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The role of head trauma and concussions in producing chronic traumatic encephalopathy: analysis of risk factors, diagnosis, treatment, and prevention

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**THE ROLE OF HEAD TRAUMA AND CONCUSSIONS IN PRODUCING
CHRONIC TRAUMATIC ENCEPHALOPATHY: ANALYSIS OF RISK
FACTORS, DIAGNOSIS, TREATMENT, AND PREVENTION**

by

ANTHONY RICHARD DECLUSIN

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Approved by

First Reader

Karen Symes, Ph.D.
Associate Professor of Biochemistry
Assistant Dean of Student Affairs

Second Reader

Gwynneth D. Offner, Ph.D.
Director M.A. in Medical Sciences Program
Associate Professor of Medicine

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ANTHONY RICHARD DECLUSIN

Boston University School of Medicine, 2013

Major Professor: Karen Symes, Ph.D., Associate Professor of Biochemistry, Assistant
Dean of Student Affairs

ABSTRACT

Traumatic brain injuries (TBIs) have become a focal point for discussion in the media today. They are an unfortunate part of many recreational activities and military participation. The long-term effects of concussions and other types of mild traumatic brain injury (mTBI) are becoming increasingly evident. It appears that they can contribute to the development of certain neurodegenerative diseases later in life, and of particular interest is chronic traumatic encephalopathy (CTE). CTE is a progressive tauopathy characterized by a variety of cognitive and behavioral changes, which is correlated with a history of repetitive brain trauma. This thesis provides a review of the pertinent literature in attempt to link the development of CTE to the neurophysiological changes associated with concussions and mTBI by providing an in-depth analysis of both concussions and CTE. However, even with the current evidence, prospective studies will be necessary to gain a better understanding of the disorder.

TABLE OF CONTENTS

Title	i
Reader's Approval Page	ii
Acknowledgements	iii
Abstract	iv
Table of Contents	v
List of Tables	ix
List of Figures	x
List of Abbreviations	xi
1. Introduction	1
2. Concussion	2
2.1 Biomechanics	5
2.2 Pathophysiology	7
2.2.1 Diffuse Axonal Injury	10
2.2.2 Excitotoxicity	14
2.2.3 Microglial Activation and the Neuroinflammatory Response	15
2.2.4 Cerebrovascular Dysfunction	15
2.3 Acute Clinical Signs/Symptoms	16
2.4 Post-Concussion Syndrome	18
2.5 Testing	21
2.6 Treatment	22

3. Chronic Traumatic Encephalopathy	22
3.1 History	23
3.2 Clinical Presentation and Course	24
3.2.1 Neuropsychological/Neuropsychiatric Changes	25
3.2.2 Neurological/Motor Changes	26
3.2.3 Disease Progression	27
3.2.3.1 Stage I	27
3.2.3.2 Stage II	27
3.2.3.3 Stage III	28
3.2.3.4 Stage IV	28
3.3 Gross Pathology	28
3.3.1 Stage I	30
3.3.2 Stage II	30
3.3.3 Stage III	30
3.3.4 Stage IV	30
3.3.5 Chronic Traumatic Encephalomyelopathy	31
3.4 Microscopic Pathology	31
3.4.1 Tau	31
3.4.1.1 Stage I	35
3.4.1.2 Stage II	35
3.4.1.3 Stage III	36
3.4.1.4 Stage IV	36

3.4.2 Transactive Response DNA-Binding Protein	43	37
3.4.2.1 Stage I		38
3.4.2.2 Stage II		38
3.4.2.3 Stage III		39
3.4.2.4 Stage IV		39
3.4.3 α -amyloid		39
3.5 Risk Factors		40
3.5.1 Sport		41
3.5.1.1 Football		42
3.5.1.2 Boxing		42
3.5.2 Military Service		43
3.5.3 Age		43
3.5.4 Sex		44
3.5.5 Genes		44
3.5.6 Cognitive Reserve		45
3.6 Testing		46
3.6.1 Biomarkers		46
3.6.2 Magnetic Resonance Imaging		46
3.6.3 Susceptibility-Weighted Imaging		47
3.6.4 Diffusion Tensor Imaging		48
3.6.5 Magnetic Resonance Spectroscopy		49
3.6.6 Positron Emission Tomography		50

3.6.7 Single-Photon Emission Computed Tomography	51
3.7 Treatment/Prevention	52
4. Discussion	53
5. Conclusion	54
References	55
Vita	78

LIST OF TABLES

Table	Title	Page
1	TBI Stratification	2

LIST OF FIGURES

Figure	Title	Page
1	Epidemiology of mTBI	3
2	Biomechanics of Concussion	6
3	Post-Concussive Neurometabolic Cascade	8
4	Neuromembrane Events in TBI	9
5	Cytoskeletal Disruption at Nodes of Ranvier	11
6	Mitochondrial and Ca ²⁺ -ATPase Dysfunction	13
7	Prevalence of Acute Concussion Symptoms	17
8	ICD-10 Classification of PCS	19
9	DSM-IV-TR Classification of PCS	19
10	Prevalence of Post-Concussion Symptoms	20
11	Gross Pathology of CTE	29
12	CTE Tau Pathology	34
13	Tau Pathology Progression	37
14	Microhemorrhagic Imaging	48
15	DTI in Athlete with CTE-Like Symptoms	49
16	PET of Athletes with CTE-Like Symptoms	51

ABBREVIATIONS

AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
AMPA	-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
AOC	alteration of consciousness
APOE	apolipoprotein E
APP	amyloid precursor protein
ATP	adenosine triphosphate
A	-amyloid
BBB	blood-brain barrier
CBF	cerebral blood flow
CBV	cerebral blood volume
CDC	Centers for Disease Control and Prevention
CMR _{gluc}	oxidative glucose metabolism
CNS	central nervous system
CPP	cerebral pulse pressure
CSF	cerebrospinal fluid
CT	computed tomography
CTE	chronic traumatic encephalopathy
CTEM	chronic traumatic encephalomyelopathy
DAI	diffuse axonal injury

DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4 th Edition, Text Revised
DTI	diffusion tensor imaging
GCS	Glasgow coma scale
GLU	glutamate
GT	glial tangle
ICD-10	International Classification of Diseases, 10 th Revision
ICP	intracranial pressure
LOC	loss of consciousness
LPP	lipid peroxidation product
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
mTBI	mild traumatic brain injury
MVA	motor vehicle accident
NFL	National Football League
NFT	neurofibrillary tangle
NMDA	<i>N</i> -methyl- <i>D</i> -aspartate
NO	nitric oxide
PCS	post-concussion syndrome
PET	positron emission tomography
PTA	post-traumatic amnesia
RNS	reactive nitrogen species

ROS	reactive oxygen species
SPECT	single-photon emission computed tomography
SWI	susceptibility-weighted imaging
TBI	traumatic brain injury
TDP-43	transactive response deoxyribonucleic acid-binding protein 43

1. Introduction

Recently, traumatic brain injury (TBI) has garnered a lot of attention in the media with reports of professional athletes experiencing detrimental outcomes as a result of repeated head injuries by their participation in contact sports [1, 2]. Of particular interest are concussions, a type of mild traumatic brain injury (mTBI), and their long-term impact in developing the neurodegenerative disorder, chronic traumatic encephalopathy (CTE) [3]. CTE is a progressive tauopathy characterized by widespread neurodegeneration that has been linked to a considerable variety of cognitive deficits and behavioral changes. Thus far, it has only been diagnosed neuropathologically in those with a history of repetitive TBI post-mortem. Therefore, CTE is believed to be caused, in large part, by TBI that can occur as a result of contact sports, military participation, and other recreational activities [4, 5].

This thesis will provide a comprehensive review and analysis of the recent literature regarding CTE and will attempt to attribute the pathological changes associated with mTBI towards the development of the disorder. In order to do so, the relevant background information regarding concussions and mTBI will be reviewed. This discussion will include the biomechanics and pathophysiology of injury, the clinical signs and symptoms of concussion, and the currently available testing and treatment guidelines. It will then detail CTE, including the clinical/neuropathological presentations, the disease course, risk factors, potential clinical diagnostic evaluations, and treatment/preventive measures.

2. Concussion

The word, concussion, is derived from the Latin “concutere,” which means “to dash together” or “to shake violently” [6]. Concussion is a complex pathophysiological process that occurs as a result of a direct or indirect external forces transmitted to the head, which can lead to a collision between the brain and surrounding structures or put excessive strain on brain tissue or cerebrovasculature. These events may or may not result in loss of consciousness (LOC) [7, 8]. The pattern and extent of the resulting damage is determined by the duration, intensity, and direction of these forces [9]. Concussions result in short-term neurologic impairment that presents with a variety of clinical symptoms, which typically resolve spontaneously [8].

As stated previously, concussions are a type of mTBI. TBIs are divided into categories of mild, moderate, and severe and are clinically diagnosed based upon the criteria presented in Table 1 below [10].

Table 1. TBI Stratification.

Current clinical diagnostic criteria to determine TBI severity in patient post-injury. Patient is assigned severity if he/she meets one or more of the below criteria within a category. LOC – Loss of consciousness; AOC – Alteration of consciousness/mental state; PTA – Post-traumatic amnesia; GCS – Glasgow Coma Scale. (Table taken from [10]).

Mild	Moderate	Severe
Normal structural imaging	Normal or abnormal structural imaging	Normal or abnormal structural imaging
LOC = 0-30 min	LOC >30 min and < 24 hours	LOC > 24 hrs
AOC = a moment up to 24 hrs	AOC >24 hours. Severity based on other criteria	
PTA = 0-1 day	PTA >1 and <7 days	PTA > 7 days
GCS=13-15	GCS=9-12	GCS=3-8

The terms “concussion” and “mTBI” are often, mistakenly, used interchangeably by the scientific community [8]. All concussions are mTBIs, but not all mTBIs are concussions. Concussions fall on the less-severe end of the spectrum of mTBIs, and thus, represent only a subset of the category [11].

An estimated 1.4-3.8 million TBIs occur in the United States annually, with mTBIs accounting for approximately 70-90% of all cases [12–14]. These incidences include approximately 1.1 million visits to the emergency department, 235,000 hospitalizations, and result in approximately 50,000 deaths every year. However, the actual number of mTBIs is most likely higher because many go unreported or are never diagnosed [13]. The leading causes of mTBIs are motor vehicle accidents (MVA), sporting activities, and falls among adults. Falls, sporting activities, and pedestrian injuries represent the largest proportion among children (Figure 1) [15].

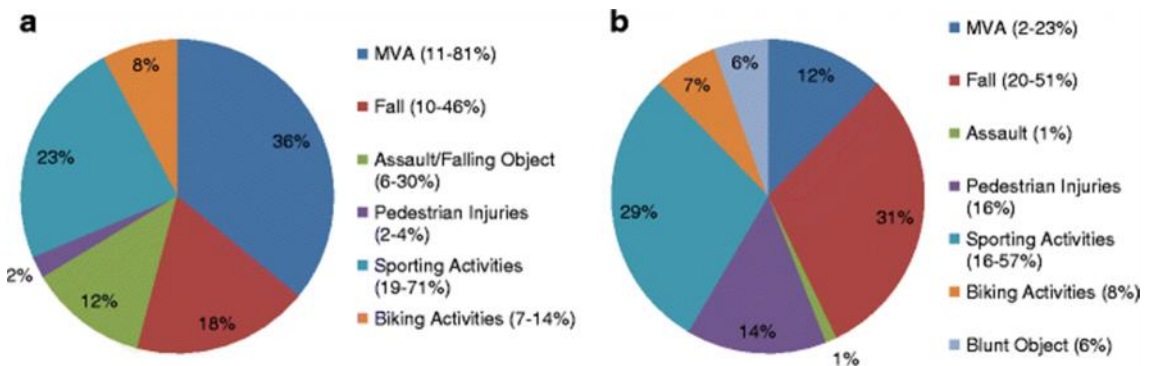


Figure 1. Epidemiology of mTBI.

The average prevalence of particular mechanisms of injury taken from multiple studies in (a) adults and (b) children. Values are modified to sum to 100%, and ranges for specific mechanisms are located in the legend. (Figure taken from [15]).

The Centers for Disease Control and Prevention (CDC) estimate that 300,000 sports-related concussions occur every year, and their rates are continually on the rise [16, 17]. This rise could be due to an increase in actual occurrence or improved concussion education and incidence reporting. Repetitive closed head injuries, which can result in concussion, occur in a considerable variety of contact sports, including football, rugby, wrestling, soccer, boxing, lacrosse, hockey, and skiing [4]. With a great proportion of America's youth participating in these sports on a regular basis, there is significant concern regarding the effects of concussion.

Several researchers have suggested that there may be a critical window of 7-10 days post-injury in which there is an increased likelihood of repeat concussion, which may have a major impact on return-to-play guidelines following sport-related concussion. Two studies examining concussion incidence in collegiate football players found that well over 75% of repeat concussions occurred within 10 days of the first injury [18, 19]. In attempts to better understand the effects of these TBIs, animal models have been used to simulate concussions in humans. Rodents subjected to a second mTBI within 24 hours of the initial injury displayed impaired memory performance, decreased astrocytic activity, and axonal injury compared to those animals with only a single injury [20]. In another model, the time of second mTBI was delayed to 3, 5, or 7 days post-injury. Those animals subjected to a second injury on the third or fifth days exhibited significantly impaired cognitive function, while animals reinjured a week later showed no significant cognitive deficits; thereby, supporting the idea of critical period of increased post-concussive vulnerability [21].

However, while many repeat concussions tend to occur within this critical window, this increased susceptibility may extend well beyond the first week. During one season of Canadian professional football, players who sustained a single concussion were over 5 times more likely to be diagnosed with a second that same season compared to players with no history of concussion [22]. Collegiate football players with a reported history of, at least, 3 concussions were, also, 3 times more likely to sustain an additional concussion during their career compared to their counterparts with no concussion history [18]. This could be due to genetic predisposition, or there may be long-term neuropathological consequences of even a single concussion.

There is, also, data that shows that athletes who suffer multiple concussions require longer recovery times. A study looking at high school athletes found there to be statistically significant enduring neuropsychological effects in subjects with a history of two or more concussions [23]. Another study found that athletes with a multiple concussion history performed significantly lower on memory tests 2 days following injury than those who had sustained only their first concussion [24]. Balance deficits have, also, been shown to require longer recovery times in athletes experiencing their second concussion [25]. Therefore, it appears that there are more long-term effects from sustaining even a single concussion.

2.1 Biomechanics

A concussion results from traumatic forces imparted on the brain induced by rapid acceleration or deceleration. The major mechanisms of brain injury are positive pressure,

negative pressure, and/or shear strain [26]. Positive pressure is developed at the site of impact, or the coup site, while negative pressure is created at the countrecoup site (Figure 2).

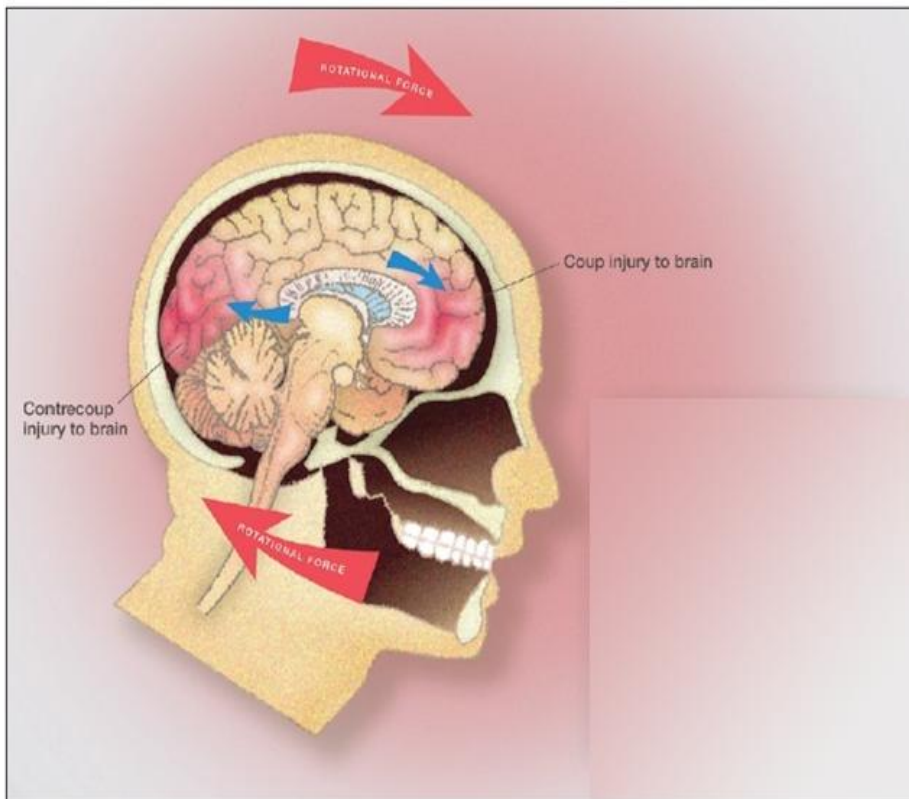


Figure 2. Biomechanics of Concussion.

A force is exerted on the brain that causes it to move within skull and impact surrounding structures. The figure illustrates both the coup site and countrecoup site. (Figure modified from [27]).

Deformation of the skull further accentuates these pressures at both sites. Positive pressure forces the skull to bend outward, while negative pressure pulls the skull inward. Positive pressure can result in brain contusion, whereas negative pressure may injure the brain by tensile loading or cavitation. Cavitation is the compressive loading that occurs

due to the collapse of vapor bubbles that are initially formed under negative pressure [28]. Lastly, shear strain elongates or stretches axons and blood vessels, which can result in diffuse axonal injury (DAI), affecting the white matter tracts of the brain [28, 29]. However, axons are not physically sheared at time of injury except during severe occurrences [4].

Rotational forces are believed to be of primary importance in producing concussion [30–32]. Brain motion is more pronounced with a large rotational acceleration vector, and it produces 90% of total strain [28, 33]. However, one National Football League (NFL) study found linear acceleration to be more highly correlated with concussive injury [34]. Thus, more research is necessary to elucidate exactly the types of forces important in concussive injury.

Several studies have attempted to quantify the necessary concussive threshold levels for linear and rotational acceleration by using kinematics data from football players [34–36]. However, their results are conflicting. There were, also, some athletes who received hits that exceeded their defined thresholds, yet did not sustain concussions. Hence, the level of force exerted on the brain appears to be only one associated risk factor for concussion.

2.2 Pathophysiology

It is the widely held belief of many neuropsychological and clinical researchers in the field that concussions produce transient neurophysiological dysfunction, but do not result in chronic neuropathologies [8, 37]. This idea is based largely on clinical

evaluations of the restoration of cognitive functioning in individuals. It is further complicated by the fact that the prevailing industry standards for brain imaging, computed tomography (CT) and magnetic resonance imaging (MRI) scans, are frequently normal due to the lack of macrostructural abnormalities [38, 39]. Yet, there is increasing evidence that neurons are potentially irreversibly harmed by concussion.

In recent years, studies have indicated that there exists an intricate complex of neurometabolic cascades, neurophysiological impairment, and cerebrovascular dysfunction as a result of biomechanical forces responsible for concussion [7, 40, 41]. Many of these changes can be identified within minutes of injury and last for hours to days, resulting in cell death and/or secondary axotomy in less than 24 hours (Figure 3) [40, 42].

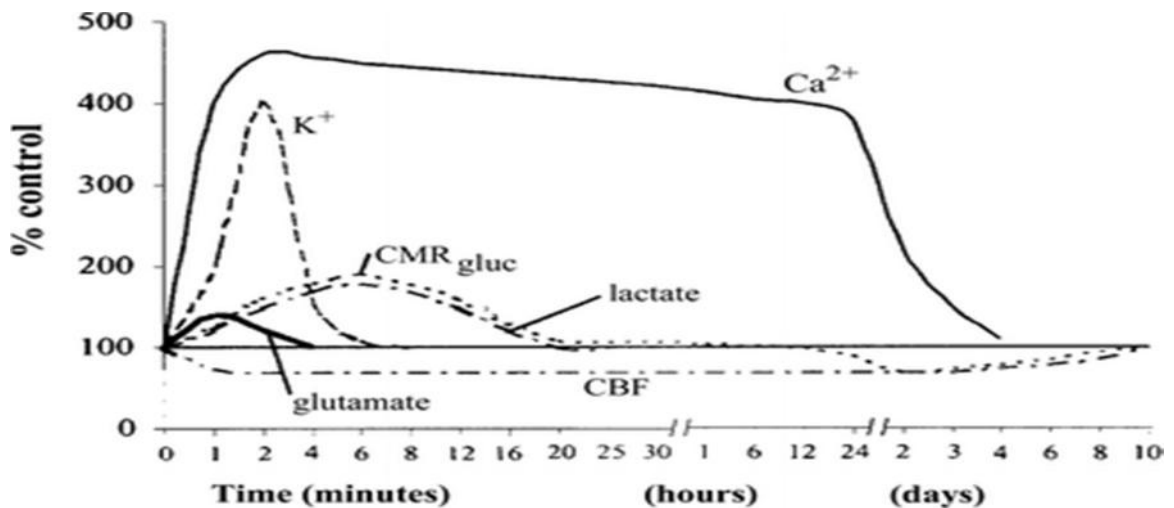


Figure 3. Post-Concussive Neurometabolic Cascade.

Metabolic cascade following experimental concussion. The large increase in Ca²⁺ release along with the long-term changes observed in oxidative glucose metabolism (CMR_{gluc}) and cerebral blood flow (CBF) may be partly responsible for the critical period of increased vulnerability following concussion. (Figure taken from [40]).

TBI-associated neurodegeneration can either be due to direct, physical damage or secondary injuries, involving diffuse, delayed mechanisms, such as, ion dysregulation, excitotoxicity, the neuroinflammatory response, apoptotic/necrotic cascades, and ischemic injury [27, 43, 44]. Many of these mechanisms are highlighted in Figure 4 below.

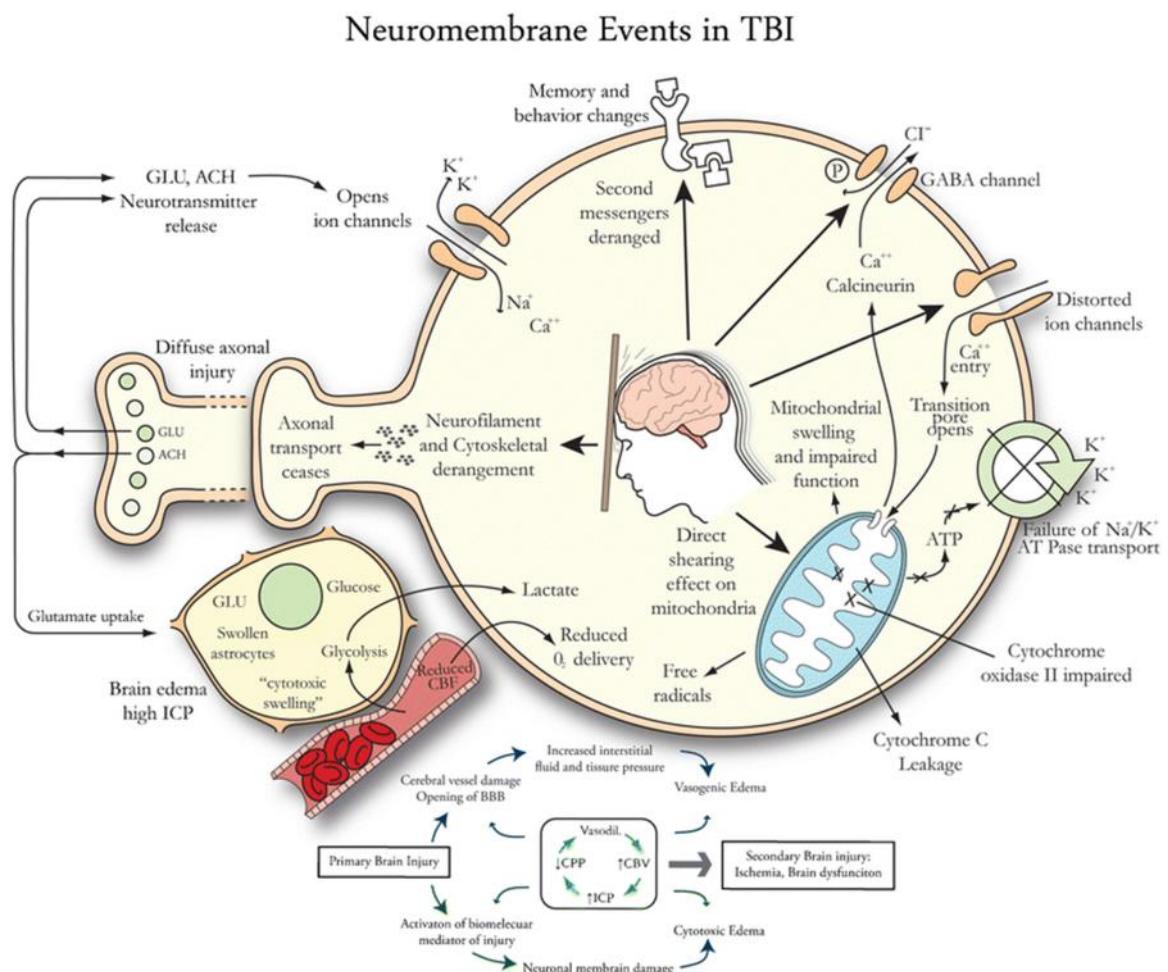


Figure 4. Neuromembrane Events in TBI.

TBI sets into motion a cascade of events that result in ion dysregulation, mitochondrial damage, and ultimately, cell death. BBB – Blood-brain barrier; CBF – Cerebral blood flow; CBV –

Cerebral blood volume; CPP – Cerebral pulse pressure; ICP – Intracranial pressure. (Figure taken from [45]).

The following subsections will detail each potential neurodegenerative mechanism of concussion. Any or all of the following may be occurring to varying degrees depending on the severity of the injury.

2.2.1 Diffuse Axonal Injury

DAI is one of the most frequently documented pathological findings of TBI [27]. The shear strains created by the traumatic biomechanical forces of concussion can stretch axons, resulting in axolemmal compromise of the cortical and subcortical white matter [28, 29]. Axons are commonly damaged when they are required to change direction due to the presence of blood vessels, to enter target nuclei, or when decussation occurs [46–50]. Thicker neurons are typically more affected, and axonal injury is often identified where changes in tissue density occur [47, 49–52].

Axons can either be injured by direct shearing or by secondary axotomy, which occurs over hours or days [53]. Axons are rarely injured as a result of primary injury in cases of concussion [4]. Hence, the majority of DAI occurs by way of a pathophysiologic process that results in the dismantling of microtubules and axonal cytoskeleton [47, 50, 54–58].

Elongation of the axon during concussive injury increases axolemmal permeability by causing certain sodium channels at the nodes of Ranvier to become leaky, resulting in a large influx of sodium and calcium ions and cell membrane

hyperpolarization [59]. This uncontrolled influx of calcium produces microtubule disruption, calpain and caspase release, mitochondrial swelling, and impairment of axonal transport that leads to axonal swelling and ultimately, secondary axotomy [40, 42, 60–62]. Rapid axonal swelling, Wallerian degeneration, and perisomatic axotomy may also occur without alterations in axolemmal permeability [4].

Elevated axoplasmic levels of free calcium result in spontaneous depolymerization of microtubules and trigger activation of calcium-sensitive neutral proteases, or calpains. Calpains initiate neurofilament proteolysis and disrupt the subaxolemmal cytoskeleton. This process causes the axolemma to become detached from the axonal cytoskeleton and produces nodal blebs (Figure 5) [63, 64].

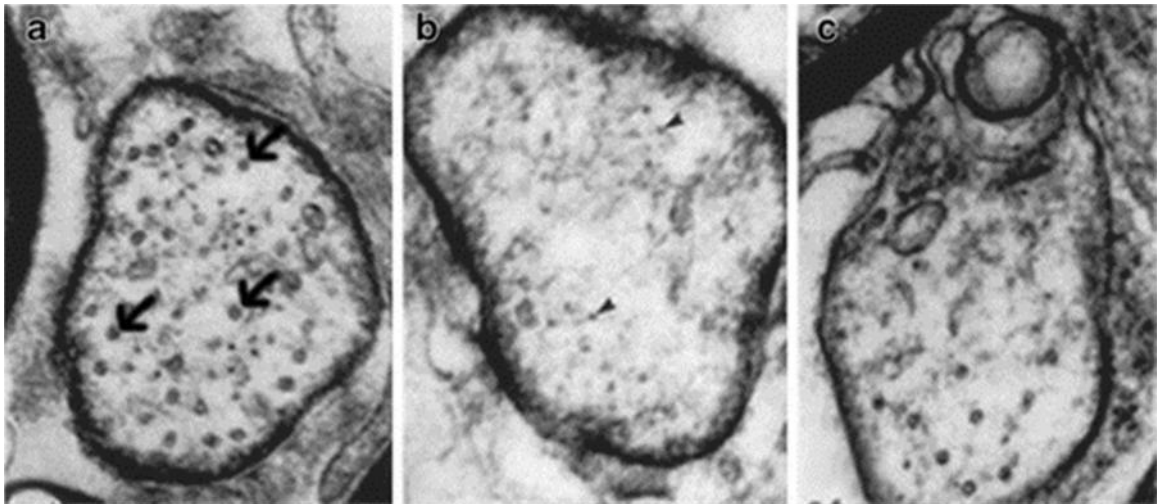


Figure 5. Cytoskeletal Disruption at Nodes of Ranvier.

Electron micrographs displaying transverse thin sections of nodes of Ranvier following stretch injury in experimental animals. Control animal (a) shows abundant microtubules (arrows) and neurofilaments at node. Section b shows no microtubules and very few neurofilaments (arrowheads) in injured animal 15 minutes post-injury. After 1 hour (c) in injured animal, subaxolemmal density is decreased and nodal bleb is evident. Original magnification $\times 54,000$. (Figure taken from [45]).

Increased axoplasmic calcium, also, results in mitochondrial damage. In an attempt to maintain axonal homeostasis, mitochondria sequester excess calcium, which ultimately, reaches toxic levels. This process results in mitochondrial swelling and interferes with oxidative phosphorylation [65]. Decreased adenosine triphosphate (ATP) production leads to failure of the membrane-associated calcium-ATPase pumps and further increases in axoplasmic calcium; thus, exacerbating the issue (Figure 6) [45]. Disruption of calcium homeostasis has been noted for up to a month following TBI in experimental animals [66].

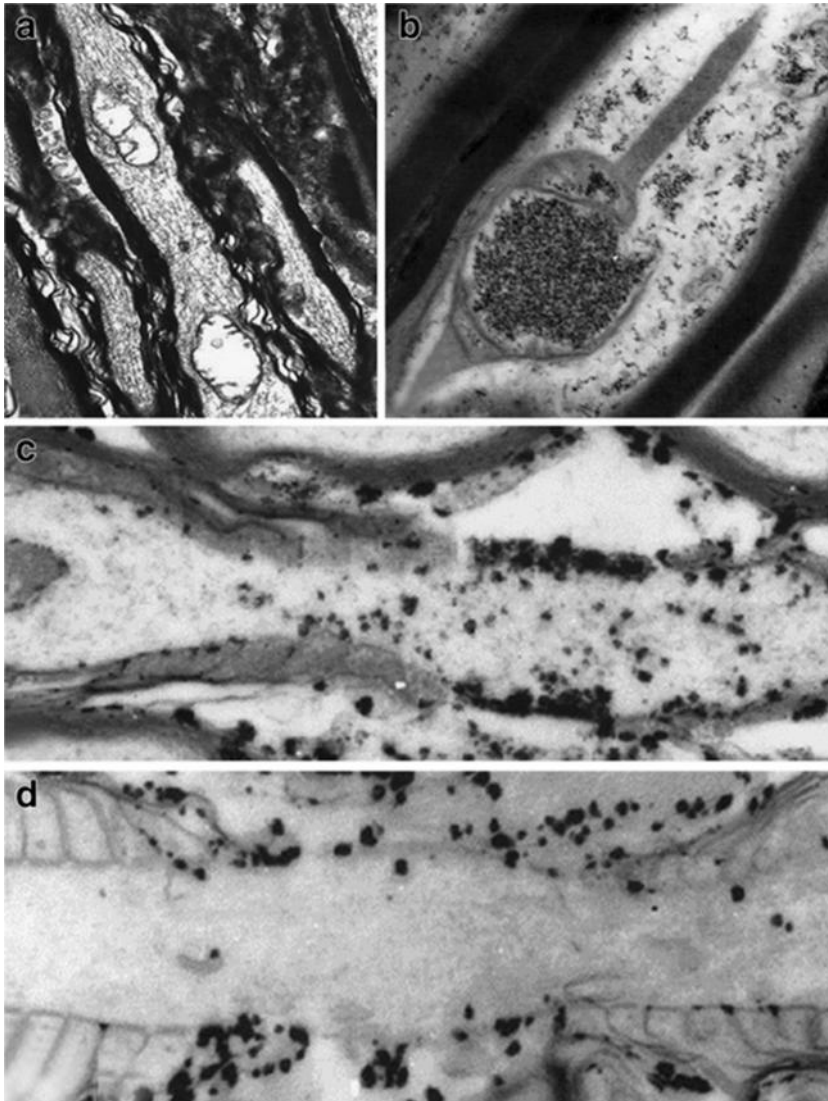


Figure 6. Mitochondrial and Ca²⁺-ATPase Dysfunction.

Electron micrographs displaying longitudinal thin internodal (a-b) and nodal (c-d) sections 2 hours after stretch injury in experimental animals. Section a shows translucent mitochondria with little trace of inner mitochondrial membranes. A lone mitochondrion (b) appears swollen and is densely stained for calcium using pyroantimonate technique. An uninjured control animal (c) exhibits dense staining for Ca²⁺-ATPase activity at node, whereas, there is little activity in an injured animal 2 hours after injury (d). Original magnification: a = ×10,230; b = 15,421; c = 12,780; d = 13, 270. (Figure taken from [45]).

Immunocytochemical evidence of axonal injury is identified within the first 2 hours of injury [67]. In humans, cytoskeletal disintegration is witnessed between 4-6

hours post-injury. Eventually, these pathophysiologic changes produce secondary axotomy. Secondary axotomy typically begins 12 hours following injury and peaks 1-3 days later, with the resulting damage potentially lasting for years [30, 68, 69].

2.2.2 Excitotoxicity

Excitotoxicity is the process by which neurons are damaged and killed from excessive release of excitatory neurotransmitters, particularly glutamate (GLU). GLU is the most common neurotransmitter found in the brain and is largely liberated from astrocytes and microglia [27]. There is supportive evidence for a mass acute accumulation of GLU and other excitatory neurotransmitters within the central nervous system (CNS) following TBI [70–72]. GLU acts on neurons by stimulating ionotropic receptors, such as, *N*-methyl-D-aspartate (NMDA), α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA), and kainate receptors, which regulate sodium and calcium channels [27]. Increased stimulation of these receptors can lead to a host of reactions within the cell.

Excitotoxicity has been found to coincide with calcium dysregulation, mitochondrial impairment, microtubule dysfunction, membrane compromise, dendritic retraction, synaptic loss, and apoptosis. Excessive GLU release can generate large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS), lipid peroxidation products (LPPs), prostaglandins, and nitric oxide (NO); all of which, can be harmful to the cell at high levels [27]. NO is particularly detrimental to cellular health by

competing with oxygen for cytochrome oxidase within mitochondria, and thereby, disrupting oxidative phosphorylation [73, 74].

2.2.3 Microglial Activation and the Neuroinflammatory Response

Microglia are known to be primed and/or activated due to disturbances in brain homeostasis, including TBI [75–77]. Microglia are the resident macrophages of the CNS, and thus, serve as an integral component of the innate immune system. They migrate into the CNS and assume a “resting” morphological phenotype [78]. When microglia first detect signs of nervous system dysfunction, they can adopt a primed state, in which they do not discharge any reactive molecules. However, once primed, any subsequent stimulation activates microglia to release large amounts of cytokines, chemokines, interferons, LPPs, ROS/RNS, prostaglandins, and excitotoxins [76, 79–81]. Cytokines, chemokines, and interferons recruit more immune-mediated cells to the site and result in further inflammation. These activated microglia are hyper-reactive as a result of priming, which causes them to release much higher levels of these molecules than normal [80].

Recent studies have found that microglial priming may exist for extended periods, from months to even years [77, 82, 83]. With each incidence of TBI, there is increased likelihood that this microglial priming and/or activation will be prolonged, resulting in further neuroinflammation [27]. This can produce a continued, low grade loss of neurons over the years.

2.2.4 Cerebrovascular Dysfunction

Cerebral blood flow (CBF) is known to decrease following TBI due to impairment of cerebral autoregulation [84]. However, the brain requires additional oxygen and glucose immediately following TBI due to the increased activity of ATP-dependent membrane pumps [39, 85]. This leads to a condition known as “concussion penumbra,” which is similar to ischemic penumbra following a cerebrovascular accident [86]. When metabolic demand can no longer be met, this process results in ischemic injury to the brain.

2.3 Acute Clinical Signs/Symptoms

Concussions present with a rapid onset of clinical signs and symptoms, which typically resolve spontaneously. However, no two concussions have similar presentations or identical outcomes [87]. Occasionally, the appearance of symptoms might be delayed until several hours after injury. Concussions may or may not involve LOC [8]. LOC only occurs in around 15% of all cases, and it is not a reliable predictor of total injury severity [13, 88, 89]. Concussions may, also, be accompanied by variety of motor phenomena, such as, convulsive movements [8].

Those who sustain a concussion can complain of a constellation of clinical symptoms. There are several somatic symptoms, including headaches, fatigue, dizziness, nausea, sleep abnormalities, noise/light sensitivity, and other visual problems. Common emotional symptoms comprise irritability, anxiety, and depression. Lastly, cognitive symptoms include attention deficits, memory dysfunction, and decreased processing speed (Figure 7) [90].

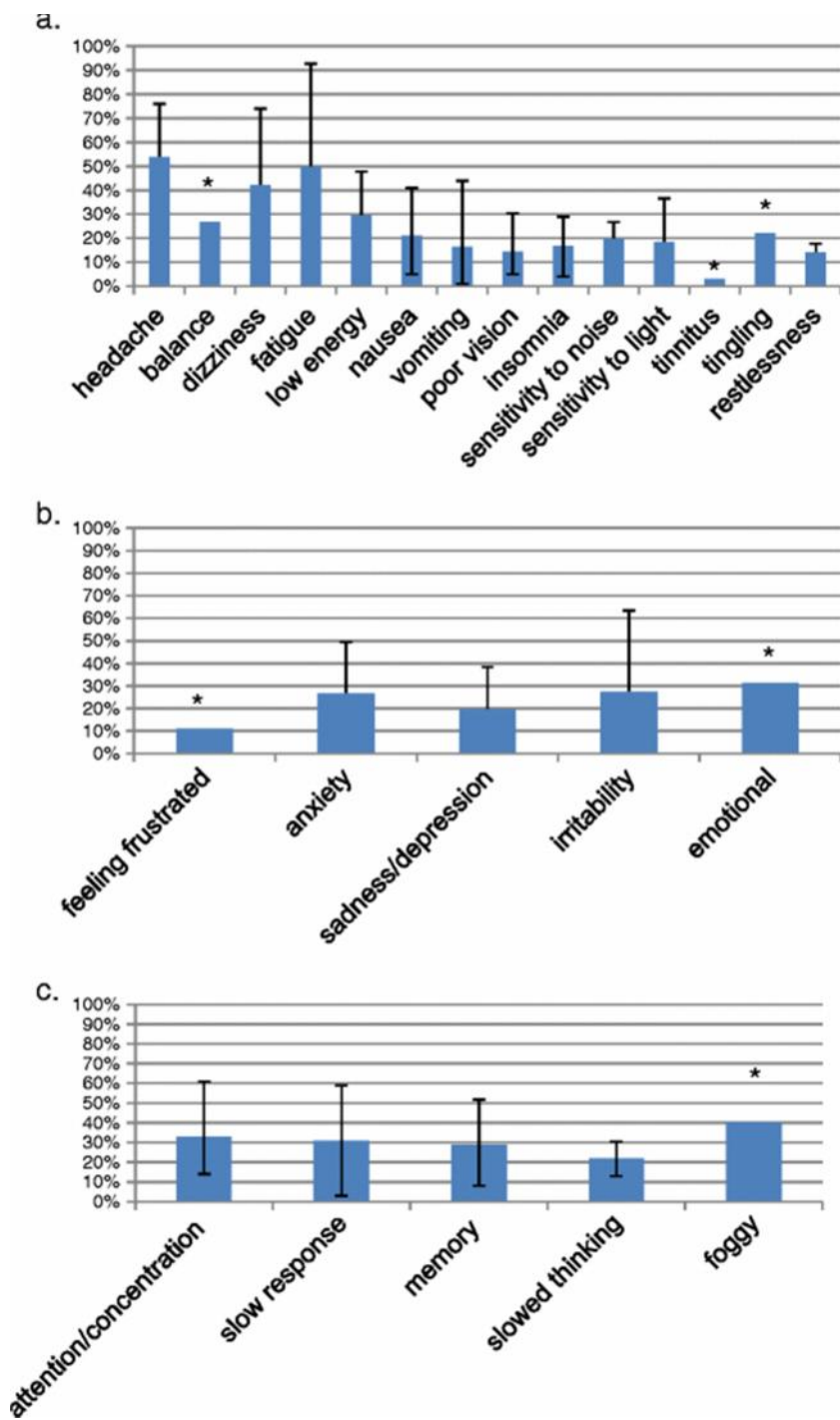


Figure 7. Prevalence of Acute Concussion Symptoms.

Prevalence (%) of acute somatic (**a**), emotional (**b**), and cognitive (**c**) symptoms based upon the findings of multiple studies. Error bars denote prevalence range across these studies. Stars indicate that the results were taken from a single study. (Figure taken from [15]).

Symptoms can resolve within a matter of days, weeks, or months [91]. Several studies have attempted to quantify the length of time it takes for individual symptoms to resolve, and they found that the majority typically improve within a week [92–94]. The resolution of these symptoms often follows a sequential course [8]. However, if symptoms linger, the patient will be diagnosed with post-concussion syndrome (PCS) [91].

2.4 Post-Concussion Syndrome

PCS is a complex, multifactorial disorder, and there is little consensus from the scientific community on how to define or diagnose the condition [95]. There are two major diagnostic systems for PCS, the International Classification of Diseases, 10th Revision (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revised (DSM-IV-TR) [96, 97]. Each system is defined in Figures 8 and 9, respectively, and Figure 10 displays the prevalence of these symptoms below.

Characteristics of postconcussion syndrome according to the ICD-10
History of head trauma with loss of consciousness precedes symptom onset by maximum of 4 weeks
<i>Three or more symptom categories:</i>
<ul style="list-style-type: none"> • Headache, dizziness, malaise, fatigue, noise intolerance • Irritability, depression, anxiety, emotional lability • Subjective concentration, memory, or intellectual difficulties without neuropsychological evidence of marked impairment • Insomnia • Reduced alcohol intolerance
Preoccupation with above symptoms and fear of brain damage with hypochondriacal concern and adoption of sick role
<i>Data From World Health Organization. The ICD-10 classification of mental and behavioral disorders: diagnostic criteria for research. Geneva (Switzerland): World Health Organization; 1993.</i>

Figure 8. ICD-10 Classification of PCS.

Symptoms must be present in 3 or more symptom categories within 1 month of injury. (Figure modified from [98]).

Characteristics of postconcussion syndrome according to the DSM-IV-R
A history of head trauma that has caused significant cerebral concussion (eg, with loss of consciousness, posttraumatic amnesia, or seizures)
Neuropsychological evidence of difficulty in attention or memory
<i>Three or more symptoms that last at least 3 months and have an onset shortly after head trauma or represent substantial worsening of previous symptoms:</i>
<ul style="list-style-type: none"> • Fatigue • Disordered sleep • Headache • Dizziness • Irritability or aggression with little or no provocation • Anxiety, depression, or affect lability • Changes in personality • Apathy or lack of spontaneity
The symptoms result in significant impairment in daily functioning that reflects a decline from previous level
<i>Data from American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edition. Washington, DC: American Psychiatric Association; 1994.</i>

Figure 9. DSM-IV-TR Classification of PCS.

Symptoms must be present in 3 or more symptom categories, at least, 3 months following injury with evidence of neuropsychological dysfunction. (Figure modified from [98]).

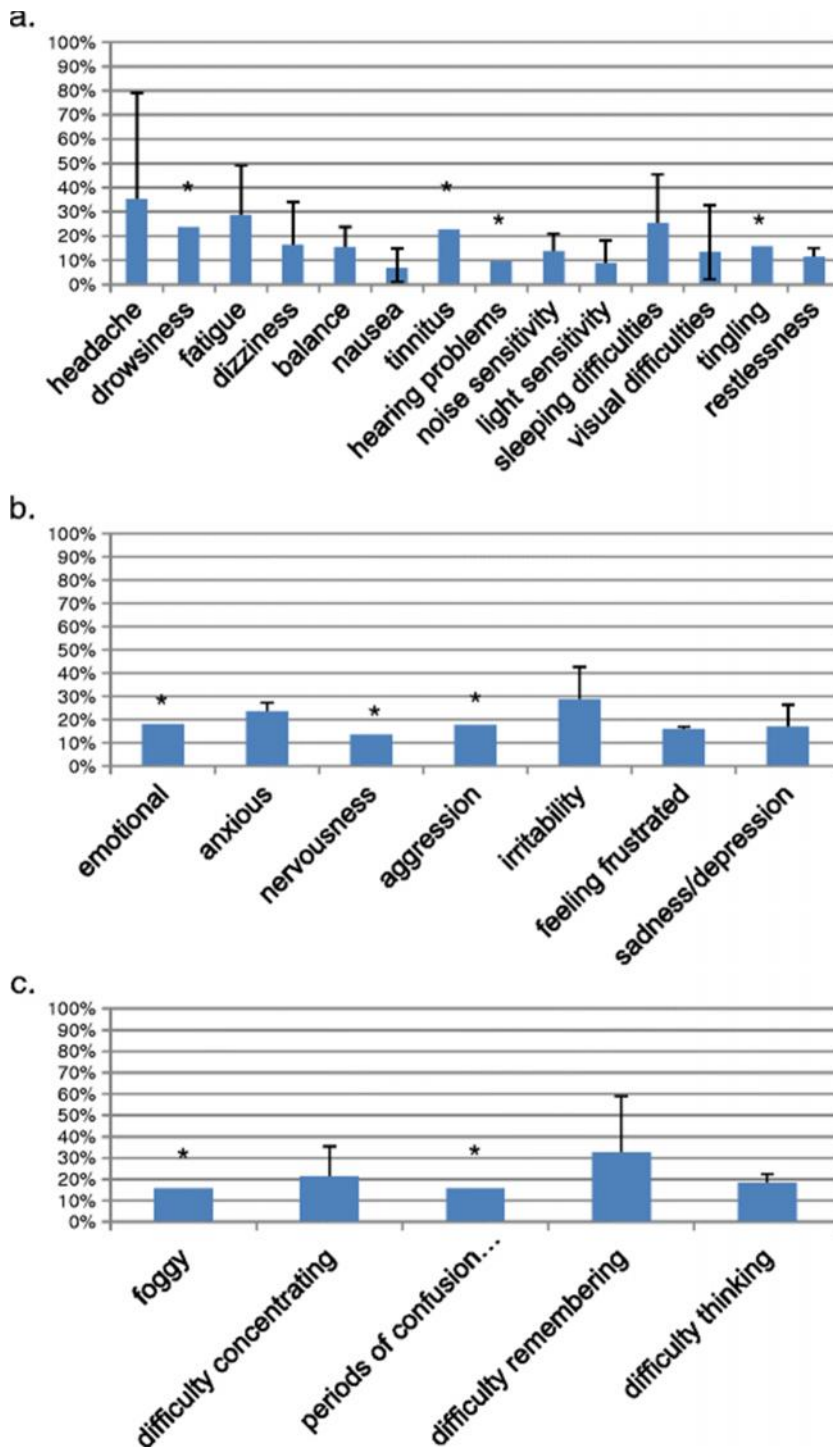


Figure 10. Prevalence of Post-Concussion Symptoms.

Prevalence (%) of chronic somatic (a), emotional (b), and cognitive (c) symptoms 3 months following injury based upon the findings of numerous studies. Error bars denote prevalence range

across these studies. Stars indicate that the results were taken from a single study. (Figure taken from [15]).

Whether PCS is experienced following injury is dependent on a number of factors, including post-injury psychological adjustment, pathophysiology, and congenital vulnerability [99]. One study found that those who possessed a more negative outlook on their injury were significantly more likely to suffer from symptoms of PCS after 3 months. In fact, this negative perception of injury severity by the subject was more predictive of PCS than were the total number of acute symptoms reported immediately following concussion [95]. Only 7-15% of people still experience any symptoms of PCS one year after injury [91].

2.5 Testing

Concussion is typically diagnosed based upon the clinical and cognitive symptoms reported by the patient, which can be non-specific and overlap with other differential diagnoses [39, 100, 101]. There are a number of available diagnostic checklists used in the field [39]. However, the most complete and widely used diagnostic tool is the Sports Concussion Assessment Tool 2, developed at the 3rd International Conference on Concussion [8]. Ideally, those who experience a concussion have had a baseline evaluation prior to injury that includes a neuropsychiatric evaluation, cognitive examination, and balance test, which can be repeated and results compared [102].

As previously mentioned, both CT and MRI imaging techniques typically fail to find any gross neurological abnormalities [38, 39]. However, more sophisticated imaging

techniques are being developed and implemented in concussion research, such as, functional MRI, susceptibility-weighted imaging (SWI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and neurochemical biomarkers, which will be detailed later in this review [103–106].

2.6 Treatment

Health professionals have been treating concussion using the same approach for decades [38]. The pathophysiology behind the injury is often overlooked. However, since no reliable measures of neurologic dysfunction currently exist, concussion treatment focuses on the resolution of symptoms [107]. Those who have sustained a concussion should be closely monitored for the first 24-48 hours, and any subsequent deterioration should be immediately reported to a physician for evaluation. While recovering, the patient should have complete physical and cognitive rest, as any increased workload could exacerbate symptoms. Once symptoms have resolved and neuropsychiatric tests appear normal, the patient may gradually increase activity. However, if any symptoms reappear during this time, workload should again be decreased until activity can be performed without issue [8].

3. Chronic Traumatic Encephalopathy

It has been known for some time that activities with a high degree of repetitive head trauma, such as, certain contact sports, can increase the risk for neurodegenerative diseases later in life, including Alzheimer's disease (AD), Parkinson's disease, and

amyotrophic lateral sclerosis (ALS) [29, 108–110]. Although, a meta-analytic study researching the association between TBI and AD could only find an correlation in men [111]. There has been only one study in recent years that has actually used neuropathologically-verified AD patients in researching this association, and it confirmed this increased risk [112]. Since most of these studies only used clinical criteria to diagnose AD, it is possible that a number of cases could have, in reality, been due to CTE, alone or in combination with other neurodegenerative disorders [113, 114].

CTE is a neurodegenerative disease believed to be caused, in large part, by the pathophysiological changes associated with repetitive brain trauma that can occur as a result of contact sports, military participation, and other recreational activities [4, 5]. This brain trauma can include mTBI, concussions, and even subconcussive injury [4, 29, 115, 116]. The symptoms of CTE include a variety of cognitive and behavioral deficits that do not typically manifest until many years after the trauma-producing activity has ended [4, 29, 117]. While CTE may have overlapping clinical characteristics of other dementing disorders, it is neuropathologically distinct from neurodegenerative diseases [4, 5]. The risk of developing CTE probably varies by activity participation and exposure, sport position, age, sex, genetic predisposition, and cognitive reserve [29].

3.1 History

In 1928, Martland first hypothesized that the repetitive brain trauma of competitive boxing could result in cognitive and behavioral detriments. He introduced the term, “punch drunk,” to characterize the spectrum of symptoms observed in these athletes

[118]. In the late 1930's, Millspaugh detailed a set of motor and cognitive dysfunctions seen in boxers, and alternatively, defined the condition as “dementia pugilistica” [119]. The term, CTE, was not coined until 1966 by Miller, and it was first described neuropathologically in 1973, famously by Corsellis et al. [117, 120]. However, it was not until recently that the disorder was attributed to more than just boxing. Contemporary studies have neuropathologically diagnosed CTE in those who have participated in a variety of other contact sports, as well as, military veterans, victims of physical abuse, a self-injurer, an epileptic, and a circus clown who was shot from a human cannon [4, 116, 121–127].

Due to the present increased concern and awareness regarding the disorder, the Center for the Study of Traumatic Encephalopathy was created in 2008 at the Boston University School of Medicine, in collaboration with the Sports Legacy Institute [128]. The NFL, also, recently donated \$30 million to the National Institutes of Health to help fund brain injury research [129].

3.2 Clinical Presentation and Course

The clinical presentation of CTE is distinct from the acute and chronic sequelae of concussion [121]. Symptoms do not usually manifest until long after the incidents of repetitive brain trauma have concluded and the neurodegeneration is severe enough to cause observable deficits [4, 29, 116, 117]. This delay of onset may be due to the effects of the chronic neuropathological changes associated with mTBI [4]. However, it typically

presents earlier than most other neurodegenerative diseases, like AD and frontotemporal lobar degeneration [116].

The observed changes in both cognition and behavior found in CTE are reflective of the neurodegeneration in brain regions most affected by the disease [130]. Early neuropathological changes may not present clinically, but they become increasingly obvious as the disease progresses [116].

3.2.1 Neuropsychological/Neuropsychiatric Changes

CTE can have effects on cognition, mood, and behavior in patients. Cognitive changes include learning/memory impairment and executive dysfunction [130]. McKee et al. identified memory impairment in greater than 60% of known cases [4]. Similar to AD, CTE presents with anterograde amnesia, which is consistent with the observed neurodegeneration of the hippocampus and associated medial temporal structures [131, 132]. The associated executive dysfunction is a result of frontal lobe atrophy found in most cases [4].

Changes in mood include depression, irritability, apathy, and suicidality [130]. Any one of these mood changes has been reported in more than 60% of cases [4]. Depression is the most commonly identified symptom in those with a history of head trauma [133]. These emotional changes are due to the neurodegeneration of the medial temporal lobe and orbitofrontal regions seen in patients [121]. These changes can be severe enough to result in a patient taking their own life [5].

Lastly, behavioral alterations include disinhibition, poor impulse control, increased aggression, and substance abuse [130]. The issues with disinhibition, impulse control, and substance abuse most likely stem from frontal lobe atrophy, while the increased aggression is due to neuropathological changes seen in the limbic system [121, 134]. Unfortunately, the frequent substance abuse associated with the disease can confound the presentation of clinical symptoms. These changes have, also, been linked to homicidal behavior and drug and alcohol overdose in some [4, 5].

3.2.2 Neurological/Motor Changes

CTE frequently produces neurologic dysfunction, which can negatively impact motor operations [130]. Signs of such impairment were found in approximately 40% of subjects by McKee et al. and included Parkinsonism, dysphagia, slurred and dysarthric speech, and ocular anomalies. The Parkinsonism arises from the atrophy of the substantia nigra, cortical and subcortical frontal lobes, and/or cerebellum. The remaining symptoms are a result of the neurodegeneration of brainstem nuclei [4].

A small subset of patients (11.8%) presented with a variant of the disorder, known as chronic traumatic encephalomyelopathy (CTEM), that affects the spinal cord and is associated with motor neuron disease, which clinically mimics ALS [5, 130, 135]. These patients are more severely affected and display signs of progressive muscle atrophy, balance and gait issues, fasciculations, and hyperactive deep tendon reflexes [135]. Typically, the onset of any cognitive and behavioral symptoms is seen several years after the initial signs of motor neuron disease [5].

3.2.3 Disease Progression

CTE has an insidious onset and gradual progression [29]. It frequently begins to manifest between the ages of 30-50, at approximately 8 years following retirement for professional athletes [4, 130]. This early presentation can help to distinguish it from other neurodegenerative disorders. The disease progresses slowly, at a rate of 11-14 years between the four separate pathological stages, which will be detailed below [5, 130]. However, in professional athletes, the disease course is much shorter, with a total mean duration of 17.5 years [4]. As the disease advances, the symptoms become more severe and numerous [116].

3.2.3.1 Stage I

During this very early stage of the disease, it is possible to not display any symptoms. However, headache and attention deficits are the most common complaints. Some patients, also, report short-term memory difficulties, depression, aggression, explosivity, and executive dysfunction [5].

3.2.3.2 Stage II

The majority of individuals display some symptoms of CTE. These commonly include depression, explosivity, attention deficits, headaches, and short-term memory difficulties. Less frequently, patients complain of executive dysfunction, suicidality,

impulsive behavior, and speech difficulties. A small subset of subjects have, also, been diagnosed with the CTEM variant by McKee et al. by this stage [5].

3.2.3.3 Stage III

It is highly unlikely that patients will still be asymptomatic. Patients frequently present with executive dysfunction, memory problems, explosivity, attention deficits, depression, aggression, and visual abnormalities. Less common symptoms include headaches, suicidality, apathy, and impulsive behavior. McKee et al. noted that approximately 75% of subjects were considered to be cognitively impaired by this stage, and a small portion developed symptoms of CTEM [5].

3.2.3.4 Stage IV

All are symptomatic and have developed varying degrees of dementia prior to this point. The only symptoms not commonly observed in these patients are typically dysarthria, impulsivity, and Parkinsonism [5].

3.3 Gross Pathology

As previously stated, CTE is pathologically distinct from other neurodegenerative diseases [4, 5]. The disease presents with diffuse brain atrophy and a reduction in brain weight [4]. The brain regions most severely affected are the cerebral cortex and medial limbic structures [29, 116]. There is obvious degeneration of the thalamus, hypothalamus, and mammillary bodies. Patients present with thinning of the corpus callosum and other

subcortical white matter, as well as, pallor of the substantia nigra and locus coeruleus. There is pronounced dilatation of the lateral and third ventricles along with anterior cavum septum pellucidum and posterior septal fenestrations (Figure 11) [4]. Cavum septum pellucidum is produced when the leaflets of the septum pellucidum are separated by cerebrospinal fluid (CSF) [136]. This accumulation of CSF is likely caused by fluid waves generated in the ventricles by repetitive brain trauma, which eventually, damage the septum pellucidum [4, 29].

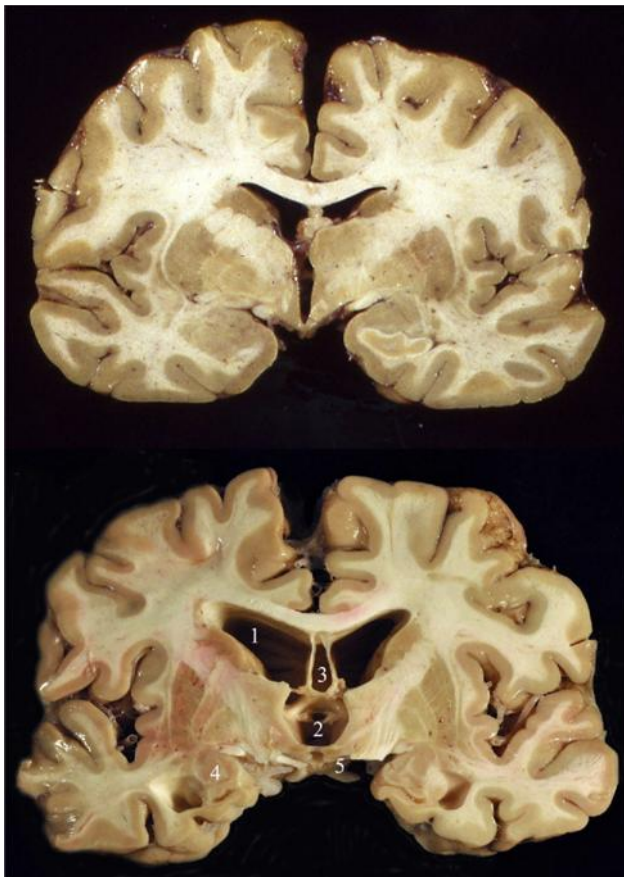


Figure 11. Gross Pathology of CTE.

Two coronal sections of human brain, control (**top**) and CTE-diagnosed brain (**bottom**). The brain with CTE shows the characteristic dilatation of the lateral (**1**) and third (**2**) ventricles,

cavum septum pellucidum (3), and atrophy of medial temporal lobe (4) and mammillary bodies (5). (Figure taken from [116]).

3.3.1 Stage I

During this first stage of pathological development, there may be mild ventricular enlargement. Other than that, there are relatively no gross abnormalities, and brain weight is normal [5].

3.3.2 Stage II

Mild ventricular enlargement is more frequent with small cavum septum pellucidum. There may, also, be pallor of the locus coeruleus and substantia nigra and mammillary body atrophy. However, brain weight still remains approximately normal [5].

3.3.3 Stage III

Most brains display ventricular dilatation and mild cerebral atrophy. Septal abnormalities and pallor of the substantia nigra and locus coeruleus are found in close to half of patients. Other common gross anatomic features include atrophy of thalamus and mammillary bodies and thinning of the corpus callosum and subcortical white matter [5].

3.3.4 Stage IV

Ultimately, patients exhibit atrophy of cerebral cortex, medial temporal structures, thalamus, hypothalamus, mammillary bodies, and white matter with significant

ventricular enlargement and septal abnormalities. Pallor of the substantia nigra and locus coeruleus is found in all cases. Brain weight is, also, significantly reduced by this point [5].

3.3.5 Chronic Traumatic Encephalomyelopathy

In those small subset of patients diagnosed with the CTEM variant, there is significant atrophy of the medullary pyramids and lateral corticospinal tracts. There is extensive loss of cells in both the anterior horn and ventral roots [135].

3.4 Microscopic Pathology

The microscopic pathology of CTE is characterized by the accumulation of hyperphosphorylated tau, transactive response deoxyribonucleic acid-binding protein 43 (TDP-43) inclusions, and in some cases, β -amyloid (A β) plaques affecting widespread brain regions [4, 5, 135]. CTE morphogenesis likely initiates within the depths of sulci of the cerebral cortex, often perivascularly, and slowly proliferates over the course of decades to affect multiple other brain regions. Axonal varicosities and axonal loss are present in all stages of CTE [5].

3.4.1 Tau

Under normal circumstances, the tau protein is predominately associated with microtubules found in the axons of healthy CNS tissue, where it remains non-toxic [5]. However, hyperphosphorylation of intracellular tau causes it to become dissociated from

microtubules. The increases in axoplasmic calcium and excitotoxicity associated with TBI are known to activate specific kinases, which phosphorylate the tau protein; thus, resulting in the dissociation from microtubules [137–140]. Once dissociated, tau is susceptible to cleavage by calpains and caspases, misfolding, and aggregation. Excess accumulation of tau aggregates, ultimately, results in neurodegeneration [29, 141–143]. TBI has been shown to lead to accumulation of hyperphosphorylated tau in the brain in less than 24 hours of injury [144].

CTE is defined by the accumulation of hyperphosphorylated tau as neurofibrillary tangles (NFTs), glial tangles (GTs), and spindle-shaped neurites. These are found throughout the frontal, insular, and temporal cortices, as well as, the diencephalon, brain stem, cerebellar dentate nucleus, and spinal cord [4].

NFTs and GTs are densely distributed within the hippocampus, entorhinal cortex, amygdala, and olfactory bulbs, frequently in greater density compared to AD. There are, also, profuse NFTs and GTs seen in the thalamus, hypothalamus, substantia nigra, locus coeruleus, superior colliculus, medial geniculate, nucleus basalis of Meynert, medial lemniscus, periaqueductal gray, dorsal and median raphe, oculomotor nucleus, trochlear nucleus, trigeminal motor nucleus, ventral tegmental area, dorsal motor nucleus of the vagus, pontine nuclei, inferior olives, hypoglossal nucleus, and reticular formation. The nucleus accumbens is only moderately affected, and the caudate, putamen, and globus pallidus are even less disturbed. The white matter tracts of the brainstem and spinal display abundant GTs, especially perivascularly, and they are, also, present in subpial and periventricular zones [4].

Tau-immunoreactive neurites are found on astrocytes dispersed throughout superficial neocortical layers. The corpus callosum and subcortical white matter, also, possess several neurites [4]. Finally, NFTs, neurites, and GTs can be identified in the dorsal and ventral horns of the spinal cord in patients with the CTEM variant [135].

CTE is distinguished from other tauopathies, like AD, by its uniquely irregular deposition of NFTs, which predominately affects superficial neocortical layers (laminae II/III) within the depths of sulci and surrounding microvasculature [4, 29, 145]. NFTs are much more uniformly distributed in AD and found in laminae III/V [4]. This process in CTE may initiate within these sulcal depths or surrounding small blood vessels and spread via the internalization of tau aggregates by nearby cells. Once internalized, tau aggregates might induce intracellular tau alterations much like prions [146]. Exactly why the pathology first presents with the depths of sulci still remains a mystery. However, the shear forces of repetitive TBI are more prone to damaging axons surrounding cerebral microvasculature and associated vessels, and thus, explain the perivascular NFT and neurite formation [123]. NFTs seen in CTE have higher levels of iron and aluminum accumulation than AD, supporting the theory for perivascular formation [147].

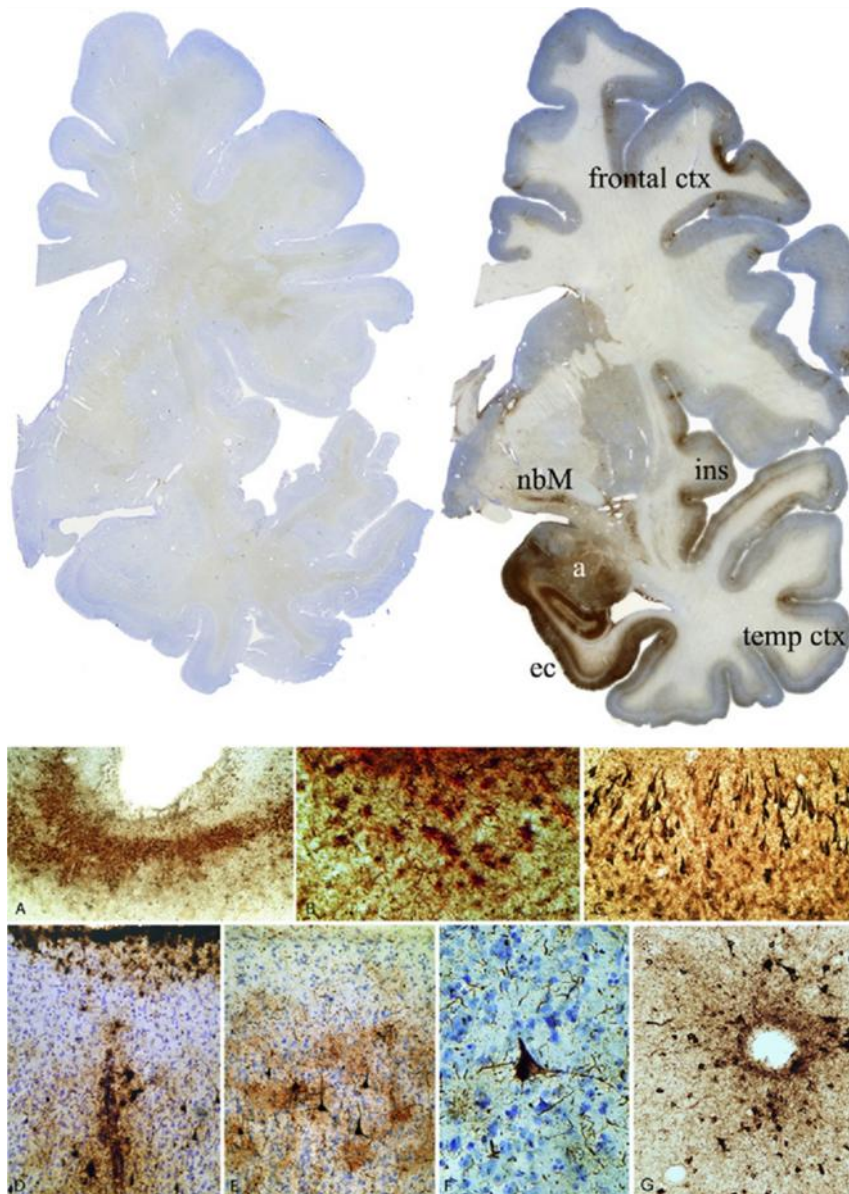


Figure 12. CTE Tau Pathology.

Top panel: Coronal hemisections of a control (**left**) and CTE-diagnosed brain (**right**) stained for phosphorylated tau using AT8. The CTE-diagnosed brain shows extensive tau immunostaining and neurodegeneration in the amygdala (**a**), entorhinal cortex (**ec**), temporal cortex (**temp ctx**), insular cortex (**ins**), nucleus basalis of Meynert (**nbM**), and frontal cortex. Cortical changes are more severe at sulcal depths. **Bottom panels:** (**A**) Dense NFT formation in depths of sulci (AT8). (**B**) Subpial NFTs found in both neurons and astrocytes [AT8 (brown); GFAP (red)]. (**C**) Dense NFT formation in CA1 of hippocampus (AT8). (**D**) NFTs and GTs found in subpial patches and surrounding microvasculature (AT8). (**E**) NFT formation in laminae II/III (AT8). (**F**) NFT in Betz cell of primary motor cortex (AT8). (**G**) Perivascular NFT deposition (AT8). Original magnification: A = $\times 60$; B = 350; C = 150; D = 150; E = 150; F = 350; G = 150. (Figure taken from [116]).

Much like AD, CTE pathology is composed of all 6 specific brain tau isoforms [148]. NFTs are composed of comprised of both 3-repeat and 4-repeat tau. However, GTs are primarily constructed of 4-repeat tau [5].

In contrast, the spindle-like shape of neurites is unique to CTE, and they are believed to originate from axons [4, 149]. NFTs and GTs are, also, found in far greater densities than other progressive tauopathies [29]. However, there have been a few reported cases associated with neurodegeneration of the cerebral cortex, hippocampus, and substantia nigra without any significant neurofibrillary pathology [4].

3.4.1.1 Stage I

There are focal epicenters of perivascular NFTs and GTs, predominantly within the depths of sulci of the superior and dorsolateral frontal cortex. Small amounts of NFTs are found in the locus coeruleus in a few cases. Axonal varicosities are present in the frontal cortex, subcortical white matter, and in the white matter of the diencephalon [5].

3.4.1.2 Stage II

Hyperphosphorylated tau is prevalent as distinct foci in areas of the frontal, temporal, parietal, insular, and septal cortices, with NFTs in the superficial layers of cortex. NFTs are, also, present in the locus coeruleus, nucleus basalis of Meynert, and amygdala in moderate densities. Lower densities of NFTs are observed in the thalamus, hypothalamus, hippocampus, entorhinal cortex, substantia nigra, and dorsal and median

raphe nuclei. Distorted axonal profiles are identified in the frontal and temporal cortices, as well as, the white matter tracts [5].

3.4.1.3 Stage III

NFTs are widely dispersed throughout areas of the frontal, temporal, insular, and septal cortices, as well as, the inferior parietal cortices. They are, also, observed in high densities in the hypothalamus, hippocampus, amygdala, locus coeruleus, substantia nigra, entorhinal cortex, olfactory bulbs, nucleus basalis of Meynert, mammillary bodies, and dorsal and median raphe nuclei. NFTs can be identified in the thalamus, cingulate cortices, dorsal motor nucleus of the vagus, nucleus accumbens, dentate nucleus of the cerebellum, and the spinal cord only in small amounts. Distorted axonal varicosities and axonal loss are prevalent in the subcortical white matter of the frontal and temporal cortices [5].

3.4.1.4 Stage IV

Severe hyperphosphorylated tau pathologies are prevalent throughout the cerebral cortex, diencephalon, basal ganglia, brainstem, and spinal cord. There is obvious axonal loss in the subcortical white matter, as well as, the presence of axonal varicosities [5].

Figure 13 below shows the progression of the tau pathology.

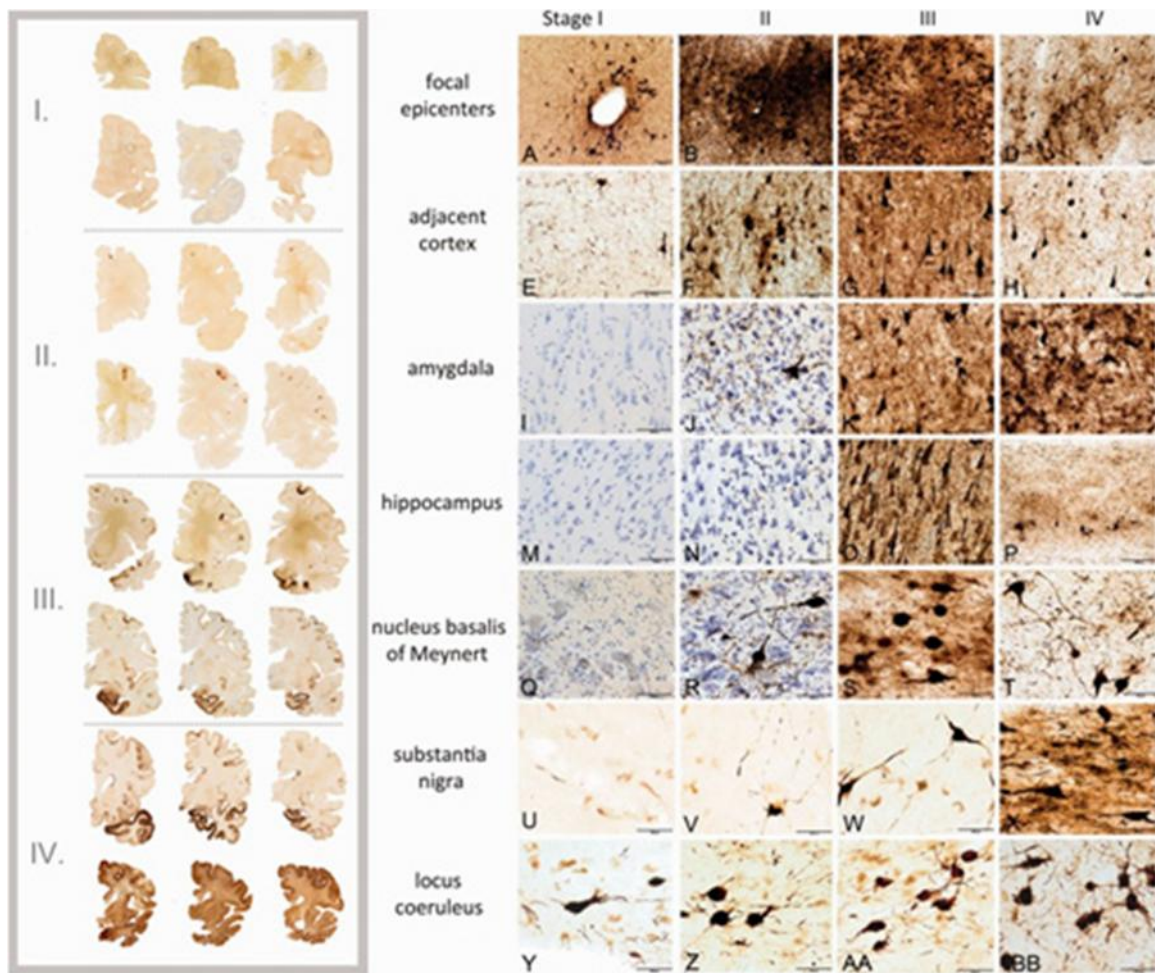


Figure 13. Tau Pathology Progression.

Left panel: Coronal hemisections of CTE-diagnosed brain show progression of tau pathology from discrete foci in the depths of sulci in Stage I to more widespread accumulation by Stage IV. Immunostained for tau using CP-13. **Right panels:** Display tau pathology progression in distinct brain regions. Immunostained for tau using CP-13, and some counterstained with cresyl violet. Scale bars = 100 μ m. (Figure modified from [5]).

3.4.2 Transactive Response DNA-Binding Protein 43

TDP-43 is normally found within the nuclei of neurons and functions in stabilizing and exporting the messenger ribonucleic acid transcript of neurofilaments. It is critical in modulating the response to cytoskeletal injury within the cell, and its expression is found to be upregulated following experimental axotomy in mice [150,

151]. However, overexpression and dislocation from the nucleus to the cytoplasm are correlated with cellular death [152–154]. Traumatic axonal injury associated with TBI may potentially expedite cytoplasmic dislocation [29, 135].

TDP-43 inclusions are found in more than 80% of CTE cases and are most commonly identified in subjects that present with a severe tau pathology [135]. It accumulates as cytoplasmic and intranuclear inclusions in neurons and glia and as neurites [4]. It is frequently observed in the frontal and medial temporal cortices, diencephalon, thalamus, hypothalamus, hippocampus, amygdala, substantia nigra, insula, caudate, putamen, brainstem, and subcortical white matter [116, 135].

In patients with CTEM, abundant TDP-43 inclusions are observed in the anterior horn of the spinal cord and motor cortex [116, 135]. They present as neuronal, glial, and neuritic inclusions in these cases [5].

3.4.2.1 Stage I

Some subjects present with TDP-43 neuritic inclusions in the subcortical white matter of the frontal cortex and fornix [5].

3.4.2.2 Stage II

TDP-43 inclusions become more common in the medial temporal lobe, brainstem, and subcortical white matter, frequently of subpial, periventricular, or perivascular formation. However, it is possible to have more severe TDP-43 distribution as neuronal and glial inclusions and neurites throughout the cerebral cortex, diencephalon, basal

ganglia, brainstem, and spinal cord. CTEM patients show marked loss of lateral and ventral corticospinal tracts and anterior horn cells [5].

3.4.2.3 Stage III

Most subjects have TDP-43-positive neurites in the cerebral cortex, medial temporal lobe, or brainstem. Those with CTEM have much more severe and widespread TDP-43 pathology, presenting with intraneuronal and intraglial inclusions and neurites [5].

3.4.2.4 Stage IV

Ultimately, TDP-43 pathology becomes severe in majority of subjects with neuronal and glial inclusions and neurites in the cerebral cortex, medial temporal lobe, diencephalon, basal ganglia, and brainstem. They are typically less dense in spinal cord. In those most severely affected, TDP-43 inclusions are observed in all layers of cortex with sporadic inclusions in the hippocampus [5].

3.4.3 -amyloid

Neurotoxic A β is a 42 residue peptide that is enzymatic cleaved from the transmembrane protein, amyloid precursor protein (APP), by β -secretase and γ -secretase. This form of A β is highly prone to misfolding and aggregation, resulting in insoluble plaque formation. Excess accumulation of these plaques culminates in neurodegeneration [155].

APP is believed to have neurotrophic functions, which help axons recover after damage [156–158]. APP is known to be upregulated in response to TBI, which can potentially result in A β plaque formation in some patients within hours of injury [159–162]. However, it is unknown how long increased levels of APP and A β exist for following TBI [29].

The role of A β pathology in CTE is still unclear. It is found in only 40-45% of those diagnosed with CTE, and typically, it is only observed in significantly older patients. Of those cases, about half are diagnosed with another neurodegenerative disorder in combination with CTE, and therefore, the neuropathological findings may be confounded by the presence of multiple disorders. This contrasts with AD, in which a severe A β pathology is identified in virtually all patients. When A β is present, there is a primarily diffuse distribution of plaques with few neuritic plaques [4, 5].

3.5 Risk Factors

CTE has only been diagnosed neuropathologically in those with a history of repetitive TBI. Therefore, TBI is considered to be a primary risk factor in CTE pathogenesis, which can occur as a result of contact sports, military participation, and other recreational activities. Of those diagnosed, greater than 90% have been athletes, yet only a small sample of brains for those who participated in other trauma-producing activities have been acquired for research [4, 5].

It is still unclear whether the severity and frequency of head trauma can affect the risk of developing CTE [130]. A history of concussive injury appears to not be

significantly correlated with the development of CTE [5]. The disorder has been diagnosed in football players with no reported history of concussions, which suggests that subconcussive brain trauma may be sufficient [4, 29]. There are measurable neurophysiologic and cognitive impairments following subconcussive injury, yet they typically go unnoticed and undiagnosed. As a result, many athletes will return to play too early, potentially increasing their risk [163]. One study found there to be a significant association between the number of hits sustained by football players and the ensuing pathophysiological changes. However, the data is inconclusive due to the use of regression analysis to determine this relationship [164].

Nevertheless, brain trauma appears to be necessary for CTE pathogenesis, yet it is not entirely sufficient. There are several individuals with a history of repetitive TBI that show no signs of the disorder upon examination [130]. There seem to be a number of other factors involved, as well. The risk of developing CTE probably varies by activity participation and exposure, sport position, age, sex, genetic predisposition, and cognitive reserve; all of which, will be detailed below [29].

3.5.1 Sport

Repetitive head trauma occurs in a considerable variety of contact sports, including football, boxing, rugby, wrestling, soccer, lacrosse, hockey, and skiing, and the risk of developing CTE most likely varies across each sport and player position [4, 29]. Thus far, it has been neuropathologically diagnosed in athletes, who have participated in football (50%), boxing (43%), hockey (4%), wrestling (2%), and soccer (1%). The

disease appears to progress much more quickly in athletes compared to other subjects.

One-third of the diagnosed athletes were symptomatic by the time they retired, and up to half experienced symptoms within 4 years [4, 5].

3.5.1.1 Football

CTE symptoms typically begin to present in early mid-life in retired football players, and the disease shows an average duration of approximately 10 years prior to death. However, symptoms have been identified in a player as young as 34, and another player lived to be close to 100 years of age. The total number of years played, years since retirement, and age at death are all significantly associated with the pathological stage of CTE [4, 5].

In football, there are significant differences in the frequency and location of TBI exposure based upon position [165, 166]. Players have been known to experience up to nearly 1,400 impacts in a single season [165]. The defensive linemen receive the greatest number of head impacts, followed by the offensive linemen, offensive skill players, and lastly, defensive skill players [167]. Of those diagnosed with CTE, the majority are offensive skill players, followed by offensive linemen, defensive skill players, and defensive linemen. Thus, position played is not significantly correlated to the pathological stage of CTE at time of death [5].

3.5.1.2 Boxing

Historically, boxing has always been the most synonymous with CTE. Although, on average, the disease progresses more slowly than in football players, with a mean duration of approximately 20 years, and thus, boxers tend to live to an older age [4]. A recent study reviewed the neuroimaging findings in boxers, and they discovered that greater than 75% had, at least, one neuroanatomical abnormality that may be associated with TBI. The severity of the injury was, also, associated with career length and total number of fights [168]. However, a meta-analytic study found there to be no significant correlation between boxing and CTE [169].

3.5.2 Military Service

Blast exposure is known to increase the risk for TBI in military veterans, and it has been linked to those diagnosed with CTE [5, 170–173]. One study examined the effects of explosive blasts on mice and found that it produces tau pathologies consistent with CTE in as little as 2 weeks after injury [170]. Blast exposure may potentially induce an inward skull flexure that generates enough positive pressure to damage the brain in unhelmeted individuals [174]. However, cognitive and memory deficits are prevented by head immobilization during blast exposure, suggesting that head acceleration is the most likely mechanism of injury [170].

3.5.3 Age

The risk of CTE development based upon age of insult still remains unclear. However, many athletes begin participating in their respective sports at a very young age

[4]. There is significant evidence that concussion produces longer-lasting cognitive impairment and prolonged pathogenesis in immature brains compared to adults [175, 176]. This could be due to a number of different characteristics, including incomplete brain development, greater head-to-body ratio, and/or a thinner, more flexible skull [177, 178]. The developing brain is, also, more sensitive to the effects of excitotoxicity following TBI, and the associated cerebral edema is more widespread and prolonged, producing greater ischemic injury [86, 175, 178]. Therefore, TBI sustained at a young age may, actually, hinder brain plasticity and development [179].

3.5.4 Sex

CTE has been predominantly diagnosed in males due to a much larger proportion of male brain donations [130]. However, females may be at greater risk for concussions, and they frequently take longer to recover than their male counterparts. This could be due to better reporting by females, weaker upper body strength, and/or sex hormones [180, 181]. What role this plays in the development of CTE is unknown.

3.5.5 Genes

A gene of particular interest in CTE pathogenesis is the apolipoprotein E (APOE) gene, as it is the strongest susceptibility gene for AD [130]. The APOE gene possesses 3 different alleles, APOE 2, 3, and 4, which occur with a frequency of 7%, 78%, and 15%, respectively, in Caucasian populations [182]. The gene encodes for apolipoprotein

E, which is believed to maintain microtubule integrity and assist in neural recovery following injury [183].

Possession of the APOE 4 allele is associated with more severe cognitive impairments and longer recovery times following TBI [184–187]. However, one large study saw no evidence of poor outcome 6 months following injury [188]. This allele may reduce the brain's capacity to repair itself after injury by affecting inflammatory processes, cell proliferation, and cellular signaling [189]. APOE 4 transgenic mice exhibit increased neuroinflammation, glial activation, A β deposition, neurodegeneration, and suffer greater mortality than controls following TBI [190, 191].

In a large study examining CTE, those diagnosed with the disorder showed no proportional difference in APOE 4 possession when compared to the general population [5]. However, in a smaller sample, greater than 40% were shown to be APOE 4 carriers, a much higher number than the general population [135].

3.5.6 Cognitive Reserve

The timing of the onset of CTE symptoms may be affected by a patient's cognitive reserve. That is, an individual with a greater cognitive reserve might be able to better mask the clinical symptoms of CTE than those with less cognitive reserve. This may be accomplished by an enhanced ability to recruit or develop alternate neural networks to compensate for the underlying neuropathology [192, 193]. Supporting this theory, pre-injury intelligence quotient has been demonstrated to be a significant

predictor of the severity of post-concussion symptoms for up to a year following injury [194, 195].

3.6 Testing

Currently, there are no conclusive clinical diagnostic criteria for CTE. The clinical presentation may be confounded by substance abuse or the presence of another neuropsychiatric disorder. CTE can only be truly diagnosed neuropathologically post-mortem, yet there is still no general consensus even on the neuropathologic criteria from the scientific community [29, 130]. Fortunately, there has been a lot of progress made in neurochemical biomarker development and neuroimaging, which may further assist in diagnosing the disease in vivo.

3.6.1 Biomarkers

Presently, there are no neurochemical biomarkers available for CTE diagnosis [4]. However, tau levels in both plasma and CSF are currently being researched for diagnosing AD, which may be applicable towards CTE diagnosis, as well [196–198]. Biomarkers are, also, being researched for diagnosis of concussion, including S100 calcium-binding protein B, neuron-specific enolase, and glial fibrillary acidic protein [199, 200]. The confirmed neurochemical diagnosis of a concussion immediately following injury may go a long way in preventing further injury, and ultimately, CTE.

3.6.2 Magnetic Resonance Imaging

MRI makes use of magnetic fields and radio frequencies to detect alterations in the spin signal of atoms, typically hydrogen atoms. It is frequently used to image the soft tissues of the body and has much better resolution than CT [201]. Conventional MRI imaging consists of a few different techniques that display various levels of contrast among tissues, including T1-weighted, T2-weighted, and T2*-weighted (gradient echo) sequences [202]. MRI is only capable of detecting some of the gross pathological changes associated with CTE, such as, ventricular abnormalities and marked cortical atrophy [4]. However, more sophisticated MRI techniques are being developed for imaging the less discernible brain pathologies.

3.6.3 Susceptibility-Weighted Imaging

SWI makes use of MRI technology to distinguish susceptibility differences among the structures and fluids within the body, such as, oxygenated versus deoxygenated blood. It is capable of detecting microhemorrhagic lesions that cannot be observed by traditional MRI [201]. Since the perivascular tau deposition associated with CTE is believed to be triggered by the microvascular compromise observed with diffuse axonal injury, SWI may be useful in differential diagnosis (Figure 14) [4, 121, 130].

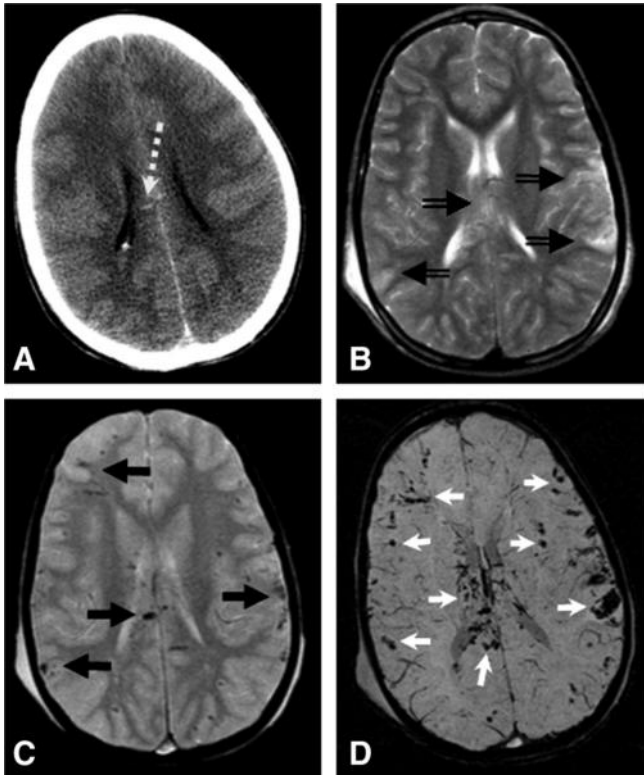


Figure 14. Microhemorrhagic Imaging.

CT (A) only finds a small focal point of microhemorrhages in the corpus callosum of child following TBI. T2-weighted imaging (B) is not sensitive to hemorrhages, but it does show areas of edema in the corpus callosum and peripheral hemispheres. T2*-weighted imaging (C) displays some areas of microhemorrhage in the corpus callosum and peripheral hemispheres. SWI (D) is by far the most sensitive to microhemorrhagic lesions; of which, it detects several throughout the brain. (Figure taken from [202]).

3.6.4 Diffusion Tensor Imaging

DTI is another MRI-based technique that makes use of the diffusion properties of water to distinguish microstructural tissue anatomy. It is capable of visualizing damage within the white matter tracts of the brain [201]. White matter damage is a hallmark of the DAI associated with mTBI, and it may be a mechanism in CTE pathogenesis [130, 203–205]. DTI was used in a small pilot study to examine the white matter integrity in athletes displaying signs of CTE, and it showed a thinning of the corpus callosum (Figure

15) [121]. DTI abnormalities are positively correlated with greater cognitive detriments in humans and are predictive of long-term outcomes in rats following TBI [206–208]. However, there is a lack of uniformity for DTI protocols, which decreases the reliability of data across multiple studies [209].

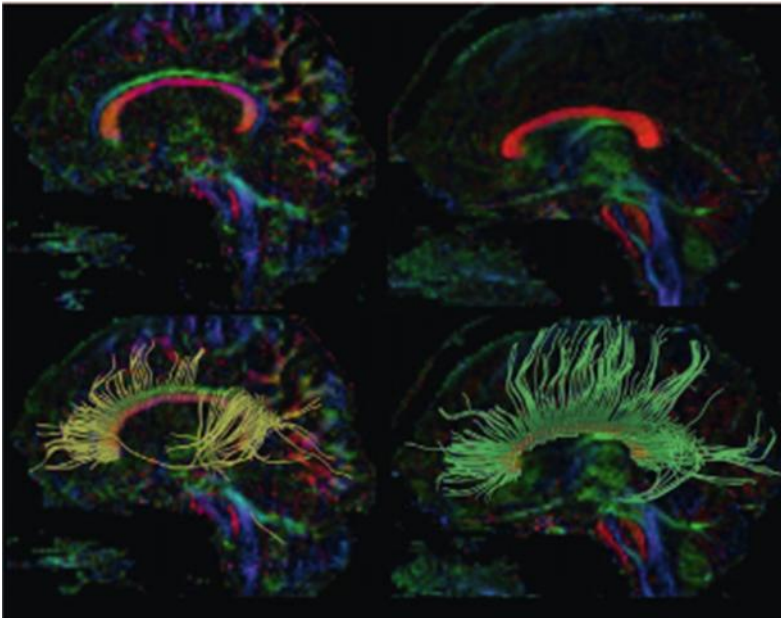


Figure 15. DTI in Athlete with CTE-Like Symptoms.

Former athlete presenting with CTE-like symptoms (**left**) and control (**right**). The top panels show an obvious thinning of the corpus callosum in the center of the brain in the athlete (red). The bottom panels use streamline tractography to trace the corpus callosum fiber bundle, and once again, the fibers are much less numerous in the athlete compared to the control. (Figure taken from [121]).

3.6.5 Magnetic Resonance Spectroscopy

MRS uses MRI-technology to measure the brain’s biochemical metabolites in vivo. Metabolite concentrations can be used to provide neurophysiological data on structural damage, neurotransmission, and several other brain functions [201]. MRS frequently measures such metabolites as, N-acetylaspartate, choline, GLU, and creatine-

phosphate [210–213]. Significant changes in concentration have been observed with each following TBI, which may be predictive of long-term outcome [213–216]. If there are chemical imbalances within the brain due to CTE, this imaging technique will be able to detect them. As with DTI, there are significant differences among MRS protocols, which can make results difficult to compare across multiple studies [38].

3.6.6 Positron Emission Tomography

Positron emission tomography (PET) uses radiolabeled isotopes to determine areas of uptake or binding within the brain, which can provide information on brain activity or chemical density [201]. A pilot study made use of a ligand developed for AD, which chemically binds to both tau and A β , in an attempt to detect CTE in former NFL players with symptoms of the disorder. They discovered characteristic deposits in areas associated with CTE, but the data may be confounded by A β binding (Figure 16) [217]. A tau-selective ligand would be useful in CTE diagnosis, but there are none currently available [130]. However, one team is already in the process of developing and researching a tau-selective ligand [218].

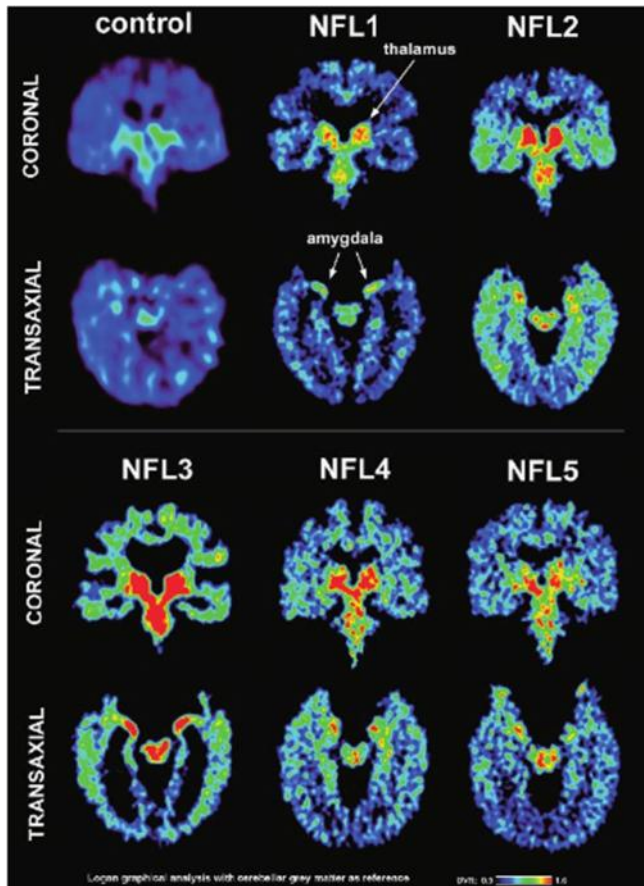


Figure 16. PET of Athletes with CTE-Like Symptoms.

Coronal and transaxial scans of 5 retired, symptomatic NFL players and a control. The players' scans display consistently high signals in the amygdala and subcortical regions, which may be indicative of the presence of CTE pathology. (Figure taken from [217]).

3.6.7 Single-Photon Emission Computed Tomography

Single-photon emission computed tomography (SPECT) uses radiolabeled tracers to determine the distribution of cerebral blood flow. This can be used to detect abnormalities in brain function, which could be useful in assisting in the diagnosis of CTE [130, 219]. However, the specificity of this technique is poor, making a differential diagnosis difficult [220].

3.7 Treatment/Prevention

There are no treatments currently available for CTE [121]. However, since the disease appears to have a long latency period prior to symptom development, there is a large window of opportunity for potential therapies to slow or even stop the neurodegenerative disease progression [135].

Since TBI is a primary risk factor in CTE pathogenesis, the most obvious way to prevent disease development is to avoid head trauma and any activity that might increase the risk for head injury. However, it is likely that many people will still engage in these precarious activities regardless of the consequences, and thus, it is important to make them safer. Protective equipment is often used to minimize the possibility of injury, but unfortunately, there is no significant evidence that the currently available protective gear, such as, helmets and mouth guards, will prevent concussive injury [8]. In fact, the very use of this protective equipment may actually increase the risk for TBI by encouraging more hazardous behavior [221]. Rule changes in sports may be necessary to decrease TBI incidence and unnecessary contact in order to minimize risk [8].

Proper concussion diagnosis and management may, also, go a long way in preventing CTE [29]. Removing individuals from any dangerous activity during the post-injury vulnerability period will prevent any further damage. The CDC recently initiated the Heads Up program, in an attempt, to better educate medical professionals and others associated with youth athletics, primarily football, on concussion identification and management [222]. Prudent return-to-play guidelines may need to be altered to

recommend a minimum of 4 weeks of recovery time following TBI to promote an improved outcome [223].

4. Discussion

Recently, there has been increased public awareness regarding the long-term consequences of repetitive TBI and its role in the pathogenesis of CTE. A history of concussions may not be necessary for the development of the neurodegenerative disorder, but the pathophysiological changes associated with brain injury are clearly important. The biomechanical forces responsible for TBI can produce diffuse axonal injury, excitotoxicity, microglial activation, and cerebrovascular compromise. Repetitive injury can result in prolonged activation of these neurodegenerative mechanisms, which can produce the hyperphosphorylated tau and TDP-43 accumulations associated with CTE. However, more research will be necessary to provide further evidence for this theory.

CTE research is still in its infancy, and thus, scientific knowledge of the disorder is still limited. The disease was only recently found to affect a much broader population than just boxers. Hence, it is more important than ever to increase understanding of CTE to reduce the potential negative impact on society. Much progress has been made in the last few years, but more work still needs to be done. Hopefully, with further research, scientists and clinicians will be able to accurately define the clinical and neuropathologic diagnostic criteria.

To date, there have been no randomized neuropathological studies, which created a selection bias among studies. This has resulted in a large proportion of athletes

diagnoses, which may not be representative of the epidemiology of the disease. CTE potentially affects a much broader population. It will be necessary to design prospective studies to elucidate the epidemiology and etiologies of the disorder, including the severity and frequency of hits necessary for disease development, genetic predisposition, and other associated risk factors. Researchers should make use of the knowledge available for related neurodegenerative disorders to increase understanding. Better knowledge of these risk factors will help to provide improved treatment and prevention.

Finally, more work is necessary to improve the neuroimaging and neurochemical techniques presented in this review, so that the disease may be diagnosed *in vivo*. If this becomes a possibility, there is a large window of opportunity for potential therapies to slow or even stop the neurodegenerative disease progression. The earlier a patient is diagnosed, the better effect interventions may have.

5. Conclusion

Concussions and mTBI appear to initiate lasting neurophysiological changes in the injured brain, which can result in CTE development later in life. While other risk factors are necessary, a history of repetitive brain trauma is the most highly correlated event associated with disease pathogenesis. However, much more research will be necessary to further elucidate this idea.

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