



Brain Injuries-A Cause of Alzheimer's Disease & Chronic Traumatic Encephalopathy

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Abstract

Objective: Determine the effects of repetitive brain injuries, whether concussive or not and its associated neurodevelopment abnormalities.

Hypothesis: Repetitive concussive and non-concussive brain injuries increase the likelihood of developing early onset Alzheimer's disease and chronic traumatic encephalopathy.

Methods: The research paper looks at numerous study designs consisting of cohort studies, longitudinal studies and systematic reviews. Studies incorporating participants with repetitive brain injuries were used in order to assess the outcomes on the brain and its long-term effects. Individuals with traumatic brain injury were monitored over time and the levels of various biomarkers and protein build-up were traced along with its effects on behavior and cognitive functioning.

Results: The results of various studies have shown that individuals who sustained chronic traumatic brain injuries are more likely to have a build-up of tau protein, amyloid plaques and neurofibrillary tangles in the brain. These individuals also exhibited elevated levels of S100 compared to those individuals who did not suffer chronic traumatic brain injuries. Studies involving individuals with traumatic brain injuries have revealed decreased levels of ApoE and higher levels of FDDNP signals in the amygdale and subcortical regions.

Conclusion: In conclusion, the results of the research conclude that repetitive traumatic brain injuries play a significant role and are a major contributing risk factor in the development of early onset Alzheimer's disease (EOAD) and chronic traumatic encephalopathy (CTE).

Keywords: Repetitive brain injury; Concussions; Alzheimer's disease; Chronic traumatic encephalopathy

Introduction

Traumatic Brain Injuries are a major cause of death worldwide and a leading source of neurological disabilities. Traumatic brain injuries frequently referred to as a "silent epidemic" pose a significant public health issue. Individuals who sustain traumatic brain injuries as a result of sports activities, violence or due to motor vehicle accidents often present with complications later in life that are not readily evident. Due to the lack of awareness of traumatic brain injuries and its

complications such as impaired memory, cognitive function and behavioral changes, the term "silent epidemic" is often used and it is very crucial that traumatic brain injuries be dealt with appropriately to avoid these unseen complications [1]. According to the Centers for Disease Control, there are approximately 1.6 to 3.8 million sports-related brain injuries occurring each year [2]. Traumatic Brain Injuries occur when there is a sudden external force applied to the head that

may be blunt or penetrating in nature. The severity of the trauma or the amount of force the brain receives determines the signs and symptoms that one may experience (National Institute of Neurological Disorders and Stroke, n.d). Traumatic brain injuries are classified using a scale known as the Glasgow Coma Scale (GCS), which assesses the individual's level of consciousness and classifies it from a range of GCS-3 to GCS-15. According to the Center for Disease Control, for a traumatic brain injury to be classified as severe, the individual must have a GCS score between 3-8. Persons with a GCS score between 9-12 are classified with moderate brain injury and those with scores of 13-15 are considered to have mild brain injury. The identification of a concussion is made using several measures such as a computed tomography (CT) scanning, magnetic resonance imaging (MRI) and neuropsychological evaluation; however, these techniques may fail to identify the injury, or the extent of axonal damage and biomarkers may be used for diagnostic and prognosis post brain injury [3].

Eye Opening (E)	Verbal Response (V)	Motor Response (M)
4=Spontaneous	5=Normal Conversation	6=Normal
3=To voice	4=Disoriented Conversation	5=Localizes to pain
2=To pain	3=Words, but non-coherent	4=Withdraws to pain
1=None	2=No words-only sounds	3=Decorticate posture
		2=Decerebrate posture
		1=None
	1= None	Total=E+V+M

Table 1: Glasgow Coma Scale.

Traumatic brain injuries have shown to increase the risk for the most common form of dementia, leading to the development of early onset Alzheimer's disease. 30% of patients who die of traumatic brain injury have an accumulation of extracellular plaques and intercellular neurofibrillary tangles that are considered to be the pathological features of Alzheimer's disease [4]. Repeated mild traumatic brain injuries linked to a later onset of neuropsychiatric signs and symptoms specifically due to contact sports is termed chronic traumatic encephalopathy [5]. Chronic traumatic encephalopathy is a largely preventable chronic neurological disturbance comprising of depressed mood, personality, cognitive, behavioral and motor

symptoms. It is one of the major concerning neurodevelopmental pathologies stemming from repetitive concussions or mild traumatic brain injuries [6]. Alzheimer's disease and chronic traumatic encephalopathy are both characterized by the deposition of hyperphosphorylated tau proteins and the accumulation of neurofibrillary tangles in the brain and have various overlapping pathognomonic features [5]. Traumatic brain injuries over time if not treated appropriately lead to the development of these proteins and plaques in the brain leading to delayed complications.

The purpose of this paper is to give an insight into the long-term neurological consequences of repetitive traumatic brain injuries and its associated pathophysiology leading to the development of early onset Alzheimer's disease and chronic traumatic encephalopathy.

Methods

PubMed, OVID, Google Scholar & JSTOR were searched from January 2004 to December 2016 to identify studies that are relevant to the research topic. Database searches combined the terms: 'Repetitive brain injury' OR 'concussions' with the terms 'Alzheimer's disease' AND/OR 'Chronic traumatic encephalopathy'. The terms were searched as both subject headings and keywords. Studies including participants with repetitive brain injuries were used in order to assess the outcomes on the brain and its long-term effects. Only individuals who sustained one or more traumatic brain injuries and presented with signs and symptoms consistent with brain injury along with the lack of follow up and appropriate care were included into the research. The participants were recruited for the study on the bases that they must be experiencing signs or symptoms of mild cognitive impairment due brain injury, and after ruling out all other possible causes for the neurological dysfunction.

Table 2: Describes the number of studies and the study designs that have been used in this paper.

Study Design	No. of studies
Systematic Review	2
Cohort studies	2
Retrospective study	2
Longitudinal study	2
Case-control	3

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Table 3: Evidence table.

First Author	Year of Publication	Study Design	Population Studied	Outcome/Results
Papa, Linda	2015	Systematic Review of Clinical Studies. Acceptable research designs included experimental, observational, and case-control studies.	11 to 52-year-old subjects >100 participants	S100b levels increased significantly after a soccer game and also correlated with the number of headers. Increased Tau, GFAP, & NSE
Alexander P Lin	2015	Small cohort study	5 former professional male athletes with 11 to 28 years of exposure to contact sports	Elevations in brain glutamate/glutamine and choline for early TBI. Increases in phenylalanine and fucose are recorded in the brains of athletes with repeated brain injury
Thor D. Stein	2015	Retrospective study of autopsy-confirmed cases A systematic review of possible and probable cases		Abnormal tau pathology in chronic traumatic encephalopathy. Chronicity and repetitive nature of impacts to the head, including subconcussive impacts, are key factors in chronic traumatic encephalopathy development.
Mario F. Mendez	2015		National Alzheimer's Coordinating Center (NACC) database	TBI is a specific risk factor for early onset Alzheimer's disease and may lead to disinhibition.
Philip H. Montenegro	2015		Group of athletes with head trauma such as: American football players, soccer and hockey players, boxers, wrestlers and soldiers who have received battlefield injuries.	Chronic traumatic encephalopathy has been diagnosed in a wide range of individuals with a history of head trauma.
Small GW	2013		NFL players with 1 or more traumatic brain injury. Age 45-73yrs	Elevated levels of FDDNP in all subcortical regions and amygdala. Tau deposits
Alan I. Faden	2015	Cohort study and a Retrospective cohort study: Meta-analysis of case-control studies examining the relationship between AD and TBI		Large cohort studies recently have raised a question about the relationship of TBI to AD. Chronic TBI appears to be considerably more frequent as a contributing mechanism of late brain atrophy and cognitive decline.
Helen L	2015	Experimental study		Acute and long-term consequences of TBI include excitotoxicity, apoptosis, inflammatory events, seizures, demyelination, white matter pathology, as well as decreased neurogenesis.
Thamil Mani Sivanandam	2012	Longitudinal study		Plaques which are pathological features of Alzheimer's disease (AD) found in TBI. Thus, acts as an important risk factor.

Furthermore, all studies were relatively recent within the last 10-13 years and all studies before 2004 were excluded. Participants that received appropriate care at the time of injury and those who followed up with their physicians following the injury were excluded.

The quality of the study was assessed and maintained by using only peer reviewed and published journals. Journals that were not peer reviewed were excluded. Throughout the research, study designs identified included cohort studies, longitudinal studies and systematic reviews. The journals were assessed to see if there are any potential risks to the validity and to see if any alternative explanations can be attributable to the outcomes obtained. If journal results were based on confounding variables or were attributable to other causes, those journals were also excluded from the research paper.

To synthesize and organize the outcomes, an evidence table (Table 3) will be included which will emphasize the key findings from various articles obtained through research.

This table will be used as a comparison to determine the effects of repetitive concussive and non-concussive brain injuries on the likelihood of developing Alzheimer's disease and chronic traumatic encephalopathy.

Results

The results of the Small et al. [2] study reveal elevated levels of FDDNP signals in the brain of individuals who

sustain mild traumatic brain injuries, suggesting a buildup of protein. Tau protein deposits were found in the amygdala and subcortical regions of the brain, causing the neurological changes in mood, behavior, personality, and motor abilities that were observed in the participants.

Results of a study conducted by Mendez, et al. [7] found a significant increase ($p=0.056$) in the prevalence of disinhibition, an indicator of frontal lobe dysfunction as a result of traumatic brain injury in individuals with early onset Alzheimer's disease when compared to the control; yet no significant increase in late onset Alzheimer's disease when compared to the control was found. Table 4 below shows that 13.3% of individuals with traumatic brain injuries developed early onset Alzheimer's disease compared to only 7.7% of individuals with traumatic brain injuries who developed late onset Alzheimer's disease.

Individuals, who sustain repetitive traumatic brain injuries and subsequently develop chronic traumatic encephalopathy, have abnormal perivascular accumulation of tau in astrocytes, neurons, and in the cell processes. This accumulating tau is in an irregular pattern found at the depths of the cortical sulci. Repetitive traumatic brain injuries have shown decreased volume of the hippocampus along with abnormalities in the biochemical and cerebral blood flow. Additionally, these individuals presented with slower reaction times and the magnetic resonance spectroscopy showed alterations in neurochemistry [8].

Table 4: The prevalence of traumatic brain injuries in development of early onset vs. late onset Alzheimer's disease [7].

	Prevalence of TBI in NACC-database groups			
	EOAD	EOAD-matched NC	LOAD	LOAD-matched NC
No previous TBI	1234 (85.2%)	1279 (88.3%)	3954 (91.2%)	3931 (90.6%)
Any TBI*	193 (13.3%)	161 (11.1)	335 (7.7%)	379 (8.7%)
Insufficient information on TBI	22 (1.5%)	9 (0.6%)	48 (1.1%)	

*Trend toward significance for EOAD vs. EOAD-matched controls: $\chi^2 = 3.64$, $p = 0.056$; TBI: Traumatic Brain Injury; EOAD: Early-onset Alzheimer's Disease; LOAD: Late-onset Alzheimer's Disease; NC: Normal Controls

A systematic review of clinical studies examining biomarkers of brain injury found that participants with a greater number of 'headers' in a soccer game had significantly increased levels of S100B a low-affinity calcium binding protein found in astrocytes [3].

Newer serum biomarkers for the detection of mild traumatic brain injury which include ubiquitin C-terminal hydrolase (UCH-L1) and alpha-II spectrin breakdown products (SBDP150) both have been associated with mild traumatic brain injury [3].

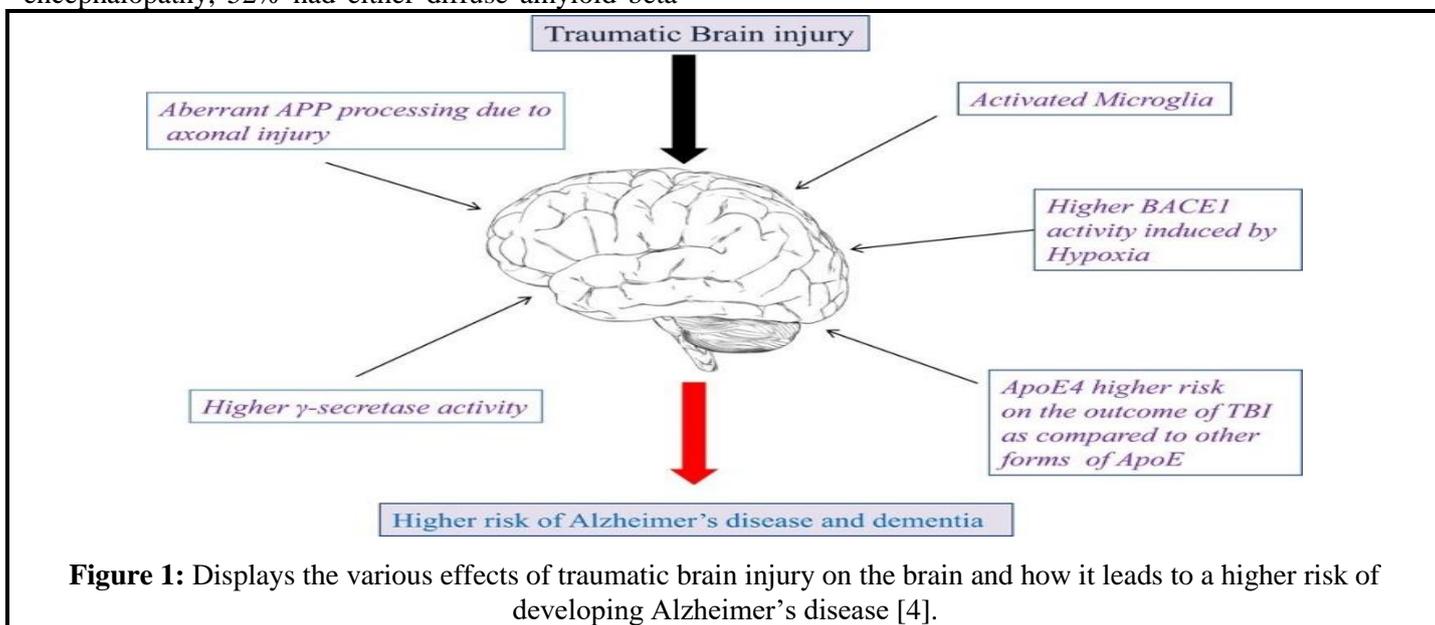
Individuals who sustained traumatic brain injuries also showed higher cerebrospinal fluid (CSF) levels of tau protein, neurofilament light protein (NFL), glial fibrillary acidic protein (GFAP), and neuron-specific enolase (NSE) regardless of whether clinical symptoms of concussion or brain injury were seen [11].

Amyloid beta precursor proteins along with various other proteins such as Neurofibrillary proteins and presenilin-1 are detected on histology of traumatic brain injury individuals as early as 2-4 hours post-injury [4,11]

Amongst the participants with chronic traumatic encephalopathy, 52% had either diffuse amyloid beta

deposition or neurotic plaques and 14% of those individuals met the criteria for Alzheimer's disease. The deposition of amyloid beta plaques was accelerated by 10-15 years in individuals with chronic traumatic encephalopathy [8].

Participants with chronic traumatic encephalopathy with amyloid beta plaques presented with significantly severe tau and lewy body pathology and were followed by poor prognosis. Anti-amyloid beta immunohistochemistry with formic acid revealed diffuse cortical amyloid beta plaques in 27 of the 28 (96.4%) participants [8].



Subjects with chronic traumatic encephalopathy had atrophy of the cerebral cortex, mostly in the frontal and temporal lobes. They had thinning of the corpus callosum, loss of white matter, enlarged ventricles and cavum and fenestrated septum pellucidum [8].

A relatively new technology, involving in vivo localized correlated spectroscopy (L-COSY) demonstrated Individuals with repetitive brain injuries had considerable changes in the neurochemistry of the athletes. The results of the localized correlated spectroscopy exhibited a 31% increase in the levels of glutamine/glutamate, a 65% increase in choline, a 60% increase in fucosylated molecules and a 46% increase in the levels of phenylalanine. These results, as established by the sample size had a p-value of 0.05 and a power of 90% [9].

Traumatic brain injury patients have a significant five-fold decrease in the levels of APOE and a 1000-fold

increase in tau levels in the cerebrospinal fluid. Mice that had insufficient levels of APOE had lower levels of defensive antioxidants following brain injury. APOE2 is known to have protective effects whereas APOE4 is considered to be a major risk factor in the development of Alzheimer's disease. CSF-tau levels in healthy individuals are low to non-existent; when high levels are present in CSF it suggests axonal damage [4].

The APO-E4 allele is a major risk factor in the development of Alzheimer's disease and those with the E4 allele have increased amyloid beta levels following brain injury and present with more severe clinical outcomes. The G219T polymorphism in the APOE promoter region has been associated with traumatic brain injuries with concussions [8].

A diffusion tensor imaging (DTI) study of white matter tracts showed that 61% of mid traumatic brain injury individuals showed significant alterations in the corona

radiate, anterior limb of the internal capsule, superior longitudinal fasciculus, optic radiation, cingulum and the genu of the corpus callosum. The acute-phase traumatic brain injury group showed considerably reduced white matter integrity across several tracts and numerous other white matter tracts not initially effected also showed decreased functioning 6 months post-injury. Participants with mild traumatic brain injury also performed significantly poorer (p-value <0.001) across most neuropsychological domains particularly language, memory and executive functioning and a great portion of the sample size worsened over time [10].

Discussion

The “PET Scanning of Brain Tau in Retired National Football League Players: Preliminary Findings” study conducted by Small et al. [2] was intended to study the effects of mild traumatic brain injuries on the development of Tau proteins in the brain and its associated neurological effects. According to this study, the retired athletes from the NFL, with a history of 3 or more concussions or mild TBI's, were three times more susceptible to being diagnosed with depression and five times more likely to be diagnosed with mild cognitive impairment. This study was performed on five retired National Football League (NFL) players aged 45 years or older. The participants were recruited for the study on the bases that they must be experiencing signs or symptoms of mild cognitive impairment (MCI) due to contact sports, and after ruling out all other possible causes for the neurological dysfunction such as strokes or tumors. The control subjects were healthy males with no signs or symptoms of MCI, and otherwise comparable in age, BMI, years of education and family history. The participants were injected with a biomarker called FDDNP, which allowed the tau tangles and the amyloid plaque deposition in the brain to be measured. Prior to the use of FDDNP as a biomarker, chronic traumatic encephalopathy would be found only when an autopsy was conducted, revealing a widespread accumulation of phosphorylated tau protein as neurofibrillary tangles [2].

A few limitations of this study carried out by Small et al. [2] include: the small sample size, the lack of autopsy confirmation of tau proteins, and the difference in genetic and cerebrovascular health along with the risk factors for the subjects and control groups. The mentioned limitations must be taken into consideration when evaluating the overall study or experiment as it helps establish the strength and credibility of the study and determines how accurate the results may be.

One of the major limitations of the Small et al. [2] study is the small sample size used to carry it out. Five retired national football league players were chosen for the study and the entire research is based on those five individuals. The results of the study indicate that the players had significant higher FDDNP signals in amygdale and subcortical regions when compared with the control group. However, none of the correlations reached statistical significance due to the small sample size. This article also consists of selection bias, as the subjects involved in the study are not representative of the population; this is due to the very small sample size and lack of random sampling. Furthermore, the results of this preliminary study need to be interpreted with caution and further investigation needs to be done.

Lack of autopsy confirmation for the build-up of tau proteins in the brain associated with mild traumatic brain injuries is also another limitation the ‘Small et al.’ study faces. Although there are elevated FDDNP signals in the brain, which suggests build-up of protein, there is no certain way of confirming this deposition, unless there is a death of a participant in which case an autopsy would confirm the accumulation of tau protein in the brain. The lack of autopsy confirmation may be due to the lack of technology available to assess the build-up of proteins prior to participant death, ultimately hindering the validity and reliability of the test.

Large cohort studies recently have raised questions about the relationship of traumatic brain injury to Alzheimer's disease. Research suggest that traumatic brain injury is a strong and specific risk factor that promotes the development of early onset Alzheimer's disease but does not necessarily cause Alzheimer's disease. A meta-analysis of 11 case control studies confirmed the association of moderate to severe traumatic brain injuries and early onset Alzheimer's disease and other studies including retrospective cohort studies have shown a greater risk for the development of Alzheimer's disease in people with traumatic brain injures [7].

Acute and long-term consequences of traumatic brain injury continue to occur due secondary injury which includes: excitotoxicity which is the over activation of the excitatory neurotransmitter receptors such as glutamate and N-methyl-D-aspartate (NMDA); demyelination which occurs when the protective coating known as myelin sheath found around nerve fibers is damaged; along with decreased neurogenesis that activates multiple apoptotic and inflammatory pathways leading to an increase in chemical mediators of injury [11].

Many pathologic features are shared in acute brain injury and Alzheimer's disease, including but not limited to amyloid beta precursor protein, tau phosphorylation and neurite degeneration. Evidence suggests there is accumulation of amyloid beta plaques and tau protein in the brain as a result of brain injury, however the location where these proteins accumulate varies compared to that seen in Alzheimer's disease not resulting from traumatic brain injury [4]. In chronic traumatic encephalopathy resulting from traumatic brain injuries, there is abnormal perivascular accumulation of tau in neurons, astrocytes and cell processes that differ from tauopathies occurring via Alzheimer's disease or various other tau-related diseases [8].

Tau protein, which is an intracellular, microtubule associated protein found in axons when measured in participants with traumatic brain injury, was found to be significantly elevated in both the plasma and cerebrospinal fluid. However, no correlation was found between the plasma and CSF tau proteins as CSF-tau correlated with the clinical outcomes of traumatic brain injury while the plasma-tau did not. Tau levels peaked significantly during the first hour after a traumatic brain injury resulting in a concussion and remained elevated post-concussion when compared to the pre-concussion samples [3,11].

Neurofibrillary proteins, amyloid precursor protein (APP) and presenilin-1 along with amyloid beta protein are detected in brain tissue samples that are harvested 4 weeks after a traumatic brain injury. Axonal damage is almost always a universal outcome of brain injury leading to the formation and accumulation of amyloid precursor protein (APP) through continued neuronal damage known as secondary injury [4,11].

16% of individuals with pathological signs and symptoms of chronic traumatic encephalopathy had no prior history of concussions; therefore, suggesting that chronic repetitive brain injury, incorporating sub-concussive effects are the key players in the development of chronic traumatic encephalopathy. Amyloid beta plaque deposition was highest at 70% in boxers, followed by 51% in football players and 41% in military veterans; further supporting that repetitive injury to the brain is what causes chronic traumatic encephalopathy [8].

Traumatic brain injury participants had enlarged ventricles along with the cavum vergae, which is also known as the 6th ventricle and cavum septum pellucidum [8]. Previous studies have determined that

the cavum septum pellucidum rarely seen in normal individuals is a significant marker for cerebral dysfunction and often presents with neurodevelopmental abnormalities. Cavum vergae is seen to some frequency in both normal and developmentally delayed individuals [12].

The elevated level of glutamine/glutamate, choline, fucosylated molecules and phenylalanine as seen via localized correlated spectroscopy (L-COSY) has a major limitation in the sample size used. The study was solely based on five retired professional male athletes and all results obtained are based on the small sample size. According to the study, N-acetyl aspartate (NAA) and myo-inositol (mI) were also expected to be elevated in individuals with repeated brain trauma as seen in previous research; however there was merely a 7% increase in the levels of N-acetyl aspartate (NAA) and a 10% increase in myo-inositol (mI) which is considered to be a relatively small change that does not meet statistical significance [8].

Elevated levels of glutamate and glutamine are considered to be a poor prognostic factor in individuals who sustain repetitive brain injury. Glutamate along with being a major excitatory neurotransmitter is also an important neuronal biomarker when elevated signifies poor outcome in traumatic brain injury patients. Glutamine is an amino acid and a glial metabolite that plays a role in inflammation of neurons and has been associated with Alzheimer's disease. Choline and several of its related membrane metabolites are found in individuals with traumatic brain injury and is reflective of diffuse axonal injury [8].

Caspases, a protease enzyme known for its essential role in apoptosis plays a significant role as a key enzyme that target cytoskeletal breakdown thus inhibiting axonal transport. Hence targeted inhibition of the caspase enzymes of the apoptotic pathway may limit secondary injury to axons thereby limiting the release of chemical mediators, which contribute to the formation of amyloid plaques and neurofibrillary tangles. ApoE can also serve as a biomarker for traumatic brain injury as high levels of apoE4 are considered to be an important risk factor for Alzheimer's disease; however, ApoE as a biomarker has not been widely researched [4].

The diffusion tensor imaging (DTI) study showed significantly reduced neuropsychological functioning. 56.7% of the individuals remained impaired in the neuropsychological domains while 33.3% of the individuals worsened. 63.3% of the participants had impaired language functioning and 3.33% of those

participants worsened with time; approximately 33.3% of the individuals had impaired memory 6 months post injury. The neuropsychological evaluations were completed approximately 4.35 hr after full GCS (Glasgow coma scale) recovery and the diffusion tensor imaging procedures were completed within approximately 10 hr post-trauma to identify structural changes. Results of the study show a significant correlation between the neuropsychological deficits and the white matter tract integrity within hours of injury as well as 6 months post injury [9].

The lack of biomarkers for the detection of traumatic brain injury is one of the main limiting factors in the advancement of therapeutics. Further research opportunities and techniques must be explored so that various biomarkers can be utilized in the detection of traumatic brain injury and the development of early neurological changes. Autopsy is one of the main ways of detecting brain changes in traumatic brain injury participants and this confirmatory test is only done when a death of a participant occurs. Hence, advancements in techniques to detect changes in the brain prior to death are needed so that individuals can be taken care of appropriately. In order to avoid neurological problems such as early onset Alzheimer's disease and chronic traumatic encephalopathy, it is imperative the long-term consequences of traumatic brain injuries if not dealt with in a timely manner are made aware to the public.

Conclusion

Traumatic brain injuries sustained repetitively over time are a major contributing risk factor and not a causative mechanism for the development of early onset Alzheimer's disease and chronic traumatic encephalopathy. Research has shown adequate data in support of tau protein, neurofibrillary tangles and amyloid plaque build-up in the brain as a result of chronic traumatic brain injury; however, this build-up occurs in areas that differ from the pathologic build-up that occurs in Alzheimer's disease. Studies have additionally shown elevated levels of various markers and signals such as S100, glial fibrillary acidic protein (GFAP), neuron specific enolase (NSE), ApoE4, FDDNP proteins which further support the indication of traumatic brain injuries being an important risk factor in the development of Alzheimer's disease and chronic traumatic encephalopathy.

With increasing support for sports related repetitive traumatic brain injuries and its associated axonal injury, the risk of developing long-term neurodegenerative

complications cannot be ignored. Many popular sports have made changes in the way they manage the sport and its rules and regulations; as such, making the public aware of the complications of traumatic brain injuries and concussions sustained whether through motor vehicle accidents, abuse, sports etc. will lead to appropriate care and follow up limiting the neurological impact in the long run.

The limitations of the research mentioned in this paper must be taken into consideration when determining the overall validity of the study as it contributes to the credibility and further investigation may be needed to confirm the results.

Conflict of Interest

None declared.

Funding

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