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The Long-Term Effects of Traumatic Brain Injuries in Professional Football

Sports-related concussions are one of the most common injuries sustained by professional football players. The acute symptoms that follow a mild traumatic brain injury are well established, with many instances of headaches, confusion, dizziness, and short spells of amnesia. The long-term effects of these injuries are less comprehensively understood. It is clear that repeated blows to the head can cause physiologic distress that develops into a degenerative neurological syndrome known as Chronic Traumatic Encephalopathy (CTE). This disease is characterized by pathologic protein aggregations that eventually lead to behavioral disturbances culminating in dementia. Several individuals diagnosed with CTE have committed suicide, though evidence conclusively linking the disease with such actions remains elusive. Original claims that the disease develops only after many years of playing football are being reevaluated as younger players are being diagnosed with CTE.

Concussion Physiology

What precisely constitutes a concussion is not universally agreed upon, but a consensus among many experts describes a concussion as a cascade of pathophysiological events brought on by a traumatic impact.[1-4] Concussive or subconcussive events may be the result of a direct blow to the head or the body, resulting in sudden rotational and acceleratory forces being transferred to the skull. Generally, these mild brain traumas are closed head injuries. The result of the violent impact is "a physiologic and metabolic insult to the neurons" that reflects a functional perturbation rather than an anatomical pathology.[2,5-7] The acute symptoms of a concussion include dizziness, prolonged headaches, concentration difficulties, memory lapse, nausea and

vomiting, difficulty balancing, and blurred vision.[8] Concussions may or may not include a loss of consciousness (LOC) and this variable is largely responsible for the gross underreporting of sports-related concussions.[8-10]

While there is no universal agreement on the exact biomechanics that accompany a concussive trauma, several physiological certainties have been established (Figure 1). The immediate result of the impact is a rapid efflux of potassium (K^+) ions from the neurons into the extracellular space as neural membranes are disrupted by the collision.[4,7,11] This 5-fold increase in extracellular potassium triggers the release of excitatory amino acids, notably glutamate, further stimulating potassium efflux.[12-14] Elevated potassium concentrations outside the cell membrane disrupt neural signaling and may be a catalyst for the LOC that occasionally follows concussions.[13,14] Large amounts of energy are used as sodium-potassium pumps labor to restore homeostasis, increasing glycosis.[13]

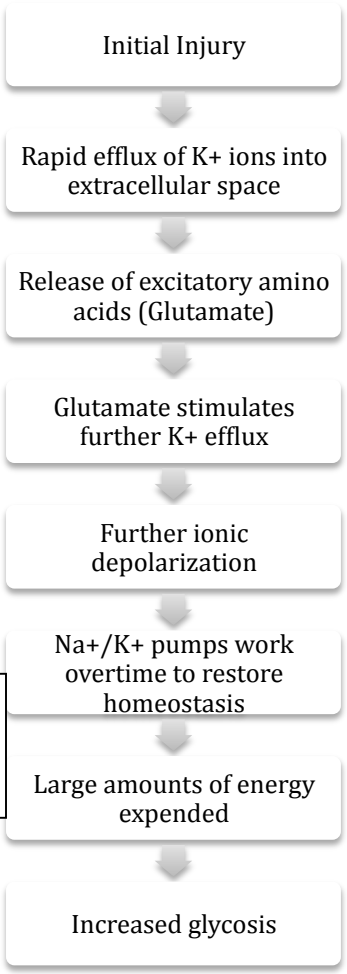


Figure 1. Showing metabolic cascade following a concussive trauma.

Neurotransmitter function is also disrupted following a concussive trauma. Extracellular concentrations of acetylcholine increase to twice the baseline level immediately after impact and remain elevated for several days.[6,13] The result of this

change is increased stimulation of muscarinic receptors, which may contribute to the LOC and lowered seizure thresholds documented in post-concussive patients.[6,14,15] Several days after the injury extracellular acetylcholine concentration drops below baseline levels and remains depressed for as long as 14 days.[13,15]

The metabolic chaos in the neurons is compounded by a 50% decrease in cerebral blood flow occurring several hours after a concussion.[14,16] Cerebral ischemia is particularly dangerous in these situations because of the high demands placed on neural tissue. More than 24 hours after the injury, cerebral blood flow increases above baseline levels for as long as 2 weeks.[14,16] Additional damage is caused by hyperemia as the sudden increase in oxygen concentration produces large numbers of oxygen free radicals, which disrupt cellular DNA and alter membrane permeability.[17]

Research shows that all of these acute disturbances are transient, with the brain returning to baseline functionality after approximately 14 days.[2,4,15] Metabolic irregularities are the first to stabilize after several hours, followed by acetylcholine regulation after 10-12 days.[6] Abnormalities in blood flow take longer to correct and are likely responsible for symptoms such as headache and dizziness reported by patients several weeks after the injury. Researchers believe adequate rest and recovery time will prevent long-term damage to brain tissue.[18,19]

Concussion Recovery Time

Precisely what constitutes adequate recovery time is disputed.[6,12] Several studies have determined that a period of at least 14 days – the average time at which symptoms

subside – is the desired minimum.[19,20] This finding is not absolute, however, as many variables including player position, equipment, surface of play, pervious injuries, and weather conditions can affect an individual's risk of head injury.[16] Many sports organizations, including the National Football League, have instituted return to play guidelines to varying effect.[21,23] While previous parameters focused on LOC and acute amnesia, new findings have forced organizations to examine each injury on an individual basis and tighten restrictions to keep injured players off the field.[1,10,11]

Multiple studies have determined a player is at greater risk for subsequent concussions after an initial trauma.[2,24,25] No conclusive reasons for higher morbidity have been found, though research suggests athletes with a history of concussive injuries face a prolonged recovery time and are likely still suffering from post-concussive symptoms when they resume activity.[19,26] In most cases the brain has not adequately recovered from the initial injury by this time, greatly increasing the probability of subsequent trauma.

A rare and controversial result of returning to play following a concussion is second impact syndrome (SIS). The disruption of neural plasma membranes that immediately follows a concussion may be severe enough to compromise the blood-brain barrier, allowing the unregulated passage of macromolecules into the cerebral milleu.[27] The compromised permeability of neural membranes can be exacerbated by a slight secondary insult, leading to massive cerebral hemorrhage and death. Data suggest the brain is so overwhelmed by the metabolic demands of the initial injury that any subsequent trauma, however trivial, exceeds the capacity for cerebral autoregulation.[27,28] SIS is extremely rare in adult male athletes, nearly to the point of being a clinical

uncertainty.[28] Nonetheless, the mechanisms responsible for SIS are crucial in gauging the long-term effects of repeated head trauma in a short time period.

Concussions and Chronic Traumatic Encephalopathy

Unlike a concussion, which is a temporary physiologic disruption, chronic traumatic encephalopathy (CTE) is a degenerative neurological disease with established pathological abnormalities.[2,19] CTE is not an accumulation of these concussive or subconcussive hits but rather a disease set in motion by these events. It is currently not known how many brain injuries are necessary to initiate CTE, but data suggest a single concussion is insufficient.[10,19] It is clear that CTE is a result of the repeated mild brain injuries suffered thousands of times each year by professional football players.

The initial clinical symptoms of CTE are akin to those documented in post-concussive patients. These include attention deficiencies, memory loss, profound confusion, dizziness, and chronic headaches. As the disease progresses more serious symptoms such as difficulty problem solving, impaired judgment, and emotional instability become apparent.[29] In the case of one former professional football player posthumously diagnosed with CTE, cognitive disturbances such as asking the same question repeatedly and the inability to recall movies he had previously seen were documented by friends and family before his death.[29-31]

The second stage of the CTE progression is characterized by impaired speech and the onset of Parkinson's symptoms such as tremors and inconsistent muscle control. Advanced cognitive dysfunction and infrequent violent or erratic behavior constitute

phase III of CTE, with intermittent bouts of depression, lethargy, or anxiety throughout.[30,31] The progression of CTE is largely dependent on the individual patient, with various factors including length of career, family medical history, and co-morbidity affecting the outcomes.[29]

Initial study of CTE in football players showed the onset of symptoms after retirement [29,30] Two frequently cited examples are of two 45-year-old former professional football players who developed CTE after they left the game and died violent deaths (though one was an accidental self-inflicted gunshot wound) (Figure 2).[29,30] Both men played professional football for at least 8 years and were diagnosed with at least 8 concussions during their careers. Neither man was diagnosed with post-concussive syndrome or required hospitalization after the head injury. Each man lost consciousness only once in his professional career.[29,30]

After retirement, the family and friends of each player noticed cognitive dysfunctions. The wife of one man noticed "he sometimes became extremely reclusive and distanced himself from all personal interactions with family and friends", a behavior pattern never before exhibited. This patient later committed suicide.[29] The family and friends of the other man documented memory loss, mood swings, and irritability.[5] The family histories of both men were negative for major depression, though both exhibited despondency and suicidal tendencies before their deaths.[32]

The behavior exhibited in these 2 men is consistent with 3 other football players diagnosed with CTE after autopsy.[19,32] Depression, consistent memory loss, paranoia, emotional outbursts, unprovoked anger, and reduced concentration were documented to

varying degrees in all 5 patients. Psychological autopsies reveal these symptoms appeared after at least 10 years of football activity in these men.

Recent data show CTE may develop in athletes at a much younger age. In April, 2010 a 21-year-old college football player with a limited history of concussions committed suicide by hanging.[2] Postmortem studies of the man's brain revealed inchoate but clear signs of CTE around cerebral vessels in the fontal cortex. Researchers are unwilling to directly link the disease to the man's suicide, though CTE is believed to be a contributing factor.[16]

The youngest player to date diagnosed with CTE is an 18-year-old high school football player with a documented history of concussions. The diagnosis in this case is consistent with pathological origins near cerebral capillaries (Figure 3).

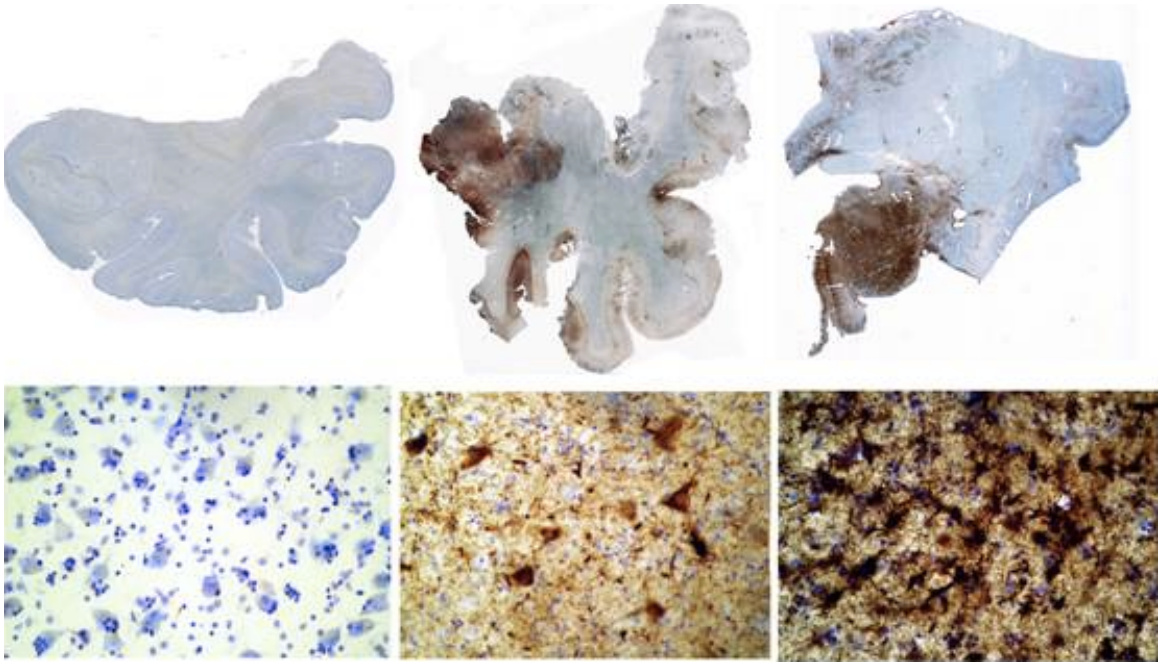
Pathology of Chronic Traumatic Encephalopathy

The primary microscopic characteristic of CTE is the pathological development of tau protein immunoreactive neurofibrillary tangles (NFTs) throughout the brain.[18,19,34] These plaque like aggregations are present in the olfactory bulbs, thalamus, hypothalamus, mammillary bodies, oculomotor nucleus, pontine nuclei, and elsewhere in the brains of patients diagnosed with CTE.[18] Tau NFTs are frequently found adjacent to small blood vessels, including the grey and white matter of the brainstem and spinal cord. Development of NFTs appears to initiate first around cerebral capillaries, with sporadic distributions throughout the brain as the disease progresses (Figure 2).

The precise mechanism for the insidious development of tau accumulations is not

fully understood, but data suggest the cerebral ischemia that follows a concussive event plays a role.[19] Decreased cerebral blood flow coupled with the degradation of the blood-brain barrier causes microvascular fissures throughout the brain; the subsequent appearance of NFTs at these sites implies correlation.[19] Further study is required to establish a direct link.

Figure 2. Shows cerebral tissue stained with tau protein antibodies. The brain on the left is not diagnosed with CTE, the 2 on the right have extensive tau NFTs, consistent with a CTE diagnosis. Image courtesy Center for Study of Traumatic Encephalopathy at Boston University School of Medicine.



Macro (top) and microscopic analysis of 65-yer-old man showing no tau protein accumulation.

Analysis of 45-year-old professional football player showing tau NFTs in the frontal cortex. This image is from the brain examined by McKee, et al 2009.

Image from 73-year-old professional boxer showing extensive tau NFT development in amygdala and thalamus. This man had severe dementia when he died.

After initial clusters appear near cerebral blood vessels tau NFTs begin to form in

the amygdala, hippocampus, hypothalamus, and mesencephalon, a continuum known as the Papez circuit.[19,24] These regions, referred to in one study as the "emotional" or "visceral" brain, play a role in emotional stability, aggression, and impulse control; tau abnormalities brought on by repeated concussive hits may underlie the serious psychological problems experienced by CTE patients.[34] In the same vein, tau NFTs in the hippocampus and entorhial cortex are likely responsible for the memory loss documented in professional football players with CTE.[35] Similar muscle control problems such as tremors or Parkinson's symptoms that appear in phase III may result from increased tau NFT concentrations in the substantia nigra of the midbrain.[35,36]

The deposition of β-amyloid plaques, a symptom associated with Alzheimer's disease, is occasionally documented in CTE patients. In the hours following a concussion, β-amyloid aggregations may appear in the hippocampus and neocortex, but are not necessarily concentrated near the injury site. The diffuse accumulations of β-amyloid plaques suggests that brain injuries trigger the overproduction of cerebral proteins and could bring about other neurological disorders such as Parkinson's and Alzheimer's at an accelerated rate.[24]

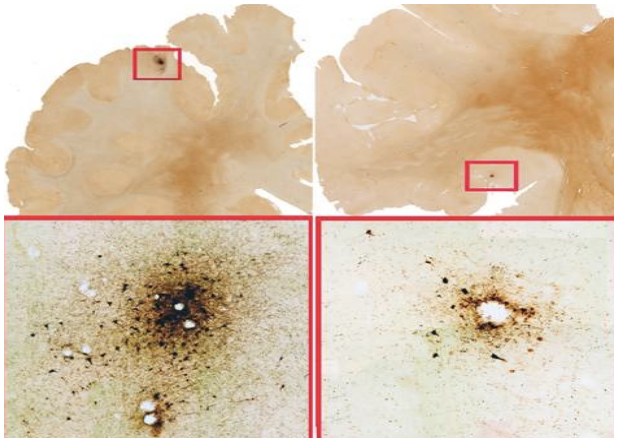


Figure 3. Showing early development of tau positive NFTs near cerebral blood vessels in frontal cortex (left) and insular cortex (right) of 18-year-old man diagnosed with CTE. Note tau concentrations adjacent to blood vessels (holes) in both bottom images. Image courtesy CSTE at Boston University School of Medicine.

Patients with CTE also develop gross anatomical pathology as the disease progresses. Earlier claims that axons tear after initial injury have been refuted as new evidence suggests axonal ability to stretch and fully heal even after repeated insults.[36-38] Neural damage originally attributed to a concussive trauma is now categorized as a gradual degeneration of axons and is described as "a process, not an event".[14,18] This process is considered distinct from cerebral apoptosis, which follows a unique signaling cascade.

Other physiological incidences documented in former professional football players include slightly reduced brain weight, thinning or fenestration of the corpus callosum, enlargement of the lateral and 3rd ventricles, and atrophy of the hippocampus, entorhinal cortex, and amygdala.[38,39] These neural disturbances, absent in the 18- and 21-year-old men and mild in the two 45-year-old men, suggest structural changes occur only after tau NFTs accumulate substantially.[40] The point at which tau clusters begin degrading neural tissue is not known.

Neural death is a consequence of acute traumatic brain injuries and factors into CTE. Claims that axons shear following injury have been reevaluated and it is now understood that the majority of neural death occurs in the hours and days that follow a concussion. Experimental data in rat studies and evidence from human autopsies suggest neuronal necrosis related to MTBIs is largely the result of high concentrations of excitatory amino acids in the intracellular space immediately following the concussion.[42] These amino acids are believed to destroy neurons for days after the initial injury. Colicos et al found lateral concussive injuries in rats to produce necrotic conditions that continue for up to 1 year after the trauma.[42] Rats in this study presented diffuse neural degradation in the hippocampus, thalamus, and neocortex and memory performance was

severely and progressively impaired. The implications for these findings on CTE in athletes is profound. CTE continues to progress in patients for decades after the repeated concussions that caused the disease have stopped, suggesting that multiple pathologic processes exert chronic effects once they are triggered. There is no point in CTE progression that represents a terminus; neural loss, cerebral atrophy, NFT propagation, and diffuse neurodegeneration continue to accumulate as the patient ages.

Genetic Considerations

There is evidence to suggest some individuals posses a genetic predisposition to CTE after repeated brain traumas. Apoliprotein E, the primary apoliprotein present in human cerebrospinal fluid, is responsible for lipid transportation in the brain and may assist with neurotransmission and neural repair following MTBI.[43,44] The ApoE gene has 3 alleles - ε2, ε3, and ε4 – which occur in 7%, 78%, and 15% of the population, respectively.[45] As related to CTE, ε4 is the most important because it is shown to result in increased risk for Alzheimer's disease, cognitive impairment, and hippcampal atrophy, particularly in the African-American community.[46,47]

There appears to be a link between the ApoE ε4 allele and negative outcomes associated with repeated head traumas. Patients with ApoE ε4 and a concurrent history of repeated head injuries are 10 times more likely to develop tau NFTs and β-amyloid plaques than people that possess ε4 with no history of MTBI.[48] The exact mechanism that links the allele to neurological disease is not clear. It is believed that β-amyloid deposits are more prevalent in individuals with ε4 than ε3 or ε2.[47,48] Reasons for this discrepancy remain unclear, but ApoE ε4's inability to bind to β-amyloid likely plays a role in chronic

neurodegeneration.

The dangerous combination of repeated head traumas and the ApoE ε4 allele is particularly important to CTE in professional football, where approximately 65% of NFL players identify themselves as African American.[49] The full impact of ApoE polymorphism on CTE in professional football players is unclear. It is not known if individuals carrying ApoE ε4 develop the disease more quickly than others, nor is it clear if players carrying the allele develop CTE after fewer concussions. Omalu et al documented 2 well-known cases of CTE in professional football players and noted that one player possessed the ApoE ε4 allele while the other did not. The authors were unable to account for this discrepancy, suggesting that ApoE ε4 genotyping is neither genetic protection from CTE nor a necessary precursor.[29] The risks associated with repeated brain traumas appear to be significantly compounded by genetic factors and more research with larger cohort sizes is necessary to elucidate the effects of genetic variation on CTE in professional athletes.[50]

Conclusions

The link between repeated concussive or subconcussive hits and long-term brain damage has been established in recent years. The physiological aftermath of a concussion coincides with the pathological findings in the brains of patients with CTE. There is overwhelming evidence showing the condition to be the direct result of these repeated sublethal hits to the head. Further data suggest the condition can be prevented by longer rehabilitation time after an initial head injury, though precisely what amounts to adequate recovery time is not yet clear and varies on an individual basis. The thousands of hits to

which professional football players are subjected over the course of the season are not necessarily damaging on their own, but the cumulative effect of these impacts over time is catastrophic. Of special concern to researchers is the development of CTE in younger players, most of whom have not yet experienced the ultra-violent hits encountered on the professional level. The appearance of tau neurofibrillary tangles in these young men suggests CTE may be extremely widespread in professional football players. The National Football League has instituted guidelines for its players, coaches, owners and medical staff designed to identify concussive traumas and keep players off the field until they are deemed fit to return to action by an independent neurologist. The effectiveness of this new protocol and the consequences on NFL players remains to be seen.

From a clinical perspective, researchers need more athletes to participate in CTE studies. The Center for the Study of Traumatic Encephalopathy and the Sports Legacy have been petitioning players to donate their brains with some success; 40 current or retired NFL players have agreed to donate their brains. This is an important step in curbing the development of CTE in professional football, but the key to stopping the disease appears to be broader education of athletes, trainers, physicians, and parents on the risks associated with repeated brain injuries. Organizational intercession to prevent injuries players from returning to the field is essential and could drastically decrease the prevalence of all brain injuries at every level.

Research about CTE is still relatively limited and there are significant questions to be answered, such as the precise relationship between ApoE polymorphism and CTE or how many concussions are necessary for the disease to occur. There remains a need to establish an accurate diagnostic test for CTE in living individuals and treatments must be

developed for these patients. Other environmental risk factors must be evaluated, such as the effects of childhood or adolescent brain traumas on athletes. It is clear that more expansive research on professional football players is required before a complete picture of the long-term effects on head trauma on these athletes can emerge.

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