stopped. People with persistent cognitive deficits following TBI should be offered function-oriented cognitive rehabilitation that includes improvement of attention and information processing skills, teaching of compensatory techniques, use of external memory aids, and acquisition of procedural learning information and principles (77-79).

Prognosis differs depending on the severity and location of lesions and access to immediate, specialized acute management. Prognosis worsens with the severity of injury (80, 81). While the majority of TBIs are mild and do not cause permanent disability, all levels of TBI have the potential to cause significant, long-term disability. Permanent disability occurs in 10% mild injury, 66% moderate injury, and 100% severe injury cases. Most mild TBI is completely resolved within three weeks, and almost all these patients are able to live independently and return to their previous jobs prior to injury, although a proportion may have mild cognitive and social impairments. Over 90% of people with moderate TBI are able to live independently, although some require assistance with physical abilities, employment, and financial managing (82). The majority of people with severe closed-head injury either die or recover enough to live independently; middle ground is rarely seen (83, 84).

7. CONCLUSIONS AND FUTURE DIRECTIONS

Injury to the brain is the leading factor in mortality and morbidity from traumatic injury. The devastating personal, social and financial consequences of traumatic brain injury are compounded by the fact that most people with TBI are young and previously healthy. While several guidelines have been proposed for the management of TBI, the molecular basis remains incompletely understood. Increasing evidence indicates that molecular responses related to growth, development and metabolism play a critical role in understanding both acute injury response and post acute recovery phases in TBI. Gene expression analysis has revealed that many of these changes occur at the transcriptional level. Other studies indicate that metabolic substrate control can be preferentially regulated through changes in transporters and enzymatic activities. Elucidation of the interrelationships between cellular metabolism and activity-dependent neuroplasticity in future studies may facilitate the development of effective therapeutic interventions.

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Abbreviations: AMPA, α-amino-3-hydroxy- 5-methyl-4-isoxazole-propionic acid; CT, computed tomography; GCS, Glasgow Coma Scale; ICP, intracranial pressure; LCMRglc, local cerebral metabolic rate of glucose; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartic acid; NO, nitric oxide; NOS, nitric oxide synthase; TBI, traumatic brain injury

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