Chronic Traumatic Encephalopathy

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Objectives

1. Examine history of disorder now referred to as CTE and previous nomenclature and descriptions.

2. Detail the stereotypic macroscopic and microscopic changes associated with CTE.

3. Discuss clinical manifestations of CTE, specifically in regards to mood and behavioral changes.

4. Describe more specific incidences of CTE in professional athletes and associated signs/symptoms.

5. Briefly
Jacked Up
History of Diagnosis

• The first known mention of neuropsychiatric deficits associated with head injuries seems to date back to the very late 1800’s.

• In 1893, a U.S. Navy football player (Joseph M. Reeves) was warned by a Navy doctor that another blow to the head could cause “instant insanity or death”. Reeves, instead of heeding the doctor’s advice, paid a shoemaker to construct the first football “helmet” of leather in order to play in Army-Navy game.

• In 1912 Glenn “Pop” Warner stated “Playing without helmets gives players more confidence, saves their heads many hard jolts, and keeps their ears from becoming torn or sore. I do not encourage their use. I have never seen an accident to the head which was serious, but I have many times seen cases when hard bumps on the head so dazed the player receiving them that he lost his memory for a time and had to be removed from the game.”

• In the 1920’s there were the beginnings of reports of neurologic deterioration associated with repetitive brain trauma, specifically as it related to the sport of boxing- hence, the term “dementia pugilistica”.
History of Diagnosis

The syndrome was first formally described in literature in 1928 by Dr. Harrison Stanford Martland with an article titled “Punch Drunk”\(^1\).

“Some time fight fans and promoters have recognized a peculiar condition occurring among prize fighters which, in ring parlance, they speak of as "punch drunk." Fighters in whom the early symptoms are well recognized are said by the fans to be "cuckoo," "goofy," "cutting paper dolls," or "slug nutty." Frequently it takes a fighter from one to two hours to recover from a severe blow to the head or jaw”.

He outlined early symptoms as a mild tremor of the extremities, a slowing of all motor function, confusion, and speech problems (slurring of words).
History of Diagnosis

- A 1956 study examined the pathology of closed head injury patients who never regained full level of consciousness but lived for between five to fifteen months (defined as without skull fracture, intracranial hematoma, brain lacerations, or signs of elevated intracranial pressure).

- Microscopic examination of brain tissue showed diffuse degeneration of white matter throughout cerebral hemispheres without fibrosis or destruction of remaining nerve fibers or myelin sheaths. There were noted to be specific areas of more severe volume loss including around ventricles, internal capsule, and thalamus.

- Important to study was fact that dementia-like states of these patients were differentiated from previously described loss of consciousness/comatose states with head injuries of various types along with histologic differentiation that this was not a result of damage to cerebral cortex, infarction, or laceration but rather a degeneration of white matter.
History of Diagnosis

In 1969, A.H. Roberts studied the cognitive functioning of 224 former boxers and found that 17% of them suffered from significant memory loss, aggression, confusion, or depression (at that time termed just traumatic encephalopathy) and that there was direct correlation of incidence to number of fights and overall length of boxing career.

In 1973, general term for syndrome changed from DP to CTE as a result of study by JA Corsellis et al which histologically analyzed the brains of 15 former boxers who had been diagnosed with “Dementia Pugilistica” and found that all showed some common characteristics: cavum septum (ranging from 1-8mm, strained thin dorsal attachment), scarring of cerebellum, degeneration of substantia nigra, and presence of neurofibrillary tangles (specifically in hippocampus and medial temporal gray matter).
In the early 1990’s, researchers used an antibody to the beta-protein known to be present in AD plaques and found similar levels of beta protein deposition in symptomatic retired boxers\(^5\).

Tokuda et al found that there were tau immunoreactive neurofibrillary tangles in addition to the beta-protein deposits\(^6\).

Dale et al proved histologically that there was ubiquitin present in the NF tangles of both boxers with clinical signs of dementia and patients with AD\(^7\).
Macroscopic Pathology in CTE

- Overall reduction in brain weight—more specifically atrophy of the medial temporal lobe as well as temporal and frontal cortices.
Stereotypic Pathology in CTE

- Enlargement of third and lateral ventricles
- Cavum septum pellucidum
- Atrophy of mammillary bodies, olfactory bulbs, thalamus
- Depigmentation or pallor of substantia nigra and locus ceruleus
- Scarring and decreased number of Purkinje cells in inferior region of cerebellum
- Atrophy of hippocampus, amygdala noted in severe cases
Stereotypic Pathology in CTE
Microscopic Pathology in CTE

- Tau immunoreactive neurofibrillary tangles in irregular pattern of deposition - most often closer to superficial cortex (as compared to AD) and concentrated in perivascular regions.

- Also a higher concentration of NFT’s in basal region of brain, especially in depths of sulci.
Microscopic Pathology in CTE

- In advanced cases, these tau immunoreactive NFT’s are also found in limbic areas, brainstem, and subcortical white matter.

- Unlike plaques in Alzheimer’s dementia, there is much lower incidence of Beta-amyloid protein deposits in cases of CTE\textsuperscript{10}.

- In addition, higher levels of hyper-phosphorylated, ubiquinated TAR DNA binding protein 43(TDP-43) are found in brainstem, basal ganglia, medial temporal lobe, frontal, temporal, and insular cortices.

- TDP-43 binds to neurofilament mRNA and plays a major role in stabilizing mRNA transcription and mediating the response of neuronal cytoskeleton to axonal injury.

- Hyperphosphorylation of TDP-43 results in NFT’s in a similar helical process to tau proteinopathy.
Microscopic Pathology in CTE

Recent evidence shows that TDP-43 proteinopathy develops at a very early stage in the course, as revealed by presence in post-mortem analyses of brains of 18 y/o high school student with history of multiple concussions who died suddenly of other causes but had experienced CTE symptoms\textsuperscript{16}, and 26 year old Chris Henry(former Cincinnati Bengals WR) who died after falling from the back of a truck but was still active in the NFL at the time of his death\textsuperscript{17}.

If significant levels of pathologic TDP-43 accumulate in the anterior horns of spinal cord and motor cortex, the result is corticospinal tract degeneration which appears clinically similar to ALS- weakness, spasticity, fasciculations, and muscular atrophy\textsuperscript{10}.
TDP-43 proteinopathy has previously been found in patients with ALS and FTLD, indicating that CTE may share similar pathogenic mechanisms\textsuperscript{15}.

Other recent studies have shown that brains of patients with a single TBI-both in acute and long-term recovery phase-do not show evidence of TDP-43 proteinopathy\textsuperscript{14}.

Figure 7. TDP-43 in FTLD-U and ALS. This figure shows the different cellular distribution of TDP-43 in normal cells (top) as opposed to neuronal cells from patients affected by FTLD-U or ALS (bottom). In these patients, no wild type TDP-43 protein can be found within the nucleus and all the pool of intracellular TDP-43 can be found accumulating in the cytoplasm. The modifications to which this cytoplasmic TDP-43 has been subjected include hyperphosphorylation, ubiquitination, and cleavage to generate C-terminal fragments\textsuperscript{18}. 
The four histologic stages of CTE

- Stage 1- pathology restricted to discrete foci in cerebral cortex, most commonly in the dorsolateral and lateral prefrontal cortices and specifically around small blood vessels at depths of sulci
- Stage 2- multiple pathologic sites in similar distribution but with associated spread of pathology to adjacent superficial cortex but, by definition, with no involvement of medial temporal lobe
- Stage 3- Widespread pathology with highest concentration of neurofibrillary degeneration in frontal, temporal, insular, and parietal cortices along with NFT’s in hippocampus and amygdala
- Stage 4- Severe pathology affecting the majority of cerebral cortex
Lack of clear clinical stages/criteria

- Mckee et al proposed in 2009 a three tier model of staging CTE¹⁰
  - Stage 1 involved affective changes and psychotic symptoms
  - Stage 2 described also social instability, erratic behavior, memory loss, and motor symptoms similar to early Parkinson’s
  - Stage 3 was progressive deterioration into dementia-like clinical picture along with Parkinsonian symptoms of dysarthria, dysphagia, shuffling gait, and ptosis

- However, still no accepted consensus among providers as to consistent method
Clinical Progression of CTE

- Earliest features tend to be deficits in attention and concentration, memory, mild disorientation and confusion, as well as headaches and dizziness.

- Progression involves worsening hypofrontality and degeneration of prefrontal cortex influencing mood regulation, poor decision-making, planning, and impulsivity/aggression as well as worsening dementia (global cognition).

- More severe cases show slowing of motor function, shuffling gait, masked facies, dysarthria, tremor, and deafness.
Mood and Behavioral Symptoms

Most commonly described associated symptoms have been depression (thought to be more refractory to treatment), apathy, mood instability, impulsivity, as well as a significantly higher incidence of substance abuse and suicidality.\textsuperscript{11}

A review was done in 2009 of the cases of 51 patients with confirmed neuropathologic changes associated with CTE to assess correlation with clinical features. It was found that in fourteen (30\%) of the cases, there was documentation of concern for mood illness, with large majority being depression and one case with description of “euphoric dementia”. Two of the cases of depression also involved manic symptoms and these patients were described as either “manic-depressive” or “bipolar”.\textsuperscript{10,12,13}

Motor abnormalities were described in cases of 21 (42\%) of these patients including Parkinsonism, staggered, slowed or shuffling gait, slowed or slurred speech, ataxia, dysphagia, and ocular abnormalities and in no cases was there described any clinical course other than progressive worsening of symptoms.
Mood and Behavioral Symptoms

- Pathologic mechanism of mood and behavioral symptoms most likely related to significant degeneration of dorsolateral prefrontal cortex (DLPFC), amygdala, and hippocampus.

- DLPC is highest cortical area involved in planning, organization, regulation/inhibition, integration of sensory information, regulation of attention and action, as well as working memory.

- Involvement of dorsal frontal cortex as opposed to more ventral areas helps explain more specific deficits with processing of memorized material as opposed to direct deficits of storage/recall of factual information.
Mood and Behavioral Symptoms

- Amygdala specifically involved in emotional and social awareness and processing—specifically as they pertain to fear and pleasure responses.

- Abnormal functioning of the amygdala has been correlated with autism, PTSD, all anxiety conditions, violent behavior, antisocial personality disorder, and unipolar depression.

- Interestingly, there has been evidence of hyperactive amygdalae in patients with bipolar I disorder—high incidence of paranoia.
Post-mortem study of 51 patients with neuropathologic CTE

- Of the 51 confirmed cases of CTE studied, 46 (90%) were athletes—more specifically, there were 39 boxers (amateur or professional), 5 football players (average involvement time of 18 years), 1 professional wrestler, and 1 soccer player. Interestingly, one of non-athletes worked as a circus clown and others were either victims of physical abuse or patients with epilepsy\(^\text{10}\).

- There was a wide range in reported age of initial onset of symptoms (25-78) with average age of 43 years old.

- At the time that these athletes retired from their playing careers, one-third already demonstrated clinical features of CTE and within four years after stopping, one-half of the sample group was experiencing symptoms.
Focus on Football

Sport Science: Concussions
Five cases of former football players

- Extremely small sample size but limited available data

- Sample group of football players died at a younger age (range of 36-50 years old at death with mean of 44) as compared to the group of former boxers (range of 23-91 with mean of 60)\textsuperscript{10}.

- All five football players played positions which, by nature, involve a high volume of repetitive impacts including three offensive linemen, one defensive lineman, and one linebacker\textsuperscript{10}.

- 4/5 players had symptoms of depression, memory loss, paranoia, and poor insight/judgment noted.

- 3/5 had outbursts of anger or aggression, irritability, and apathy.

- 2/5 had confusion, hyperreligiosity, reduced concentration
Five cases of former football players

Out of the five players, only one experienced a death that could easily be deemed unrelated to CTE (had severe CAD) as two committed suicide, one died during a high speed police chase, and the fifth described below died from what was deemed as an accidental gunshot wound to the chest while cleaning a gun.

Example is case of a 45 year old retired NFL linebacker who was described by his wife to have had at least three concussions during college career and at least eight concussions during NFL career (only one documented in medical chart review) but without any instances of losing consciousness for more than 1-2 seconds, being carried off the field, seeking treatment or requiring hospitalization for cognitive or behavioral deficits.

Around age 40, family noticed impairments in his short-term memory, attention, concentration, organization, planning, problem-solving, judgment, and multi-tasking ability. Language skills were unaffected and he continued to work as a hunting/fishing guide until time of death. However, towards the end of his life, family describes anger, verbal aggression, emotional lability, and alcohol abuse.
Football and Closed Head Trauma

- It has been estimated that, during a course of a college football season, linemen in particular can experience up to 1500 subconcussive head impacts while some high school players (who play both offense and defense) may experience upwards of 2000 of these collisions\(^{19}\).

- A research study recorded data about 300,000 head impacts by implanting a sensor in helmets. It showed that while quarterbacks and running backs suffered the most severe blows to the head, linebackers as well as offensive and defensive linemen experience a significantly higher volume of head impacts than any other position.

- Data indicated that hits to the top of the head carried greater risk of concussion than hits to back front, or lateral areas.
Dr. Bennet Omalu

- Forensic pathologist who happened to be working in Pittsburgh when bodies of former Steelers Mike Webster and Terry Long came in for autopsy.

- After discovering similar anatomic abnormalities, he sought out brain tissue from other athletes including former NFL players and professional wrestler Chris Benoit and found these same brain changes.

- He authored recent book titled “Play Hard, Die Young: Football, Dementia, Depression, and Death”.
Mike Webster (1952-2002)

- NFL Hall of Fame Center (played 1974-1990)
- Nicknamed “Iron Mike” for never missing plays
- Experienced severe decline of cognitive functioning as well as behavioral and personality changes after retirement from football.
- His son described an incident during a family dinner when his father got up from eating the meal, walked around in a confused fashion, opened up the oven door and urinated in the oven.
- His son also describes the family having to always have a specific flag on the porch outside their home so Mike would recognize the house.
- In his last years of life, he exhibited extreme paranoia, resulting in the ending of his marriage and him living homeless for periods of time, refusing the help of friends and family. He eventually passed away as a direct result of a heart attack.
Dave Duerson (1960-2011)

- **NFL safety from 1983-1993**

- After retirement, he built a very successful food services company before he began experiencing symptoms of CTE per family.

- Per family members, Duerson experienced severe memory loss, poor impulse control, and displayed abusive behavior towards family and employees, leading to the collapse of the business, declaration of bankruptcy, ending of his marriage. He later completed suicide by gunshot wound to the chest.

- This case was particularly prominent in media due to Duerson’s role on NFL’s six-person committee which decided disability claims filed by former NFL players, his growing concern that his own struggles may have been a result of football-related injuries, and text message to family that his brain be studied by Boston University’s Center for the Study of Traumatic Encephalopathy, which, after biopsy, confirmed diagnosis of CTE.
Chris Henry (1983-2009)

- NFL WR from 2005-2009 when he passed away in tragic accident after he fell from back of a pickup truck driven by his fiancee as she attempted to drive away following a domestic dispute.

- In the last four years of his life, Henry was arrested more than five times on a variety of charges including aggravated assault with a firearm, driving while intoxicated, supplying alcohol to underage females at a hotel, and multiple assault and battery charges.

- His brain was studied by the Brain Injury Research Institute at West Virginia University and he was found to have CTE.

- He was the first still-active NFL player to be diagnosed with CTE.

- He had never been formally been diagnosed with concussion throughout college and NFL playing career.
Relevant stories of other Professional Athletes

Chris Benoit (1967-2007) - Professional wrestler who placed copies of Bible alongside bodies of wife and son after strangling them and then hanging himself. His brain was tested and showed signs of CTE. Neurosurgeon Julian Bailes commented “Benoit’s brain was so severely damaged it resembled the brain of an 85 year old Alzheimer’s patient.”

Bob Probert (1965-2010) - NHL player infamous for fighting and being an “enforcer”. He was arrested in 2004 after getting into physical altercation over drugs but police had to use tasers and stun guns to subdue him. In 2005, he was arrested for breach of peace, resisting arrest, and assaulting a police officer. After death from cardiac arrest in 2010, his brain was studied at Boston University and showed evidence of CTE.
Future of Research

With similarities in protein deposition between CTE, AD, FTD, and ALS, what role does head trauma play in the development of all of these disorders?

Similarities/differences

What can be done to prevent damage associated with repetitive head trauma (helmets, banning of certain types of impact, age limits on certain sports, rules on return to sport after known head injury)?

Is there a way to design studies of at-risk persons currently in regards to specific symptoms and follow them longitudinally to better be able to identify odds ratios to help provide guidance with risk analysis regarding retirement?
References


References


