Understanding The Cumulative Effects of Concussion

From headaches, dizziness, and emotional/behavioral changes to pathology suggestive of AD and PD, the effects of chronic traumatic encephalopathy are under investigation.

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Chronic Traumatic Encephalopathy (CTE) is a progressive neurodegenerative syndrome believed to be caused by single, episodic, or repetitive head trauma or via the transfer of angular and rotational forces to the brain. However, a recent review paper concluded that it is not possible with any certainty to determine the causality or risk factors for CTE. In addition, there is insufficient evidence at this time to classify CTE as a clinical syndrome.

Once thought to be exclusive to boxers, the neuropathological changes associated with CTE have been found in former and current professional football, hockey, and soccer players, professional wrestlers, as well as military personnel who have suffered blast injuries and individuals with repetitive physical abuse.1-6,8,12,18,19 Currently there are two large study groups looking at CTE in high impact sport athletes and the military: Omalu/Bales, and the Boston University group (McKee and colleagues).

WHAT’S IN A NAME?

Historically CTE has undergone an evolution with over 28 synonymic terms.12 In 1928 Martland published a paper in the Journal of the American Medical Association entitled “Punch Drunk.” In it he described a group of what he termed “poor fighters” who tended to “take considerable head punishment.” According to the author, early symptoms included occasional clumsiness, slight ataxia and periods of confusion. He noted that many never progress beyond this stage, however, while others would go on to develop tremors, dysarthria, deafness, physical slowing, “dragging legs while walking” and mental deterioration to a point where some required institutionalization. Some would go on to develop a progressive neurological syndrome leading to mental or physical helplessness.4

In 1937 Millsopagh,5 in describing effects in Navy boxers, coined the term dementia pugilistica. Crichley9 in the mid-1950s reported on 69 cases of boxers with both chronic and insidious onset of mental and physical abnormalities marked by what he termed “euphoric dementia” characterized by emotional labiality, poor insight, speech difficulties, and memory problems. These individuals also experienced behavioral problems including mood swings, “fatuous cheerfulness,” depression, paranoia and sometimes even aggressive or disinhibited behavior. The patients also complained of persistent headaches, dizziness and unsteady gate.

In 1969 Roberts10 published a report on 224 boxers with progressive memory loss, aggression, confusion and
depression and correlated this with the number of fights and the length of the boxer’s career.

The term CTE first appeared in the literature in the mid 1960s and in 1973 Corsellis, Bruton, and Freeman-Browne described three stages of clinical deterioration in CTE, which have yet to be validated. Then in 2002 Dr. Bennet Omalu after examining the brain of a former NFL player, Mike Webster, initially found what appeared to be a normal brain; however, microscopic examination demonstrated Tau deposition. He subsequently diagnosed Mr. Webster as having CTE. This was the first documented case in an American football player. He presented his findings to the chair of the Mild Traumatic Brain Injury Committee of the NFL, who rejected the findings both privately and later in a published paper.

Finally in 2009, McKee et al. examined the brains of one retired professional football player and two boxers. They found pathological changes almost identical to those described above and correlated the findings with memory loss, behavioral and personality changes, along with parkinsonism, speech and gait abnormalities. Since its inception, Boston University’s Center for the study of CTE has identified 85 suspected cases of CTE in athletes and military personnel with evidence of CTE in 80 percent (68/85) of the cases. Interestingly, in 15/85 cases (37 percent) there was significant comorbid pathology consistent with AD, Lewy body disease (LBD), motor neuron disease (MND), or Frontal Temporal Lobe Dementia (FTLD).

**PATHOLOGY**

Pathologically CTE is defined by reduction in brain weight, enlargement of the lateral and third ventricles, thinning of the corpus callosum, cavum septum pellucidum with fenestrations, scarring and neuronal loss of the cerebellar tonsils and atrophy of the frontal, temporal, and parietal lobes. However the brain can also appear grossly normal. Older individuals with CTE can demonstrate changes similar to patients with other neurodegenerative diseases, i.e. diffuse atrophy.

Histologically there are diffuse changes in all brain regions. These changes can include mild neuronal loss, isomorphic astrogliosis, increased perivascular neuropil histiocytes, reduced pigmentation of the substantia nigra and locus coeruleus with pigmented laden histiocytes in Virchow-Robin spaces. Subcortical and brainstem structures may show mild neuronal loss as well. Unlike other neurodegenerative disorders, loss of neurons in the hippocampus is typically absent.

Routine staining is normal in CTE, with immunohistochemical analysis with a battery of proteomic antibodies being required for diagnosis. The classic features of the disorder include the presence of neurofibrillary tangles (NFTs), neuropil/neurite threads (NTs) and astrocytic tangles (only reported by McKee) made up of paired helical filamentous aggregates of hyperphosphorylated tau protein (all 6 tau isomers) which are distributed throughout the brain and according to McKee tend to be more densely distributed than in Alzheimer’s disease (AD). However, in contrast to McKee’s findings, Omalu has reported a sparse, distribution of NFTs with what he terms a “skip phenomenon” whereby NFTs and NTs are “haphazardly” located in one region of the neocortex within the same lobe of the brain. They can also be found in a perivascular distribution and with clusters around small intracortical blood vessels and a unique regional involvement of subcortical and brainstem structures. McKee has reported the presence of NFTs and astrocytic tangles in the large white matter tracts including the corpus callosum and subcortical U-fibers along with the extreme and external capsule, and anterior and posterior commissures. This tends to correlate with findings seen in DTI MRI studies in patients with mTBI and TBI. Unlike AD, deposition of beta amyloid occurs in fewer than half the cases. Secondary amyloid deposition may accompany tau deposition in about 20-30 percent of cases and is not required to diagnose CTE. Older and advanced CTE patients can develop a pattern very similar to AD with the presence of neuritic amyloid plaques to a point that may be difficult to distinguish from non-CTE AD neuropathologically.

There is still considerable uncertainty on how the neuropathological changes in CTE develop. It is suspected that...
traumatic and mild traumatic brain injury induces the activation of kinases which hyper-phosphorylate tau (the specific cascade is unknown). Hyper-phosphorylated tau results in microtubule disassembly, impaired axonal transport, neuronal and synaptic dysfunction and eventually cell death. Others have proposed a prion like self-propagation whereby hyper-phosphorylated tau spread transsynaptically to recruit unaffected neurons in other regions of the brain. Finally, multiple sub-concussive hits can result in white matter inflammation and the deposition of NFTs and astrocytic tangles which in turn can result in white matter dysfunction and degeneration which has been demonstrated with DTI studies on retired NFL players (Conidi unpublished data). Likely a combination of the above occur and future research is needed and underway. Clinically, Stern and colleagues have suggested that the neuropathological changes (i.e. neurofibrillary tangles) seen in the locus coeruleus and amygdala may account for early behavioral changes, whereas difficulties with memory and executive function, which occur as the disorder progresses, may be associated with degeneration of frontal and hippocampal structures.

Prior to death, patients with CTE are suspected of suffering from neurocognitive and behavioral changes, along with chronic headache and cerebellar dysfunction. Early studies were based on case reports in boxers. Individuals with a younger onset had a predominance of mood and behavioral symptoms, whereas those with older onset had more pronounced cognitive impairment and motor disturbance. Recent evidence (also case reports, a majority in non-boxers), has shown a predominance of early behavioral (depression, paranoia, agitation, social withdrawal, and aggression) symptoms, followed by the development of neuropsychological/cognitive impairment (orientation, short and long term memory, executive function, language and attention/concentration). The dementia associated with CTE is quite similar to that associated with AD and other age related neurodegenerative diseases.

One of the largest studies, Stern et al. (2013) looked at the clinical presentation and APOE genotype (a genetic risk factor for sporadic AD) in 36 pathologically confirmed CTE cases. The group conducted postmortem phone interviews with next of kin and when available reviewed the patient’s medical record. Cognitive deficits were reported in all but two subjects who were asymptomatic at time of death. Two distinct clinical presentations were found: behavioral and/or mood disturbances in those with a younger presentation and neurocognitive impairment whose initial presentation developed at an older age. In addition, there were significantly more APOE e4 homozygotes than expected in the general population (one to three percent) with two of 11 of the cognition group testing positive when compared to one of 22 for the behavioral group. It is hypothesized that the APOE 34 isoform may have direct neurotoxic effects resulting in mitochondrial dysfunction and cytoskeletal changes, resulting in an increased risk of neurodegeneration.

The media has been quick to attribute suicide among current and former contact sport athletes with underlying CTE. Wortzel et al. looked published case reports form McKee and Omalu. The authors asked the question: “What is the existing evidence in support of a relationship between CTE and suicide.” The abstracts were individually reviewed by two of the authors and rated using the New Castle-Ottawa Quality Assessment Scale. After single case studies were excluded, two case series were included and there was “very low” probability that CTE was associated with an increased risk of suicide. The authors identified issues with the observational nature of the investigations, potential for bias, methodological issues and confounding factors as reasons for the poor rating.

A major focus of CTE research is in the development of biomarkers for the early detection of the disorder. Tau can be measured in the CSF and our group is currently looking at this biomarker in retired NFL players, however less invasive studies are preferred. PET scans also have the potential to examine the level of tau pathology by utilizing the tracer 2-(1-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene) malononitrile (FDDNP). One such study employed FDDNP PET scans to look at the brains of retired NFL players. Retired alumni had significantly greater levels of tau pathology when compared to healthy controls.

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in the amygdala and all subcortical ROIs including caudate, putamen, thalamus, subthalamus, midbrain and cerebellar white matter.\textsuperscript{44}

A second PET ligand [(18)F]-T807, also known as [(18)F]-T807 PET imaging also currently under investigation. This ligand binds to both tau and NFTs. Two case reports of retired NFL players have been published.\textsuperscript{45,46} One involved a 71 year old with a history of multiple concussions and progressive cognitive decline. He initially underwent [(18)F]-Florbetapir PET imaging (a ligand used to detect AD) which was negative. CTE was suspected clinically, and [(18)F]-T807 PET imaging revealed striatal and nigral [(18)F]-T807 retention consistent with the presence of tauopathy.

Interestingly, the distribution of the tauopathy mimicked that of progressive supranuclear palsy (PSP), however the patient did not have any signs or symptoms of a movement disorder. The key distinguishing factor was hippocampal involvement which is frequently seen in CTE and not with PSP. The second individual was 56 years old and suffered a single severe TBI (SDH from a fall). He carried a diagnosis of frontotemporal dementia and had also had a progressive cognitive decline as well as personality changes. [(18)F]-Florbetapir PET imaging one year post-injury was negative for an AD pattern of amyloid accumulation in this subject. Focal [(18)F]-Florbetapir retention was noted at the site of impact suggesting focal amyloid aggregation.

ALZHEIMER’S DISEASE, PARKINSON’S DISEASE AND ALS

In addition to CTE, patients who suffer repetitive mild traumatic and traumatic brain injury are at risk for other neurodegenerative disorders.\textsuperscript{28-30} A growing body of research supports the hypothesis that professional football players are at an increased risk of neurodegeneration, however cause and effect have yet to be established.\textsuperscript{38} Epidemiological studies have demonstrated an increased risk of head trauma and the development of ALS.\textsuperscript{24} In addition, other studies have demonstrated an increased risk of ALS in Italian professional soccer players and NFL players.\textsuperscript{20,24-27}

McKee et al.\textsuperscript{20} examined 12 cases of Chronic Traumatic Encephalopathy and, in 10, found a widespread TAR DNA-binding protein of approximately 43kd (TDP-43). Three of the athletes with CTE also developed signs and symptoms of progressive motor neuron. In these three cases, there were abundant TDP-43-positive inclusions and neurites in the spinal cord in addition to tau neurofibrillary changes, motor neuron loss, and corticospinal tract degeneration. The results suggest that TDP-43 proteinopathy seen in CTE can extend into the spinal cord and is associated with motor neuron disease.

Head trauma has also been implicated as a risk factor for the development of Parkinson’s disease (PD).\textsuperscript{31-33} In fact Parkinson himself in the early 1800s suggested the “the shaking palsy may stem from injury to the superior portion of the medulla spinalis.”\textsuperscript{33} In the mid-1980s Muhammad Ali brought world-wide attention to the disorder and remains today the classic example of athletic related trauma induced PD. Studies have shown otherwise healthy former athletes demonstrate abnormalities in the primary motor cortex (i.e. excessive intra-cortical inhibition) which clinically correlated with slowness in motor execution (i.e. bradykinesia) when compared to non-concussed counterparts.\textsuperscript{34-37}

Perhaps the most comprehensive study looking at head trauma as a risk for the development of PD was conducted by Jafari et al.\textsuperscript{33} After reviewing over 636 articles, 22 studies (19 case controlled, two “nested” case controlled and one cohort study) underwent meta-analysis and multi-varied statistical analysis. They found that a history of head trauma the results in concussion with a loss of consciousness has a statistically significant association with the risk of developing PD.

A Canadian epidemiological study (Harris et al.) looked at all types of head injury (i.e. a self-report of a single injury related to work, motor vehicle accidents, sports and hobbies) also found that a history of concussion and loss of consciousness has a statistically significant association with the risk of developing PD.
Also, there is the use of proton magnetic resonance spectroscopy in conjunction with serial reaction time testing. De Beaumont et al.,\textsuperscript{31} studying former university-level athletes found a disproportionate reduction in glutamate/H\textsubscript{2}O ratio in the primary motor cortex of concussed athletes as they age. This reduction correlated with motor sequence learning.

Finally, there was a strong negative correlation between the number of concussions and both sequence specific learning and glutamate/H\textsubscript{2}O levels. Although there are several possible mechanisms as to how head trauma could result in PD, the most likely mechanism is via an inflammatory response.\textsuperscript{29,30,33} Head injury can result in blood brain barrier disruption with infiltration by neutrophils, lymphocytes and monocytes, along with microglial activation.\textsuperscript{29,33} Mitochondrial dysfunction and excitatory neurotransmitter release occur, which eventually can result in cell death.\textsuperscript{33} Neuro-inflammation has also been implicated in the pathogenesis of PD in genetically susceptible individuals.\textsuperscript{33}

There are currently no published studies directly linking a single/multiple concussion(s) or sub-concussive hits in athletes with an increased risk for AD. There are numerous case reports (our group included) showing progressive neuro-cognitive deficits in retired athletes with a history of concussion. AD has a long prodromal phase prior to presentation, therefore mTBI and TBI early in life would not impact the individual until decades later. In addition, seventy five percent of all TBI’s are concussion and a history of TBI predisposes individuals to AD.\textsuperscript{39}

With that said, advancing age remains the biggest risk factor for the development of the disorder.\textsuperscript{31} The average neurologist is well aware of the underlying pathology of AD i.e. amyloid beta deposition (ABeta peptides), NFTs, widespread loss of cortical neurons and inflammation of the brain’s glial support cells.\textsuperscript{31}

Many may not be be aware that NFTs and beta amyloid pathology are present in one-third of TBI patients, with beta amyloid developing in the acute phase of TBI (NFTs are seen later on in the disorder as the symptoms become more chronic).\textsuperscript{31} Animal models have demonstrated that axonal swelling immediately after TBI results in amyloid beta production as well as impaired protein transport and cytoskeletal alterations. Furthermore, studies using transgenic mice have shown that amyloid beta may also spread from the initial TBI site to more distant brain regions,\textsuperscript{43} which is similar to what is hypothesized with tau in CTE. In addition to its presence in the acute phase of TBI, beta amyloid (beta amyloid peptide AB42) has been shown to be present many years after TBI. This protein is highly neurotoxic and predisposed to aggregation, which in turn can result in cell death.\textsuperscript{40-42}

Despite a growing body of research to suggest that professional football players are at an increased risk of neurodegeneration, cause and effect have not yet been established.

In addition to beta amyloid deposition, neuro-inflammation and microglial activation likely play a role in the development of AD in patients with a history of TBI. Animal models have shown an association between TBI and microglial activation and the development of anti-inflammatory cytokines the later of which may be neuroprotective due to their ability to clear beta amyloid. However, activated microglia and pro-inflammatory cytokines can persist for many years after the initial traumatic event where they can have detrimental effects on brain parenchyma.\textsuperscript{31} Taken together it is possible that a vicious cycle involving microglial and cerebral amyloid beta activation with spreading may result in the development of AD pathology in patients with a history of TBI.

It is now quite evident that multiple concussions, sub-concussive hits and perhaps even a single concussion can place an athlete at increased risk for the early development of neurodegenerative disorders. Could this signal an end to American football? It is unlikely given the strength of the NFL, which continues to report revenues in the billions. In fact it would not be difficult to argue that professional...
football has replaced professional baseball as America’s favorite sport.

It may, however, influence younger athletes to choose other sports such as basketball, volleyball and golf. This trend has actually already begun with a decrease in the number of children playing Pop Warner football over the past few years, and even at the professional level with the retirement of NFL and NHL players in their prime for fear of the effects of head injury. In addition, over the next few years retired NFL alumni are going to begin to be screened for all of the neurodegenerative discussed above.

If preliminary results hold true we are about to see a wave of individuals with significant neurological issues. Major questions remain including: What factors influence the development of neurodegenerative disorders (i.e. genetics etc.)? Is CTE a separate clinical entity? Or are the neuropathological findings a precursor to AD? The later may be the case as new yet to be published evidence from the Mayo Clinic suggests Tau may be a major player in the development of AD. Clearly more research is needed including longitudinal studies looking at cause and effect, neuropsychological and neuropsychiatric symptoms, early diagnosis (i.e. biomarkers and neuroimaging) and treatment. Expect neurologists to be at the forefront of this research.

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