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# Secondary Tissue Damage in Acute Traumatic Brain Injury

**Rakhimova Gulnoz Shamsievna**
Bukhara State Medical Institute

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**ABSTRACT**

Traumatic brain injury (TBI) remains one of the leading causes of morbidity and mortality among civilians and military personnel worldwide. Every year, more than 50 million people worldwide suffer from TBI. Despite advances in our knowledge of the complex pathophysiology of TBI, the underlying mechanisms have yet to be fully elucidated.

According to the unique physical mechanisms of TBI injury , it can be divided into three categories: 1. Closed; 2. Penetrating; 3. Explosive TBI.

Closed craniocerebral trauma usually occurs as a result of blunt force trauma, mainly as a result of road accidents, falls and sports. The incidence of this form of TBI is the highest among the civilian population.

Neural tissue damage associated with TBI is divided into two categories: 1. Primary injury that is directly caused by mechanical forces during the initial stroke; and 2. Secondary damage, which refers to further damage to tissues and cells after the primary damage.

**Primary brain injuries**

The direct impact of various mechanical damage to the brain can cause two types of primary damage: focal and diffuse brain damage. As a result of lacerations, compression and concussion, with a closed head TBI and penetrating TBI, there is focal brain damage with signs of a skull fracture and localized contusion in the center of the injury site. The necrotic area of neuronal and glial cells is concentrated in places with impaired blood supply, causing the occurrence of hematomas, epidural, subdural and intracerebral hemorrhages in limited layers of the brain. A strong blunt and compressive contact force disrupts the normal functioning of the brain directly under the impact site, which leads to immediate damage to brain vessels and neural cells. Displacement of the brain due to vibrations and shocks that occur during impact can also lead to compression of brain tissues and a decrease in cerebral blood flow. Both mechanisms

eventually lead to focal localized bruises or diffuse damage to other areas of the brain.

**Secondary brain injuries**

Biochemical, cellular and physiological phenomena that occur during primary damage often develop into delayed and prolonged secondary damage, which can last from several hours to several years. Mechanically, a number of factors contribute to secondary damage, including excitotoxicity, mitochondrial dysfunction, oxidative stress, lipid peroxidation, neuroinflammation, axon degeneration and apoptotic cell death.

BBB dysfunction caused by TBI injury ensures the transmigration of activated leukocytes into the damaged parenchyma of the brain, which is facilitated by the activation of cell adhesion molecules. Activated leukocytes, microglia and astrocytes produce ROS and inflammatory molecules, such as cytokines and chemokines, which contribute to demyelination and destruction of the axonal cytoskeleton, leading to axonal edema and accumulation of transport proteins at the terminals, thereby disrupting the activity of neurons. Progressive damage to axons leads to neurodegeneration. In addition, astrogliosis at the site of the lesion causes the formation of a glial scar, which creates a non-permissive environment that prevents the regeneration of axons. On the other hand, excessive accumulation of neurotransmitters glutamate and aspartate in the synaptic space due to leakage from ruptured neurons, glutamate-induced enhanced release from presynaptic nerve endings and disruption of reuptake mechanisms in the traumatic and ischemic brain activate NMDA and AMDA receptors located on postsynaptic membranes that provide an influx of calcium ions. Together with the release of Ca2+ from the intracellular depot (ER), these events lead to the production of ROS and activation of calpains. As a result of mitochondrial dysfunction, molecules such as apoptosis-inducing factor (AIF) and cytochrome C are released into the cytosol. These cellular and molecular events, including the interaction of the Fas-Fas ligand, eventually lead to the caspase-dependent and -independent death of neurons.

**Excitotoxicity**

Studies in both animals and humans have shown that the destruction of the BBB and the primary death of neurons during TBI cause excessive release of excitatory amino acids, such as glutamate and aspartate, from presynaptic nerve endings. The presence of excess glutamate during TBI is also facilitated by a violation of glutamate reuptake due to dysfunction of glutamate transporters. Activation of NMDA receptors by glutamate promotes the production of reactive oxygen species and nitric oxide, which further aggravates secondary damage to cells. Excess Ca 2+ in the cytosol also activates a number of proteins that cause apoptotic cell death, such as calcineurin, calpain and caspases. Thus, excessive stimulation of glutamate receptors due to the massive release of excitatory neurotransmitters leads to post-traumatic oxidative stress and excitotoxic cell death over a long period.

**Mitochondrial dysfunction**

Mitochondrial dysfunction is one of the characteristic signs of TBI, which contributes to metabolic and physiological disorders that cause cell death. The sequestration of intracellular Ca 2+ and the influx of excess ions into the mitochondria leads to the production of ROS, depolarization of the mitochondrial membrane and inhibition of ATP synthesis. Electron microscopic analysis of mitochondria revealed significant swelling and structural damage, such as destruction of the crist membrane and loss of membrane potential. In addition, mitochondrial proteins such as cytochrome C and apoptosis inducing factor (AIF) are released into the cytosol, which play a crucial role in apoptotic cell death.

**Release of reactive oxygen species and lipid peroxidation**

Endogenous ROS and free radicals are constantly generated after TBI from various sources, such as enzymatic processes, activated neutrophils, excitotoxic pathways and dysfunctional mitochondria. On the other hand, the accumulation of Ca 2+ after TBI increases the activity of nitric oxide synthase (NOS), which contributes to the formation of NO. The reaction between excess NO and superoxides of free radicals leads to the formation of peroxynitrite (PN), which causes oxidative damage.

**Neuroinflammation**

In the acute 24-hour period after TBI, BBB dysfunction promotes the infiltration of circulating neutrophils, monocytes and lymphocytes into the damaged parenchyma of the brain. Polymorphonuclear leukocytes release complement factors and pro-inflammatory cytokines such as IL-1ß, IL-6 and TNF-α, as evidenced by an increase in the corresponding mRNA and protein 24 hours after injury.

**Axonal degeneration**

Wallerian degeneration is widely observed within a few minutes after TBI. Direct mechanical damage leads to disorganization of the axonal cytoskeletal network consisting of longitudinally oriented neurofilaments and microtubules. Along with permanent calcium-mediated proteolysis, acute axon damage can progress and develop into delayed and secondary axotomy a few days and months after the initial injury, which is characterized by degradation of the myelin sheath, axonal transport disruption and accumulation of axonal transport proteins.

**Glial scar and myelin-associated axon growth inhibitors**

Damage to the central nervous system often causes activation and proliferation of astrocytes. The formed reactive astrocytes infiltrate into the lesion and undergo reactive astrogliosis, which involves hypertrophy and complication of their processes. The mixing of astrocytic processes with oligodendrocytes, meningeal cells, microglia and fibroblasts gradually turns into a scar structure, which has long been considered the main physical obstacle to axon regeneration and counteracts recovery after TBI.

**Apoptotic cell death**

Apoptotic death of neurons and oligodendrocytes is a sign of secondary brain damage, the death of neurons in the human hippocampus is observed within 1 year after TBI. These apoptotic events include activation of cysteine proteases such as caspases and calpain, and can be triggered by the interaction of various neurochemical, cellular, and molecular pathways.

**Violation of autophagy and lysosomal pathways**

Autophagy is an adaptive homeostatic process that regulates the turnover of cellular organelles and proteins through a lysosome-dependent degradation pathway. Autophagy plays an important role in cytoprotection, maintaining cell stability and survival by eliminating abnormal intracellular proteins or organelles when cells are damaged or under stress, although it is also involved in the regulation of apoptotic cell death, inflammation and adaptive immune responses. In fact, many neuroprotective drugs alleviate secondary damage caused by TBI by activating autophagy. Nevertheless, lysosomal function is often impaired in TBI, which is associated with an increase in the permeability of the lysosomal membrane. This leads to disruption of autophagic flow and pathological accumulation of autophagosomes and their cargo, causing the death of neurons and aggravating the severity of injury.

**Conclusion:** Studies of traumatic injuries of the central nervous system have significantly expanded our understanding of the underlying pathophysiology and molecular mechanisms. While primary injuries in TBI are mostly irreversible, subsequent secondary injuries that develop

and progress over months or years are amenable to therapeutic interventions. Since this delayed phase of damage involves many events that include excitotoxicity, apoptotic cell death, inhibition of axon regeneration, neuroinflammation and oxidative stress, the development of effective therapeutic strategies should target several mechanisms over a long period of time.

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