

Postconcussion Syndrome: A Review of Pathophysiology and Potential Nonpharmacological Approaches to Treatment

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FROM ABSTRACT

The incidence of all-cause concussions in the United States is 1.6 to 3.8 million annually, with the reported number of sport-or recreation-related concussions increasing dramatically, especially in youth sports.

The use of roadside bombs in Iraq and Afghanistan has propelled the incidence of concussion and other traumatic brain injuries to the highest levels ever encountered by the US military. The wars in Iraq and Afghanistan cause about 300 concussions per month.

There is a marked increase in post-concussion syndrome (PCS) and the associated cognitive, emotional, and memory disabilities associated with the condition.

There have been no significant advancements in the understanding or treatment of PCS for decades.

The current management of PCS mainly consists of rest, reduction of sensory inputs, and treating symptoms as needed.

Recently, researchers have proposed that activation of the immune inflammatory response may be an underlying pathophysiology that occurs in those who experience prolonged symptoms after a concussion. This immune inflammatory response is known as immunoexcitotoxicity.

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KEY POINTS FROM THIS ARTICLE:

1) Most traumatic brain injuries (TBIs) are mild traumatic brain injuries (mTBIs) and are often referred to as concussions. These concussions can cause long-term disability.

2) Most signs and symptoms of a cerebral concussion spontaneously resolve within 2 to 7 days, including:

- Headache
- Nausea
- Visual disturbance
- Balance abnormalities

3) Up to 15% of concussion individuals “may experience prolonged and intractable physical, cognitive, emotional, and/or sleep disturbances that result in severe debilitation—the so-called post-concussion syndrome (PCS). These symptoms often result in significant disruption and even withdrawal from school, job, or military activity.”

4) Post-concussion syndrome requires at least 3 symptoms for a minimum of 4 weeks following a head injury, including:

- Headache
- Dizziness
- Sleep problems
- Psychological disturbances
- Cognitive disturbances

5) Management of PCS includes rest and reduction of sensory input from schoolwork, computers, and any processing of new information.

6) In PCS, imaging technology (CT, MRI, diffusion tensor imaging, PET) are less than optimal because they do not document changes in brain neurochemistry.

7) “Following an impact to the head, a cascade of biochemical, immunological, and excitotoxic events occur, mediated by the innate and adaptive immune systems in the central nervous system.”

8) “When a person sustains a TBI, it is well recognized that there is a massive release of glutamate and aspartate, primarily from astrocytes and microglia cells, which overstimulate glutamate receptors. This results in an influx of calcium through the cellular membrane and subsequent neuronal toxicity and cell death.” This is called the “excitotoxic reaction,” and contributes to PCS and to “chronic traumatic encephalopathy (CTE).”

9) Microglia are the macrophages of the brain and spinal cord. In brain injury, the microglia become activated, releasing a series of immune factors, such as reactive oxygen species (ROS), inflammatory prostaglandins, and “excitotoxins in the form of glutamate, aspartate, and quinolinic acid.”

10) Immunoexcitotoxicity and microglial activation is central to a number of neurodegenerative diseases, including Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and vascular dementia.

11) The lingering symptom of headache, cognitive disturbances, and memory impairment of PCS are linked to excitotoxic neurotransmitters and inflammatory cytokines. “PCS following TBI may represent a persistent, low-grade, chronically smoldering neuroinflammatory response.”

12) The short-term symptoms of concussion, such as immediate confusion and disorientation, usually resolve within minutes to several hours and are probably due to electrochemical changes.

13) A limited activation immunoexcitotoxicity inflammatory response produces protracted headaches, fogginess, and poor concentration, which resolve within a week in most cases.

14) After a concussion it is extremely important to prevent a second injury before the brain is completely healed. A second impact initiates brain

vasoreactive edema with resultant severe malignant brain swelling, which “if not recognized and treated promptly, it may be fatal.”

15) A second brain injury before complete recovery accelerates microglia activation. “The initial injury primes the microglia—a state in which microglia upregulate the production of proinflammatory cytokines. Primed microglia release significantly higher levels of proinflammatory cytokines/chemokines and excitotoxins than normal, causing prolonged brain immunoexcitotoxicity.”

16) Both glutamate and quinolinic acid can produce tau proteins and stimulate β amyloid accumulation in both Alzheimer’s disease and in CTE.

17) “A number of natural plant products and extracts, such as fish oil, resveratrol, green tea, and curcumin, among others, may offer similar effects in the treatment of AD and other immunoexcitotoxicity-associated neurodegenerative disorders. These compounds work by suppressing or affecting microglial activation states as well as the excitotoxic cascade and inflammatory mediators, and promoting the release and generation of neurotrophic factors essential for CNS healing.”

18) “Nonsteroidal anti-inflammatory drugs are the most common cause of drug-related morbidity and mortality reported to the US Food and Drug Administration and other regulatory agencies around the world.”

19) “Omega-3 essential fatty acids (EFAs), vitamin D3, curcumin, resveratrol and other polyphenols, and magnesium have all been shown to clinically reduce inflammation, reduce microglial activation, affect excitotoxic cell signaling processes, and are used worldwide to treat inflammatory-related conditions.”

20) The major components of omega-3 EFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can inhibit production of proinflammatory eicosanoids.

21) “The proinflammatory prostaglandin E2 (PGE2), made from omega-6 EFA (arachidonic acid [AA]) found in all cellular membranes, can be downregulated through competitive inhibition due to the enhanced production of prostaglandin E3 (PGE3) from EPA, which is also incorporated into cellular membranes.”

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- 22) CTE's mechanisms of immunoexcitotoxicity and microglia activation are reduced by both EPA and DHA.
- 23) Docosahexaenoic acid (DHA) constitutes > 25% of brain phospholipids, "maintaining membrane integrity, fluidity, excitability, and function."
- 24) Oral supplementation of DHA for 30 days following TBI significantly decreases the number of swollen, disconnected, and injured axons, attenuates glutamate-induced neuronal injury and death.
- 25) Omega-3 EFAs increase neuronal survival following brain injury by reducing excitotoxicity through inhibition of glutamate-induced neuronal toxicity.
- 26) Therapeutic EPA+DHA dosing for TBI is a total of 1.5 to 5.0 g per day.
- 27) Vitamin D significantly promotes immune function and reduces the inflammatory response.
- 28) Vitamin D can limit the extent of TBI injury by reducing cerebral edema, inflammatory response, necrosis, and apoptosis. Vitamin D decreases glutamate-induced neuronal death.
- 29) "Curcumin is a flavonoid compound found in the Indian spice turmeric." It has potent anti-inflammatory, antioxidant, and antineoplastic effects.
- 30) Curcumin's anti-inflammatory actions arise from inhibition of proinflammatory mediators, including cytokines and NF- κ B and inhibition of COX-1 and COX-2. It may be a comparable alternative to NSAIDs without the unacceptable side effects.
- 31) "Curcumin has been found to prevent apoptosis, as well as decrease edema following TBI and ischemia."
- 32) The suggested dosage of curcumin supplementation for TBI is 400 to 600 mg taken 3 times per day.
- 33) Resveratrol is a plant-based polyphenol antimicrobial. It is a powerful antioxidant with cardioprotective, antineoplastic, and anti-inflammatory effects.

34) Resveratrol may extend the life span, slow the development of chronic neurodegenerative disease, and improve patient outcome following stroke, cerebral ischemia, spinal cord injury, and TBI.

35) Resveratrol is anti-inflammatory by suppressing pro-inflammatory PGE2 synthesis, and inhibiting TNF- α -and IL-1 β -induced NF- κ B activation.

36) Resveratrol significantly reduces glutamate release TBI.

37) Moderate resveratrol wine consumption “significantly reduced the risk of AD in population studies.”

38) “Resveratrol can exist in either the cis-or trans-form, but only the transform is believed to be bioactive.” The typical supplementation range is between 50 to 500 mg/day.

39) Magnesium is “required for > 300 metabolic processes and plays an essential role in modulating transmembrane electrical activity.” It is also “essential for protein synthesis, energy metabolism, maintenance of ionic gradients, immune system regulation, smooth muscle tone, and calcium regulation.”

40) “Magnesium decline is thought to play a major role in the neuronal pathogenesis following TBI.” “Its most predominant neuroprotective action is by acting as a noncompetitive inhibitor of NMDA excitotoxicity by receptor blockade or by decreasing glutamate release.”

41) About 63% of adult Americans have insufficient magnesium, and especially those who use proton pump inhibitors [antacids].

42) “Food sources for magnesium include legumes, nuts, whole grains, and most vegetables. The recommended dosage of magnesium is approximately 80 to 420 mg/day.”

43) Green tea is a powerful antioxidant, containing numerous polyphenolic compounds called catechins, of which epigallocatechin-3 galate (EGCG) is the most abundant. These polyphenols in green tea are anti-inflammatory, helping prevent cardiovascular disease, cancer, and arthritis.

44) “The typical recommendation is 3 to 4 cups of green tea per day, or 1 serving of extract, which contains between 300 and 400 mg.”

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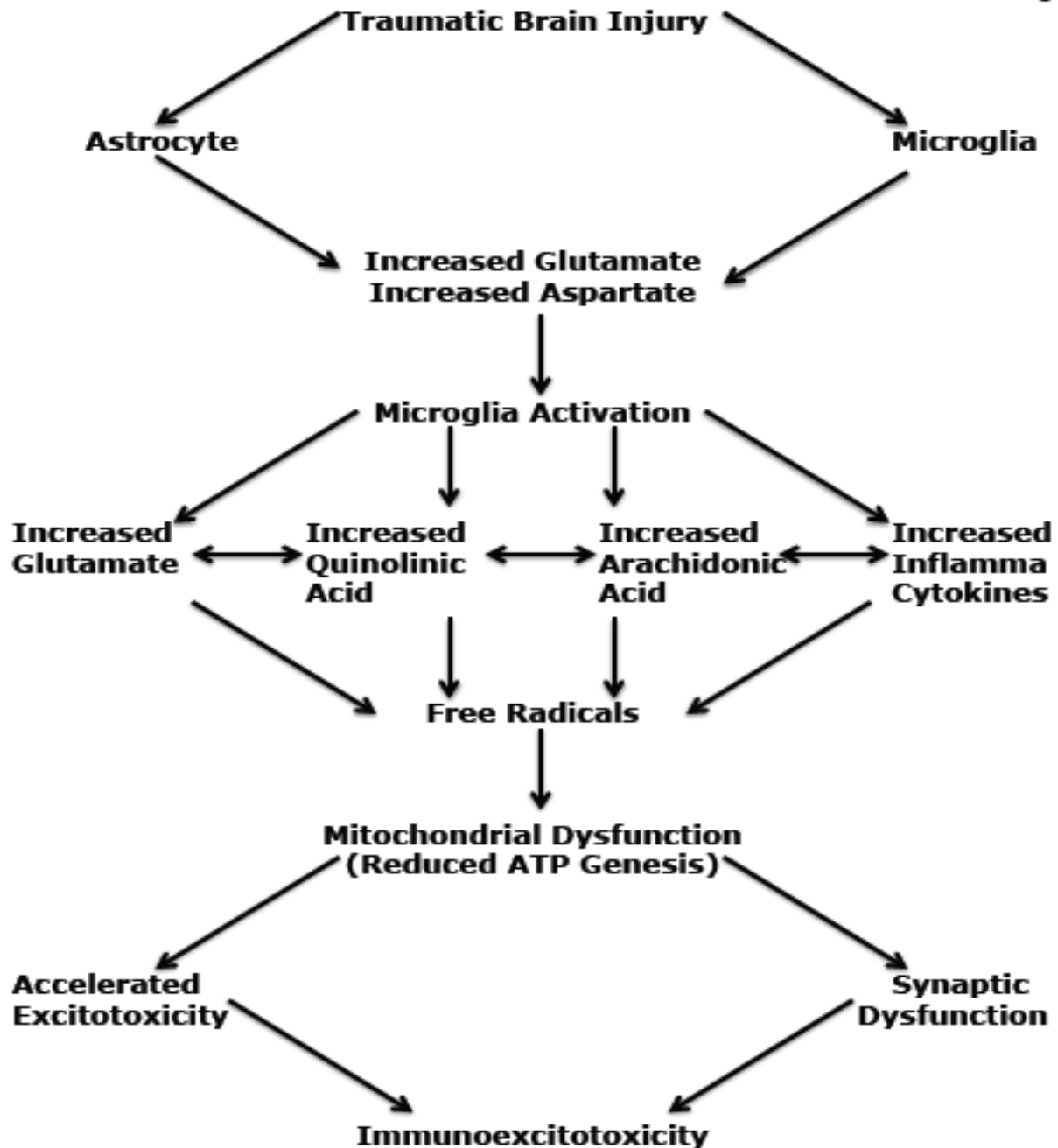
45) These nutritional approaches for TBI and PCS attack the pathophysiology of the disorder, shortening its duration, and not just ameliorating the symptoms.

46) “By supporting neuronal function and countering key immunoexcitotoxicity mechanisms, non-pharmaceutical treatments may offer an effective alternative for treating post-concussion syndrome.”

COMMENTS FROM DAN MURPHY:

The suggested natural products to be used to halt the pathophysiological cascade of TBI and PCS were:

- Omega-3s EPA+DHA
- Vitamin D3
- Curcumin
- Resveratrol
- Magnesium
- Green Tea (EGCG)



Quinolinic acid activates the N-methyl-d-aspartate receptor (NMDAR) and can lead to axonal neurodegeneration. Quinolinic acid is a potent neurotoxin. Quinolinic acid is an excitotoxin in the CNS.

Quinolinic acid may be involved in many psychiatric disorders, neurodegenerative processes in the brain, as well as other disorders.

Within the brain, quinolinic acid is produced by activated microglia cells and macrophages. The quinolinic acid produced in microglia is then released and stimulates NMDA receptors resulting in excitatory neurotoxicity.

Quinolinic acid destabilizes the cytoskeleton of the astrocytes and brain endothelial cells contributing to the degradation of the Blood Brain Barrier.

Quinolinic acid reaches pathological levels in response to inflammation in the brain, which activates the microglia and macrophages. High levels of quinolinic acid can lead to hindered neuronal function or even apoptotic death.

When inflammation occurs, quinolinic acid is produced in excessive levels. This leads to over excitation of the NMDA receptor, which results in an influx of Ca^{2+} into the neuron. High levels of Ca^{2+} in the neuron trigger an activation of destructive enzymatic pathways that degenerate crucial proteins and increase NO levels, leading to an apoptotic response by the cell, which results in cell death.

Glutamate further stimulates the NMDA receptors, thus acting synergistically with quinolinic acid to increase its neurotoxic effect.

Increased levels of quinolinic acid are linked to:

- Mood disorders • Depression
- Schizophrenia • Neurodegenerative conditions
- Amyotrophic lateral sclerosis (ALS) • Mitochondria dysfunction
- Alzheimer's disease • Brain ischemia, stroke
- Huntington's disease • Parkinson's disease
- Bacterial infections of the CNS • Systemic lupus erythematosus
- Traumatic Brain Injury • Cognitive decline with ageing
- Other brain infections, including polio, Lyme disease

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Antioxidants provide protection against the pro-oxidant properties of quinolinic acid. Natural phenols such as catechin hydrate, Curcumin, and epigallocatechin gallate (found in green tea) reduce the neurotoxicity of quinolinic acid.

COX-2 [controls the production of pro-inflammatory eicosanoids from omega-6 fatty acid arachidonic acid] is upregulated in neurotoxic disorders and is associated with increased ROS production.

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