Published in final edited form as:
Clin Sports Med. 2011 January ; 30(1): 179–xi. doi:10.1016/j.csm.2010.09.007.

Chronic Traumatic Encephalopathy: A Potential Late Effect of Sport-Related Concussive and Subconcussive Head Trauma[1]

Brandon E. Gavett, Ph.D.[a,b], **Robert A. Stern, Ph.D.**[a,b], and **Ann C. McKee, M.D.**[a,b,c,d]

[a]Center for the Study of Traumatic Encephalopathy and Alzheimer's Disease Center, Boston University, Boston, MA

[b]Department of Neurology, Boston University School of Medicine, Boston, MA

[c]Department of Pathology, Boston University School of Medicine, Boston, MA

[d]Bedford Veterans Affairs Medical Center, Bedford, MA

Synopsis

Chronic traumatic encephalopathy (CTE) is a form of neurodegeneration that is believed to result from repeated head injuries. Originally termed *dementia pugilistica* due to its association with boxing, the neuropathology of CTE was first described by Corsellis in 1973 in a case series of 15 retired boxers. CTE has recently been found to occur following other causes of repeated head trauma, suggesting that any repeated blows to the head, such as those that occur due to American football, hockey, soccer, professional wrestling, and physical abuse, can also lead to neurodegenerative changes. These changes often include cerebral atrophy, cavum septum pellucidum with fenestrations, shrinkage of the mammillary bodies, dense tau immunoreactive inclusions (neurofibrillary tangles, glial tangles, and neuropil neurites), diffuse axonal injury, and, in some cases, a TDP-43 proteinopathy. In association with these pathological changes, affected individuals often exhibit disordered memory and executive functioning, behavioral and personality disturbances (e.g., apathy, depression, irritability, impulsiveness, suicidality), parkinsonism, and, occasionally, motor neuron disease. At the present time, there are no formal clinical or pathological diagnostic criteria for CTE, but the distinctive neuropathological profile of the disorder lends promise for future research into its prevention, diagnosis, and treatment.

Keywords

Encephalopathy; Post-Traumatic; Neurodegenerative Disorders; Concussion; Athletic Injuries; Dementia; Motor Neuron Disease

[1]This work was supported by NIA P30AG13846, supplement 0572063345-5, National Operating Committee on Standards for Athletic Equipment, and by the Department of Veterans Affairs. This work was also supported by an unrestricted gift from the National Football League. The funding sources were not involved in the preparation, review, or approval of this manuscript.

Address correspondence to Ann C. McKee, M.D., Bedford VA Medical Center, 200 Springs Road, Bedford, MA, 01730; amckee@bu.edu; telephone: (781) 687-2913; fax: (781) 687-3515.
Brandon E. Gavett, Ph.D., Boston University School of Medicine, 72 East Concord St., B-7800, Boston, MA, 02118; begavett@bu.edu; telephone: (617) 414-8388; fax: (617) 414-1197.
Robert A. Stern, Ph.D., Boston University School of Medicine, 72 East Concord St., B-7800, Boston, MA, 02118; bobstern@bu.edu; telephone: (617) 638-5678; fax: (617) 414-1197.

It has been understood for decades that participation in certain sporting activities may increase an athlete's risk of developing a neurodegenerative disease later in life. Not surprisingly, this association was originally noted in boxers, athletes who receive numerous blows to the head during training and competition. In 1928, Harrison Martland, a New Jersey pathologist and medical examiner, first described the clinical spectrum of abnormalities found in "nearly one half of the fighters who have stayed in the game long enough" [1.] Boxers exhibiting cognitive, behavioral, or motor abnormalities were well known to lay persons, sportswriters, and others within the boxing community and were referred to by a variety of terms, such as "punch drunk," "goofy," and "slug-nutty" [2,3;] later, the more formal term *dementia pugilistica* was introduced in order to lend medical validity to the condition [4.] By the 1970s, a sufficient number of boxers with *dementia pugilistica* had been studied pathologically to support the conclusion that this form of neurodegeneration was similar to, but distinguishable from, other causes of neurodegenerative disease [5.] As evidence pertaining to the clinical and neuropathological consequences of repeated mild head trauma grew, it became clear that this pattern of neurodegeneration was not restricted to boxers, and the term chronic traumatic encephalopathy (CTE), originally coined by Miller [6,] became most widely used.

Over the last several decades, clinical and neuropathological evidence of CTE has emerged in association with a variety of sports, including American football, professional wrestling, professional hockey, soccer, as well as other activities associated with repetitive mild head trauma, such as physical abuse, epileptic seizures, and head banging [7,8,9,10,11,12,13.] Although the incidence and prevalence of CTE is currently unclear, it likely varies by sport, position, duration of exposure, and age at the time of initial or subsequent head trauma, as well as with additional variables such as genetic predisposition. To date, there have been no randomized neuropathological studies of CTE in deceased athletes, and as such, there is a selection bias in the cases that have come to autopsy. If one considers the prevalence in deceased professional American football players who died between February 2008 and June 2010, there were 321 known player deaths [14] and the brains of 12 of the 321 underwent postmortem neuropathological examination at Boston University Center for the Study of Traumatic Encephalopathy (BU CSTE). All 12 examined neuropathologically showed evidence of CTE, suggesting an estimated lifetime prevalence rate of at least 3.7%. If one assumes that all deceased players who did not come to autopsy did not have CTE, and that the amount of head trauma in professional football has remained fairly constant over the past 5 decades, a prevalence rate of 3.7% would result. Although this represents a conservative estimate, it suggests a significant public health risk for persons who suffer repetitive mild traumatic brain injury.

Clinical signs and symptoms of CTE

Whereas concussion and post-concussion syndrome represent temporary states of neuronal and axonal derangement, CTE is a neurodegenerative disease that occurs years or decades following recovery from the acute or post-acute effects of head trauma. The exact relationship between concussion and CTE is not entirely clear, although repetitive axonal perturbation may initiate a series of metabolic, ionic, membrane, and cytoskeletal disturbances that trigger the pathological cascade that leads to CTE in susceptible individuals [15,16.] The onset of CTE is often in mid-life, usually after the athlete has retired from his or her sport. In some individuals, the early manifestations of CTE affect behavior; in particular, individuals with neuropathologically-documented CTE have been described by family and friends as being more irritable, angry, apathetic, or having a shorter fuse. Increased suicidality appears to be a particularly salient symptom caused by CTE [17.] In other cases, cognitive difficulties may be the first signs to emerge, with poor episodic memory and executive functioning being two of the most common cognitive dysfunctions

reported. Later in the disease, movement (e.g., parkinsonism), speech, and ocular abnormalities may emerge in the context of declining cognition and worsening comportment. A minority of cases with neuropathologically-documented CTE developed dementia before death; the relative infrequency of dementia in individuals with CTE may be due in part to the fact that many individuals with CTE have either committed suicide or died from accidents or drug overdose at an early age [11,17].

Neuropathology of CTE

Gross Pathology

Neuropathological studies of athletes with a history of repeated mild head injuries have produced a number of consistent findings that, together, make CTE a distinctive disorder. Upon gross examination, there is often anterior cavum septum pellucidum and, usually, posterior fenestrations. These changes may be caused by the force of the head impact being transmitted through the ventricular system, thereby affecting the integrity of the intervening tissue. Enlargement of the lateral and third ventricles is also a common feature seen in CTE; the third ventricle may be disproportionately widened. Additional gross features include atrophy of the frontal and temporal cortices, atrophy of the medial temporal lobe, thinning of the hypothalamic floor, shrinkage of the mammillary bodies, pallor of the substantia nigra, and hippocampal sclerosis. Atrophy of the cerebrum, diencephalon, basal ganglia, brainstem, and cerebellum, may result in an overall reduction in brain mass [11].

Microscopic Neuropathology

Tau—Microscopically, CTE is characterized by an abundance of neurofibrillary inclusions, in the form of neurofibrillary tangles (NFTs), neuropil threads (NTs), and glial tangles (GTs). The main protein composing NFTs is the microtubule-associated protein tau, and NFTs are aggregates of filamentous tau polymers. While CTE shares many microscopic similarities with Alzheimer's disease (AD) and other tauopathies, it has several distinguishing features. First, the distribution of tau pathology is unique; it is most commonly found in the more superficial cortical laminae (II and III), whereas tau NFTs in AD are preferentially distributed in large projection neurons in layers III and V. Further, the regional tau pathology is extremely irregular, largely confined to uneven foci in the frontal, temporal, and insular cortices, unlike the more uniform cortical NFT distribution seen in AD. Tau NFTs, NTs and GTs are found throughout the medial temporal lobe, often in densities greater than those found in severe AD, and are also prominent in the diencephalon, basal ganglia, and brainstem. NTs and GTs are also found in the subcortical white matter. Finally, NFTs in CTE are most dense at the depths of cortical sulci, and are typically perivascular, which might indicate that disruptions of the cerebral microvasculature and the blood brain barrier that occur at the time of the traumatic injury play a critical role in the formation of NFTs [11.]

Although the precise pathological mechanisms that tie repeated mild head injuries to NFT formation are not known, they may involve a series of diffuse axonal injuries (DAI) set in motion by the initial trauma and aggravated by subsequent mild traumatic injuries. During a traumatic brain injury, the brain and spinal cord undergo shear deformation producing a transient elongation or stretch of axons. Traumatic axonal injury results in alterations in axonal membrane permeability, ionic shifts including massive influx of calcium, and release of caspases and calpains that might trigger tau phosphorylation, misfolding, truncation, and aggregation, as well as breakdown of the cytoskeleton with dissolution of microtubules and neurofilaments [15,18,19].

There is also increasing evidence that tau phosphorylation, truncation, aggregation, and polymerization into filaments represents a toxic gain of function and continued accumulation of tau leads to neurodegeneration. This is supported by tau's involvement in some genetic forms of frontotemporal degeneration [20] and by work that shows that plasmids containing human tau cDNA constructs microinjected into lamprey neurons in situ produce tau filaments that accumulate and lead to neuronal degeneration [21,22.] However, it is also possible that the intracellular NFTs, in and of themselves, are byproducts, rather than the cause, of cellular injury, and that NFT formation indicates neurons that survived the initial injury and sequestered the abnormally phosphorylated, truncated and folded tau [23.] How a neurodegeneration that starts multifocally around small blood vessels or in the depths of cortical sulci ultimately spreads to involve large regions of brain as a systemic degeneration such as CTE may be explained by a possible tau toxic factor or trans-cellular propagation by the misfolded tau protein [24].

Beta-amyloid—Beta-amyloid (Aβ) deposits are found in 40–45% of individuals with CTE; this is in contrast to the extensive Aβ deposits that characterize nearly all cases of AD. While neuritic plaques are typically abundant in AD and are essential to the diagnosis, Aβ plaques in CTE, when they occur, are less dense and predominantly diffuse [11.] Despite the relatively minor role Aβ plaques appear to play in the neuropathological manifestation of CTE, the role of Aβ in the pathogenesis of CTE has yet to be elucidated. It is known that acute head injuries cause an up-regulation of amyloid precursor protein (APP) production, and that Aβ plaques may be found in up to 30% of patients who die within hours following TBI [25,26,27.] DAI, often a consequence of mild TBI, is thought to influence changes in Aβ following head injury. Interruption of axonal transport causes an accumulation of multiple proteins in the axon, including APP, in varicosities along the length of the axon or at disconnected axon terminals, termed axonal bulbs [28.] Although the axonal pathology in TBI is diffuse in that it affects widespread regions of the brain, typically the axonal swellings are found in multifocal regions of the subcortical and deep white matter, including the brainstem. Due to the rapid and abundant accumulation of APP in damaged axons after TBI, APP immunostaining is used for the pathological assessment of DAI in humans. Accordingly, this large reservoir of APP in injured axons might be aberrantly cleaved to rapidly form Aβ after TBI [25,29,30.] However, it remains unclear whether the large quantities of APP and Aβ found in damaged axons after TBI play any mechanistic role in either neurodegeneration or neuroprotection [28,31,32.] Moreover, it is unknown how long the increased APP and Aβ lasts or what mechanisms may result in variable clearance.

TDP-43—Recently, in addition to severe tau neurofibrillary pathology, we found a widespread TDP-43 proteinopathy in over 80% of our cases of CTE [13.] Moreover, in 3 athletes with CTE who developed a progressive motor neuron disease several years prior to death, there were extensive TDP-43 immunoreactive inclusions in the anterior horns of the spinal cord, in addition to tau immunoreactive GT, neurites, and, occasionally, extensive NFTs. These findings suggest that a distinctive, widespread TDP-43 proteinopathy is also associated with CTE and that, in some individuals, the TDP-43 proteinopathy extends to involve the spinal cord and is clinically manifest as motor neuron disease with a presentation that may appear similar to amyotrophic lateral sclerosis [13.] The shared presence of two aggregated phosphorylated proteins associated with neurodegeneration in the great majority of cases of CTE suggests that a common stimulus, such as repetitive axonal injury, provokes the pathological accumulation of both proteins [33.] Recent studies *in vitro* and *in vivo* suggest that over-expression of wild-type human TDP-43 and its dislocation from the neuronal nucleus to the cytoplasm are associated with neurodegeneration and cell death [34,35,36.] By virtue of its capacity to bind to neurofilament mRNA and stabilize the mRNA transcript, TDP-43 plays a critical role in mediating the response of the neuronal

cytoskeleton to axonal injury. TDP-43 is intrinsically prone to aggregation, and its expression is upregulated following experimental axotomy in spinal motor neurons of the mouse [37.] Traumatic axonal injury may also accelerate TDP-43 accumulation, aggregation, and dislocation to the cytoplasm, thereby enhancing its neurotoxicity.

Clinical Implications

CTE is a potential late effect of repeated head injuries

CTE is not thought to be a long-term sequela following a specific head trauma. Rather, its clinical symptoms emerge later in life, usually after an athlete retires from his or her sport. Like most other neurodegenerative diseases that cause dementia, CTE has an insidious onset and gradual course. Based on a recent review of neuropathologically-confirmed CTE in athletes [11,] the mean age of onset is 42.8 years (SD = 12.7; range = 25 – 76 years). On average, onset occurs approximately 8 years after retirement (SD = 10.7), although approximately one-third of athletes were reportedly symptomatic at the time of retirement. In athletes, the course appears to be considerably protracted (mean duration = 17.5 years, SD = 12.1), especially in boxers. The average duration of the disease in boxers is 20 years (SD = 11.7) and 6 years in American football players (SD = 2.9) [11.] If the affected individual does not die of other causes, full-blown clinical dementia may occur late in the course of the disease.

Diagnosis of CTE

At the present time, the clinical diagnosis of CTE is difficult because there are no consensus diagnostic criteria or large-scale longitudinal clinico-pathological correlation studies. The differential diagnosis of CTE will often include AD [38] and frontotemporal dementia (FTD) [39,] depending on the age of onset and the presenting problem. Older individuals with memory difficulties may appear to have AD, and, in fact, may have both evidence of AD and CTE neuropathologically [11.] When the age of onset is earlier (e.g., when an individual is in his/her 40s or 50s) and the patient presents with behavioral dysregulation or apathy, it may be difficult to rule out FTD. While a history of remote head trauma may be suggestive of CTE, head trauma has been implicated as a risk factor for AD, Parkinson's disease (PD), ALS, and other neurodegenerative diseases [40,41,42.] Therefore, without neuropathological confirmation, at the present time, a clinical diagnosis of CTE cannot be made with a high degree of confidence. Furthermore, the clinical phenotype of CTE may be confounded by alcohol or other drug abuse. A number of individuals with neuropathologically-confirmed CTE are thought to have developed problems with drug abuse as a consequence of the loss of inhibitory control caused by the neurodegenerative disease. From a clinical perspective, however, it can be difficult to determine whether the drug abuse problems are a cause of symptoms or simply one of many ways in which CTE is manifest.

Although the neuropathological features of CTE appear to be distinct from other neurodegenerative diseases, there are also no current neuropathological criteria that have been agreed upon for the diagnosis of CTE. Once these criteria are established, they can be applied at autopsy in large-scale, prospective longitudinal studies of athletes with a history of repetitive head injuries. Establishing neuropathological diagnostic criteria will allow for the identification of clinical criteria and biomarkers to improve the accuracy of CTE diagnosis in the living.

A number of biomarkers are believed to have the potential to contribute to identifying CTE in vivo. For instance, the changes to white matter integrity caused by repeated head trauma may be amenable to detection using diffusion tensor magnetic resonance imaging [43.] Magnetic resonance spectroscopy may be capable of detecting changes in glutamate/

glutamine, N-acetyl aspartate, and myo-inositol, molecular abnormalities that may serve as markers of brain damage caused by head injuries [44.] Further, measuring tau and phospho-tau in cerebrospinal fluid may yield diagnostically useful markers of CTE [45].

Risk and Protective Factors

Clearly, CTE research is in its infancy, and decades of research are likely necessary to move the field to the point where CTE can be diagnosed early in its course using a combination of clinical tools and biomarkers. However, the research that has currently been conducted has profound implications for current practice by medical professionals, athletic trainers, and related specialists, as well as policy makers in both government and athletic organizations. CTE is the only known neurodegenerative dementia with a specific identifiable cause; in this case, the cause is head trauma. It is unknown whether a single blow to the head is sufficient to initiate the metabolic cascade that precedes the clinical and neuropathological changes characteristic of CTE, as all confirmed cases of CTE to date have had a history of multiple head injuries. Therefore, the most obvious way to prevent CTE is, in theory, to prevent repetitive head injuries from occurring. In some sports, such as boxing and American football, it may be impossible to prevent repetitive head injuries, especially the repeated subconcussive blows that are characteristic of the impacts felt by offensive and defensive linemen in football on nearly every play. In sports where repeated blows to the head are unavoidable, proper concussion assessment and management may be paramount for preventing long-term consequences. At the present time, it is unknown whether returning to play while symptomatic from a previous concussion, or sustaining a second concussion while symptomatic, is a risk factor for developing CTE. However, other strategies to reduce the number and severity of head trauma are possible, such as limiting full-contact practices, implementing rules of play which diminish the likelihood of repeated head trauma (e.g., removing the three-point stance in football), or increasing the use of newer protective headgear aimed at absorbing force and thus diminishing the impact to the brain.

Along these same lines, there are many potential variables surrounding head trauma in athletes that may be important for preventing CTE later in life. The sport played and the position played within each sport may be relevant; for instance, boxers receive a greater proportion of rotational forces to the head, while American football players receive a greater proportion of linear forces to the head [46.] Even within the same sport, athlete exposure to head injuries can differ considerably. In the case of American football, some positions such as wide receiver may receive occasional severe blows with the potential to cause unconsciousness, while other players, such as linemen, may take hundreds of small impacts per season, most of which are not, in and of themselves, forceful enough to cause symptoms [47.] It is unknown whether CTE is more likely to occur following a small number of severe head injuries, a large number of subconcussive injuries, or other forms of head trauma. Currently, investigations are ongoing that attempt to quantify the force of head impacts across different sports and positions [48.] These findings will play an important role in understanding the specific head injury variables that influence CTE risk.

The age at which an athlete suffers his or her head injuries may also influence future CTE risk. At younger ages, the brain may be more vulnerable to injury [49]. On the other hand, the increased plasticity of the young brain may be better able to compensate for specific difficulties such as behavioral dysfunction [50.] It is also not clear whether particular lifestyle factors may be protective against CTE in the context of repetitive head injuries. In other neurodegenerative diseases such as AD, the neuropathology is thought to precede the clinical symptoms, possibly by several decades [51.] The same may be true for CTE, as evidenced by the presence of CTE neuropathology in asymptomatic individuals studied at autopsy. Conceivably, health and medical factors that are absent or present during this preclinical stage may influence the extent of neurodegeneration or the brain's ability to

compensate for any neurodegeneration. For instance, the presence of chronic inflammation, such as that which accompanies medical conditions such as obesity, hypertension, diabetes mellitus, atherosclerosis, and heart disease, may facilitate neurodegeneration and NFT formation [52,53,54,55.] In addition, as with other neurodegenerative diseases like AD, some individuals may have greater "cognitive reserve," thus increasing the threshold for the clinical manifestation of the underlying neuropathological condition.

Genetic variations may also play an important role in moderating the relationships between head trauma, neuropathological changes, and disordered cognition and behavior. One of the genes thought to influence CTE risk is the apolipoprotein E (APOE) gene. The APOE ε4 allele, important in the genetics of AD, may also increase the risk of CTE. Based on genetic testing conducted in conjunction with neuropathological examinations of individuals with a history of repeated head injuries, approximately 57% of individuals with neuropathologically-confirmed CTE possessed at least one APOE ε4 allele. When contrasted with the estimated 28% of the population possessing at least one APOE ε4 allele [56,] the frequency of this allele in those with CTE appears higher than expected. This genetic link is currently speculative, as formal epidemiological studies have yet to be conducted. However, individuals carrying the APOE ε4 allele may be more likely to have a poor outcome following TBI, especially in individuals less than 15 years of age [57,58,59.] Epidemiological data have also implicated the APOE ε4 genotype as a risk factor for the development of AD following TBI [60,61] and carriers of the APOE ε4 allele were found to be at increased risk of Aβ deposition following TBI [62].

Conclusion

CTE is a neurodegenerative disease that occurs later in the lives of some individuals with a history of repeated head trauma. The exact relationship between repetitive mild traumatic brain injury, with or without symptomatic concussion, and CTE is not entirely clear, although it is possible that repetitive axonal injury sets up a series of metabolic, ionic, and cytoskeletal disturbances that trigger a pathological cascade leading to CTE in susceptible individuals. CTE has been reported in association with the play of American football, professional wrestling, soccer, hockey, as well as in association with physical abuse, epilepsy, and head banging behaviors, suggesting that mild TBI of diverse origin is capable of instigating CTE. CTE often manifests in mid-life and produces clinical symptoms of disordered cognition, memory loss and executive dysfunction, depression, apathy, disinhibition, irritability, and parkinsonian signs. The characteristic neuropathological features of CTE include extensive tau-immunoreactive inclusions scattered throughout the cerebral cortex in a patchy, superficial distribution, with focal epicenters at the depths of sulci and around the cerebral vasculature; and widespread TDP-43-immunoreactive inclusions that may occasionally be associated with symptoms of motor neuron disease. Currently, neuropathological examination of brain tissue is the only way to diagnose CTE, although intense research efforts are underway to identify biomarkers to detect the disease and monitor its progression, and to develop therapies to slow or reverse its course. Longitudinal research efforts are underway to shed additional light on the specific variables related to head trauma, neuropathology, and clinical presentation of CTE that remain unanswered.

References

1. Martland HS. Punch Drunk. JAMA 1928;91:1103–1107.
2. Critchley M. Medical aspects of boxing, particularly from a neurological standpoint. Br Med J 1957;1:357–362. [PubMed: 13396257]

3. Parker H. Traumatic encephalopathy (‘punch drunk') of professional pugilists. J Neurol Psychopathol 1934;15:20–28.
4. Millspaugh JA. Dementia Pugilistica. U S Nav Med Bull 1937;35:297–303.
5. Corsellis JA, Bruton CJ, Freeman-Browne D. The aftermath of boxing. Psychol Med 1973;3:270–303. [PubMed: 4729191]
6. Miller H. Mental after-effects of head injury. Proc R Soc Med 1966;59:257–261. [PubMed: 5909768]
7. Geddes JF, Vowles GH, Nicoll JA, Révész T. Neuronal cytoskeletal changes are an early consequence of repetitive head injury. Acta Neuropathol 1999;98:171–178. [PubMed: 10442557]
8. Omalu BI, DeKosky ST, Hamilton RL, et al. Chronic traumatic encephalopathy in a national football league player: part II. Neurosurgery 2006;59:1086–1092. [PubMed: 17143242]
9. Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH. Chronic traumatic encephalopathy in a National Football League player. Neurosurgery 2005;57:128–134. [PubMed: 15987548]
10. Cajigal S. Brain Damage May Have Contributed to Former Wrestler's Violent Demise. Neurology Today 2007;7:1–16.
11. McKee A, Cantu R, Nowinski C, et al. Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury. J Neuropathol Exp Neurol 2009;68:709–735. [PubMed: 19535999]
12. Omalu BI, Bailes J, Hammers JL, Fitzsimmons RP. Chronic Traumatic Encephalopathy, Suicides and Parasuicides in Professional American Athletes: The Role of the Forensic Pathologist. Am J Forensic Med Pathol 2010;31:130–132. [PubMed: 20032774]
13. McKee AC, Gavett BE, Stern RA, et al. TDP-43 Proteinopathy and Motor Neuron Disease in Chronic Traumatic. J Neurol Exp Neuropathol. in press.
14. Oldest Living Pro Football Players. 2009 – 2000 Necrology. [Accessed May 15, 2010]. Available at: http://www.freewebs.com/oldestlivingnfl/20092000necrology.htm
15. Giza C, Hovda D. The neurometabolic cascade of concussion. J Athl Train 2001;36:228–235. [PubMed: 12937489]
16. Yuen TJ, Browne KD, Iwata A, Smith DH. Sodium channelopathy induced by mild axonal trauma worsens outcome after a repeat injury. J Neurosci Res 2009;87:3620–3625. [PubMed: 19565655]
17. Omalu BI, Hamilton RL, Kamboh MI, Dekosky ST, Bailes J. Chronic traumatic encephalopathy (CTE) in a National Football League Player: Case report and emerging medicolegal practice questions. J Forensic Nurs 2010;6:40–46. [PubMed: 20201914]
18. Binder LI, Guillozet-Bongaarts AL, Garcia-Sierra F, Berry RW. Tau, tangles, and Alzheimer's disease. Biochim Biophys Acta 2005;1739:216–223. [PubMed: 15615640]
19. Serbest G, Burkhardt MF, Siman R, Raghupathi R, Saatman KE. Temporal profiles of cytoskeletal protein loss following traumatic axonal injury in mice. Neurochem Res 2007;32:2006–2014. [PubMed: 17401646]
20. Spillantini MG, Bird TD, Ghetti B. Frontotemporal dementia and Parkinsonism linked to chromosome 17: a new group of tauopathies. Brain Pathol 1998;8:387–402. [PubMed: 9546295]
21. Hall GF, Chu B, Lee G, Yao J. Human tau filaments induce microtubule and synapse loss in an in vivo model of neurofibrillary degenerative disease. J Cell Sci 2000;113:1373–1387. [PubMed: 10725221]
22. Hall GF, Yao J, Lee G. Human tau becomes phosphorylated and forms filamentous deposits when overexpressed in lamprey central neurons in situ. Proc Natl Acad Sci U S A 1997;94:4733–4738. [PubMed: 9114060]
23. de Calignon A, Fox LM, Pitstick R, et al. Caspase activation precedes and leads to tangles. Nature 2010;464:1201–1204. [PubMed: 20357768]
24. Frost B, Jacks RL, Diamond MI. Propagation of tau misfolding from the outside to the inside of a cell. J Biol Chem 2009;284:12845–12852. [PubMed: 19282288]
25. Gentleman SM, Nash MJ, Sweeting CJ, Graham DI, Roberts GW. Beta-amyloid precursor protein (beta APP) as a marker for axonal injury after head injury. Neurosci Lett 1993;160:139–144. [PubMed: 8247344]

26. Roberts GW, Gentleman SM, Lynch A, Murray L, Landon M, Graham DI. Beta amyloid protein deposition in the brain after severe head injury: implications for the pathogenesis of Alzheimer's disease. J Neurol Neurosurg Psychiatry 1994;57:419–425. [PubMed: 8163989]
27. Roberts GW, Gentleman SM, Lynch A, Graham DI. beta A4 amyloid protein deposition in brain after head trauma. Lancet 1991;338:1422–1423. [PubMed: 1683421]
28. Johnson VE, Stewart W, Smith DH. Traumatic brain injury and amyloid-beta pathology: a link to Alzheimer's disease? Nat Rev Neurosci 2010;11:361–370.
29. Gorrie C, Oakes S, Duflou J, Blumbergs P, Waite PME. Axonal injury in children after motor vehicle crashes: extent, distribution, and size of axonal swellings using beta-APP immunohistochemistry. J Neurotrauma 2002;19:1171–1182. [PubMed: 12427326]
30. Sherriff FE, Bridges LR, Sivaloganathan S. Early detection of axonal injury after human head trauma using immunocytochemistry for beta-amyloid precursor protein. Acta Neuropathol 1994;87:55–62. [PubMed: 8140894]
31. Smith DH, Chen XH, Iwata A, Graham DI. Amyloid beta accumulation in axons after traumatic brain injury in humans. J Neurosurg 2003;98:1072–1077. [PubMed: 12744368]
32. Chen XH, Johnson VE, Uryu K, Trojanowski JQ, Smith DH. A lack of amyloid beta plaques despite persistent accumulation of amyloid beta in axons of long-term survivors of traumatic brain injury. Brain Pathol 2009;19:214–223. [PubMed: 18492093]
33. Uryu K, Chen XH, Martinez D, et al. Multiple proteins implicated in neurodegenerative diseases accumulate in axons after brain trauma in humans. Exp Neurol 2007;208:185–192. [PubMed: 17826768]
34. Barmada SJ, Skibinski G, Korb E, Rao EJ, Wu JY, Finkbeiner S. Cytoplasmic mislocalization of TDP-43 is toxic to neurons and enhanced by a mutation associated with familial amyotrophic lateral sclerosis. J Neurosci 2010;30:639–649. [PubMed: 20071528]
35. Tatom JB, Wang DB, Dayton RD, et al. Mimicking aspects of frontotemporal lobar degeneration and Lou Gehrig's disease in rats via TDP-43 overexpression. Mol Ther 2009;17:607–613. [PubMed: 19223871]
36. Wils H, Kleinberger G, Janssens J, et al. TDP-43 transgenic mice develop spastic paralysis and neuronal inclusions characteristic of ALS and frontotemporal lobar degeneration. Proc Natl Acad Sci U S A 2010;107:3858–3863. [PubMed: 20133711]
37. Moisse K, Mepham J, Volkening K, Welch I, Hill T, Strong MJ. Cytosolic TDP-43 expression following axotomy is associated with caspase 3 activation in NFL−/− mice: support for a role for TDP-43 in the physiological response to neuronal injury. Brain Res 2009;1296:176–186. [PubMed: 19619516]
38. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944. [PubMed: 6610841]
39. Neary D, Snowden JS, Gustafson L, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546–1554. [PubMed: 9855500]
40. Mortimer JA, van Duijn CM, Chandra V, et al. EURODEM Risk Factors Research Group. Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. Int J Epidemiol 1991;20:S28–S35. [PubMed: 1833351]
41. Goldman SM, Tanner CM, Oakes D, Bhudhikanok GS, Gupta A, Langston JW. Head injury and Parkinson's disease risk in twins. Ann Neurol 2006;60:65–72. [PubMed: 16718702]
42. Chen H, Richard M, Sandler DP, Umbach DM, Kamel F. Head injury and amyotrophic lateral sclerosis. Am J Epidemiol 2007;166:810–816. [PubMed: 17641152]
43. Jones DK, Dardis R, Ervine M, et al. Cluster analysis of diffusion tensor magnetic resonance images in human head injury. Neurosurgery 2000;47:306–313. [PubMed: 10942003]
44. Ross BD, Ernst T, Kreis R, et al. 1H MRS in acute traumatic brain injury. J Magn Reson Imaging 1998;8:829–840. [PubMed: 9702884]
45. Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. Ann Neurol 2009;65:403–413. [PubMed: 19296504]

46. Viano DC, Casson IR, Pellman EJ, et al. Concussion in professional football: comparison with boxing head impacts--part 10. Neurosurgery 2005;57:1154–1172. [PubMed: 16331164]
47. Rowson S, Brolinson G, Goforth M, Dietter D, Duma S. Linear and angular head acceleration measurements in collegiate football. J Biomech Eng 2009;131:061016. [PubMed: 19449970]
48. Brolinson PG, Manoogian S, McNeely D, Goforth M, Greenwald R, Duma S. Analysis of linear head accelerations from collegiate football impacts. Curr Sports Med Rep 2006;5:23–28. [PubMed: 16483513]
49. Field M, Collins MW, Lovell MR, Maroon J. Does age play a role in recovery from sports-related concussion? A comparison of high school and collegiate athletes. J Pediatr 2003;142:546–553. [PubMed: 12756388]
50. Anderson V, Spencer-Smith M, Leventer R, et al. Childhood brain insult: can age at insult help us predict outcome? Brain 2009;132:45–56. [PubMed: 19168454]
51. Näslund J, Haroutunian V, Mohs R, et al. Correlation between elevated levels of amyloid beta-peptide in the brain and cognitive decline. JAMA 2000;283:1571–1577. [PubMed: 10735393]
52. Arnaud LT, Myeku N, Figueiredo-Pereira ME. Proteasome-caspase-cathepsin sequence leading to tau pathology induced by prostaglandin J2 in neuronal cells. J Neurochem 2009;110:328–342. [PubMed: 19457109]
53. Ke YD, Delerue F, Gladbach A, Götz J, Ittner LM. Experimental diabetes mellitus exacerbates tau pathology in a transgenic mouse model of Alzheimer's disease. PLoS One 2009;4:e7917. [PubMed: 19936237]
54. Duong T, Nikolaeva M, Acton PJ. C-reactive protein-like immunoreactivity in the neurofibrillary tangles of Alzheimer's disease. Brain Res 1997;749:152–156. [PubMed: 9070642]
55. Arnaud L, Robakis NK, Figueiredo-Pereira ME. It may take inflammation, phosphorylation and ubiquitination to 'tangle' in Alzheimer's disease. Neurodegener Dis 2006;3:313–319. [PubMed: 16954650]
56. Hill JM, Bhattacharjee PS, Neumann DM. Apolipoprotein E alleles can contribute to the pathogenesis of numerous clinical conditions including HSV-1 corneal disease. Exp Eye Res 2007;84:801–811. [PubMed: 17007837]
57. Teasdale GM, Murray GD, Nicoll JAR. The association between APOE epsilon4, age and outcome after head injury: a prospective cohort study. Brain 2005;128:2556–2561. [PubMed: 16033781]
58. Friedman G, Froom P, Sazbon L, et al. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. Neurology 1999;52:244–248. [PubMed: 9932938]
59. Sundström A, Marklund P, Nilsson LG, et al. APOE influences on neuropsychological function after mild head injury: within-person comparisons. Neurology 2004;62:1963–1966. [PubMed: 15184597]
60. Mayeux R, Ottman R, Maestre G, et al. Synergistic effects of traumatic head injury and apolipoprotein-epsilon 4 in patients with Alzheimer's disease. Neurology 1995;45:555–557. [PubMed: 7898715]
61. Mayeux R, Ottman R, Tang MX, et al. Genetic susceptibility and head injury as risk factors for Alzheimer's disease among community-dwelling elderly persons and their first-degree relatives. Ann Neurol 1993;33:494–501. [PubMed: 8498827]
62. Nicoll JA, Roberts GW, Graham DI. Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. Nat Med 1995;1:135–137. [PubMed: 7585009]