Medicolegal Aspect of Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) still represents the leading cause of morbidity and mortality in individuals under the age of 45 years in the world. Numerous experimental and clinical analyses of biomechanical injury and tissue damage have expanded the knowledge of pathophysiological events which potentially serves as the basis to define new or refine established treatment strategies. Traumatic brain injury (TBI) is usually caused by motor vehicle accidents, falls and assaults. „ TBI can be classified based on severity (mild, moderate or severe) mechanism (missile or blunt) and pathology (primary or secondary. Of all regional injuries, those of the head and neck are the most common and most important in forensic practice. These are the reasons of this dominance of head injuries. Significantly increased risk of mortality, the secondary complications of traumatic brain injury (TBI) must be recognized early and managed appropriately. Conditions such as spasticity, venous thromboembolism, paroxysmal sympathetic hyperactivity, neuroendocrine dysfunction, heterotopic ossification, nutritional deficits, and sleep disturbances can all negatively affect functional outcomes and community reintegration.

Keywords: Medicolegal Aspect, Traumatic Brain Injury

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Introduction:

Traumatic brain injury (TBI) still represents the leading cause of morbidity and mortality in individuals under the age of 45 years in the world. Numerous experimental and clinical analyses of biomechanical injury and tissue damage have expanded the knowledge of pathophysiological

events which potentially serves as the basis to define new or refine established treatment strategies (1).

Traumatic brain injury (TBI)—the "silent epidemic"— a growing public health concern, contributes to worldwide death and disability more than any other traumatic insult. Yet, TBI incidence and distribution across regions and socioeconomic divides remain unknown. In an effort to promote advocacy, understanding, and targeted intervention, the authors sought to quantify the case burden of TBI across World Health Organization (WHO) regions and World Bank (WB) income groups (1).

❖ ***Biomechanical and neuropathological classification of injury:***

Traumatic brain injury (TBI): Traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force (2).

The principal mechanisms of TBI are classified as (a) focal brain damage due to contact injury types resulting in contusion, laceration, and intracranial haemorrhage or (b) diffuse brain damage due to acceleration/deceleration injury types resulting in diffuse axonal injury or brain swelling. Outcome from head injury is determined by two substantially different mechanisms/stages: (a) the primary insult (primary damage, mechanical damage) occurring at the moment of impact. In treatment terms, this type of injury is exclusively sensitive to preventive but not therapeutic measures. (b) The secondary insult (secondary damage, delayed non-mechanical damage) represents consecutive pathological processes initiated at the moment of injury with delayed clinical presentation. Cerebral ischaemia and intracranial hypertension refer to secondary insults and, in treatment terms, these types of injury are sensitive to therapeutic interventions (2).

❖ ***Pathophysiology:***

TBI is characterized by two injury phases, primary and secondary. The primary brain injury includes cerebral contusions, extra-axial hematomas (epidural, subdural, and subarachnoid hemorrhages), and diffuse axonal injury, is the direct injury to the brain cells incurred at the time of the initial impact. This results in a series of, biochemical processes which then result in secondary brain injury. The secondary brain injury is caused by a dynamic interplay between ischaemic, inflammatory and cytotoxic processes (3).

Traumatic brain injury (TBI) can be categorized in several ways; physical mechanism (e.g., penetrating versus non-penetrating; direction of acceleration), magnitude of force, single versus multiple, and temporal spectrum from acute to chronic. Relatively mild injuries such as concussions, by definition, have no gross or histologic findings, but may have occurred in individuals who died as a consequence of trauma to another part of the body or drug/alcohol toxicity. More severe brain injuries, which can cause death, usually present with intracranial hemorrhages (e.g., epidural, subdural, subarachnoid, and intraventricular) and parenchymal lesions (e.g., contusions, lacerations, or diffuse axonal injury [DAI]). If the victim survives, the

evolving lesion can develop cerebral edema and swelling, anatomical herniations, secondary hypoxic-ischemic (HI) damage, inflammation, and (with penetrating injury) infection **(4).**

Vascular lesions frequently accompany trauma, or they can occur in the clinical situation of stroke. These are categorized as ischemic (focal interruption of blood flow) or hemorrhagic (rupture of a subarachnoid or parenchymal blood vessel). Diffuse HI brain injury can follow arterial hypotension, hypoxia, cardiac arrest, or respiratory arrest. The first stages of cerebral injury after TBI are characterized by direct tissue damage and impaired regulation of CBF and metabolism. This 'ischaemia-like' pattern leads to accumulation of lactic acid due to anaerobic glycolysis, increased membrane permeability, and consecutive oedema formation. Since the anaerobic metabolism is inadequate to maintain cellular energy states, the ATP-stores deplete and failure of energy-dependent membrane ion pumps occurs **(1).**

TBI is characterized by an imbalance between cerebral oxygen delivery and cerebral oxygen consumption. Although this mismatch is induced by several different vascular and haemodynamic mechanisms, the final common endpoint is brain tissue hypoxia **(5).**

TBI is primarily and secondarily associated with a massive release of excitatory amino acid neurotransmitters, particularly glutamate. This excess in extracellular glutamate availability affects neurons and astrocytes and results in over-stimulation of ionotropic and metabotropic glutamate receptors with consecutive Ca2þ, Na þ, and Kþ-fluxes **(5).**

Although these events trigger catabolic processes including blood–brain barrier breakdown, the cellular attempt to compensate for ionic gradients increases Naþ/Kþ-ATPase activity and in turn metabolic demand, creating a vicious circle of flow–metabolism uncoupling to the cell **(6).**

Two different types of cell death may occur after TBI: necrosis and apoptosis (programmed cell death). Necrosis occurs in response to severe mechanical or ischaemic/ hypoxic tissue damage with excessive release of excitatory amino acid neurotransmitters and metabolic failure. However, apoptosis (programmed cell death) becomes evident hours or days after the primary insult **(1).**

❖ ***Classification of traumatic brain injury:***

Traumatic brain injury (TBI) is usually caused by motor vehicle accidents, falls and assaults. „ TBI can be classified based on severity (mild, moderate or severe) mechanism (missile or blunt) and pathology (primary or secondary) **(2).**

The primary selection criterion for inclusion in a TBI clinical trial is the Glasgow Coma Scale (GCS), a clinical scale that assesses the level of consciousness after TBI. Patients are typically divided into the broad categories of mild, moderate, and severe injury. While the GCS has proved to be extremely useful in the clinical management and prognosis of TBI, it does not provide specific information about the pathophysiologic mechanisms responsible for the neurological deficits **(7).**

There are different systems for classifying traumatic brain injury (TBI). Systems include classifying traumatic brain injury by severity, which is generally based on clinical indexes at the time of presentation. TBI can be classified by pathoanatomic type i.e., type of injury such as diffuse axonal injury, haematoma and haemorrhages. Further classification systems include classification of TBI by outcome and prognosis **(7).**

Multiple criteria are used in each diagnosis including loss of consciousness, post-traumatic amnesia (PTA), skull fracture, and evidence of neuroradiological abnormalities including subdural haematoma (SDH), cerebral contusion, and hemorrhagic contusion. A TBI would be classified as definite moderate-severe if one or more of the following criteria apply: death due to this TBI, loss of consciousness of 30 minutes or more, PTA of 24 hours or more, and worst GCS full score in first 24 hours is <13 providing this not invalidated by other factors such as intoxication or sedation. In addition, if there is evidence of neurological injury such as haematoma, contusion, haemorrhage then the TBI would be in the definite moderate-severe category **(8).**

A TBI would be classified as probable mild if there is loss of consciousness below 30 minutes, PTA is less than 24 hours, and there is a depressed, basilar, or linear skull fracture (dura intact). A possible TBI is diagnosed if there are one or more of the following symptoms: blurred vision, confusion, feeling dazed, dizziness, headache, or nausea **(9).**

Medicolegal aspect of traumatic brain injury:

Of all regional injuries, those of the head and neck are the most common and most important in forensic practice. These are the reasons of this dominance of head injuries: **(Adelson, 1974).**

1. The head is the target of choice in the great majority of assaults involving blunt trauma.
2. When the victim is pushed or knocked to the ground, he often strikes his head.
3. The brain and its coverings are vulnerable to degrees of blunt trauma that would rarely be lethal if applied to other areas.

Forensic anatomy of the head: There are three main components of the head: scalp, skull and brain (Fig.1). „ The term 'craniocerebral injuries' can be used to describe the presence of skull ('cranio') and brain ('cerebral') injury. **(2).**

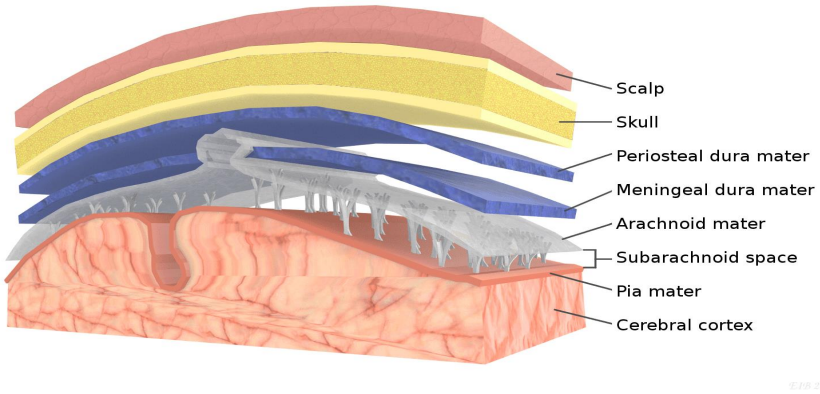

figure 1. Layers of the head.

Cranio-cerebral injuries are either focal or diffuse: (2).

focal	diffuse
Scalp lacerations.	Axonal injury (DAI).
Skull fractures.	Ischaemic.
Contusions/lacerations.	Vascular.
Intracranial hemorrhage.	Brain swelling.
Lesions due to increased intracranial pressure.	

Table 1. classification of craniocerebral injuries.

On the basis of localization of injuries, it is possible to conclude if they resulted from blows (assault), brain shows much larger contusions underlying the area of impact (coup) than on the site opposite to impact (contrecoup) figure 2. Contrecoup lesions are rare (2).

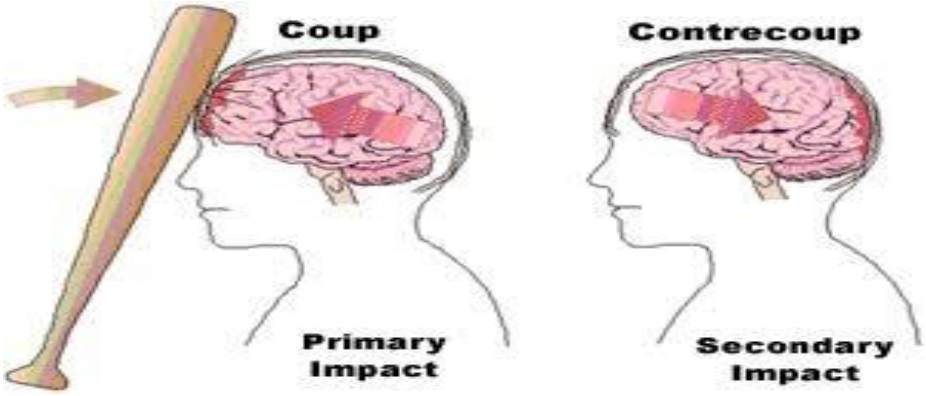

Figure 2. coup and countercoup injury

Complications of traumatic brain injury:

Significantly increased risk of mortality, the secondary complications of traumatic brain injury (TBI) must be recognized early and managed appropriately. Conditions such as spasticity, venous thromboembolism, paroxysmal sympathetic hyperactivity, neuroendocrine dysfunction, heterotopic ossification, nutritional deficits, and sleep disturbances can all negatively affect functional outcomes and community reintegration **(10).**

Intracranial hemorrhage is a common complication of head injury, and is the most common cause of death in patients who experienced a lucid interval, 'talk and die', or 'talk and deteriorate after injury'. „ Clinical complications associated with a hematoma are related to the size/volume of the lesion, the anatomical location and the rapidity with which it develops. „ Hypovolemic shock cannot happen from intracranial bleeding; there is not enough space inside the head for the amount of blood loss needed to produce shock **(2).**

Histopathological changes of traumatic brain injury:

Histology should be used to augment macroscopic diagnoses, particularly in the absence of gross evidence of intracranial trauma. Histology can detect nontraumatic causes of seemingly traumatic lesions. Histology can help estimate the survival interval after an insult. However, even detailed documentation of cytologic, inflammatory, and immunohistochemical changes is at best an approximation. Note that the legal time of death might not be the same as the biological time of death **(11).**

An integrated consideration of the macroscopic and microscopic features, along with historical and medical evidence is necessary to distinguish TBI from HI from artifact. Even if TBI is definite, examination of the brain in isolation cannot help distinguish between accidental and nonaccidental etiologies **(11).**

Inflammatory reactions are somewhat helpful in estimating the stage of intracranial lesions. Histologic aging can help determine if an insult occurred within an alleged time frame. This involves estimating the time between when an insult occurred and death (the posttraumatic interval or survival interval). The general tempo of changes is similar in intracerebral and meningeal (i.e., subdural and epidural) hematomas, but there are major cytologic differences. The meninges lack the microglial reaction but exhibit a much more exuberant fibrovascular proliferation in the resolution phase. The phases of healing after traumatic tissue injury can be categorized by distinct, chronologic, partially overlapping morphological changes that have been established by numerous experimental investigations **(11).**

In general, neuronal pathology of brain trauma includes necrosis, apoptosis, gliosis, and atrophy. Neurons' response to external damage by several morphological changes, such as swelling, chromatolysis, pyknosis, hypochrome, and hyperchrome **(12).**

Apoptosis of neurons and glia contribute to the overall pathology of traumatic brain injury (TBI) in both humans and animals. In both head-injured humans and following experimental brain injury, apoptotic cells have been observed alongside degenerating cells exhibiting classic necrotic morphology. Neurons undergoing apoptosis have been identified within contusions in the acute port-traumatic period, and in regions remote from the site of impact in the days and weeks after trauma. Apoptotic oligodendrocytes and astrocytes have been observed within injured white matter tracts **(13).**

Owing to their high metabolic needs and vulnerability to excitotoxicity, neurons are generally more sensitive to hypoxic-ischaemic injury (HI) than macroglia (i.e., astrocytes and oligodendrocytes), microglia, or endothelia **(14).**

In the mature brain, the most sensitive populations (or at least the most obvious victims) are the long-projection large neurons of the third and fifth neocortical layers, the neurons of the hippocampal CA1 regions, and the Purkinje neurons of the cerebellum. Histologic changes following HI are determined by the pathobiology **(15).**

Early subtle changes can be difficult to define in autopsy samples. Also, not all cellular processes are energy dependent and morphology is not immediately frozen after death; passive water movements can continue after death. Swelling with cytoplasmic pallor of neurons and astrocytes occurs within 15-30 minutes of HI because the Na+-K+ exchange pumps are dependent on ATP; water passively follows the altered ion gradients. This can give the tissue a spongy or pale appearance at low magnification as early as one hour after the insult. Occasionally, swelling of specific organelles including Golgi apparatus and endoplasmic reticulum can be identified in compromised neurons **(16).**

The cerebral vasculature possesses a blood-brain barrier (BBB) that is necessary for homeostasis of the neuronal extracellular environment. So-called “vasogenic edema” is the result of a disrupted BBB and subsequent movement of plasma proteins into the brain. Histologically, enlarged extracellular spaces are expanded by acellular, faintly eosinophilic material. Macroglia can ingest plasma proteins, presumably by pinocytosis, whereupon they become engorged and uniformly eosinophilic (figure 3) **(17).**

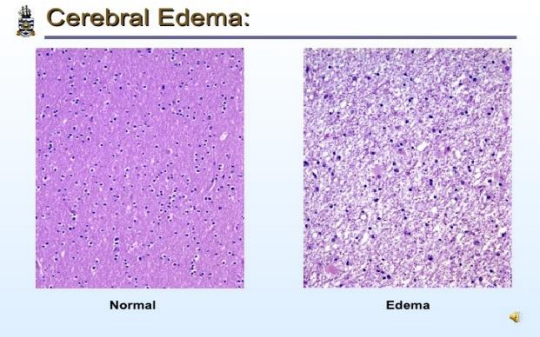

Figure 3. cerebral edema

Cortical contusions (figure 4) are more complex lesions because the blood collections are interspersed with viable and damaged brain parenchyma. Immediately after trauma, ruptured blood vessels release blood cells and plasma into the extracellular spaces. Some neurons are subject to HI damage because the vascular supply is interrupted while others are compromised by plasma enzymes (e.g., thrombin and plasmin) **(17).**

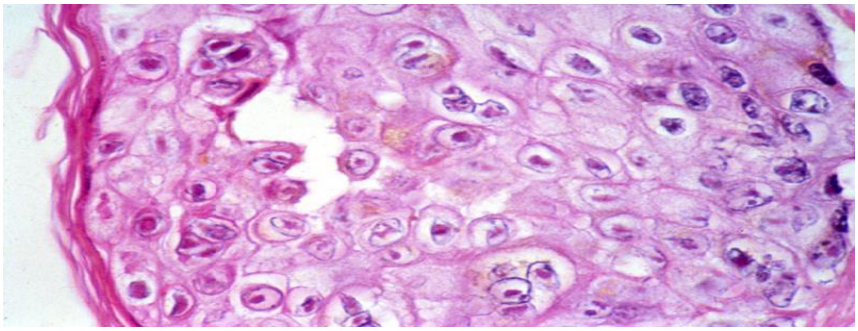

Figure 4 . cortical contusion

Diffuse Axonal Injury (DAI) figure 5. Defined as a focal lesion in the corpus callosum, focal lesions in one or both dorsolateral sectors of the rostral brainstem adjacent to the cerebellar peduncles, and diffuse damage to axon. Such a distribution of injured axons has been achieved in only on animal models, as its diagnosis is only made postmortem depending on presence of injured axons **(18).**

Diffuse Axonal Injury (DAI) is one of the most common and important pathological features of traumatic brain injury (TBI). Axons in the white matter appear to be especially vulnerable to injury due to the mechanical loading of the brain during TBI. As such, DAI has been found in all severities of TBI and may represent a key pathologic substrate of mild TBI (concussion) **(18).**

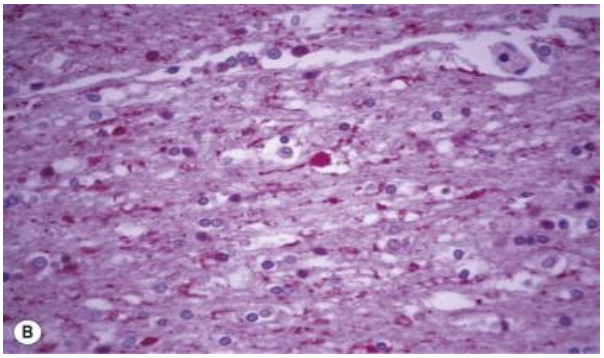

Figure 5. Diffuse Axonal Injury

Tumor necrosis factor alpha (TNF-α):

Decades ago, the brain was thought to be refractory to immune activation due its isolation from the bloodstream. Despite being modest compared to the immune activation occuring in peripheral organs or in infectious diseases of the nervous system, the brain is capable of eliciting immune response acutely following trauma **(19).**

Experiments in animal models of TBI have revealed a plethora of inflammatory mediators that are expressed in the brain following injury. Many of these exhibit rapid changes in expression, reaching peaks of over 1000 orders of magnitude greater than physiological levels within hours of injury **(20)**.

Traumatic brain injury (TBI) is associated with secondary injury to the central nervous system (CNS) via inflammatory mechanisms. The combination of polytrauma and TBI further exacerbates the inflammatory response to injury **(21)**.

The cytokine tumor necrosis factor (TNF-alpha) is a pleotrophic polypeptide that plays a significant role in brain immune and inflammatory activities. TNF-alpha is produced in the brain in response to various pathological processes such as infectious agents [e.g., human immunodeficiency virus (HIV) and malaria], ischemia, and trauma. TNF-alpha mRNA is rapidly produced in response to brain ischemia within 1 h, reaches a peak at 6-12 h post ischemia, and subsides 1-2 days later. TNF-alpha mRNA expression corresponds in a temporal fashion to other cytokines such as interleukin (IL)-6, cytokine-induced neutrophil chemoattractant (KC), and IL-1 and precedes the infiltration of inflammatory cells into the injured zone. TNF-alpha is present early in neuronal cells in and around the ischemic tissue (penumbra), yet at later time points, the peptide is found in macrophages in the infarcted tissue **(22)**.

TBI induces increased production of tumor necrosis factor (TNFα) by brain resident cells. There is conflicting evidence on the role of this response in the injured brain, showing its potential effect in both processes of repair and of damage, its inhibition by pharmacologic agents, neutralizing antibodies or soluble receptors has protective effects. In contrast, there are reports (from in-vitro studies or knock-out mice) on the beneficial effects of TNFα **(23)**.

Active upregulation of the synthesis and release of various molecules can also drive immune cell reactivity **(20)**. It is well established that TNF-α, IL-6, and IL-1β are major drivers of neuroinflammation while IL-10 acts as an anti-inflammatory molecule. TNF-α mRNA and proteins are rapidly generated, producing detectable levels within minutes and reaching peak concentrations within a few hours after TBI in pre-clinical animal models. The varying intensity of immune responses reported in individuals affected by brain trauma (figure 6) has spurred several investigations that support a predisposition to higher and prolonged cytokine production in female patients **(19)**.

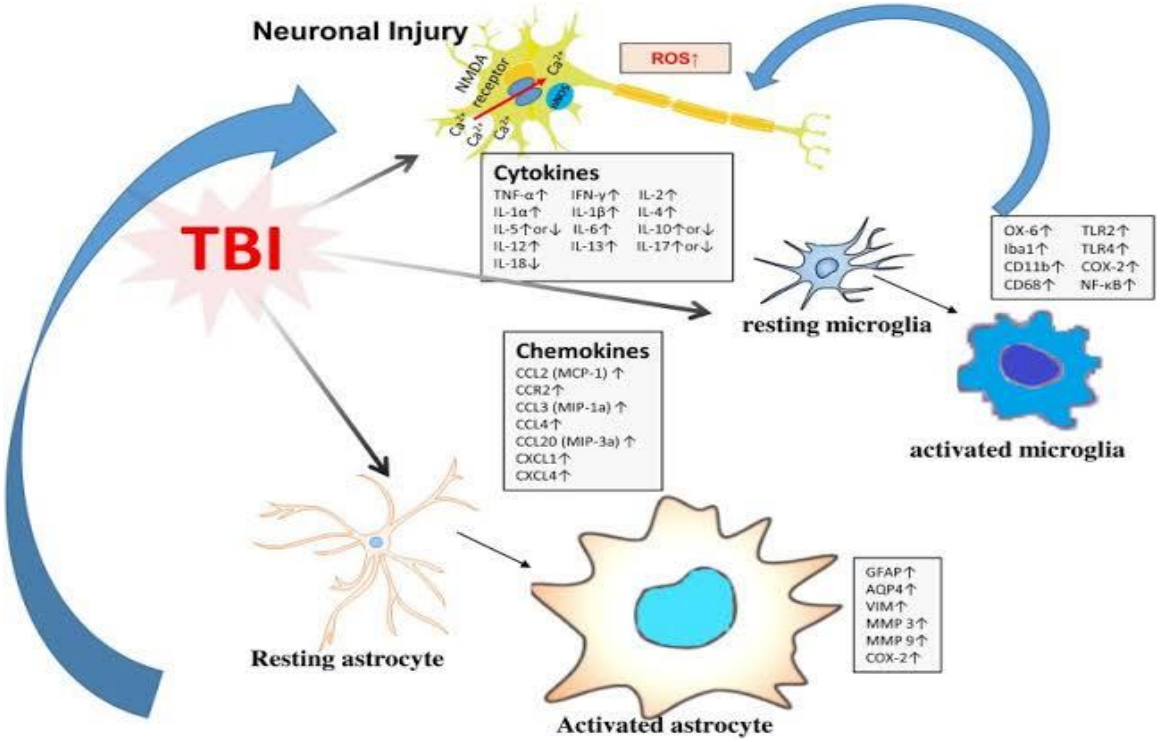

Figure 6. Neuroinflammation following TBI

P 53:

P53 is a tumor suppressor and its 19 kb gene (TP53) is situated on chromosome 17p13.1. It consists of 11 exons resulting in a transcript of 2,629 bp and a protein of 393 amino acids. In half of all human cancers, the tumor suppressor p53 is damaged by somatic mutation in tumor cells. This protein is at the centre of cell regulatory pathways, influencing transcription and activity of several replication and transcription factors, and is known as the guardian of the genome **(24).**

The p53 molecule is a tumour suppressor that prevents the outgrowth of aberrant cells, by inducing cell cycle arrest, DNA repair or programmed death. In healthy cells, p53 is barely detectable; in contrast, most tumour cells manifest accumulation of p53 protein. Tumour-associated p53 accumulation may activate p53 autoimmunity; thus, autoantibodies to p53 can serve as markers for established or even incipient tumours. However, p53 accumulation may also occur in non-tumour cells under various forms of stress; thus, it has become clear that the occurrence of p53 antibodies is not restricted to cancer, but can also happen in a variety of autoimmune diseases. Moreover, the p53 antibodies found in autoimmune disease appear to be associated with autoantibodies to DNA. The pathogenic relevance of p53 autoantibodies is currently not clear **(25).**

A growing body of evidence suggests that neurons undergo apoptotic cell death following traumatic brain injury (TBI). Since the expression of several tumor suppressor and cell cycle genes have been implicated in neuronal apoptosis, studies have proved upregulation and participation in molecular response of tumor suppressor gene p53 in TBI. Recent studies indicated that p53 played a crucial

role in neuronal apoptosis and regeneration following TBI. However, the detailed mechanism of p53-induced neuronal apoptosis in TBI remains largely elusive. The P53 gene is important in the regulation of apoptosis; this gene exhibits a common polymorphism that results in either proline or arginine at amino acid 72. Arg/Arg genotype of the Arg72Pro polymorphism in p53 is associated with an increased likelihood of a poor outcome at discharge from the surgical intensive care unit following TBI **(26).**

Multiple studies concluded that after experimental TBI in mice p53 rapidly accumulated in the injured brain tissue and translocated to the nucleus of damaged neurons. The signal responsible for inducing p53 in injured neurons is not presently known, although DNA damage is the most likely candidate for such a stimulus. Recent evidence suggests that DNA strand breaks, but not other DNA lesions, are capable of inducing p53 accumulation **(27).**

The regulation of p53 expression and the consequences associated with its activation in the nervous system may vary as a function of the intracellular environment and perhaps the injury stimulus as well. The role of p53 in neuronal cell death in the posttraumatic brain thus remains elusive. Although it was previously demonstrated that experimental TBI in mice resulted in accumulation of p53 protein in the nuclei of damaged neurons and that administration of the p53 inhibitor pifithrin-alpha (PFT) significantly reduced neurodegeneration and inhibited nuclear p53 accumulation **(28).**

Tomasevic et al., (29), demonstrated that deletion of the tumor suppressor gene p53 results in improved neuromotor functional recovery, without attenuation of cell or tissue loss in the cortex, thalamus, or hippocampus, following experimental brain trauma in mice.

Interestingly, p53 also appears to have a variety of pro-oxidant activities in the CNS which may further exacerbate cellular injury associated with oxidative stress. . In support of a role for p53 in cell death after CNS injury, increased levels of total p53 and phosphorylated p53 were noted in the contused rat spinal cord **(30).**

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