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One Test Forward: Finding Diagnostic Tools for Chronic Traumatic Encephalopathy

Chronic Traumatic Encephalopathy is an aggressive degenerative brain disease caused by subconcussive blows and other trauma to the brain. An abnormal buildup of the tau protein ransacks white matter within the brain. The effects of CTE are devastating: dementia, little to no fine motor skills, and a severe lapse in judgement are only a few symptoms recorded. Currently, the only way to confirm a diagnosis of CTE is to conduct a posthumous brain examination. As the amount research and data increases, the number of athletes falling prey to this disease grows. Sports organizations such as the National Football League (NFL) have taken strides to create safety protocols and incorporate protective standards for all helmets. Nevertheless, a diagnostic tool that can be used on living patients must be created in order to begin the process of treatment. In this paper, I am going to argue that the prevalence of the disease increases the urgency for an antemortem diagnosis. I will also talk about a potential diagnostic tool for chronic traumatic encephalopathy and treatment method in living patients.

The Boston University Chronic Traumatic Encephalopathy Center has classified five stages. Stage 1 consists of symptoms such as headaches, attention and concentration problems, and disorientation. The second stage builds on these features and adds impairment of short-term memory, emotional explosivity, poor judgement, psychotic symptoms, and depression. Stage 3 deals with cognitive impairment and problems with executive function such as judgement, organization, and multitasking. Finally, stage 4 is the most severe: dementia, slowing of muscular movements, vertigo, and possible Parkinsonism. Most cases that are dealt tend to be classified as the later stages, and many athletes are classified as stage 3 or 4.

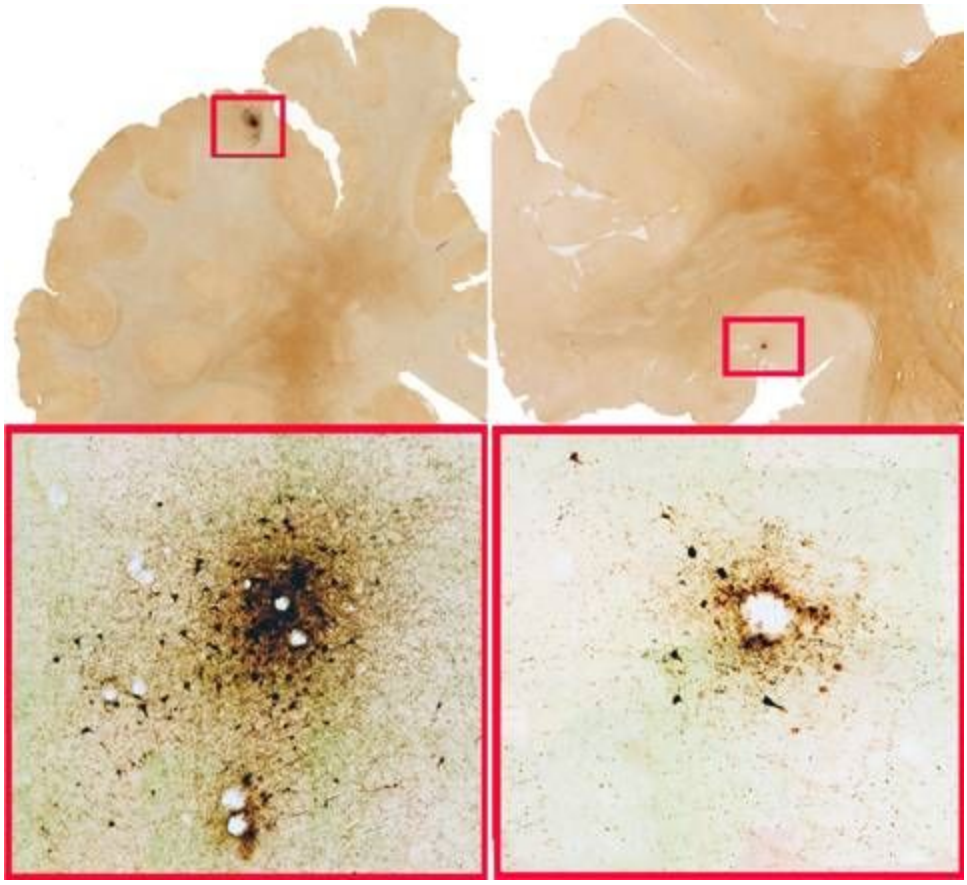
The pathology of CTE is nuanced, and is still being researched. However, there is general consensus on the mechanisms of the disease, and how the disease progresses. As said before, the main aggressor of CTE is tau. These proteins are primarily located in the distal portions of axons in neurons, and are essential in stabilizing the microtubules. They work with other proteins called tubulin to organize the microtubules. Proliferation of the tau protein is triggered by the concussive or subconcussive blows to the head; patterns of tau within the frontal and temporal cortex are irregular and patchy distribution, called neurofibrillary tau tangles. These neurofibrillary tau tangles are the driving force behind CTE. Yet it is important to note that tau does not have an inherently malicious purpose: this protein is designed to bring stability to the microtubules of neurons in the central nervous system. Normally, tau is present in the axons, where it provides flexibility, which means that tau is very soluble. In CTE, the hyperphosphorylation of tau results in insoluble fibers of tau, which leads to the assembly of neurofibrillary tangles. The danger of these hyperphosphorylated tangles is that axonal transport is disrupted, and the microtubules of the neurons become destabilized. Since the microtubules of a cell and the axons of a neuron are crucial to brain function, the widespread accumulation of hyperphosphorylated neurofibrillary tau tangles is detrimental to all areas of the brain. Furthermore, the tangles cause a loss of general neurons, called cerebral atrophy, and scarring of brain tissue due to trauma often appears upon examination of brain tissue. Atrophy often occurs in the cerebral hemisphere, medial temporal lobe, thalamus, and brainstem. Thinning of the corpus callosum, the white matter that connects the left and right hemispheres of the brain, attributes to the loss of hand-eye coordination that CTE progresses to. Moreover, diffuse axonal injury to white matter in the form of lesions and damage to the cerebellum affect the severity of motor control, fine movement, and equilibrium symptoms (Mckee). Immune activation, knows as resistance to infection, also aids in the progression of chronic traumatic encephalopathy. Helper T-cells and macrophages promote inflammation by expelling pro-inflammatory proteins, like cytokines, activate kinases which promote tau hyperphosphorylation (Collins-Praino). Kinases are enzymes that catalyze the transfer of phosphate groups from ATP to another molecule. The lack of regulation of pro-inflammatory cytokines encourages tau hyper-phosphorylation. Although not the primary factor, cytokines aid the progression of the detrimental tau tangles.

CTE was pushed into the spotlight by the Dr. Bennett Omalu, a forensic neuropathologist who published pioneering studies on the results of multiple professional football players' autopsies. Currently, ninety of the ninety-four brains of deceased National Football League players have tested positive for CTE (Boston University CTE Center). Thus, the notion of the brain disease being solely a football issue was born. Yet the truth is far different; CTE has been diagnosed in a wide range of sports, from boxers to baseball players. Furthermore, the autopsies of war veterans with and without post-traumatic stress disorder have shown CTE. This particular disease is rooted in trauma to the brain, like a series of sub-concussive blows to the head. Therefore, any profession which involves danger to the head is vulnerable to CTE, proving the pervasiveness of this disease. Contrary to popular belief, this neurodegenerative disease was first documented in boxers, not football players. Some of the symptoms that accompanied the disease were paranoia, slurred speech, constant state of confusion, and unsteady gait and balance. The condition was often called "punch drunk", because of the common devolution into alcohol abuse. A particular case involved an 80-year-old African American boxer who began exhibiting symptoms during his twenties. A posthumous cerebral computerized axial tomography revealed progressive cerebral and cerebellar atrophy, which meant the neurons were severely degenerated, and mild ventricular enlargement. Similarly, a 77-year-old rugby player was found to have CTE with alike symptoms. After playing for the Manly Rugby Union for an astounding 17 years, the player had severe cognitive difficulties and severe dementia. Ann Mckee, the leading neuropathologist who examined the rugby player, stated that the lining of the ventricles and the septum pellucidum, a double membrane separating the left and right ventricles of the brain, had lacerations. Another case of CTE was presented in a deceased 29-year-old soccer player. Amyotrophic lateral sclerosis, a fatal neurological disease which attacks the neuron cells responsible for voluntary movements, and extensive frontal lobe damage accompanied the athlete (New York Times).

Even sports which are not known for head collisions, such as baseball, have had cases of CTE. A former MLB player who committed suicide at 36 years old was revealed to have chronic traumatic encephalopathy. He was being treated for depression, and had alcohol abuse that was linked to his concussions. Lastly, an Iraqi war veteran was in close quarters with explosive devices has been found with CTE. He was 27 years old and dealt with post-traumatic stress disorder as well. The brain tissue analyzed from the war veteran

did not show the usual loss of neurons, but changes to the newest part of the cerebral cortex leaned towards chronic traumatic encephalopathy. Many of the athletes and veterans studied are far past adolescence, but evidence points towards a rising number of teenage athletes being at risk for chronic traumatic encephalopathy. Boston University's CTE Center published findings on the analysis of the brain of a deceased 18-year-old multi-sport athlete. The brain tissue scan revealed deposits of tau protein in and around blood vessels, making this athlete the youngest documented case of CTE. While the spectrum of symptoms is wide, all deal with a form of cognitive dysfunction and neural damage. The relationship between concussive blows during each athlete's career cannot be anything but inextricably linked their diagnosis of CTE. Moreover, the studies display a startling reality: chronic traumatic encephalopathy is not a "football issue", but a disease that has no limits.

Figure 1: Brain tissue of 18-year-old multi-sport athlete. The top and bottom left is the frontal cortex with a dense tau deposit around small blood vessels. The top and bottom right is another section of the frontal and insular cortex with more tau deposits around blood vessels.



A second test and potential treatment is dealing with an antibody for hyperphosphorylated tau. There are many formations that tau can shift into, but the pathogenic cis-tau conformation is the one that creates a destructive environment in the brain. A study exploring the effects of this antibody on cis-tau conformation levels on mice with traumatic brain injury found that levels of cis-tau surged within neurons hours after stress was applied to the neurons (Lu). This process is called cis-tauosis, and the antibody is designed to convert cis-tau formations into trans-tau formation, restoring original tau function. Cis-tauosis is the process in which tau-mediated neurodegeneration and brain atrophy ensues. Prolyl isomerase Pin1, the antibody, not only converts tau conformations but also targets the intracellular phosphorylated cis-tau and prevents extracellular cis-tau from spreading to other neurons. The patient could be tested for their phosphorylated cis-tau levels, which would indicate the stages leading up to or the earliest stages of chronic traumatic encephalopathy. If tests come back with high levels of cis-tau, prolyl isomerase Pin1 could be a treatment introduced. Although these methods have not been tested on

human subjects, the findings published give a promising outlook on endoplasmic reticular stress inhibitors and cis-tau antibodies (Lu). More specifically, these methods can be used to combat the pervasiveness of hyperphosphorylated tau and turn the protein back into its original, positive function: stability to the neurons.

Current research is looking for antemortem methods of CTE diagnosis. If people can be diagnosed while living, a treatment plan can be tailored to the specific individual to help manage, like Alzheimer's Disease. Patients with chronic traumatic encephalopathy range from athletes from a myriad of sports to war veterans, highlighting the extensivity of this disease. For athletes, guidelines for protective gear are not enough. Helmets are not fully effective in warding of diseases caused by concussive blows and brain trauma. Focus should be centered around creating approaches for diagnosing CTE as early as possible, and using said diagnostic techniques to find different treatment methods. All of the professions that are affected by chronic traumatic encephalopathy are an integral part of today's society. Banning American football will not be the end of this disease. Soldiers are needed to fight for their countries. Media and awareness centered around patients diagnosed with CTE should spread the message that everyone is susceptible to this neurodegenerative disease. If studies are targeted towards the tau tangles that plague the brain, identifying and treating Chronic Traumatic Encephalopathy will be one test easier.

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