Beyond the Game: Understanding the Neuropathology and Enduring Impacts of Chronic Traumatic Encephalopathy

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Abstract:

Chronic Traumatic Encephalopathy (CTE) is a progressive neurodegenerative disease characterized by aggregation of phosphorylated tau as well as astrogliosis. Currently, CTE can only be diagnosed post-mortem and is most likely to be found in former professional athletes, especially in contact sports. However, military veterans and domestic violence victims may also suffer from this disease, increasing the prevalence. CTE is correlated to the number of traumatic brain injuries (TBI) or subconcussive impacts received, usually in childhood or adolescence. Mild TBI induces mechanisms to regain homeostasis which include a hypermetabolic state, increased intracellular calcium, and inflammatory signaling molecules in the acute phase. After the acute phase, all of these proteins and mechanisms are downregulated to create depressed neuronal signaling, neuronal death, and glial cell pathology. The immune response to mTBI causes a permeable blood-brain barrier (BBB) which leads to further neuroinflammation and further vascular injury. Post-mortem studies on brains with CTE show progressive aggregation of phosphorylated-tau neurofibrillary tangles (NFTs), diffuse axonal injury (DAI), and accumulations of thread-like astrocytes. Gross cerebral atrophy, widening of the ventricles, and wider sulcal depths are also indicative of CTE diagnosis. The McKee Staging Scheme allows for characterization and comparison of varying severities of CTE between individuals. These changes in brain chemistry can be seen through behavioral, motor, and memory symptoms in patients, similar to those in Alzheimer's Disease. A common symptom of CTE is abnormal mood changes which include apathy, depression, and aggression. The NFTs of p-tau have neurotoxic effects and destabilize microtubules. Astrocyte pathology also leads to decreased gliotransmitter release and therefore fewer neuronal depolarizations. Due to plasticity of the brain, this may lead to neuronal death and pruning. Though there are no conclusive results of the

mechanisms which make TBI or repetitive head injury (RHI) transform into the neurodegenerative disease, research into connections between the two is ongoing. Chronic neuroinflammation, a permeable BBB, and an autoimmune response may contribute to the pathophysiology and progression of CTE. Currently, researchers are working to find a way to diagnose CTE before patient death. So far, blood-based biomarkers demonstrate the most promising possibilities. Drawbacks of blood-based biomarkers, such as lack of protein specificity, still exist. The studies reviewed in this paper highlight significant findings in current academic research, identify those most at risk for development of CTE, and suggest possible modes of CTE development after TBI or RHI. The findings demonstrate the importance of education and prevention in youth sports and demand major sports organizations to take responsibility for the health and safety of their athletes. The data also finds that future research will be critical for diagnosis, treatment, and prognosis for patients with CTE.

Assessing Vulnerability: Who is at Risk?

With the rise in popularity of sports throughout the centuries, children and young adults face a higher prevalence of concussive or subconcussive injuries to the head (Gessel, 2007). Throughout this review, mild traumatic brain injuries (mTBIs) will be discussed as these are the most common and most likely to be received through recreational and professional sports (WebMD, 2024). Mild TBI also correlates to mild concussions. Through contact sports such as American football, soccer, rugby, hockey, children face a great likelihood of obtaining a serious head injury. Additionally, the societal and peer pressure that surround sports and create a culture can be very damaging to the young athletes (NATA, 2015). However, sports are not the entire cause of mild traumatic brain injury (mTBI). Veterans and active military personnel, those who have been in horrible accidents, and survivors of domestic violence are also very susceptible to

one or more head injuries (Kaunzer, 2024). Interestingly, military members do not have to see combat to endure damage. Some daily activities including riding in vehicles and regular training exercises may contribute to mTBIs as well as subconcussive impact (Phillips, 2024).

Annually, 1.7 million people worldwide receive a diagnosed concussion (CDC, 2019). This is likely an underestimation of the true number of people that experience a TBI due to patient refusal to see a doctor, social inequalities in health care, and mild concussions that may not cause severe enough symptoms to cause alarm (NATA, 2015). According to the Mayo Clinic, a concussion is defined as a mild traumatic brain injury that alters functioning of the brain. Symptoms can include headache, concentration, issues with executive function and decision making, poor coordination, and memory problems. Age groups that are at the highest risk for mTBI are children from birth to four years, adolescents from ages fifteen through nineteen, and adults over the age of sixty-five (CDC, 2019). Young children have relatively heavy and large craniums with less developed neck muscles. The weight of their head is 25% of their body weight compared to 6% of body weight at adulthood (CDC, 2019). The delicate, developing neck muscles put them at a higher risk for whiplash and other head motions which could lead to a shearing of neurons and mTBI symptoms (Bey, 2009). Many adolescents are involved in extracurriculars, including contact sports. The sports with the highest risk of mTBI include: American football, soccer, lacrosse, rugby, and hockey (Knauzer, 2024). Female players are at twice the risk of males in the same sport due to longer and weaker neck muscles than their male counterparts (Gessel, 2007). The tough culture and competitive nature of sports also increases the risk of players returning to the field before their injuries have completely healed (NATA 2015). For weeks to months after a mild concussion or mTBI, the brain is more prone to receiving another concussion (Bey, 2009). The second TBI can lead to Second Impact Syndrome.

Second Impact Syndrome occurs when a player acquires a first concussion but then returns to play and receives another concussion before the first one heals. The second TBI can be mild but may have very dangerous and inflammatory consequences (Bey, 2009). Occasionally, Second Impact Syndrome may lead to death from global cerebral swelling so intense that the brain herniates through the foramen magnum of the skull (Bey, 2009). Not only do women tend to have more reported symptoms post-mTBI, but also there is a longer average recovery period (McKee, 2023). Studies have even shown that women may have more microstructural white matter alteration than men after performing the same actions such as heading a soccer ball (McKee, 2023). Throughout adulthood, vehicle or other accidents, military service, or domestic violence serve as major causes of mTBI and concussion (NATA, 2015). Adults over the age of sixty-five are most likely to receive their brain injuries from accidental falls due to loss of balance (CDC, 2019).

Traumatic Brain Injury and multiple brain injuries, have been implicated and are likely related to the development of Chronic Traumatic Encephalopathy (CTE) (Mayo Clinic, 2023). CTE is a progressive neurodegenerative disease that affects people who have suffered repeated mTBI and concussions. It is linked to a collection of abnormal proteins that result in brain damage and neuron cell death (CDC, 2021). The mechanisms driving repeated mTBIs to develop into CTE are unknown, so it is critical that more research is done to find definitive answers. Though, there is emerging evidence that frequent subconcussive impacts may also play a role in CTE pathophysiology. Although CTE affects many different populations, prevention of mTBI in youth is critical due to the correlation between the years and level of the sport played (Emami, 2023). Per year of play in a professional American football team, there is a 1.20 increased probability of a future CTE diagnosis (Emami, 2023). Additionally, there is a positive correlation

between the number of years an individual played a contact sport and the number of concussions, mTBI, and sub-concussive repetitive head injuries (RHI) (Emami, 2023). Essentially, the more time spent in contact sports allows for more mTBIs and frequent subconcussive impacts which may build the foundation for long-term impacts. Hypothetically, the earlier that intervention and prevention begin in youth sports and collegiate sports, the better the outcomes later in life and hopefully CTE development is avoided completely. Hopefully these efforts will also lead to a decrease in the prevalence of CTE. It has been observed that 41% of contact sport athletes under the age of thirty show neuropathological markers that are consistent with future development of CTE (Emami, 2023). Though the prevalence of CTE in the general population is unknown, it has been found that development may not occur until decades after the last time of play (Emami, 2023). Interestingly, 20% of people diagnosed with CTE did not have a diagnosed or reported concussion in their life, indicating that even mTBIs that are subclinical or subconcussive impacts may have an effect on CTE development (Tagge, 2017).

The demographics that are most often associated with the development of CTE are those who play or have played American football (Emami, 2023). Of the eleven brains donated from former professional American football players, all eleven were diagnosed post-mortem with CTE (Emami, 2023). Furthermore, of the forty-eight brains of American football players on both professional and amateur levels, thirty-seven of them were diagnosed with CTE (Emami, 2023). Another study of 152 brains provided by former contact sport athlete donors, found that 63 had CTE Stage I or Stage II (McKee, 2023). The average age at death was 22.97 and 93% of the brains came from males (Mckee, 2023). A post-mortem diagnosis of CTE was associated with more years of participation in their respective sport as compared to those who were not diagnosed with CTE (Mckee, 2023). Those diagnosed with CTE were also more likely to

identify as Black and have a higher (college) level of education (Emami, 2023). While a large percentage of former athletes diagnosed with CTE played American football, CTE was recently confirmed in thirteen former male soccer players (Van Amerongen, 2023). The average age of death for those who had CTE is between twenty-four and eighty-three (Van Amerongen, 2023). This large age range could be attributed to the level of play, the number of years involved in the sport, and number of RHI, mTBI, and even subconcussive impacts. It also accounts for differences in genetics, predispositions, substance use, and personal variations in anatomy and progression of pathology (Emami, 2023). Interestingly, many former athletes are diagnosed with dementia before their deaths due to the dementia-like symptoms (Van Amerongen, 2023). Also, 71% of athletes diagnosed with CTE only played at the amateur level and never professionally, indicating that current high school and collegiate athletes are at an extreme risk of receiving RHI and mTBI that will predispose them to CTE (Emami, 2023). These studies also controlled for substance abuse and alcohol abuse and found no significant correlation of substance ingestion between the affected athletes and the general population (Emami, 2023). The studies done to find prevalence and demographics most affected need to be expanded to account for a general population and not just those suspected to have CTE before their diagnosis.

Hundreds of millions of children, adolescents, and adults play sports worldwide (Van, Amerongen, 2023). The constant risk of mTBI, especially in contact sports, for adolescents playing non-professional sports rightfully sanctions much concern. Overall, the people in the most danger of receiving a RHI and mTBI are adolescent, black males who play collegiate American football (Emami, 2023). It is still vital to consider other contact sport and non-contact sport athletes, military personnel, and domestic violence victims. The devastating effects of neurocognitive decline provide a viable reason to begin prevention early.

After the Impact: Post - Concussive Cascade and Subconcussive Impact

The mechanical force on the brain, especially on the fragile neurons, is what leads to the damage done by concussions or mTBI. The mechanics of injury and where and how much force is applied has a huge role in determining the extent of damage (Kornguth, 2017). However, it is possible for concussions to be asymptomatic, making it difficult to ensure treatment and adequate recovery time for those affected (Simpson, 2023). Knowing the mechanisms and mechanics behind mTBI and concussions is crucial for accurate clinical diagnosis and treatment management.

A main cause of concussion and mTBI involves a water hammer effect (Kornguth, 2017). In physics, the water hammer effect is described as fluid flowing through a pipe and creating a shock wave as the flow abruptly meets a sealed area, leading to a powerful increase in pressure opposite the blockage. Physiologically, the skull is a likely place for a water hammer injury to occur due to the unyielding and uncompromising bones of the skull (Kornguth, 2017). The skull acts as the abrupt halting mechanism and the cerebrospinal fluid operates as the flowing liquid (Kornguth, 2017). Due to the small area of the closed system, a powerful shock wave could cause damage to the fragile neurons. The intense direction and pressure change can lead to shear stress on the axons, which is the primary cause of concussion (CDC, 2021). The shear force on the axons of neurons can also lead to damage to the vasculature surrounding the axons, resulting in an increased permeability of the blood brain barrier (Kornguth, 2017). The primary strike or impact can be quite traumatic to structures in the torso, neck, and skull. For example, a two hundred pound football player who runs five meters per second will hit a target at an average of nine hundred newtons (Kornguth, 2017). This force, even over a fairly short duration, can still

cause considerable tissue damage and broken bones as well as an mTBI. Additionally, helmets may not always be effective, especially if the contact is to the lower part of the body and causes whiplash of the neck, causing enough radial force to generate a water hammer effect and subsequent shearing of axons and perivascular damage (Kornguth 2017). There may be shearing of both white and gray matter, and intense pressure may lead to vascular injury (Kornguth, 2017). White matter is stiffer and therefore is less able to respond to rapid changes in mechanical pressure (Kornguth, 2023). Women are also at twice the risk of men for such injuries due to the longer and less-developed muscles in the neck which further increase risk of whiplash (Katsumoto, 2019). Understanding the mechanical mechanism and causation of concussion is important and directly correlates to the diagnosis of a mTBI or concussion.

After receiving a mTBI, players can undergo potential diagnosis and treatment. ImPACT (immediate post-concussion assessment and cognitive testing) is a fairly common test for clubs, high schools, and colleges and allows for comparison between preseason working memory, attention span, and visual problem solving abilities, reaction time, and a post-injury score (Children's Healthcare of Atlanta). Though not a diagnostic test, ImPACT can identify vast changes between initial and current performance. It may also indicate player progress in the healing process by showing slow improvement over time (Children's Healthcare of Atlanta). A limitation to ImPACT testing is the occurrence of invalid responses which has been found as high as 27.9% of baseline tests (Szabo, 2013). Poor effort on baseline tests can skew interpretation of later ImPACT testing results (Szabo, 2013). Diagnostic testing for mild TBI includes computed tomography (CT) and magnetic resonance imaging (MRI) to find abnormalities intracranially (Silverberg, 2023). MRI is more sensitive and likely to pick up a mild TBI than CT, though both are used clinically as diagnostic tests (Silverberg, 2023). MRI

assessments make it possible to see progressive atrophy of regions by comparing results over time (Van Amerongen, 2023). Once officially diagnosed by a doctor, a period of physical and mental recovery is needed. Depending on the individual circumstances, this less strenuous recovery time may take weeks to months (Giza, 2001). Unfortunately, many times, athletes are pressured or desire to return to play before their concussion has completely healed (NATA, 2015). The danger in returning to play too early is that receiving another head injury could lead to Second Impact Syndrome which is a serious problem with a rapid onset of cerebral swelling (Bey, 2009). If not managed, brain herniation and death are possible within minutes of the injury (Bey, 2009). Women tend to be at a higher risk for Second Impact Syndrome and had worse outcomes after mTBI than males (McKee, 2023). Women tend to also have a different response to repetitive brain trauma than men (McKee, 2023). In summary, there are a multitude of tests which are able to ensure that players do not return to play before a mild TBI or concussion has healed, though that does little to influence the culture and mindset of the players and coaches whose objective is a quick return to play (NATA, 2015).

The effects of a mTBI are immediate and initial responses come from the cardiovascular, nervous, metabolic, and immune systems. There tends to be an initial hyperactive and hypermetabolic state which is followed by a steep metabolic depression that may last for weeks to months (Giza, 2001). In the moments after a shearing force has been applied to a section of neurons, there is an immediate need to restore homeostasis (Giza, 2001, 2011). Calcium transporters in the brain quickly elevate their activity (Giza, 2001, 2011). These transporters require abundant ATP and initiate an increased metabolic demand in the local area (Simpson, 2023). Especially with potential perivascular damage, there may be problems with maintaining adequate cerebral blood flow to match the metabolic demand (Giza, 2011). The calcium pumps

may require so much ATP that other areas of the brain are deprived of sufficient energy resources (Simpson, 2023). The superfluous amount of intracellular calcium leads to major cellular function problems such as disrupting mitochondrial function and neurofilament connectivity and assembly (Giza, 2001). After this surge of metabolic demand and transporter activity, in yet another attempt to revert to a state of homeostasis, there is a severe metabolic depression after this period of time (Simpson, 2023). Some metabolic pathways were repressed for over six months post injury (Simpson, 2023).

The immune system also has an immediate strong response to mTBI and then depression (Halicki, 2023). In human models, gene expression of interleukin receptor genes were upregulated, indicating cerebral inflammation and swelling post-injury (Simpson, 2023). It also demonstrates an upregulation of cytokine production and systematic activity (Simpson, 2023). Up to two days post-injury, natural killer cell-mediated cytotoxicity and MAPK signaling pathway were all upregulated (Simpson, 2023). Differential expression of serine and threonine protein phosphatases impacted their targets, Raf, MEK, and AKT (Simpson, 2023). Compared to controls who were non-contact sport athletes, measurements taken from blood in contact sport athletes and injured players showed an upregulation of these pathways, revealing that the pro-inflammatory and immune response is a direct consequence of the impact to the head or body (Simpson, 2023). In animal models, there is also evidence to support that the extra intracellular calcium facilitates upregulation of proteases, leading to neuronal cell death (Giza, 2011). Within a day, both the neutrophils and natural killer cells within systemic circulation return to normal levels (Simpson, 2023). As another immune response, the spleen releases monocytes into systemic circulation (Kornguth, 2017). If the perivascular areas of the brain have been damaged, then there is a potential that the Blood-Brain Barrier (BBB) becomes

compromised and more permeable to the monocytes (Kornguth, 2017). Furthermore, athletes may have cerebral vascular injury whether they have diagnosed concussions or not (Kornguth, 2017). Activated macrophages (M1 or M2) have the ability to cross the BBB conducting more interferon release, inflammation, and neuronal cell death (Kornguth, 2017). Glial and neuronal neurofilament protein production may prompt the production of antibodies, which may be the cause of clinical signs of TBI (Kornguth, 2017). Not only can immune factors pass through the BBB, but there is also a possibility that the increased permeability allows pathogens and toxins to cross. Adaptive immunity response allows for antibody creation against some neuronal proteins that are released during injury (Kornguth, 2017). The immune response to such proteins during subsequent head injuries can be elevated and more severe. This immune process may play a role in developing neurodegenerative disorders such as CTE (Kornguth, 2017).

In examining the post-concussive cascade, patients experience a period of intense metabolic demand and overactivity of calcium and potassium ion transporters immediately after injury and lasting for 24-48 hours (Simpson, 2023). There is also an upregulation of interferon, cytokine, and neutrophil production which leads to cerebral inflammation and increased permeability of the BBB (Kornguth, 2017). The spleen also releases many monocytes which travel to the brain and cross through the BBB to have their aforementioned effects in the space around neurons (Simpson, 2023). Both immune and metabolic systems downregulate quickly into a state of repression (Simpson, 2023). This depression may span from a few weeks to months or even years depending on the severity of the TBI and how quickly medical intervention was sought (Giza, 2001). Evidence of autoimmune mechanisms for increasing intensity of symptoms and brain injury after multiple TBIs is still being investigated but acts as a promising

avenue for discovering processes that lead to neurodegenerative diseases and permanent alterations to brain chemistry (Simpson, 2023).

Post-Mortem CTE Findings

While mTBI and concussions represent acute brain injuries with rapid but temporary symptoms, chronic traumatic encephalopathy (CTE) highlights the long-term and progressive impacts of RHI, mTBI, and subconcussive impacts, warranting more research into the pathophysiology of CTE and its implications. Unfortunately for patients and their families, diagnosis of CTE can only happen post-mortem (Van Amerongen, 2023). During life, patients with CTE usually present with symptoms similar to other neurodegenerative diseases such as Alzheimer's Disease (AD) (Van Amerongen, 2023). Symptoms include forgetfulness, short-term memory loss, disorientation to time and place, inability to maintain finances or the household, delusions, sleep disturbances, and abnormal motor behavior (Halicki, 2023). Interestingly, patients with CTE are different from AD patients because symptoms tend to be emotion and mood based (Tagge, 2017). These emotional symptoms can manifest commonly as apathy but can also include explosive and unexpected anger or depression (Van Amerongen, 2023). However, other types of dementia such as Frontotemporal Dementia are also associated with emotional symptoms and the impulsivity seen in CTE, making distinction between the neurodegenerative disorders difficult (National Institute of Aging, 2022). Clinical testing usually reveals deficits in executive functioning, processing speed, and memory consolidation (Van Amerongen, 2023). In subjects with CTE, especially younger men, the leading cause of death is suicide followed closely by unintentional drug overdose (Tagge, 2017).

The McKee Staging Scheme ranks the severity and level of progression of the CTE (Alosco, 2020). The stages, which are defined by the National Institute of Neurological

Disorders and Stroke (NINDS), range from I, which is mild, to IV, which constitutes severe CTE (Alosco, 2020). The staging is based mostly on the density and location where the hyperphosphorylated tau have aggregated in neurons and astroglia in specific regions of the brain. In general, those who are older tend to have a higher score on the scale of CTE (Alosco, 2020). In post mortem studies, the areas of the brain commonly tested and most affected by CTE are the dorsolateral frontal cortex, superior temporal cortex, entorhinal cortex, amygdala, and locus coeruleus (Van Amerongen, 2023). In Stage I of CTE, small and isolated hyperphosphorylated tau neurofibrillary tangles are found in perivascular areas of the frontal cortex, more specifically, the dorsolateral frontal cortex (Alosco, 2020). Stage II is indicated by at least three substantial aggregations of hyperphosphorylated tau proteins in multiple cortical regions. Usually, these larger lesions are found in the locus coeruleus and nucleus basalis (Alosco, 2020). Stage III is defined by confluent and large phosphorylated tau neurofibrillary tangles. These tangles are found perivascularly and in the depths of the foci (Alsco, 2020). Astrocytes are misshapen and thread-like (Van Amerongen, 2023). At this point in the progression of CTE, the astrocytes have developed reactivity and pathology which changes their structure into dot and thread-like neurites (Van Amerongen, 2023). The regions of the brain impacted usually are the hippocampus, entorhinal cortex, amygdala, and entorhinal cortex (Sanacora, 2013). There may be hyperphosphorylated tau within the brain stem as well (Van Amerongen, 2023). Stage IV is severe and is signified by global cerebral atrophy, especially in the medial temporal lobe and the diencephalon (Alosco, 2020). There are extensive phosphorylated tau neurofibrillary tangles, mostly found in perivascular areas and even in the brain stem (Alosco 2020). Atherosclerosis of the carotid arteries was detectable and hypothesized to be from repeated vascular injury (Van Amerongen, 2023). The amount of

arteriosclerosis found is also positively correlated with density of p-tau in nearby brain tissue (Alosco, 2020). There is pathology within astrocytes and gliosis is present (Alosco, 2020). Grossly, there is cerebral atrophy, enlargement of ventricles and frontal horns, and septum pellucidum widening. Damage in the hippocampus includes regions CA1, CA2, and CA4 (Alosco, 2020). Changes to brain structure are associated with mood, motor, and cognitive abilities (Kaunzer, 2024). Patients who were younger at time of death usually had fewer symptoms, lower stages of CTE, and had not been diagnosed with dementia or Alzheimer's Disease (Tagge, 2017). Antemortem magnetic resonance imaging (MRI) studies have shown bilateral medial temporal lobe atrophy as well as global cortical atrophy which are consistent with the post-mortem findings (Van Amerongen, 2023). The global atrophy continues to progress over time and new symptoms arise as well as increasing severity of existing symptoms until death (Van Amerongen, 2023). The gross anatomical changes seen in the varying stages of CTE, which include ventricle enlargement, regional atrophy, global atrophy, and astrogliosis, all demonstrate the anatomical impact and give possible reason to the behavioral, emotional, and motor symptoms patients experience (Alosco, 2020).

The hyperphosphorylation of the tau proteins and neurofibrillary tangles is largely what defines CTE (Van Amerongen, 2023). Tau is a protein used to bind and stabilize neuronal microtubules (Kornguth, 2017). Abnormal phosphorylation can lead to tau no longer binding to other molecules but instead binding to other tau proteins (Emami, 2023). Additionally, there are six distinct isoforms of the tau protein found in the brain. Some of the isoforms are correlated with disease such as CTE, frontotemporal dementia, Alzheimer's disease, and other tauopathies (Katsumoto, 2019). Over eighty phosphorylation sites are located on the tau protein and usually include serine or threonine residues (Halicki, 2023). Some of these sites include T175, T181,

T231, S199, S202, S205, T231, Y394, Y396, and S422 (Katsumoto, 2019). Perhaps the most clinically important phosphorylation site is Thr231 (Katsumoto, 2019). While there are few replicable studies on the conformation of tau proteins, studying the usual conformations and potential changes to conformations with pathology is necessary to understand CTE. Tau normally exists in its trans-isomer form which allows it to be destabilized when phosphorylated (Katsumoto, 2019). Essentially, this allows for easy dephosphorylation and the tau protein mostly exists in an unphosphorylated state. Templated misfolding or faulty post-translational modifications may change the tau protein to its cis conformation. The cis isomer is substantially more stable in the phosphorylated state than the trans isomer (Katsumoto, 2019). After the misfold, normal regulatory phosphorylation of the tau protein can occur. Phosphorylation may happen at many sites but a common phosphorylated site found in CTE is Thr231 (Katsumoto, 2019). The tau protein then may become hyperphosphorylated (Katsumoto, 2019). The hyperphosphorylation results in the tau protein being resistant to binding microtubules and degradation by protein phosphatases (Katsumoto, 2019). Additionally, in normal brains 3R and 4R tau isoform expressions are balanced (Van Amerongen, 2023). Both 3R and 4R isoforms are misfolded to cause CTE (Van Amerongen, 2023). Misfolded 4R tends to be in higher concentration in early stages of the disease and misfolded 3R is expressed more often in the later stages (Cherry, 2021). Normally, tau exists as a monomer but when it is in a misfolded or pathological state, in a prion-like fashion, it can cause normal tau proteins to change or misfold. Then, it can begin to accumulate and form into oligomers (Katsumoto, 2019). The oligomers serve as precursors to formation of fibrils and neurofibrillary tangles (Katsumoto, 2019). Tau aggregates into oligomers of around forty tau monomers (Hsu, 2018). The presence of the oligomers elicits granular tau fibrils (Cherry, 2021). Furthermore, hyperphosphorylated tau, after

unbinding to microtubules, may translocate to the cell body of neurons where they aggregate into neurofibrillary tangles (Katsumoto, 2019). The tangles then hinder neuronal, specifically axonal, function (Katsumoto, 2019). A major concern is that tau aggregates are able to, in a prion-like fashion, recruit other tau aggregates to themselves, causing templated tau misfolding, which creates larger networks of neurofibrillary tangles and may propagate to additional brain regions (Katsumoto, 2019). Aggregation of the tau NFTs instigate microtubule destabilization, synapse loss, disrupt intracellular signaling, and eventually cause neuronal death (Halicki, 2023). These complex conformational changes in tau structure and phosphorylation state not only disrupt neuronal function but also drive the progressive spread of tau pathology throughout various brain regions (Katsumoto, 2019).

Another pathway contributing to neurodegeneration involves gliosis which is characterized by pathological changes in glial cells (Hsu, 2018). A subtype of the glia which are most directly involved with the progression of CTE is astrocytes (Halicki, 2023). Astrocytes reside in the central nervous system (CNS) where they provide structure for neurons and connect adjacent neurons, aid in vasomodulation, including management of the blood-brain barrier (BBB), monitor synaptic transmission, and even facilitate repair mechanisms post-neuronal injury (Hussaini, 2018). There are nine types of astrocytes throughout the brain and each type is typically associated with a specific region of the brain (Hussaini, 2018). Furthermore, the higher the metabolic demand of neurons, the more astrocytes reside in the surrounding area (Hussaini, 2018). Gray-white matter junctions and subcortical regions are a standard site of localization (Hsu, 2018). Typically, astrocytes are star-shaped, but in the pathological state, such as those found in CTE, they become beaded or thorn-shaped (Hussaini, 2018). In this reactive state, deformed astrocytes have neurotoxic qualities, which may induce degeneration of white or gray

matter as well as corticobasal degeneration and palsies (Hsu, 2018). Astrogliosis refers to astrocytes being turned into their reactive states. This reactivity can be seen in multiple neurodegenerative diseases including Alzheimer's Disease (AD) and CTE (Hsu, 2018). However, astrogliosis tends to be more diffuse throughout the brain and in closer proximity to the sulcal depths in CTE than in AD (Hsu, 2018). There have been no research findings that prove a correlation between the amount of p-tau and the extent of astrocytic reactivity degeneration, demonstrating that astrogliosis has its own distinct mechanism of development and is independent from tauopathies (Hsu, 2018). One of the major roles of astrocytes lies in their abilities to secrete and uptake neurotransmitters such as glutamate and gamma-aminobutyric acid (GABA) (Hussaini, 2018). Astrogliosis represses synaptic transmission and may lead to the pruning of neurons as a result of inadequate transmission (Hsu, 2018). This process may lead to atrophy of specific brain regions. Moreover, the astrocytes connect to each other via gap junctions, forming an electrical syncytium and allowing for spontaneous excitation of the glia (Sanacora, 2013). Furthermore, astrocytes can spontaneously depolarize, given that there is enough intracellular calcium which triggers glutamate release, capable of depolarizing other astrocytes or neighboring neurons (Hussaini, 2018). The hippocampus and other brain regions possess the ability to have quick depolarizations in succession, perhaps hinting at why it is one of the most affected areas by CTE (Hussaini, 2018). Gliotransmitter release is done through calcium activation of the SNARE complex and exocytosis of vesicles of glutamate molecules (Hussaini, 2018). Astrocytes can also undergo neuron-dependent excitation when receiving glutamate, GABA, acetylcholine (Ach), nitric oxide, and brain-derived neurotrophic factor (Hussaini, 2018). These communication functions facilitate synapse formation, maintaining neurons, and contribute to blood flow control (Hussaini, 2018). Interestingly, astrocytes possess the capacity

to recognize the synapses of certain axon pathways and react differently to the neurotransmitters produced by different pathways (Hussiani, 2018). This is thought to facilitate memory consolidation as well as different behavior and mood-associated pathways (Hussaini, 2018). Reactivity of astrocytes is not a normal product of aging but instead a result of p-tau infiltration into surrounding neuronal space as well as a disruption of the BBB (Hsu, 2018). Astrogliosis can be detected through an increased expression of glial fibrillary acidic protein (GFAP) and its immunoreactive properties surrounding specific vascular areas of the cerebral cortex (Tagge, 2017). Axonal injury and subsequent increase in astrogliosis was demonstrated in subcortical white matter as well as the frontal and temporal lobes in CTE (Emami, 2023). There are reductions in overall glial cell numbers and density, including astrocytes, oligodendrocytes, and microglia (Sanacora, 2013). The GFAP is a dominant biomarker in stages III and IV of CTE (Hsu, 2018). The loss of functional astrocytes in neuroanatomical areas leads to the behavioral modifications, repressed ability to form memories, and a leaky BBB due to inability to properly regulate tight junctions (Hsu, 2018). Overall, the tau pathology can cause formation of neurotoxic neurofibrillary tangles which induce astrocyte reactivity and increase neuroinflammation. Both can degrade the BBB and cause neuronal death due to underuse of neuronal pathways, leading to atrophy of the brain and causing behavioral, mood, and memory consolidation impairment (Hsu, 2018).

Mechanisms of Disease: TBI to CTE

Chronic Traumatic Encephalopathy (CTE) has been documented since the 1920s but had not been taken seriously on a cultural level until the early 2000s when more in-depth biomedical research established its prevalence and severity of symptoms (Concussion Legacy Foundation). There is a relationship between repetitive head injuries and CTE, though more research is

necessary to understand the extent and nature of the relationship. Understanding the mechanisms which reestablish homeostasis following post-concussive or sub-concussive events and the progression to CTE are the focus of current research efforts. The following section will draw on published research to hypothesize possible mechanisms of disease that lead to progression of CTE.

As previously discussed in post-concussion cascade data, for the few hours after mTBI, there is a hypermetabolic state to regain a homeostatic state (Giza, 2001). This includes a massive release of the excitatory neurotransmitter glutamate and increases in intracellular potassium and calcium, ATP utilization, and overall metabolic demand (Giza, 2011). This is coupled with a lower cerebral blood flow, meaning that overall metabolic demand is not met (Giza, 2001). The damaged neuronal cell membranes increase their ion influx which disrupts calcium-dependent signaling and disproportionally uses ATP, which in turn will starve the brain of energy (Simpson, 2023). Glutamate clearance is depressed, indicating that there is damage not only in the neurons but also from the glial cells (Sanacora, 2013). This metabolic starvation of brain regions could lead to further efforts to restore homeostasis and therefore increased damage to the neurons and glia in the surrounding areas, perhaps leading to CTE development (Giza, 2001, 2011). Since astrocytes can spontaneously depolarize when triggered by calcium, the extreme influx of calcium following an mTBI may lead to many depolarizations in quick succession (Hussaini, 2018). Some astrocytes are able to endure quick excitations, such as those in the hippocampus, but others are not (Hussaini, 2018). There may also be elevated neuronal firing after glutamate release from the astrocytes which is why there is an increase in metabolic activity and demand (Hussaini, 2018). The decrease in cerebral blood flow due to astrocytic changes post-TBI may also contribute to the inadequate supply of ATP and calcium, leading to

brain starvation and ischemia (Sanacora, 2013). Yet, it is not necessary for a mild TBI to occur in order to develop CTE. The number of subconcussive injuries can also damage vasculature and neurons. For example, military members in speedboats experience enough jostling to cause shear force on neuronal axons and elevate blood levels of tau protein, indicating that enough axons are being damaged that the microtubules can enter systemic circulation (Phillips, 2024) This ischemia can lead to permanent brain damage and incite an immune response specifically in areas such as the hippocampus, prefrontal cortex, and amygdala, all of which we see as directly impacted by p-tau and astrogliosis decades after TBI. For example, mice models have proven that there are fewer hippocampal astrocytes five weeks post brain injury (Sanacora, 2013). Due to these specific areas increasing their metabolic demand, intracellular calcium, and increased gliotransmitter release in the first 24-48 hours after concussion or sub-concussive event, and then their high levels of astrogliosis and p-tau density decades later, it is clear that there is a direct correlation between the two (Simpson, 2023). Potentially, the initial response can lead to an ischemic state which induces responses utilizing the mechanisms which include hyperphosphorylation of tau proteins.

Another possible progression of mTBI to CTE could be through immune responses and disruption of the BBB (Simpson, 2023). The immune signaling pathways, including cytokines, are activated as soon as mTBI occurs. Neutrophil and natural killer cell concentrations are also increased in the blood (Simpson, 2023). Directly after an mTBI, the spleen releases activated M1 and M2 macrophages into systemic circulation and even circulates to the brain (Kornguth, 2017). Those who have vascular injuries due to shearing of gray and white matter have a significantly disrupted BBB (Kornguth, 2017). Potentially, immune factors which are not normally found in the brain, could wreak havoc. Activated macrophages crossing the BBB will lead to higher

amounts of interferon which increase expression of markers such as MHC/ HLA on neurons, contributing to neuron silencing and death (Kornguth, 2017). BBB permeability also allows for neuronal proteins to leak into systemic circulation (Kornguth, 2017). Tau proteins, which are released by broken neuronal axons, are able to leak into circulation and allow for white blood cells to form anti-tau antibodies (Kornguth, 2017). A large concentration of p-tau is necessary for the blood to show significant elevation (Halicki, 2023). Even though these are self-proteins, because they are circulating in unusual spots, they may not be recognized by systemic immune cells and a response against them is created (Kornguth, 2017). Now the blood serum with anti-tau antibodies can also leak through the BBB where NFTs are made of tau aggregations and the antibodies may recognize them, even within the tangles. The antibodies are able to increase local inflammatory response and have destructive properties towards neurons. This is a mechanism to form an autoimmune response (Kornguth, 2017). With repeated head injury (RHI), more NF antibody is produced and each subsequent inflammatory response and immune reaction will grow in magnitude. Higher levels of NFLs (neurofilaments) can be found in the blood up to five years after a single mTBI (Halicki, 2023). Furthermore, the microglia can recruit the peripheral immune system and cause chronic neuroinflammation (Halicki, 2023). This sustained inflammatory response can play a role in CTE pathogenesis and progression. In fact, reactive microglia can be found even 28 years after one mTBI (Halicki 2023). Reactive astrocytes have a neurotoxic quality and can expand effects to synaptic communication and blood flow control (Hsu, 2018). Chronic neuroinflammation also allows continuous increased BBB permeability which further allows peripheral cytokines, chemokines, and leukocytes access to neurons (Halicki, 2023). All of these factors amplify creation of reactive oxygen species (ROS) and can lead to neuronal cell death (Halicki, 2023). Further evidence of peripheral immune response in

the brain includes serum immunoglobulin G consolidation in perivascular brain matter (Tagge, 2017). The autoimmune theory can explain the atrophy and loss of neurons throughout brain regions which is consistent with CTE. Moreover, the cis conformation of p-tau was found in pre-fibrillary tangles within hours of TBI in mice models, though no oligomers or NFTs are seen until later (Katsumoto, 2019). If the damage caused by mTBI can quickly cause templated misfolding or post-translational modification of tau and therefore hyperphosphorylation of the misfolded protein, RHI could lead to vast amounts of this p-tau accumulation (Katsumoto, 2019). Activated microglia causing permeability of BBB to inflammatory signaling peripheral immune molecules combined with build up for p-tau could indicate how early processes after mTBI could lead to the neurodegenerative disease of CTE.

Advancements in CTE Research

Though CTE currently can only be diagnosed post-mortem, current research aims to challenge this and find specific biomarkers which could lead to an ante-mortem diagnosis and improve prognosis. Biomarkers found in the systemic blood can aid in the diagnosis of mTBI, specifically concussions (Halicki, 2023). Ideally, research into biomarkers will progress, allowing clinicians to diagnose specific neurodegenerative disorders and staging of the disease.

In systemic circulation, factors associated with immune response and markers of metabolism can be found (Halicki, 2023). Post-mTBI, blood tests within the first day of an injury will reveal upregulated interferon, cytokines, and neutrophils as well as a decrease in blood glucose and calcium (Kornguth, 2017). TBI and shear force also causes diffuse axonal injury (DAI) which can destroy axons and release their proteins into the cerebrospinal fluid (Katsumoto, 2019). Axonal proteins cross into systemic circulation where they can be collected and analyzed in blood draws (Halicki, 2023). Then, within a few days to a few weeks, those

factors will be lower due to the immunologic and metabolic depression starting a few days post-injury (Giza, 2001). Additionally, blood-based biomarkers are also being used to aid in the diagnosis of patients with other neurological disorders such as Parkingson's disease (PD) and Alzheimer's disease (AD) (Halicki, 2023). In diseases such as AD and PD, the blood biomarkers are found ante-mortem (Halicki, 2023). Additionally, exosomes are an important blood biomarker due to their ability to contain intracellular signaling molecules and cellular waste, demonstrating the state and activity of the neurons (Halicki, 2023).

In patients with CTE, the BBB has been compromised by RHI and even subconcussive events (Kornguth, 2017). This means that the barrier is more permeable for factors to enter the brain in the acute stage of TBI which lasts one to three days post-injury (Kornguth, 2017). Hyperphosphorylated tau, which aggregates into neurofibrillary tangles (NFTs) at the cortical sulcal depths, promotes neurotoxic mechanisms such as microtubule destabilization, loss of synapse, and decreased neuronal signaling (Alosco, 2020). If tau proteins or protein fragments reach systemic circulation, then these proteins are detectable in the plasma and patient blood samples (Halicki, 2023). Total phosphorylated tau protein concentration in the blood could reveal neuroinflammation and neurodegeneration (Halicki, 2023). After mTBI, patients have more neurofilament in their blood; neurofilament provides neuronal structure integrity (Halicki, 2023). Thus, increased blood neurofilament levels demonstrate potential pathology in the brain. Elevated neurofilament levels can be detected in the blood up to five years after mTBI (Halicki, 2023). In retired athletes with confirmed CTE diagnosis, tau is phosphorylated at threonine-181 (Halicki, 2023). This specific phosphorylation also correlates with decreased corpus callosum volume (Halciki, 2023). Tau has a short half-life in blood so if it is found in high amounts,

especially post-mortem, then it is likely that there is abundant damage to the neurons (Halicki, 2023).

The main drawback of using blood biomarkers is the lack of specificity (Halicki, 2023). For example, exosomal contents may look similar between patients with AD, CTE, frontotemporal dementia, and other types of dementia, not leading to a clear diagnosis (Halicki, 2023). There are thirty locations on tau proteins which can be phosphorylated, though only a few are commonly found in people diagnosed with CTE (Katsumoto, 2019). Essentially, the test may yield the result that there is a tauopathy but not be able to demonstrate which sites of tau are phosphorylated. As CTE, AD, and other forms of dementia have their own unique sites which are usually phosphorylated, this is useful information when it comes to diagnosis. Additionally, there are six isoforms of phosphorylated tau isoforms (Katsumoto, 2019). The blood-based tests for CTE lack specificity, complicating differential diagnosis between CTE and AD which also has misfolded tau proteins (Halicki, 2023). Another problem with this is that there must be an abundant amount of exosome, phosphorylated tau, and neurofilaments to find significant concentrations of it in the blood (Halicki, 2023). That means that the patient must be suffering from a high level of neuroinflammation, neuronal death, and steep increase in permeability of the BBB caused by astrocyte dysfunction before its evidence is at clinical levels in blood (Halicki, 2023). To be a viable avenue for ante-mortem CTE diagnostic testing, the specificity of the test would need to be improved. This also has monetary and clinical implications. Advantages of this type of test are that it can occur before death of a person suspected to have CTE and it is a relatively non-invasive procedure (Halicki, 2023). There are many promising studies to understand the mechanism and progression of CTE as well as research about how to diagnose CTE ante-mortem. These studies will directly impact patients and their families and lead to

potential future studies involving pharmaceutical therapies and treatment options to improve prognosis.

Conclusion

Chronic Traumatic Encephalopathy, originally called punch-drunk syndrome, has been documented since the 1920s (Concussion Legacy Foundation). Despite knowing its existence for a century, research still has a long way to go as far as understanding the causes and pathophysiology of CTE. However, there is notable progress in the area of neurodegenerative disease.

With the increase in worldwide participation in sports and idolization of professional athletes, CTE prevention and education is critical (NATA, 2015). Potentially, mild TBI and RHI can lead to the development of CTE. Though, the number of subconcussive impacts may also be a driving factor of CTE development. These injuries are most likely to be acquired in football, soccer, rugby, and hockey (Emami, 2023). Culture and competitiveness around these sports drives adolescent athletes to continue playing, even through devastating injuries such as concussions (NATA, 2015). Younger athletes are at an increased risk due to the disproportionate weight of their head compared to the rest of their body (CDC, 2019). Female athletes are also at an increased risk due to their longer and thinner neck muscles (CDC, 2019). The highest risk athletes are black male football players at the collegiate level due to their high participation in mTBI-inducing situations (Emami, 2023). Elevated CTE risk has been correlated to more years playing contact sports, both at the amateur and professional levels, as well as the number of RHIs received (Emami, 2023). However, subconcussive impacts and movements may also be implicated in CTE development, meaning not only do the mTBIs cause damage, but the everyday drills and movements may also be causing as much damage (Phillips, 2024). Before

death, CTE presents with dementia-like symptoms, including motor issues and memory consolidation disruptions (Van Amerongen, 2023). An additional symptom in younger patients tends to be emotional disturbances which include apathy, depression, and explosive anger, though patients with other types of dementia may also exhibit these symptoms (Tagge, 2017). Efforts to prevent mTBI may be essential for reducing CTE prevalence and protecting future generations.

Mild TBI can disrupt regular brain function and cause symptoms such as headaches, memory problems, and impaired coordination (CDC, 2011). Asymptomatic concussions and subconcussive events exist and may pose a bigger threat. The “water hammer injury” effect can cause shearing of axons as well as cerebrovascular injury and subsequently disrupt BBB (Kornguth, 2017). Immediately after TBI, bodily homeostatic responses cause cerebral swelling, hypermetabolic state, increased intracellular calcium, and disruption of blood flow (Giza, 2011). This hyperactive state turns to a depressed state for weeks to months post-injury (Giza, 2001). The immune system also releases cytokines and interferon which lead to neuroinflammation (Kornguth, 2017). This constant activation and transfer of the peripheral immune system to the brain in RHI, may lead to CTE-inducing mechanisms (Halicki, 2023).

CTE is distinct from other neurodegenerative diseases, though ante-mortem presentations include many of the same symptoms of Alzheimer’s Disease and other forms of dementia (Van Amerongen, 2023). Emotional symptoms unique to CTE also increase the probability that patients will die of accidental drug overdose or suicide (Emami, 2023). There is a progression of CTE through multiple stages which are defined by the McKee Staging Scheme (Alosco, 2020). The higher the level of p-tau density, astrogliosis, and cerebral atrophy, the more severe the stage of CTE (Alosco, 2020). The hyperphosphorylation of tau leads to microtubule destabilization

and formation of toxic neurofibrillary tangles (Halicki, 2023). The NFT aggregates spread throughout specific brain regions such as the amygdala and hypothalamus, causing neuronal dysfunction and death in those regions (Alosco, 2020). Therefore, progressive neurodegeneration occurs.

The mechanisms to regain homeostasis after mTBI, both the hypermetabolic state and the depressed state, may contribute to the pathophysiological progression of CTE (Giza, 2011). The hypermetabolic state leads to starvation of neurons and glial cells, ending in neuron ischemia (Giza, 2001). The calcium influx may also disrupt mitochondrial function, creating more ROS and producing less ATP (Simpson, 2023). Astrocytes may also decrease their activity, leading to less neuronal activation, and therefore the neuroplastic effect of pruning (Hsu, 2018). The disruption of the BBB allows more peripheral immune cells such as interferon and cytokines into the brain, inducing more inflammation (Simpson, 2023). RHI creates chronic inflammation in the brain and therefore sustained permeability of the BBB, allowing both systemic proteins and toxins into the brain (Simpson, 2023). Furthermore, tau proteins from axonal projections may enter systemic circulation and cause production of anti-tau antibodies (Simpson, 2023). These circulate into the brain and begin attacking self-proteins in an autoimmune response (Simpson, 2023). Over time, both the inflammatory and adaptive processes of the immune system exacerbate the progression of CTE. These processes remain only theories of the pathophysiology of CTE.

Research into ante-mortem diagnosis of CTE indicates that blood-based biomarkers may prove promising for future development (Halciki, 2023). Tau proteins can be found in exosomes in the blood (Halicki, 2023). Though these have a short half-life, their presence in the blood demonstrates considerable neural degeneration (Halicki, 2023). A drawback of this approach is

that there is a lack of specificity in the test for these proteins (Halciki, 2023). Presence of tau proteins in blood biomarkers would indicate a diagnosis of AD or CTE, but cannot definitively provide a diagnosis between these diseases (Halicki, 2023). Ongoing research into CTE ante-mortem diagnosis may improve the prognosis for patients. Additionally, ante-mortem diagnosis would support educational efforts for patients that experience RHI and their families.

CTE remains a challenging disease to diagnose and treat. Further research is needed to truly understand the pathophysiology and progression of the disease. With so many young children and adolescents around the world playing competitive amateur sports, education and prevention should be a primary focus (Van Amerongen, 2023). Professional athletes play a crucial role in current culture and are idolized by fans. Therefore, it is important to educate viewers on the extreme risk and potential health consequences of playing contact sports (NATA, 2015). Additionally, professional leagues such as the NFL, NHL, and MLS should take responsibility for keeping their players safe with the proper equipment and game rules. Professional and amateur sport organizations need to heed the research findings and change rules and equipment to accommodate player safety and safeguard the futures of their athletes.

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