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Long-Term Neurological Effects of Multiple Concussions in Athletes Who Perform Contact Sports: The Development of Chronic Traumatic Encephalopathy

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ABSTRACT

Contact-sports are often regarded as one of the most dangerous athletic events to participate in, as countless injuries could occur. Traumatic brain injuries (TBI's) can occur by repeated concussions or severe impacts to the skull in these sports, and can unfortunately lead to various neurodegenerative diseases such as CTE. The accumulation of p-tau from the oxidative stress of these blows to the brain destabilizes neurons and causes the brain to collapse in function. This secondary literature review aims to identify possible diagnostics and treatment options in the early stages of CTE when the patient is still alive. Through solely online sources, the paper, which is focused on neurology, delves in-depth into how radiology, environmental hazards, biomarkers, genetics, aptitude tests, and updated safety equipment and rules can hopefully prevent, diagnose, and treat CTE. These online sources contained keywords such as "CTE", "neurodegenerative diseases", "contact sport risks," and "biomarkers" to be utilized as evidence. These categories presented varied methods in which technology could advance in the future to combat this neurodegenerative disease, such as utilizing cognitive domains from Alzheimer's and Parkinson's disease to see parallel patterns in CTE and identify unique ones in cognitive screening exams. Most causes of death of those associated with CTE are suicide and substance abuse, and nobody can know why their behaviors are so different in life after athletics due to CTE only being discovered in autopsies after death. These aforementioned ways could help solve a critical issue many researchers have faced ever since contact-sports were invented.

Introduction

The human brain is widely regarded as one of the most vulnerable organs in the body, even more delicate than the heart. While our skeletons and layers of tissue are able to protect most of our organs, the human brain only has the skull for defense. This highlights a major issue in terms of contact sports such as hockey, American football, and boxing, as athletes repeatedly make physical contact that often involves huge blows to their heads. These repeated collisions can severely affect the brain through concussions, which are events of temporary unconsciousness or confusion caused by a blow on the head. Multiple instances of concussions over a long period of time can result in the development of a neurodegenerative disease such as Chronic Traumatic Encephalopathy (CTE). In the NFL, an average of 91 percent of former players contracted some forms of CTE after their retirement, indicating the severity of neurodegenerative diseases in such physical sports (McKee, 2023). Unfortunately, there is no way to treat CTE or any likewise diseases as it is a progressive ailment that worsens over time. While this disease can only be detected in an autopsy after death, the development of biomarkers and other prevention methods can be utilized to detect neurodegenerative diseases early to lessen the catastrophic impact.

Since CTE has been linked to repetitive head injuries, even non-athletes can still experience this disease, and as such is being heavily studied and monitored across the globe. A quantitative study in Australia conducted an analysis of former athletes and non-competitive athletes who had all participated in contact sports in their lifetimes. This study found that twenty out of twenty-one participants had developed some sort of neurodegeneration, with 13 participants having CTE and other neurological pathologies (Suter et al., 2022). Another interesting fact to note is that six members with CTE and one without it died by suicide, which is continuosly reported as the leading cause of death for those afflicted with this condition (Sutter et al., 2022). As shown, there is quite a clear correlation between these repetitive head injuries and the neurodegeneration of the brain as most participants in the study had some sort of neurological ailment. The brain scans of these participants (dead during time of study, volunteered for brains to be scanned) show high concentrations of phosphorylated tau (p-tau) in cell nuclei, which is a protein that helps stabilize neurons, specifically axon microtubules. This accumulation of the protein occurs by oxidative stress with repetitive injury to the brain, which then causes the brain to malfunction. This results in the microtubules becoming unregulated, causing the brain to waste away in a state known as atrophy. The takeaway is that p-tau can be found in blood plasma, and has previously been studied in hopes of being utilized as a biomarker for its easy sampling (Holper et al., 2022).

As previously stated anyone that does activities or careers that could potentially have risks of head trauma should always be monitored by regular checkups. A mixed methods study in Maryland focuses the research of CTE specifically on military personnel. The study discovered that of the 225 participants, only ten individuals had CTE. However, these ten were the only people to have heavily played in a contact sport and have intense blast exposure during their service (Priemer et al., 2022). This correlation further explains the link between repeated head injury and the possible development of neurodegenerative diseases. But this study also finds that there are a wide range of cases in which diseases like CTE can be developed, not just in contact sports. Suicide again was the leading cause of death with the group that had any head injuries. The participants with CTE also demonstrated high instances of alcohol and substance abuse, and while the sample size was not large enough to make a generalization, it is definitely interesting to note. This was all possible due to an MRI that scanned the brains in five chambers during these bodies' autopsies. As of now, there are no radiology machines or other imaging techniques to see if the brain contains any clusters of p-tau, but researchers are continuing to develop possible methods in the future.

Many neurological diseases like Alzheimer's include a behavioral assessment to identify if the patient has the disease or not. While CTE has not been found to have specific triggers in the brain or any significant negative impacts on cognitive function, some repeatedly common behaviors have been observed. Possible aptitude tests could test for increased aggression, memory loss, loss of impulse control, balance issues, and loss of productivity have all been associated symptoms in people with varying degrees of CTE (Cleveland Mayo Clinic, 2022). A mixed methods study done in South San Francisco and the University of Pittsburgh go in depth of a brain donor who had played high school, college and professional football for a total of 25 years. Personal accounts show that before his death at the age of fifty years old, there were repetitive signs of a dysthymic disorder, as well as frequent memory loss and early signs of Parkinson's disease (Omalu et al., 2005). Another finding discovered was on the possible influence of genetic factors in late-onset development of neurological diseases. The study focuses on the apolipoprotein E (APOE) allele in the patient's genotype as it has been known to increase the chances of Alzheimer's disease. The APOE isoforms differ with many variations of amino acids like APOE2 and APOE3, but any instance with these alleles have been found to have lower cognitive scores from athletes and higher risk of neurodegeneration. However, the study found that there was no clear connection between this allele and CTE, and that the disease could be contracted without the allele, too (Omalu et al., 2005). There could be hope in the future for researchers to identify if any alleles increase the risk of developing CTE, which would assist greatly in tracking down the disease while victims are still alive.

The latest research shows the definite correlation of repetitive head injuries, like concussions, that can lead to neurodegeneration of the brain. While most cases of such neurological diseases like CTE can be found in instances of athletes who played contact sports like football, rugby, and boxing, there can be other instances as well such as military combat and huge traumatic brain injury accidents (TBI). Specifically speaking, it is known that the oxidative stress creates a cascading effect that releases surplus amounts of p-tau that end up deteriorating the brain to a state of

atrophy, which leads to these diseases. However, there are a few developing treatments that physicians can utilize to detect the early stages of CTE. Advanced safety measures could be utilized in the said contact sports to reduce the impact on the brain. Biomarkers on neurological proteins such as p-tau itself could be utilized to track the amount in the brain. Even more simple diagnosing advancements such as a behavioral prognosis standard for CTE should be set in place like the systems for Parkinson's and Alzheimer's diseases, so unusual behavior can be identified as an effect of a possible neurological disorder. The development of these possible treatments could not only help patients live longer with proper care but also advance neuroscience in more severe cases across the globe.

Methodology

The main objective of this research paper is to identify any methods that could greatly assist in detecting the onset of CTE in the early stages of the disease. The end result will be to compile a list of several reasons that could increase the risk in contact sports and how to prevent it using modern day technology. This study is a secondary literature review and does not utilize any physical materials or tools beyond the evidence used from online databases. This review is being done through solely online sources and no experimentation was conducted, with a majority of the evidence being found in specific websites such as Mayo Clinic and the NIH (National Institute of Health) with keywords related to the discussion. These keywords included "CTE", "neurodegenerative diseases", "contact sport risks," and " protein biomarkers" in the aforementioned databases. Any quantitative data that were concluded from the key studies were cross-analyzed for validity and accuracy with multiple certified online sources. This evidence was used to support the following inquiries into the research in differing kinds of diagnoses for neurodegenerative diseases such as ALS (Amyotrophic lateral sclerosis) and Alzheimer's disease and to discover if any correlations can be made to CTE. Another method is identifying proteins to utilize for biomarkers for detecting differences in neuron cell chemistry and applying that to developing technology to use for imaging techniques in the future for detection in living people. The third form of discussion would center around environmental and genetic factors that could influence a person's susceptibility to be affected by traumatic brain injuries (TBI) and if CRISPR technologies could be implemented to identify said genes (or certain pollutants in the air etc.). The last configuration of research would be to delve into concussion management and safety protocols in the highest-performing contact sport leagues across the world. This would include reviewing rule changes and potential advancements in gear to reduce the risk of neurodegenerative diseases, and even looking at the data to see if youth leagues should ban any contact with the head like headers in soccer or helmet-to-helmet collisions in football. By implementing data from the online sources and combining it into a thoughtful discussion and analysis on CTE and the chances of early onset detection many athletes and others who suffer TBI can hopefully be treated earlier on in their lives before it's too late.

Symptoms of Neurodegenerative Diseases and Correlation to CTE

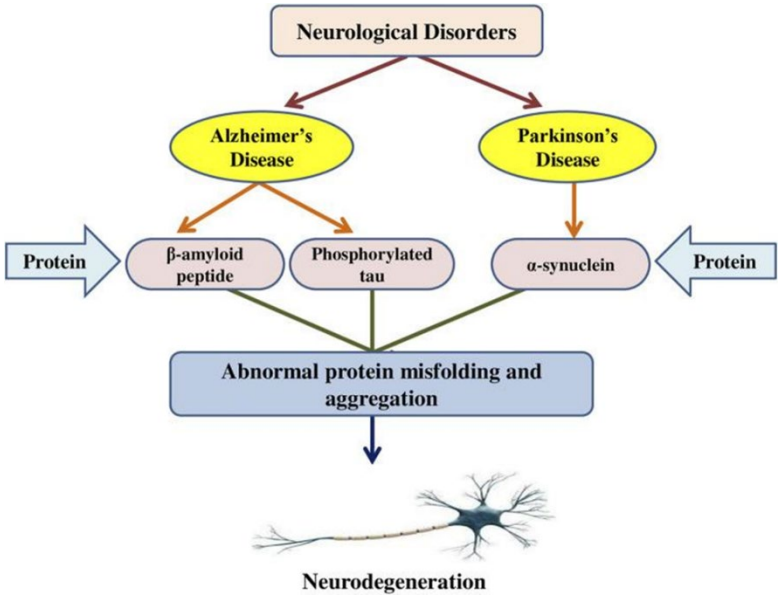

Figure 1. Main Causes of Neurodegenerative Disease**.** Source: Nabi & Tabassum, 2022**.** Description: A simple diagram that focuses on Alzheimer's and Parkinson's diseases to show how excess p-tau and other proteins like beta-amyloid peptide can cause irregular protein aggregation.

The 1960's were the most critical era in the field of Neuroscience, as remarkable discoveries and countless bounds of progress were made regarding the complex human brain. The primary focus of all these studies were not on how the brain transfigures after obtaining a disease or what occurs to the neurons over time with an ailment, but rather how do brains contract these diseases that greatly affect these people's lives? Initial tests began with using different substances to discover neural pathways and astounding progress was created with many intracellular processes being recorded and heavily examined. From then on, many drugs were administered to hopefully treat these diseases, like L-DOPA (dopamine) for Parkinson's or GABA (gabapentin) for Huntington's disease. But the most important discovery of all was the discovery of protein aggregates in relation to Alzheimer's disease, where the proteins would "fold" and "become toxic" in a sense (Neurosci et al., 2009). As time went on and imaging techniques developed, researchers were able to look specifically for these abnormalities through technology such as MRI and PET scans. These imaging techniques unfortunately cannot be used to diagnose CTE in living patients, as the protein buildup is nearly impossible to discuss. However, one strategy that could be practiced is to scan patients who show signs of loss of neurological functions such as memory loss or terrible balance control. While these scans may not be able to confirm a case of CTE it can eliminate other neurological disorders that can help narrow down the probable sickness. Another method could be to utilize aptitude tests. These cognitive assessments are most commonly done on patients with symptoms of Alzheimer's disease, with six categories tested: memory, attention, executive, language, behavior, and visuospatial (Neurol et al., 2021). Each category has a specific version of the test designed to discover any mishaps in that cognitive function. If these tests are used on patients with CTE, perhaps their disorder could be narrowed down even further to eliminate other potential neurodegenerative disorder options. Better yet, these tests could be administered to hopefully recognize any patterns with specific parts of the brain that are most susceptible specifically in correlation to CTE, to one day diagnose living patients with no need of an autopsy.

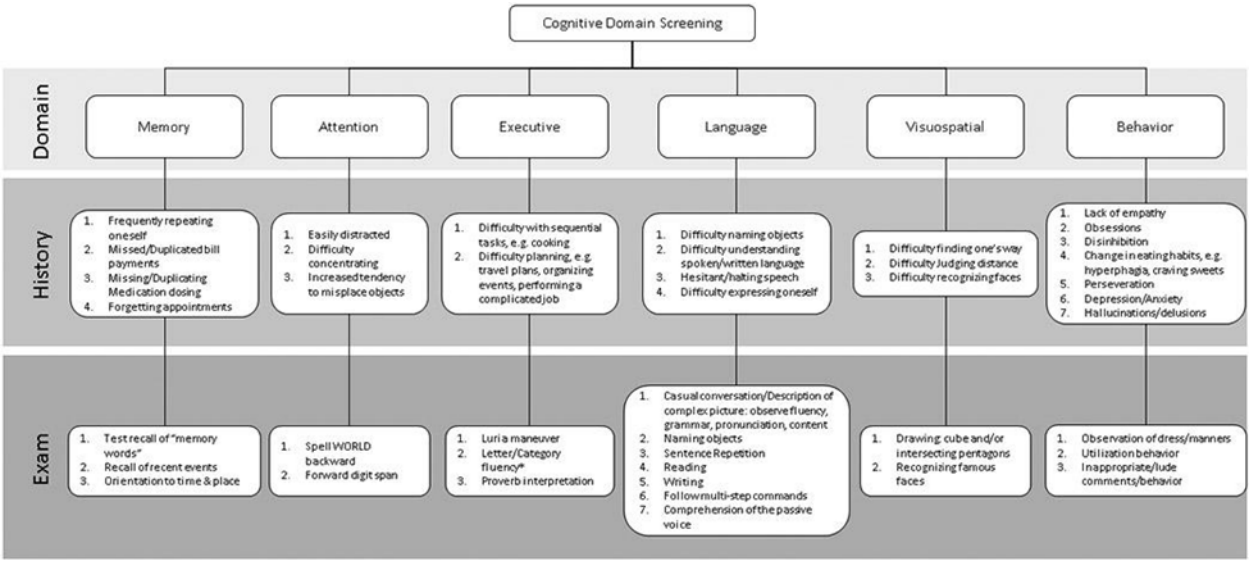

Figure 2. Types of Cognitive Domain Screening Tests**.** Source: Tipton et al., 2021**.** Description: A bubble flowchart that breaks up cognitive domains into six categories for their behavioral associations and how to examine them in patients with neurological disorders.

Environmental and Gene Factors for Increased Risk in Injuries from TBI's

Another possible test could be done through the field of genetics, as two genes have been linked to higher susceptibility in obtaining CTE. One was already discussed previously, the APOE allele, but another one was discovered. This gene is called TMEM106B and is a missense which is linked to excessive neuroinflammation (Cherry et al., 2018). This inflammation is associated with higher levels of p-tau, which has also been discussed to be a primary cause for CTE. The study unveiled a clear correlation that this gene does not cause CTE but actually increases a risk in those vulnerable to TBI's. In brief terms, it magnifies the negative effects caused by repeated blows to the head. While the allele has to be further studied, it may be early evidence of why some athletes in contact sports get significantly more affected by concussions than others who have the same amount of blows to the head. Finally, a final factor which will be discussed is probable environmental causes. Environmental neurotoxins could pollute the air and enter the central nervous systems through the lungs, where long-term damage to neurons could be sustained through inflammation (which stops these organs from functioning). Heavy metals pesticides, solvents, air pollutants, and dietary components are all responsible for triggering innate immune system responses when it is not needed, causing the system to break down (Nabi & Tabassum, 2022). While the mixed methods study discovers a clear correlation on these factors and neurodegeneration, the research only delves into the specific diseases of Parkinson's and Alzheimer's. However, most of the end results such as oxidative stress of mitochondria in neurons, neurological inflammation, and protein aggregation are also heavily associated with CTE. These two overarching components, if further studies, could inevitably save lots of individuals with afflicted minds to hopefully treat or cure patients in the future.

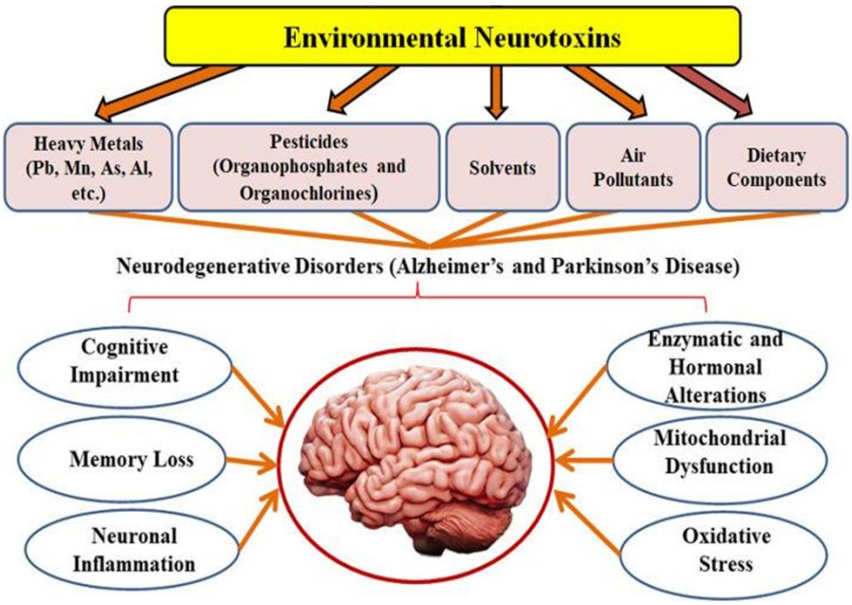

Figure 3. Environmental Causes for Neurodegenerative effects. Source: Nabi & Tabassum, 2022**.** Description: A flowchart that visualizes types of environmental neurotoxins and their respective effect on the brain for ALzheimer's and Parkinson's Disease.

Biomarkers to Identify Neuron Cell Chemistry Alterations

Biomarkers are used to capture what is occurring in the targeted cell at any given moment. Common biomarkers could be BMI (body mass index), blood pressure, and body temperature. This method of testing can include types of molecules or imaging techniques to illuminate intracellular activities for numerous variations of diseases. As already discussed, the primary cause of neurodegeneration is the extreme buildup of p-tau, which can be caused due to a variety of reasons. In the field of neuroscience, most biomarkers consist of liquids that target specific proteins through certain methods of testing. There are MRI, PET, Cerebrospinal fluid (CSF), and bloodstream biomarkers, of which MRI and PET scans have not shown any effectiveness for CTE (Ehrenberg et al., 2020). The remaining methods of utilizing biomarkers for diagnosing CTE would be blood and CSF, and fortunately both show signs of progress. One general, non-specific test for any sign of neurodegeneration is neurofilament light testing, which consists of a plasma-based test to detect axonal damage through either the blood or CSF (Coppens et al., 2023). This form of testing has not been studied for identifying specific disorders but shows heavy signs of promise to be federally administered in future clinics due to its strength in confirming signs of brain damage after a TBI or strokes. Because of this, these tests are considered mainly complementary with the two other following diagnostics: Amyloid Beta testing through blood and identifying levels of CCL11 in the CSF. Amyloid Beta plaques are most frequently associated as a symptom of Azlhimer's, any instance of a TBI has been shown to increase this protein in the brain, just like p-tau (Halicki et al., 2023). A promising figure is that the exosomal Amyloid Beta peptides have been discovered to differentiate from CTE and Alzheimer's and have successfully been used as a blood biomarker as well. A correlation was made that the higher amount of TBI leads to higher levels of this molecule. Further studies could end in a narrow focus on this protein to utilize as a biomarker in living patients from their plasma samples extracted from the blood. The other procedure is through the CSF, in which a protein previously observed to cause a diminishment of cognitive functions with increased age has been discovered to also be associated with CTE as well. The protein is called CCL11, and is found in the CSF. In a quantitative study the experiment had a control group, a deceased CTE group, and an Alzheimer's group. Of the three groups, the deceased athletes with CTE had the highest levels of this protein, even

compared to the non-contact sport individuals with Alzheimer's as well. The results clearly displayed a strong connection between multiple TBI's and the protein indiciating high levels of neurodegeneration. This investigation could optimistically result in further experiments for this novel biomarker in the near future for solely CTE. Of these two biomarker configurations the CSF route seems to be the most accurate but consistent tests for everyday clinics seem rather impossible for now. However, blood biomarkers seem to be more feasible and an effective strategy for patients experiencing trouble with their cognitive functions. These new breakthroughs in neuroscience provide tons of hope for tons of people who have experienced TBI's to one day be able to get tested and diagnosed before the onset of the disease.

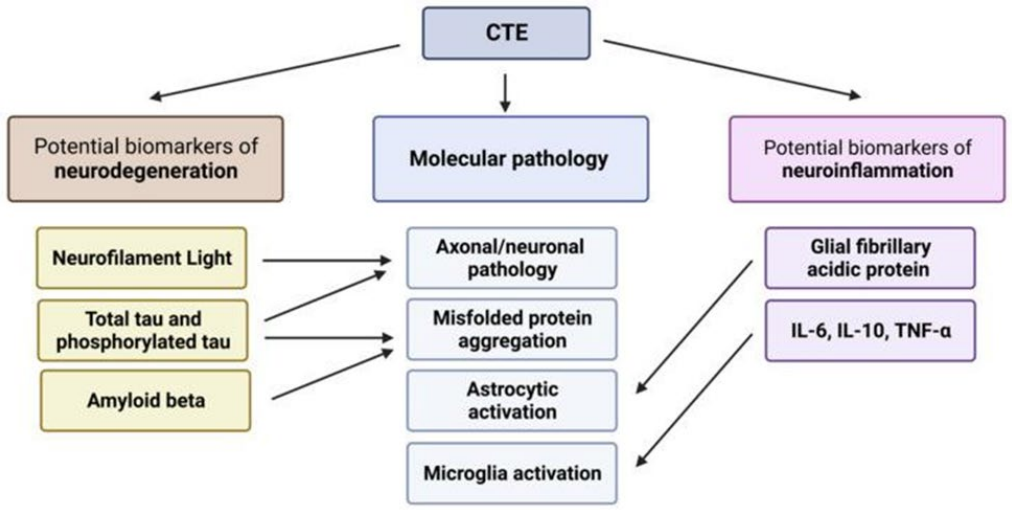

Figure 4. Differences in Neurodegeneration and Neuroinflammation**.** Source: Halicki et al., 2023**.** Description: A flowchart that visualizes how CTE can be analyzed through biomarkers associated with certain causes of the neurodegenerative disease.

Possible Improvements in Sport Safety and Protective Equipment and Techniques

While many researchers hone in on how to treat and diagnose CTE at a much earlier stage in life, another point of focus could be in preventing it almost entirely. By identifying the root cause, which is high-impact TBI's in these contact sports, we can achieve a workaround entirely. The solution is not to abolish the game, but instead to improve and upgrade the safety equipment being used, especially for helmets. In major sports leagues like the NFL and even F1, protecting the head is the number one priority, however, outdated equipment is commonly used by the athletes and newer safety standards could be implemented. The reason for this is because American football helmets were originally primarily designed to stop linear acceleration induced forces to the head. These standards were added by the National Operating Committee on Standards for Athletic Equipment (NOCSAE) in the early days of the game in hopes of reducing the frequency of severe brain injuries (Daneshvar et al., 2010). While these new designs were successful, they do not (even in newer designs) completely stop rotational impacts from lower forces to the head. Essentially, if a player is tackled from a lower position (which is almost always certain) and has contact made to the helmet, the gear can rotate and distribute the energy of the impact throughout the skull and eventually, the brain. While these hits are not as severe in terms of damage, they still can easily cause concussions which over time can lead to many neurodegenerative diseases like CTE. Many researchers have studied the biomechanics of a concussion and have all found in common that novel safety procedures should be in place to reduce the amount of concussions

annually. One proposed design is adding extra padding or foam to the outside layer of the helmet to absorb most of the blow before it reaches the brain. In one purely quantitative study, scientists determined to test how this protection would be able to perform compared to regular helmets. In this study, a helmet was dropped down and made contact with another helmet at a force of thirty G's, and that the sensor data showed that the resulting force was greater on regular helmets than padded ones, but only before the point of diminishing returns, which was more than three layers (Nakatsuka and Yamamoto., 2014). The research also discovered that a smooth finish of the padding would decrease the total force impact as well, as the helmets are able to slide off each other, redirecting the force. This study provides evidence of an updated helmet design that could prevent concussions across many contact sports like ice hockey and rugby as well.

There is already a product being sold to the market with this type of design, called the Guardian Cap. As of the 2024-2025 NFL season, players are permitted to wear these external helmet additions for the first time in league history. According to the NFL, tests were conducted on these helmets from 2018 to 2021 and discovered that concussion percentage averages reduced by fifty percent (Quigley et al., 2023). The study also found that these helmets made the most significant impact in other impact sports like ice hockey, where the players are only covered by two thin layers of interior padding. Even other equipment like mouthguards and shoulder pads could be enhanced in the future to soften blows to athletes bodies'. Another area of improvement could be concussion management protocols, in which more tests and checkups could be done on players with a significant blow to the head in any contact sport. But most crucially, implementing severe concussion policies in youth sports leagues should be the number one priority. When children and adolescent's brains are developing it is a necessity that no events should sidetrack and permanently affect growth. Annually, 300,000 children receive concussions from sports alone, rather it be from football, lacrosse, soccer, etc. (Feiss et al., 2020). Some basic rule changes should be helmets always required in any sport where heads may be impacted, immediate timeouts after an athlete has a significant blow to the head and are showing any signs of a concussion, and no use of the head when necessary. Specifically on the last rule and example is headbutts (or "headers:) in soccer. This move is when a player, usually in the opponents' penalty box off a corner kick, tries to use their head to redirect the ball coming from an angle into the goal. An average professional soccer player could head the ball for around 2000 times only from games alone, not including practices as well (Rodrigues et al., 2016). With this much contact with a ball that normally travels at very high speeds for these plays will almost certainly result in lasting impacts on the brain that could lead to multiple concussions that might wound up in neurological defects in the athletes' respective future careers. The best option for younger soccer players would be to ban this rule until past the early years of pubescence to ensure proper brain development without any concussions which could be detrimental for these kids' futures. If all these rule changes are implemented and the suggested safety equipment updates are considered then the rate of TBI's and concussions would certainly decrease which could avoid many cases of CTE in the future.

Figure 5. Heading a ball in Soccer. Source: Fatsis, 2014. Description: American soccer player Abby Wambach (right) suffered a concussion from being struck by the ball due to an impact to the head on a NWSL game on April 25th, 2013.

Discussion

There are multiple methods to diagnose and possibly treat CTE if the aforementioned scientific advancements could be made. Not only can living people be tested, but also could be helped to stop the deterioration much sooner to avoid permanent brain damage in many contact sport athletes. CTE's primary cause is the oxidation of neurons in the brain which causes p-tau to accumulate in the brain. This occurs due to the repeated stress of TBI's. These hits can range from minor to major blows, and can cause concussions, which can stack up over time and drastically alter the brain chemistry of these athletes. This could affect any one of the six cognitive domains such as memory loss or odd behavioral activities. These activities could be increased aggressiveness or even substance abuse, for example. There are also other causes, like beta-amyloid peptide overflow, which can lead to abnormal protein aggregation. Unfortunately, modern day radiology like the MRI and PET scans are unable to detect CTE, but can be utilized in the process of elimination to figure out if it is a similar neurological disease like Alzheimer's or Parkinson's. Another technique could be to analyze the genetic front for neuroligcally-prone alleles like the APOE4 or TMEM106B genes. These genes have some supporting evidence that it could increase the risk for acquired chances of a neurological disease, but further research is required. However, these genes may have a possibility of being influenced by the environment. Many environmental toxins and heavy metals could enter an individual's system and, over time, degrade the DNA in neurons or other cells linked to the brain. A way to trace if these procedures could realistically function would be through biomarkers, which can track specific molecules and be used by researchers to identify the state of the surrounding matter through blood or the CSF. Perhaps the most important procedure would be to prevent these scenarios from happening in the first place. Preventative measures like stricter rules in youth leagues for soccer, lacrosse, and football could delay any incidence of concussions and other brain-related injuries. If multiple steps like these are taken and put into place, many neurodegenerative disorders like CTE could have delayed onset effects and possibly even treatment in the future to shine a bright light of hope in the neurology field.

Conclusion

While no treatments or advanced diagnostics for CTE have officially been set into place, multiple scientific advancements are being made to one day aid ailing former athletes and other individuals with multiple TBIs or concussions to hopefully recover. Data has proven that multiple concussion and other blows to the brain can permanently affect neurological functions, even if the impact was low in terms of force. Also, most people who have CTE die by suicide or substance abuse if not by natural causes. Through genetic engineering, improvements in radiology, accurate cognitive assessments, biomarkers, improved safety for environmental hazards, and upgrades in safety equipment and rules, many concussions can be prevented and the deadly impacts can be delayed. If these precautions and discoveries are terminated, then afflicted persons can realize their illness before their loved ones solely discover it after their passing.

Limitations

This study has potential limitations, there were no experiments conducted for this paper. There were also no physical publish studies used, as every source was found from online websites with accurate and trusted writers. In terms of sample size for the utilized evidence, every study had at least ten participants for any data that was quantitative. Only one person created and edited this literature review and was only peer edited by one other researcher. There has been a great extent of previous research committed to studying CTE and other related topics as well, and no novel ideas

were discussed in this paper, they only were researched and connected for preventative measures for the neurological disease.

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