Post-Concussion Syndrome-Adults

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NEUROPATHOLOGY

In this Forensic Science Newsletter we will discuss **post-concussion syndrome (PCS)**, its definition, background (general information), pathophysiology and epidemiology.

Definition

PCS occurs after the injury that caused the **concussion (mild traumatic brain injury, mTBI).** Having stated this definition, it's a disorder with complicated origins, with confusing and conflicting findings reference symptom duration, absence of objective neurologic findings, inconsistent presentation and poorly understood etiology. For example, there are no criteria to define the role of either physiologic or psychological factors in the etiology of PCS. The name itself is somewhat misleading for those suffering from PCS need not have lost consciousness.

Approximately 40% of those who have suffered minor or serious injuries to the head complain of dizziness, fatigue, insomnia, restlessness and an inability to concentrate. Not uncommonly these symptoms are associated with anxiety and depression. It is these symptoms that may persist for weeks or up to years that is known as PCS.

Although there is no universally accepted definition of PCS, much of the literature describes the syndrome as one in which at least 3 of the following symptoms occur: headache, dizziness, fatigue, irritability, impaired memory and concentration, insomnia, and lowered tolerance for noise and light.

In a general sense, PCS is represented by the persistence of concussive symptoms lasting more than a month. Some in the literature suggest the symptoms must persist for a least 3 months to qualify as PCS, whereas others define it as symptoms appearing within the first week.

There are two well defined scholastic definitions of PCS. One is by the **Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Criterial for Post-Concussion Syndrome:**

A. History of severe concussion.

B. Neuropsychological evidence of attention or memory impairment.
C. At least three of the following symptoms occurring shortly after injury lasting for 3 months:

1. Fatigue
2. Sleep impairment
3. Irritability or aggression
4. Anxiety, depression or labile affect
5. Headache
6. Dizziness
7. Personality changes
8. Apathy

The other well recognized definition of PCS is by the **International Classification for Diseases, tenth revision, Clinical Criteria for Post-Concussive Syndrome.**

A. Head injury usually severe enough to cause loss of consciousness within 4 weeks of symptom onset.
B. Preoccupation with symptoms and fear of brain damage with hypochondrial concern and adoption of sick role.
C. Three of the following symptoms:

1. Headache, dizziness, malaise, fatigue, noise intolerance
2. Irritability, depression, anxiety, emotional lability
3. Concentration, memory or intellectual deficit without neuropsychological evidence of deficit
4. Insomnia
5. Reduced alcohol intolerance.

GENERAL INFORMATION

Before continuing with our discussion of PCS we need to clarify an issue which involves the terms **concussion** and **mild (minor) head injury (mTBI)**. The terms concussion and mTBI tend to be used interchangeably. However, the traditional definition of concussion does not allow for intracranial hemorrhage, whereas mTBI does. Also, mTBI typically is associated with a blow to the head in which there is a brief period of loss of consciousness or posttraumatic amnesia or disorientation. Another interesting feature to keep in mind is traditionally, a patient with mTBI could have a Glasgow Coma Scale (GCS) ranging from 13-15. However, more recent studies have shown those with a concussion have a GCS of 14-15. These studies have also shown those with a concussion, have sustained trauma to the head with a much less chance of having associated intracranial injury then those with a GCS of 13. Another interesting feature is although there is no evidence of intracranial trauma seen by CAT scans and MRIs in concussions, more advanced neuroimaging techniques, such as Diffusion Tensor Imaging (DTI) have shown finite white matter structural changes in those who are classified as having a concussion rather than a mTBI. Thus, these more recent

neuroimaging techniques, as well as the research into what is occurring at the molecular level (immunoexcitotoxicity) within the brain following a TBI, whether mild or severe, suggest such a distinction between concussion and minor head injury may not have the clear separation scientifically as has been suggested. In many respects the ambiguity of the terms concussion and mild(minor) head injury is a reflection of our lack of a clear understanding as to the pathophysiologic process of TBI, whether mild or severe, at the molecular level, which will be discussed shortly.

Continuing with our discussion of PCS, patients may be severely disabled but have normal findings on neurologic examination with no evidence of brain injury on MRI. There is poor correlation between the severity of the original injury and the severity and duration of later symptoms. As an example, much of the literature suggest the incidence of PCS is not related to the duration of retrograde amnesia, coma, or posttraumatic amnesia. However, there are some studies, which suggest the length of loss of consciousness or posttraumatic amnesia may be correlated with the probability of developing PCS. In some instances, symptoms may be related to brain damage, whereas in others they appear to be entirely psychogenic. To underscore this point, there is a study in which it was found higher educational levels, along with mild symptoms and no extracranial symptoms, predicted a minimal probability of developing PCS with significant dysfunction.

The symptoms of PCS have some similarities to **post-traumatic stress disorder**.

In the past PCS has been referred to as **post-traumatic nervous instability syndrome** and **traumatic neurasthenia**, which was coined by Sir Charles Putnam Symonds, an English neurologist.

Before discussing the pathophysiology of PCS, there is a disorder which appears in the literature called **persistent post-concussive syndrome (PPCS).** This entity is defined as symptoms lasting more than 6 months. However, like PCS there is confusion in the literature as to this definition of PPCS. Some define PPCS as one in which symptoms last more than 3 months. In my opinion, this term only adds to the confusion of our understanding of PCS, for there are reports where PCS symptoms may take as long as 5 years to clear up after trauma.

PATHOPHYSIOLOGY

For some time there has been much discussion in the literature as to the pathophysiologic process in PCS. It has been postulated the early PCS symptoms have an organic basis (defined pathological lesions), whereas the PCS symptoms that persist beyond 3 months have a non-organic, functional, physiological foundation, the foundation of which cannot be detected by existing laboratory procedures. Considering the latest research into the mechanisms underlying TBI, this traditional definition of the pathophysiologic processes in PCS may no longer be true.

Another issue that adds to our lack of understanding of TBI is the anatomical basis of a concussion has not been clearly defined. There is a thought PCS may represent a transient dysfunction of the neuron or it may be associated with structural changes, such as localized traumatic axonal injury (TAI). This concept is supported by animal models, which have shown localized axonal damage after mTBI.

Although, CAT scans and MRIs often fail to demonstrate any structural injury in a patient with a concussion, newer neuroimaging techniques, such as DTI, as discussed above, have shown white matter structural changes in those with concussion. DTI changes have been correlated with axonal injury demonstrated by sliver stains in animal models with mTBI. A meta-analysis of human mTBI DTI studies have shown the posterior corpus callosum to be especially susceptible to white matter changes. MRI volumetric studies of mTBI patients have also demonstrated loss of brain volume over several months.

There is one study by Blumberg et al, involving 5 patients with mTBI who died from other causes, which demonstrated axonal β-APP (beta-amyloid precursor protein) immunostaining in the fornices and corpus callosum of all 5 patients and variable changes within the brainstem and cerebral white matter. β-APP is the primary component of amyloid plaques found in the brains of Alzheimer's disease patients.

Recently, researchers investigating the underlying mechanisms of PCS have suspected activation of the immune inflammatory response (immunoexcitotoxicity) may be the underlying pathophysiologic mechanism that occurs in those patients who go on to develop PCS symptoms, most especially prolonged symptoms. The activation of the immune inflammatory response involves an interaction between immune receptors within the central nervous system (CNS) and excitatory glutamate receptors. This interaction triggers a series of events, such as extensive reactive oxygen species/reactive nitrogen species generation, accumulation of lipid peroxidation products and prostaglandin activation, which then leads to dendritic retraction, synaptic injury, damage to microtubules, and mitochondrial suppression.

Reactive oxygen species are chemical species containing oxygen. Examples are peroxides, superoxide, hydroxy radical, and singlet oxygen. Although reactive oxygen species are a normal byproduct of metabolism, during times of stress, such as in TBI, the ROS levels increase dramatically, which can in turn damage cell structures. Reactive nitrogen species (RNS) are a family of antimicrobial molecules derived from nitric oxide and superoxide produced via the enzymatic activity of inducible nitric oxide synthase 2 (NOS2) and NADPH oxidase respectively. NOS2 is expressed primarily in macrophages (microglia in the brain) after the induction by cytokines and microbial products, most especially interferon-gamma (IFN-γ) and lipopolysaccharide (LPS). The RNS act together with the ROS to damage cells.

NADPH oxidase is a membrane-bound enzyme complex that face the extracellular space. NADPH oxidase generates reactive oxygen species, such as superoxides. These oxygen species are also generated through the activity of myeloperoxidase.

Superoxides are biologically quite toxic and are deployed by the immune system to kill invading microorganisms.
Lipid peroxidation process involves the oxidative degradation of lipids, in which the free radicals produced steal electrons from the lipids in cell membranes, resulting in cell damage.
Prostaglandins are lipid autacoids (biological factors which act like local hormones, have a brief duration, and act near the site of synthesis) derived from arachidonic acid. They both sustain homeostatic functions and mediate pathogenic mechanisms, including the inflammatory response. They are generated from arachidonate by the action of cyclooxygenase (COX) isoenzymes and their biosynthesis is blocked by nonsteroidal anti-inflammatory drugs (NSAIDs), including those selective for inhibition of COX-2.
Lipopolysaccharides (LPS) are another mechanism which can activate microglia. LPS accomplishes this activation by stimulating immune responses through interacting with membrane receptor CD14 on the surface of the microglia. This interaction induces generation of cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6. The exact mechanism by which LPS signal is transduced from the extracellular environment to the nuclear compartment is not well known.

There are also a number of studies, both in humans and experimental animals, which show massive acute accumulation of **glutamate, aspartates** and other **excitotoxins** in the cells following TBI.

Immunoexcitotoxicity

The term **excitotoxicity** was coined by Dr. John Olney in 1969. Dr. Olney used this term to describe a reaction that occurs when neurons are exposed to excess glutamate extracellularly. In his study, Dr. Olney noted that when neurons are exposed to excess glutamate, there is a delayed reaction, which ultimately results in the death of the neuron. **How this came about was determined by subsequent studies, which showed the excessive glutamate allows for uncontrolled intracellular entry of calcium into the neuron through glutamate receptor controlled calcium channels. This uncontrolled entry of calcium into the neuron activates cell death (apoptosis) signaling pathways that lead to cell death.**

Apoptosis can be initiated through one of two cell death signaling pathways. In the **intrinsic pathway** the cell kills itself because it senses cell stress, while in the **extrinsic pathway** the cell kills itself because of signals from other cells. Both pathways induce cell death by activating caspases, which are proteases, or enzymes that degrade proteins. The two pathways both activate initiator caspases, which then activate executioner caspases, which then kill the cell by degrading proteins indiscriminately.

Calcium plays a role in apoptosis by having the cell initiate intracellular apoptotic signaling in response to stress, which may cause cell death. The binding of nuclear receptors by **increased calcium concentration,** cause damage to the cell membrane, which trigger the release of intracellular apoptotic signals by the damaged cell.

Before the actual process of cell death is precipitated by enzymes, caspases, apoptotic signals must cause regulatory proteins to initiate the apoptosis pathway. This step allows those signals to cause cell death, or the process to be stopped, should the cell no longer need to die. Several proteins are involved, but two main methods of regulation have been identified: the targeting of **mitochondria** functionality, or directly transducing the signal via adaptor proteins to the apoptotic mechanisms. An extrinsic pathway for initiation identified in several toxin studies is **an increase in calcium concentration within a cell** caused by drug activity, which cause apoptosis via **calcium binding protease calpain.**

The excitatory neurotransmitters in the brain are **acetylcholine, aspartate, glutamate, purinergic and cholinergic receptors, and serotonin**. **Dopamine** can be both excitatory and inhibitory. **Glutamate** mediates most of the excitatory signaling in the vertebrate brain. For example the main neurotransmitters for the descending corticospinal tract are aspartate and glutamate.

Glutamate is the most abundant neurotransmitters in the brain. It is used in 50% of the synapses in the CNS overall and 90% in the cortex.

The primary sources of glutamate are the **microglia** and **astrocytes** with astrocytes serving as the main repository for glutamate, as well as aspartate. Immune mediators and excitatory amino acids in the brain are also secreted by oligodendroglia. Glutamate and aspartate are the only excitatory amino acid in the brain, the other amino acids serving as neurotransmitters, glycine and g-aminobutyric acid [GABA] are inhibitory.

Glutamate and aspartate are products of the Kreb's cycle. They are produced in the mitochondria, transported into the cytoplasm, and packaged into synaptic vesicles. Specific high-affinity enzymes are responsible for packaging glutamate into vesicles. The actions of glutamate are terminated by high-affinity uptake systems in neurons and glia. Under normal circumstances the glutamate is then put back into the neuron and glia by these uptake systems, where it is immediately pumped into vesicles for subsequent release. What is important to remember is extracellular glutamate is not permeable to the plasma membrane. To recycle the glutamate so that it can be taken up into glial cells and neurons, an enzymatic reaction catalyzed by glutamine synthase is required to produce glutamine from glutamate. Glutamine is freely permeable to the glial and neuronal plasma membranes and diffuses back into the neuron and glia. The neuronal and glial enzyme glutaminase then metabolizes glutamine into glutamate where it can be packaged into synaptic vesicles for another round of release. **In excitotoxicity, not only cannot the neurons and glia uptake the excess glutamate, but the enzymatic reaction catalyzed by glutamine synthase is also overwhelmed thus, allowing an excess of extracellular glutamate, which contributes to the genesis of immunoexcitotoxicity.**

There are two types of **glutamate receptors**: **ionotropic** and **metabotropic**.

Ionotropic glutamate receptors are a group of transmembrane channel proteins, which open to allow ions such as sodium (Na^+), potassium (K^+). calcium (Ca^{2+}) and chloride (Cl^-) to pass through the membrane in response to the binding of a chemical messenger such as a neurotransmitter glutamate. They are built for rapidly converting extracellular chemical signals in to electrical signals at chemical synapses. The channels are concentrated in a specialized region of the postsynaptic plasma membrane at the synapse and open transiently in response to the binding of neurotransmitter molecules, thereby producing a brief permeability change in the membrane. Transmitter-gated channels are relatively insensitive to the membrane potential and therefore cannot by themselves produce a self-amplifying excitation. Instead, they produce local permeability increases, and hence changes of membrane potential, that are graded according to the amount of neurotransmitter released at the synapse and how long it persists there. Only if the summation of small depolarizations at this site opens sufficient numbers of nearby voltage-gated cation channels can an action potential be triggered. This may require the opening of transmitter-gated ion channels at numerous synapses in close proximity to the target nerve cell. **This may in part explain what occurs in immunoexcitotoxicity in which an overwhelming quantity of glutamate is released, which cannot be metabolized by glutamine synthase, allowing the excess of glutamate to open a massive number of voltage-gated channels thus, triggering an abundance of unregulated action potentials.**

A **metabotropic receptor** is one which acts through a secondary messenger. Metabotropic receptors may be on the surface of the cell, like ionotropic receptors, or within a cell in a vesicle. Metbotropic receptors are indirectly linked with ion channels on the plasma membrane through a signal transduction mechanism, often a G protein. Thus, G protein coupled receptors are inherently metabotropic. As stated, when an ionotropic receptor is activated, it opens a channel that allows ions such as Na^+, K^+, Ca^{2+} or Cl^- to pass through. In contradistinction, when a metabotropic receptor is activated, a series of intracellular events are triggered, which result in ion channels opening but must involve a range of second messenger chemicals.

There are four types of ionotropic glutamate receptors, which bind the neurotransmitter glutamate: AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor); Kainate receptors; NMDA (N-methyl D-aspartate) receptors; and delta receptors.

AMPA receptors mediate fast synaptic transmission in the CNS. They are the main charge carriers during basal transmission, permitting influx of Na^+ to depolarise the postsynaptic membrane.

NMDA receptors are activated when glutamate and glycine bind to it. When activated, the NMDA receptors open ion channels that are nonselective as far as cations are concerned such as Na^+, K^+, Ca^{2+}, Mg^{2+} and Zn^{2+}. However, when Mg^{2+} and Zn^{2+} bind to

specific sites in the receptor, they can block the passage of other cations. What is important to remember is Na^+, K^+ and Ca^{2+} not only pass through the NMDA receptor channel but also modulate the activity of NMDA receptors. In addition, NMDA glutamate receptors can alter the intracellular concentration of calcium as calcium waves, which activate cell signaling molecules utilized by the neuron to trigger various cellular events, including death signals, as well as action potentials. Although glutamate receptors are the primary excitatory neurotransmitter, cholinergic and purinergic receptors are also excitatory neurotransmitters.

There are three classes of **purinergic receptors: P1, P2Y and P2X. Purinergic P2X receptors** are widely distributed throughout the CNS and PNS (peripheral nervous system) in neurons and glial cells. These receptors have been implicated in integrating functional activity between neurons, glia, and vascular cells in the CNS, thereby mediating effects of neural activity during development, neurodegeneration, inflammation, and cancer.

Cholinergic receptors, of which there are two, nicotinic and muscarinic, will not be discussed for the term 'cholinergic' means "having to do with acetylcholine." The neurotransmitter acetylcholine is released from the terminals in all preganglionic neurons in both the sympathetic and parasympathetic divisions of the autonomic nervous system (ANS).

Calcium dysregulation plays a major role in excitotoxicity. In one study using a fluid concussion model for moderate TBI, it was found calcium remained elevated in the CA3 hippocampal neurons for 30 days and never returned to baseline levels. The calcium elevation was due to over-activation of NMDA and AMPA receptors by glutamate. **Another important observation in this study was the calcium dysregulation in moderate TBI might be permanent.**

Usually, the AMPA receptors are not permeable to Ca^{2+}. However, in TBI, hypoxia/ischemia and in neurodegenerative diseases, there is a switch to Glu2-lacking AMPA receptors that are calcium permeable. Mild frontal TBI has been shown to cause a rapid switching to calcium permeable AMPA type receptors within cerebellar Purkinje cells, which normally lack functional NMPA receptors.
There is evidence of a synergistic interaction between the glutamate receptors and certain cytokines the net effect of which is to substantially increase neuronal injury and precipitate chronic neurodegeneration. This synergistic interaction is called immunoexcitotoxicity.

Microglia

The foundation of this synergistic interaction is the activation of the brain's **microglia** in TBI. Although neurons, astrocytes, oligodendroglia, endothelial and microglia can release proinflammatory cytokines, **the principle immune cell of the brain is the microglia.**

The initial primary event involving the microglia involves an interaction between proinflammatory immune cytokine receptors and glutamate receptors. The microglia contribute to the immune response by acting as antigen presenting cells, as well as promoting inflammation and homeostatic mechanisms within the body by secreting cytokines and other signaling molecules. Some of the released proinflammatory cytokines, such as IL-Iβ, IL-4, and IFNγ, can in turn stimulate the microglia to proliferate.

Microglia are also responsible for overall maintenance of the CNS. They are constantly scavenging the CNS for plaques, damaged or unnecessary neurons and synapses, and infectious agents. This process must be, and is, very efficient to prevent fatal damage by any pathological change, hence, microglia are extremely sensitive to even small pathological changes in the CNS.

The origin of the microglia/macrophages within the CNS has been much debated. Currently, the thought is blood derived monocytes move into the brain during early embryonic development, then differentiate into microglia that share many surface markers or antigens with their blood borne and systemic visceral counterparts, monocytes and macrophages. Microglia are estimated to represent 15% of cells in some parts of the CNS.

Although, there are six types of microglia, we are primarily interested in three types: **resting (ramified), activated (non-phagocytic and phagocytic) and ameboid phagocytic microglia.** The other three are gitter cells, perivascular and juxtavascular microglial.

The **resting** or **ramified** form of microglia are composed of long branching processes and a small cellular body. Unlike the amoeboid forms of microglia, the cell body of the ramified form remains in place while its branches are constantly moving and surveying the surrounding area. The branches are very sensitive to small changes in the CNSs physiological condition. Although the ramified microglia are in a resting state, they are extremely active in chemically surveying the environment. Ramified microglia can be transformed into an activated form at any time in response to an injury. The normal population of ramified microglia is maintained by macrophage colony stimulating factor (M-CF), which is produced b astrocytes.

The **activated** form of microglia exist in one of two states: **non-phagocytic** and **phagocytic.**

The **non-phagocytic** state represents a graded response of the microglia as they move from the ramified form to their fully active phagocytic form. This transition requires the ramified microglia to be activated, which can be accomplished by a variety of factors including: glutamate receptor agonists, proinflammatory cytokines, cell necrosis factors, lipopolysaccharides, and changes in extracellular potassium, which is caused by ruptured (injured) cells. Once activated the non-phagocytic cells undergo morphological changes including thickening and retraction of their branches, uptake of MHC class I/II

proteins, expression of immunomolecules, secretion of cytotoxic factors, secretion of recruitment molecules, and secretion of proinflammatory signaling molecules, which results in a proinflammatory signal cascade. Activated non-phagocytic microglia generally appear as “bushy,” “rods,” or small ameboids depending on how far along the ramified to full phagocytic transformation continuum they are.

The phagocytic state is the activated phagocytic microglia, which are the maximally immune responsive form of microglia. It is this form of microglia that has the antigen presenting, cytotoxic and inflammatory mediating signaling. They also can phagocytose foreign materials and display the resulting immunomolecules for T-cell activation. These cells travel to the site of injury, engulf the foreign or injured cellular material and in the process secrete proinflammatory factors to promote more cells to proliferate and come to the site of injury.

The **amoeboid** state is one in which the microglia moves freely throughout the CNS, scavenging any foreign or cellular debris. This form of microglia is able to phagocytose this debris, however, unlike the activated phagocytic microglial form, they are not able to serve as antigen-presenting and inflammatory roles. This form of microglia is most prevalent during embryonic development, when there are large quantities of extracellular debris and apoptotic cells to remove.

It is very evident, microglia have numerous functions within the CNS. Besides serving as immunological sensors and antigen presenting cells, they also produce a variety of **cytokines** and **chemokines**.

Cytokines are low molecular weight proteins, which include interleukins (ILs), tumor necrosis factors (TNFs), interferons (IFNs), transforming growth factors (TGF), and colony stimulating factors (CSFs). Cytokines are important elements in not only the modulation of inflammation and immune responses but also the physiological processes vital to CNS growth and development.

Chemokines are small (8-10 KDa) inducible, secreted proinflammatory molecules, which play a role in various immune and inflammatory responses.

Thus, microglia, when activated can secrete a number of anti- and proinflammatory cytokines, prostaglandins, trophic factors, free radicals, LPP (lipid peroxidation products), NO, and three-forms of excitotoxins: glutamate, aspartate, and quinolinic acid (QULN). Whether microglia are major producers of NO (nitric oxide) is somewhat controversial.

Quinolinic acid is a downstream product of the kynurenine pathway, which metabolizes the amino acid tryptophan. It acts as an NMDA receptor agonist (a chemical that binds to a receptor and activates the receptor to produce a biological response). It has a potent neurotoxic effect. Studies have demonstrated that quinolinic acid may be involved in many psychiatric disorders, neurodegenerative processes in the brain, as

well as other disorders. **Within the brain, QULN is only produced by activated microglia and macrophages.**

Studies have shown proinflammatory cytokines can cause a release of excitotoxins from microglia as well as astrocytes at the same time the released excitotoxins can cause the further release of immune proinflammatory cytokines from the same cells. What is important to understand is exposure to individual proinflammatory cytokines in-of-themselves in not neurodestructive. However, certain combinations of these proinflammatory cytokines can be very neurodestructive, such as the combination of IL-1 and TNF-α. What the evidence suggest, it is the combination of proinflammatory cytokines and excitotoxins that leads to neurodegeneration, rather than inflammation alone. What is also important to recognize, is subtoxic concentrations of glutamate, when combined with subtoxic concentrations of LPS or proinflammatory cytokines, becomes fully neurotoxic.

What appears to occur is because proinflammatory cytokines and excitotoxins release occurs simultaneously, a synergistic neurodestructive cascade is set in motion. This synergism between the immune cytokines and excitotoxic levels of glutamate, aspartate, and QULN also have similar effects on the blood brain barrier (BBB), brain vasculature, development of edema, and metabolic changes seen within TBI.

Epidemiology

The life time incidence of single and repeated concussions in unknown but it is believed to occur in several million people annually in the United States alone. In one study, the overall incidence rate of mTBI for persons not hospitalized was 503 per 100,000 population or 1,367,101 visits per year to hospital EDs in the United States. Another study pointed out the incidence of all-cause concussions in the United States is estimated to range from 1.6 to 3.8 million annually, with the reported number of sport or recreation related concussions increasing dramatically, especially in youth sports.

The epidemiology follows a trimodal pattern over lifetime with peaks in the first few months of life, followed by adolescence, and followed by a third peak in the elderly. Contributions to concussion etiology among the very young who have begun to walk and very old are likely primarily related to accidental falls, although concussions or mTBI in the first few months of life and in those children who are preverbal must always raise a suspicion of non-accidental trauma as to causation.

Concussions in adolescents may relate to risk taking behaviors, involving driving, violence, and exposure to increasing competitive athletics. The annual incidence of sports related concussions is at least 300,000 in the United States alone, although it is generally agreed this is likely an underestimate given the poor recognition of affected players.

It is estimated that 50% of those with mTBI have symptoms of PCS at 1 month and 15% at 1 year. These percentages are dependent upon the definition one uses for PCS and the age group, and gender examined. For example, it is estimated between 14 and 29% of children with mTBI will continue with PCS symptoms at 3 months.

Although men experience minor head injury more frequently than women, the incidence of PCS is greater in women than men.

In one study, 50% of those who experienced mTBI are between the ages of 15-34 years. However, PCS has no predilection for a specific age group.

Summary

The recent research into the mechanisms underlying PCS following TBI, including mTBI, have suggested the evolution within the brain of a central pathological mechanism, which involves activation of an immune inflammatory response as the primary pathophysiologic process responsible for PCS. This inflammatory response involves a process called **immunoexcitotoxicity**, which plays a key role not only in PCS but many neurodegenerative diseases including chronic traumatic encephalopathy.

Understanding the various pathways involved in immunoexcitotoxicity leading to PCS as well as these neurodegenerative diseases will allow us to develop nonpharmacological and pharmacological agents to interrupt these pathways and thus prevent the often tragic consequences of immunoexcitotoxicity.