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The Extreme Effects of 'Not-so-minor' Concussions: Chronic Traumatic Encephalopathy Literature Review

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Abstract

Many of the concerns that people have with chronic traumatic encephalopathy (CTE) have already been researched for almost a century, but recently, there has been a big push in CTE research. Previous research was done on boxing and football and has now expanded to other contact sports and the military. Risk factors for CTE include repetitive head trauma, the Apoε4 allele, and age of first exposure to brain trauma. A wide range of symptoms may present with CTE, from motor impairment to suicidal ideation. It is believed that a biopsychosocial model should be used when approaching the symptoms of CTE patients. Current research is trying to determine the main pathology or pathologies of CTE and have determined that there are both macroscopic and microscopic pathologies. The only definitive cases of CTE have been determined by an autopsy, but with the use of biomarkers and advances in neuroimaging, hopefully CTE can be diagnosed in living persons and work can be done to find a treatment.

Background

The overall concept of chronic traumatic encephalopathy (CTE) and brain trauma dates back almost a century ago. Osnato and Gilberti (1927) are credited with the original concept that chronic neurodegeneration might occur after minor brain trauma. They studied 100 clinical cases of concussions of the brain, which was defined back then as a blow to the head with loss of consciousness with or without posttraumatic amnesia or skull fracture. Through this study, they found that several instances in which the clinical symptoms persisted, and secondary degenerative changes developed, they termed this 'traumatic encephalitis'. The following year, in 1928, Martland studied the effects of repetitive brain trauma in boxers, he called it "punch-drunk syndrome". Boxers did not like the term "punch-drunk syndrome" so it was later named dementia pugilistica, which described a physical-psychic syndrome that accumulated over a lengthy boxing career. (Tharmaratnam et al., 2018). In 1973, Corsellis, Bruton and Freeman-Browne described the clinical and neurological features of 15 retired boxers. The study conducted in 1973 introduced a relatively stereotyped pattern of structural brain abnormalities. These abnormalities included: cerebral atrophy, enlargement of the lateral and third ventricles, thinning of the corpus callosum, cavum septum pellucidum with fenestrations and cerebellar scarring (Corsellis, Bruton, & Freeman, 1973). Currently, many people follow the guidelines set by Omalu and colleagues who were the first to demonstrate the CTE phenomenon in 2005 through a series of case reports based on autopsy findings of deceased players' brains. CTE is currently defined as brain trauma that is either repetitive, episodic, or a single precipitating event, leading to progressive brain neurodegeneration (Tharmaratnam et al., 2018).

Epidemiology and Incidence

Studies aiming to identify the prevalence of CTE in football players have shown remarkable, indisputable findings. In the largest ever case series of CTE, involving 202 deceased former football players, 87% of them had signs of CTE, including 99% ex-NFL players. The magnitude of the disease burden was correlated to level of play, with high school athletes having mild CTE, and NFL players showcasing the most severe form of CTE. In this same study, it was found that Ex-NFL players were also, if over the age of 50, five times more likely to be diagnosed with dementia than the national population averages (Tharmaratnam et al., 2018). The exact incidence of CTE is still unknown but it is believed to be attributed to duration of play, position, sport, age of first exposure, and genetics.

Risk Factors

The primary risk factor for CTE is believed to be repetitive head trauma, which is very common in football players, especially NFL football players. In a study done on NFL football players, 61% of them have experienced at least 1 concussion within their careers; but, remember that brain trauma without a concussion can also lead to CTE. In general, most people recover from a single head impact with no CTE, however, experiencing 3 or more concussions is correlated to an increased risk of prolonged symptoms. In a sample of 1721 cases of contact sport athletes, CTE was reported to be found in 32% of the cases, whereas no cases of CTE was found in patients with no prior brain trauma in the control group. This suggests that participating in contact sports is a predisposing risk factor in the development of CTE (Tharmaratnam et al., 2018).

Research has shown that there may be a genetic susceptibility risk factor for CTE. There is an apolipoprotein (Apoε), a 34-kDa glycosylated protein, that is implicated as the primary

source of cholesterol transport in the brain for neuronal repair. Individuals possessing Apoε4 allele have been shown to have an increased risk of poor functional outcome. Compared to other isoforms, the Apoε4 variant has been associated with longer recovery times from neurotrauma, increased injury severity, and greater cognitive deficits in football players (Tharmaratnam et al., 2018).

Another risk factor is age of first exposure (AFE) which is associated with neurological and psychiatric dysfunction later in life. Ages 9-12 have been identified as key periods corresponding to peak gray and white matter volumes and neurological maturation of the hippocampus and amygdala. AFE <12 was associated with more than double the risk of cognitive impairment later in life, which included impairments in correlates of apathy and depression, but not cognition (Tharmaratnam et al., 2018).

Mechanisms of Injury

The literature to date is not sufficient to determine whether the development of CTE is associated with head injury frequency or head injury type (Aldag et al., 2017). It has been demonstrated that brain trauma without concussion can also lead to CTE. Over time, tau oligomers develop into paired helical, and straight filamentous neurofibrillary tangles (NFTs), which interfere with white matter tracts in the brain and cause signaling and communication abnormalities through denervation injury (Tharmaratnam et al., 2018). The increased blood-barrier permeability is due to the inflammatory state which activates cytokine and chemokines, allowing unwanted chemicals and hormones in.

Symptoms

Clinical symptoms associated with CTE include chronic psychiatric illness, headache, cognitive dysfunction, motor impairment, irritability, aggression, episodic memory impairment,

suicidal ideation, rampant mood fluctuations and depression (Aldag et al., 2017). Usually, behavioral and mood changes appear before the onset of neurocognitive decline; with the most commonly described behavioral features including explosivity, impulsivity, and hopelessness followed by suicidality and anxiety (Asken et al., 2016). In 2014, Montenigro and colleagues coined the term "traumatic encephalopathy syndrome" (TES) along with various TES subtypes. They included five general criteria derived from calculated prevalence of cognitive and emotional deficits across reported cases of CTE, three core clinical features, and nine supportive features (Asken et al., 2016). The most recent rendition of TES has different requirement and was established by Reams and colleagues. This new criterion requires persistence of symptoms for at least two years, a history of head trauma exposure, delayed onset following head trauma, progressive course, and formal neuropsychological testing corroborating self- or observer-report of cognitive dysfunction in the executive, visuospatial, memory, and/or language domain(s) (Asken et al., 2016). Symptoms do not present immediately and typically occur in midlife, usually decades after the original injury. On average, symptom onset usually occurs around 8 years after retirement, but it is unclear why this latency period exists. Some researchers believe that it is a result of tau propagation from focal to widespread areas, as a consequence of progressive axonal disruption.

Pathologies

The neuropathology of CTE is usually looked at in two different categories: macroscopic and microscopic. The macroscopic changes that are seen are commonly found in the advanced forms of CTE and rarely manifest in the early stages. Macroscopically, there may be cerebral atrophy, reduced brain mass, enlarged lateral and third ventricles, cavum septum pellucidum, pale locus coeruleus, and diencephalon atrophy (Tharmaratnam et al., 2018). The microscopic

pathologies are more debated and are multifactorial, they include tau protein aggregation, transactive response DNA-binding protein (TDP-43), beta-amyloid plaque (Aβ), and neuroinflammation. Tau progression is classically found in the perivascular spaces around the blood vessels, deep in the cortical sulci (Tharmaratnam et al., 2018). The perivascular accumulation of hyperphosphorylated tau (p-tau) at the depths of cortical sulci is thought to be unique to CTE and has been proposed as a diagnostic requirement of CTE. The normal function of tau protein is to stabilize microtubules; however, aberrant p-tau causes the formation of protein aggregates and NFTs, which may contribute to the development of CTE (Lucke-Wold et al., 2014). TDP-43 functions as a transcriptional regulator in the central nervous system and this pathological feature is not unique to CTE, it is also observed in other neurodegenerative diseases (Armstrong 2009; Bosque, Boyer, & Mishra 2013). TDP-43 is a ubiquitously expressed nuclear protein and has a high binding affinity for either TG repeats in DNA or UG repeats in RNA. It is commonly found co-localized with p-tau NFTs (Tharmaratnam et al., 2018). TDP-43 bound to (UG)n elements at the 3'-UTR of tau mRNA and promoted its instability, resulting in a negative regulation of tau expression (Gu et al., 2017). Phosphorylated TDP-43, previously identified as the common pathologic proteinopathy linking frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) is found in more than 80% of CTE cases (McKee et al., 2016). As tau and TDP-43 deposition increases, it has been shown that there is a parallel increase in axonal pathology and loss (Stein, Alvarez, & McKee 2014). Beta-amyloid plaque may be found in a diffuse pattern in sporadic loci or none at all, so it is not a tell-tale sign of CTE. Neuroinflammation is associated with microglial and astroglial activation, potentially playing a role in long-term neurodegeneration (Faden, Wu, Stoica, & Loane 2015).

There are four phenotypes that were proposed by Omalu and co-workers (Omalu et al., 2011) that were thought of as parallel pathologies. Phenotype I has sparse to frequent NFTs and neuritic threads (NTs) in the cerebral cortex and brainstem. Phenotype II also includes NFTs and NTs in the basal ganglia and cerebellum in addition to diffuse amyloid plaques. Phenotype III has a combination of moderate to frequent NFTs and NTs predominately in the brainstem with absent to sparse NFTs and NTs in the cerebral cortex and basal ganglia with none in the cerebellum. Phenotype IV is a combination of absent to sparse NFTs and NTs in the cerebral cortex, brainstem, and basal ganglia, an absence of NFTs and NTs in the cerebellum, and an absence of diffuse amyloid plaques in the cerebral cortex.

Although the process begins focally, it gradually spreads to involve widespread regions of the brain including the frontal and temporal lobes, medial temporal lobe, diencephalon, and brainstem. McKee and colleagues (2013) determined that CTE could be classified into four pathological stages based on a stereotyped pattern of structural change and tau pathology. Stage I brains are grossly unremarkable, although mild enlargement of the frontal horns of the lateral ventricles may be found occasionally. Microscopically, there are isolated perivascular foci of p-tau NFTs, neurophil threads and astrocytic tangles. This is most commonly seen at the depths of cerebral sulci of the superior, dorsolateral, lateral, and inferior frontal cortices. P-tau-positive astrocytes are usually found in the subpial region directly overlying the perivascular foci. In stage II, macroscopic abnormalities are found in approximately one-half of the cases, including mild enlargement of the frontal horns of the lateral ventricles and third ventricle, a cavum septum, and pallor of the locus coeruleus and substantia nigra. Microscopically, multiple foci of tau pathology are found at the depths of the sulci commonly in the superior, dorsolateral, lateral and inferior frontal, the anterior inferior and lateral temporal, inferior and superior parietal,

insular and septal cortices. Deep structures such as the substantia nigra, dorsal and median raphe and thalamus show mild neurofibrillary degeneration. Beta-amyloid pathology is not found in stage II CTE. Most stage III cases of CTE show a reduction in brain weight, mild atrophy of the frontal and temporal lobes and enlargement of the lateral and third ventricles. Microscopically, NFTs are present diffusely in the frontal, temporal and parietal cortices and are most concentrated around small vessels and at the depths of sulci. The majority of cases show TDP-43-positive neurites and inclusions in the cerebral cortex, medial temporal lobe, diencephalon and brainstem. Although most stage III cases of CTE show no beta-amyloid deposition, sparse diffuse and neuritic beta-amyloid plaques are found in approximately 13%. Brain weight in stage IV is significantly decreased, there may be marked global atrophy of the brain. There is usually pronounced atrophy of the frontal and temporal lobes, medial temporal lobe and anterior thalamus. The hypothalamic floor is thinned, mammillary bodies are darkly discolored and atrophied, and there is marked enlargement of the lateral and third ventricles. Approximately two-thirds of subjects will have septal abnormalities including cavum septum, fenestrations, or absence. Microscopically, there is widespread neuronal loss, as well as severe tau deposition, as clusters of glial tangles and small NFTs in a patchy irregular distribution throughout frontal, temporal and parietal cortices. NFTs are found widely distributed throughout the hippocampal formation including the dentate gyrus, CA3, CA2, and CA4 regions. The CA1 region is typically severely sclerotic, with few remaining neurons. The fourth stage generally involves the cerebellum where there is marked loss and distortion of axons throughout the cerebral and cerebellar white matter. TDP-43 deposition is severe and widespread with dense accumulations of dot-like and thread-like inclusions in neurites and intro-neuronal cytoplasmic inclusions in all cases (McKee et al., 2013).

Biopsychosocial Model Approach

Many researchers believe that to obtain a more comprehensive diagnosis, a biopsychosocial model should be applied. Existing research has examined convenient samples of athletes who donated their brains and were experiencing clinical symptoms prior to their death- this has unfortunately led to misleading headlines about the risk of developing CTE pathology and estimates of its prevalence which are almost certainly inflated (O'Keefe 2015)**.** Attribution of pathological burden and symptom expression needs to be considered in a broad biopsychosocial explanatory framework that incorporates these factors in the casual model instead of focusing only on a history of repetitive brain trauma as the sole causative factor in the development or degree of CTE symptoms (Asken et al., 2016).

The environment a particular person develops in may have a large impact on their behavior or psyche. Disadvantaged SES predisposes to increased aggression and higher susceptibility to depression, two symptoms also seen in CTE (McLoyd 1997). Interaction of SES and prenatal development, as well as delayed development, could affect cognitive and neural functioning into adulthood as well.

Some research takes normal aging into account, and compares CTE to the normal aging brain, but a lot of the effects seen in CTE are also found in normal aging. Structural brain changes associated with normal aging are well-known and include neurofibrillary tangle (NFT) development, decreased grey and white matter volume, increased ventricular volume, increased white matter hyperintensities on MRI, and default mode network (regions of highly correlated functional activity) dysfunction on MRI as well (Andrews-Hanna et al. 2007). Decreased white matter integrity is also associated with slowed processing speed and impaired executive function (Asken et al., 2016). NFT deposition accompanies the normal aging process and the recently

proposed “primary age-related tauopathy” (PART) describes the continuum of severities with and without associated cognitive changes (Crary et al. 2014) However, the unique distribution of tau deposition in the perivascular spaces of cortical sulci described in CTE differentiates CTE from PART, which is associated with NFT formation in the medial temporal lobe and several subcortical nuclei. So, contrary to other research, the pathological features of CTE do not represent normal or accelerated aging.

Sleep disturbances may also impact the behavior of a particular person. Sleep is very important, recent evidence indicates that sleep enhances the clearance of metabolic waste products from interstitial space in the brain via the “glymphatic system (Xie et al. 2013). The glymphatic system is thought to rely on the sleep state to relax interstitial spaces enabling cerebrospinal fluid (CSF) and interstitial fluid (ISF) to move through and clear metabolic waste (Jessen, Munk, Lundgaard, & Nedergaard, 2015). Interstitial space actually expands by up to 60% during sleep which accelerates the flow of fluids through the glymphatic system. Disruption to this system may be particularly relevant to collision sport athletes, who are likely to consistently accumulate metabolic waste from concussive and subclinical brain insults, including beta-amyloid from recurrent trauma (Giza and Hovda 2014). In many cases, sleep is disturbed after a concussion and disordered sleep can be a significant factor in the development of a wide range of cognitive, mood, and behavioral problems.

A Case Study

A case study was reported by Mez et al. in 2016 of a 25-year-old Division I college football defensive linebacker and special teams player. He began playing football at the age of six and stopped playing at the beginning of his junior season of college because of the ongoing symptoms he experienced. In his football career, he experienced more than 10 concussions, the

first of which occurring at age eight. Although CTE was considered, the lack of delay in symptom onset, his young age and his family history of depression were the reasons against CTE as a primary diagnosis for his death. Focal lesions of CTE have been found in athletes as young as 17 years; however, widespread CTE pathology is unusual in such a young football player. Prospective studies that include neuropsychological testing with imaging and fluid biomarkers will be essential to future improvement in diagnosing CTE in living patients.

Prevention

Currently there are no treatments for CTE, primarily because CTE hasn't been diagnosed in a living person yet. Without treatment strategies available, it is important to prevent severe head injuries to mitigate CTE. Protective head gear is important in protecting against penetrating injuries, skull fracture, and intracranial hemorrhage, but they do not appear to mitigate the incidence or severity of sports-related concussions (Harmon et al., 2013). It is important to understand that repeated blows to the head without a concussion can still lead to CTE, kids need to be protected from this rick factor. Putting kids into non-contact sports will help mitigate the incidence of blows to the head, concussions and CTE.

Future Research

Neuroimaging using positron emission tomography (PET), diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI) may lead to the diagnosis of CTE in living patients. One approach is the depletion of molecules associated with CTE pathology (e.g., tau, Aβ). The second approach is detecting structural or molecular changes as associated with head injury, which is thought to contribute to the development of CTE (Aldag et al., 2017). PET can detect the presence and distribution of specific molecules using trace amounts of radioactive ligands that bind to molecules of interest. Investigators are developing PET radioligands to

image pathology associated with CTE, such as aggregations of tau and Aβ (Villemangne & Okamura 2014; Barrio et al., 1999). Several PET radioligands targeting tau have shown potential as CTE biomarkers, some are even in clinical trials. Some challenges with PET are that p-tau aggregates are expressed intracellularly, which requires the corresponding imaging ligand to cross the blood brain-barrier and cell membrane (Villemagne, Fodero-Tacoletti, Masters, & Rowe 2015). DTI revealed significant white matter changes in a high school contact sport athlete after a single concussion and have supported a link between axonal abnormalities and executive impairment after traumatic brain injuries (Bazarian et al., 2012; Lipton et al., 2009). Researchers have used functional magnetic resonance imaging (fMRI) to evaluate functional disruptions in both concussive and subconcussive injury groups, even in the absence of overt clinical symptoms (Talavage et al., 2010).

Biospecimen-based biomarkers would be able to provide a more accessible, cost-effective, and deployable method for identifying CTE *in vivo* than neuroimaging modalities. Neuroimaging modalities are resource dependent, very expensive, and located in fixed buildings. Cerebral spinal fluid has been thought to be a prime biospecimen, but some challenges have been met, and not overcome. Although CSF is considered a potential source of TBI biomarkers given its direct contact with the brain and nervous system, the lumbar puncture required to sample CSF poses many disadvantages (Turner et al., 2013). Blood plasma has less risks than CSF lumbar punctures, but there are still some drawbacks including: dilution of the brain-specific protein by the large volume of plasma and in the extracellular fluid of peripheral organs, degradation of the biomarker candidate by blood proteases, clearance of the protein by hepatic metabolism or renal excretion, and analyses of brain proteins in blood that can be confounded by release of the same protein from peripheral tissues (DeKosky, Blennow, Ikonomovic, & Gandy 2013).

Currently, a definitive CTE diagnosis has only been confirmed with a post-mortem autopsy and immunohistochemistry for p-tau. It is believed that in the future, the use of biomarkers in along with diagnostic imaging such as PET and MRI will offer a promising opportunity for early diagnosis, monitoring of progression, and timely therapeutic interventions (Tharmartnam et al. 2018).

References (80)

Aldag M, Armstrong RC, Bandak F, Bellgowan PSF, Bentley T, Biggerstaff S, Caravelli K, Cmarik J, Crowder A, DeGraba TJ, Dittmer TA, Ellenborgen RG, Greene C, Gupta RK, Hicks R, Hoffman S, Latta RC, Leggieri MJ, Marion D, Mazzoli R, McCrea M, O'Donnell J, Packer M, Petro JB, Rasmussen TE, Sammons-Jackson W, Shoge R, Tepe V, Tremaine LA, Zheng J. (2017). The Biological Basis of Chronic Traumatic Encephalopathy following Blast Injury: Literature Review. Journal of Neurotrauma 34, 26-43.

Andrews-Hanna JR, Snyder AZ, Vincent JL, Lustig C, Head D, Raichle Marcus E, Buckner RL. (2007). Disruption of Large-Scale Brain Systems in Advanced Aging. Neuron. 56(5), 924–935.

Armstrong, R.A., Ellis, W., Hamilton, R.L., Mackenzie, I.R., Hedreen, J., Gearing, M., Montine, T., Vonsattel, J.P., Head, E., Lieberman, A.P., and Cairns, N.J. (2009). Neuropathological heterogeneity in frontotemporal lobar degeneration with TDP-43 proteinopathy: a quantitative study of 94 cases using principal components analysis. J. Neural. Transm. 117, 227–239.

Asken B, Sullan M, Snyder A, Houck Z, Bryant V, Hizel L, McLaren M, Dede D, Jaffee M, DeKosky S, Bauer R. (2016). Factors Influencing Clinical Correlates of Chronic Traumatic Encephalopathy (CTE): A Review. Neuropsychol Rev. 26(4), 340-363.

Barrio, J.R., Huang, S.C., Cole, G., Satyamurthy N., Petric A., Phelps M.E., and Small, G. (1999). PET imaging of tangles and plaques in Alzheimer disease with a highly hydrophobic probe. J. Labelled Compd. Radiopharm. S194–S195.

Bazarian, J.J., Zhu, T., Blyth, B., Borrino, A., and Zhong, J. (2012). Subject-specific changes in brain white matter on diffusion tensor imaging after sports-related concussion. Magn. Reson. Imaging 30, 171–180.

Bosque, P.J., Boyer, P.J., and Mishra, P. (2013). A 43-kDa TDP-43 species is present in aggregates associated with frontotemporal lobar degeneration. PLoS ONE 8, e62301.

Chen L. (2018). What triggers tauopathy in chronic traumatic encephalopathy? Neural Regeneration Research 13(6), 985-986.

Corsellis JA, Bruton CJ, Freeman-Browne D. (1973) The aftermath of boxing. Psychol Med 3, 270–303.

Crary JF, et al. (2014). Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol. 128(6), 755–766.

DeKosky, S.T., Blennow, K., Ikonomovic, M.D., and Gandy, S. (2013). Acute and chronic traumatic encephalopathies: pathogenesis and biomarkers. Nat Rev Neurol 9, 192–200.

Faden, A.I., Wu, J., Stoica, B.A., and Loane, D.J. (2015). Progressive inflammation-mediated neurodegeneration after traumatic brain or spinal cord injury. Br. J. Pharmacol. 173, 681–691.

Giza CC, Hovda DA. (2014). The new neurometabolic cascade of concussion. Neurosurgery. 75(Suppl 4), S24–33

Gu J, Wu F, Xu W, Shi J, Hu W, Jin N, Qian W, Wang X, Iqbal K, Gong CX, Liu F. (2017). TDP-43 suppresses tau expression *via* promoting its mRNA instability. Nucleic Acids Res. 45, 6177–6193.

Harmon, K.G., Drezner, J.A., Gammons, M., Guskiewicz, K.M., Halstead, M., Herring, S.A., Kutcher, J.S., Pana, A., Putukian, M., and Roberts, W.O. (2013). American Medical

Society for Sports Medicine position statement: concussion in sport. Br J Sports Med 47, 15–26.

Jessen NA, Munk AS, Lundgaard I, Nedergaard M. (2015). The Glymphatic System: A Beginner's Guide. Neurochem Res. 40(12), 2583–2599.

Ling JP, Pletnikova O, Troncoso JC, Wong PC. (2015). TDP-43 repression of nonconserved cryptic exons is compromised in ALS-FTD. Science. 349, 650–655.

Lipton, M.L., Gulko, E., Zimmerman, M.E., Friedman, B.W., Kim, M., Gellella, E., Gold, T., Shifteh, K., Ardekani, B.A., and Branch, C.A. (2009). Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. Radiology 252, 816–824.

Lucke-Wold, B.P., Turner, R.C., Logsdon, A.F., Bailes, J.E., Huber, J.D., and Rosen, C.L. (2014). Linking traumatic brain injury to chronic traumatic encephalopathy: identification of potential mechanisms leading to neurofibrillary tangle development. J. Neurotrauma 31, 1129–1138.

McKee AC, Cairns NJ, Dickson DW, Folkerth RD, Keene CD, Litvan I, Perl DP, Stein TD, Vonsattel JP, Stewart W, Tripodis Y, Crary JF, Bieniek KF, Dams-O'Connor K, Alvarez VE, Gordon WA TBI/CTE group. (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. Acta Neuropathol. 131, 75–86.

McKee AC, Stein TD, Nowinski CJ, Stern RA, Daneshvar DH, Alvarez VE, Lee H-S, Hall G, Wojtowicz SM, Baugh CM, Riley DO, Kubilus CA, Cormier KA, Jacobs MA, Martin BR, Abraham CR, Ikezu T, Reichard RR, Wolozin BL, Budson AE, Goldstein LE,

Kowall NW, Cantu RC. (2013). The spectrum of disease in chronic traumatic encephalopathy. Brain 136, 43–64.

McLoyd VC. (1997). The impact of poverty and low socioeconomic status on the socioemotional functioning of African-American children and adolescents: Mediating effects. Social and emotional adjustment and family relations in ethnic minority families. 7, 34.

Mez J, Solomon T, Daneshvar D, Stein T, McKee A. (2016). Pathologically Confirmed Chronic Traumatic Encephalopathy in a 25-Year-Old Former College Football Player. JAMA Neurol. 73(3), 353-355.

Neumann M, Sampathu DM, Kwong LK, Truax AC, Micsenyi MC, Chou TT, Bruce J, Schuck T, Grossman M, Clark CM, McCluskey LF, Miller BL, Masliah E, Mackenzie IR, Feldman H, Feiden W, Kretzschmar HA, Trojanowski JQ, Lee VM. (2006). Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science. 314, 130–133.

O'Keefe, M. (2015). Study finds 96 percent of former NFL players had CTE.

Omalu, B., Bailes, J., Hamilton, R.L., Kamboh, M.I., Hammers, J., Case, M., and Fitzsimmons, R. (2011). Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. Neurosurgery 69, 173–183.

Osnato M. (1927). Postconcussion neurosis-traumatic encephalitis – a conception of postconcussion phenomena. Arch NeurPsych 18, 181–214.

Stein et al. (2014). Chronic traumatic encephalopathy: a spectrum of neuropathological changes following repetitive brain trauma in athletes and military personnel. Alzheimer's Research & Therapy 6, 4.

Thamaratnam T, Iskandar M, Tabobondung T, Tobbia I, Gopee-Ramanan P, Tabobondung T. (2018) Chronic Traumatic Encephalopathy in Professional American Football Players: Where Are We Now? Front. Neurol. 9.

Turner, R.C., Lucke-Wold, B.P., Robson, M.J., Omalu, B.I., Pet- raglia, A.L., and Bailes, J.E. (2013). Repetitive traumatic brain injury and development of chronic traumatic encephalopathy: a potential role for biomarkers in diagnosis, prognosis, and treatment? Front. Neurol. 3, 186.

Villemagne, V.L. and Okamura, N. (2014). In vivo tau imaging: obstacles and progress. Alzheimers Dement. 10, Suppl, S254–S264.

Xie L, et al. (2013). Sleep drives metabolite clearance from the adult brain. Science, 342(6156), 373–377.