The Role of Medical Imaging in the Diagnosis of Chronic Traumatic Encephalopathy In Vivo

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Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with repetitive head impacts (RHI). CTE is characterized by the deposition of hyperphosphorylated tau proteins at the depths of the cortical sulcus in the brain. The symptoms of CTE include changes in mood and behavior, memory loss, cognitive impairment, and motor dysfunction. There has been a growing focus on this topic recently due to increased media attention. Currently, CTE can only be diagnosed postmortem via an autopsy and brain tissue analysis. Criteria to diagnose CTE in life will provide clinicians with the resources to develop a quality treatment plan to help their patients manage their symptoms. Researchers are exploring imaging techniques to diagnose CTE in vivo, such as MRI, fMRI, DTI, and CT scans. Studies show that MRI is the most established method, where scans show significant changes in brain volume, organization of white matter fibers, cortical thinning, and functional connectivity. The current state of CTE has limitations, such as biased methodology, insufficient data, and small sample sizes. However, more research with improved methods will allow researchers to conduct higher-quality studies and better understand CTE.

Introduction

Annually, traumatic brain injury (TBI) affects about 1.5 million Americans[1]. With this number growing, there has been increasing concern about the long-term health effects these TBIs contribute to[2]. Repetitive head impacts (RHI) occur in contact sports like American football, featuring dangerous tackles and helmet-to-helmet contact. These athletes are regularly exposed to RHI, which makes them susceptible to developing the neurodegenerative disease called chronic traumatic encephalopathy (CTE)[3] . However, CTE can develop in anyone who has experienced head trauma[4]. Cases of CTE have been observed in other contact sports athletes and military veterans[5].

The clinical symptoms associated with CTE include issues with mood and behavior, and cognition that can lead to impairment and motor dysfunction[3]. Further symptoms of CTE are commonly linked with suicide and impaired cognition throughout the rest of a patient's life[6]. CTE may occur in those who have experienced severe brain damage and been exposed to minor injuries, so it is essential for research to understand CTE better. As CTE results in several disabilities, diagnosis techniques must be found as helping prevent the spreading of CTE can potentially put a stop to symptoms that come with CTE and save lives. Current studies show a strong link between the development of CTE and repetitive head trauma[4]. Therefore it can be inferred that repetitive head trauma makes one more susceptible to developing CTE; however, more studies must be conducted to confirm this4. The main issues related to CTE are that it is an incurable disease and can only be diagnosed postmortem[7].

The fact that CTE cannot be currently diagnosed in vivo underscores the urgent need for improved assessment and diagnostic methods and calls for further research[8]. CTE has been reported as a factor contributing to suicidal behavior, which has been identified as a potential cause of suicides among professional athletes: a study that reported on retired National Football League (NFL) athletes and their CTE diagnosis calculated that the expected number of deaths by suicide was 21.8%[6]. Of 376 deceased former NFL players, 345 were diagnosed with CTE, about 92%[9]. So, a clarification on the diagnosis of CTE is needed to understand what must be done to help stop the development of CTE in brains. Currently, CTE can only be diagnosed through brain tissue analysis, where brain tissue is sliced, and chemicals are used to make the abnormal tau protein visible while analyzing a pattern unique to CTE in the tauopathy[10]. Repetitive head trauma triggers the accumulation of abnormal tau protein aggregates within brain cells, disrupting normal cellular function and leading to the degeneration of nerve cells over time. The tau aggregates form neurofibrillary tangles (NFT), a characteristic feature of CTE. As CTE progresses over time, the accumulation of tau aggregates and the resulting NFTs can spread throughout different brain regions. This widespread distribution of tau pathology is thought to contribute to the worsening of symptoms and cognitive decline in individuals with CTE[10]. To address this, researchers have explored different techniques to develop a method to diagnose CTE. While Computed Tomog-

raphy (CT) and Positron Emission Tomography (PET) been used to examine the possibility of a diagnosis, mag resonance imaging (MRI) has been reported to be the established and promising method[11].

This review paper aims to explore CTE in vivo diag tic methods, focusing on MRI. The first section of the cussion provides an essential background of CTE. The ond section, the core of the debate, reviews the state-of art methods to diagnose CTE in-vivo and summarizes rel studies that have used these methods to diagnose CTE. Fi the promises and limitations of CTE diagnosis in vivo are cussed and concluded with an overall analysis of the suit ity of MRI as a tool for diagnosing CTE compared to imaging methods.

Discussion

Background of Chronic Traumatic Encephalopathy

Through postmortem brain dissections of CTE-diagnosed patients, the accumulation of tau protein in the brain has been connected with CTE (see Figure 1)[10]. In healthy brains, tau proteins are necessary to properly function the brain's nerve cells, which transmit signals throughout the body. However, in individuals with CTE, tau protein becomes abnormally phosphorylated and forms insoluble aggregates, leading to NFTs and the disruption of normal brain function[12]. NFTs are a hallmark of CTE found in various brain regions, including the cortex, hippocampus, and amygdala[13]. The accumulation of NFTs is associated with the degeneration of neurons and subsequent brain damage that leads to the clinical symptoms of CTE[13]. The severity and distribution of NFTs in the brain correlate with the severity of clinical symptoms, with more severe cases of CTE associated with a higher number of NFTs. McKee et al. described that tau protein accumulation leads to the development of CTE through the abnormal phosphorylation of tau, which disrupts the protein's normal function and leads to the formation of NFTs[10].

The four stages shown in Figure 1 are the four steps of CTE, where clusters of NFTs gradually spread throughout the whole cross-section. Stage I CTE is characterized by 1 or 2 isolated perivascular epicenters of NFTs in the cortical sulci. In stage II, it can be observed that three additional cortical CTE lesions are found, and this can be connected to an early site of tau phosphorylation in NFT formation. Multiple CTE lesions and diffuse neurofibrillary degeneration of the medial temporal lobe are found in stage III. Multiple lesions are also found in the frontal cortex and insula, and neurofibrillary degeneration of the hippocampus. Finally, in stage IV, large groups of CTE lesions in the frontal, temporal, and insular cortices can be found, and there is diffuse neurofibrillary degeneration of the amygdala.

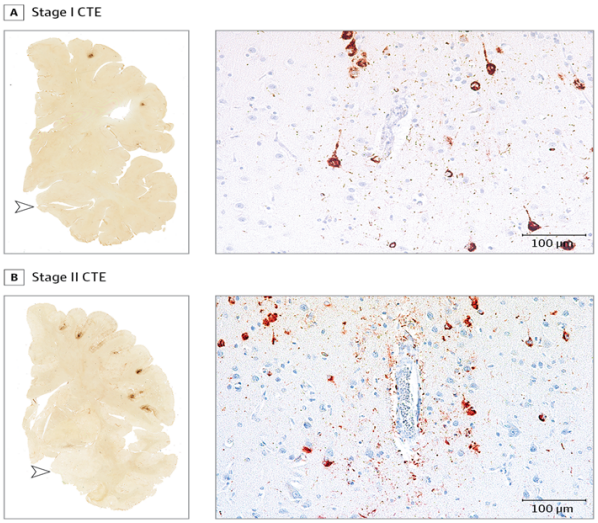

Fig. 1 The four stages of CTE, represented by the concentration of tau accumulation. The red spots represent the accumulation of abnormal tau protein stained by Immunohistochemistry. As the stages progress, tau accumulation increases (Modified, Mez et al.)[14]

According to McKee's classification, a typical CTE patient in stage I is asymptomatic or may complain of mild short-term memory deficits and depressive symptoms[14]. In Stage II, the mood and behavioral symptoms could include behavioral outbursts and more severe depressive symptoms. In Stage III, patients typically present with more cognitive deficits, including memory loss, executive functioning deficits, visuospatial dysfunction, and apathy. In Stage IV, patients present with advanced language deficits and psychotic symptoms, including paranoia, motor deficits, and Parkinsonism. As CTE progressively worsens through each stage, NFT formation is widespread in specific locations of the brain, which evidently impacts the cognition and function of the brain.

One main goal for CTE research is to observe the relationship between tau protein accumulation and microstructural level changes[15]. Recent evidence suggests that misfolded tau protein and its distribution in the brain might be more closely related to cognitive decline and tissue atrophy in Alzheimer's patients, a neurodegenerative disease closely related to CTE in terms of their tau accumulation[15]. The exact connection between tau pathology and brain tissue shrinkage remains unclear. To address this, the study created personalized models of tau-induced atrophy using clinical images from Alzheimer's patients. Using longitudinal clinical data, the study developed personalized tau-atrophy models for each individual. Surprisingly, the tau-induced atrophy rate was found to be consistent across subjects, suggesting a strong

link between tau pathology and tissue shrinkage. Furthermore, it was found that atrophy rates were higher in symptomatic Alzheimer's patients than in healthy controls. Subjects with high tau burden showed higher gray matter loss in the medial and lateral temporal lobes compared to those with low tau burden, representing a significant correlation between tau pathology and atrophy dynamics. As shown in Figure 2, gray matter, in yellow, is brain tissue that consists of a high concentration of neurons, allowing it to process information.

The presence of white matter abnormalities in the brain has also been connected to CTE[16]. White matter is found in the subcortical region of the brain, composed of axons (nerve fibers), arising from the nerve cells (neurons) and glial cells, forming connections between brain regions[16]. These connections are grouped into fascicles called white matter tracts, which allow for communication between different regions of the brain ascribed to other functions. Research has shown that there may be a correlation between CTE and the deposition of abnormal tau in the white matter, indicating that white matter also undergoes important alterations[17].

Medical Imaging and In Vivo Diagnosis of CTE

While there is currently no definitive way to diagnose CTE in vivo, techniques to diagnose CTE in vivo have been studied with MRI and CT scans and other imaging methods. The current hypothesis predicts a relationship between microstructural changes within white matter and tau proteins that reflect changes at the macrostructural level, which can be captured using medical imaging that correlates with CTE symptoms[10,18]. Studies have used this approach to attempt to diagnose CTE through imaging, where features of the brain tissue after death and imaging scans are used to connect specific features.

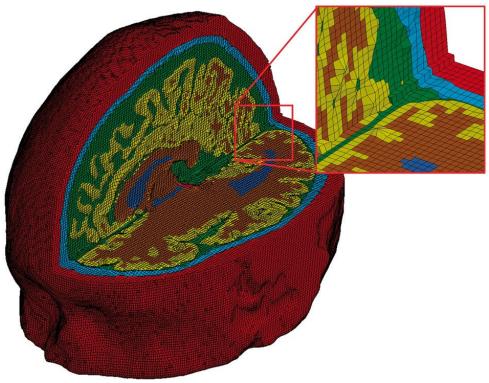

Fig. 2 An element mesh of a high fidelity 3D model of a cross-section of traumatic brain injury. In the cross-section, the colors indicate skin (red), skull (light blue), cerebrospinal fluid (green), gray matter (yellow), white matter (brown) and ventricles (dark blue) (Modified, Ghajari et al.)[19]

The techniques used include standard MRI, diffusion tensor imaging (DTI) MRI, functional MRI (fMRI), and CT. Standard anatomical MRI is used to capture changes in the brain's structure[18]. MRI scans are also helpful in detecting changes in the brain's white matter, represented by the color brown in Figure 2, the tissue that connects different brain regions[18,20]. White matter connects different brain regions that send and receive signals, impacting the ability to perform mental operations. An advanced MRI technique, DTI, has been used in studies to provide information on white matter microstructure in the brain because it is sensitive to axonal injury and changes in the myelination of white matter[21]. DTI measures the direction and magnitude of water diffusion in brain tissue to examine microstructural changes in white matter in the brain[22]. Resting-state fMRI measures the spontaneous, low-frequency blood oxygen level-dependent signals of the brain at rest and can identify networks of connected brain regions[23]. The main difference between standard MRI and fMRI is that MRI and DTI scans show structural details of the brain, while fMRI can show brain activity during a task or functional connectivity at rest[24]. Finally, CT uses X-rays to detect acute bleeding or skull fractures in those with recent head trauma[25]. CT scans come with an accompanying radiation dose and are less accurate than MRI, providing information about the size, location, and severity of brain damage related to concussions[11]. Out of all three techniques, standard MRI is the most established as it has been historically used to diagnose other progressive brain diseases similar to CTE, such as Alzheimer's disease[26].

Standard MRI techniques were used to analyze the brains of 55 CTE-confirmed men and 31 men with normal cognition at the time of the scan[18]. The MRI discovered that those with CTE had reduced brain volume in the frontal and temporal lobes and cortical thinning compared to those without CTE. Another study compared the MRI scans of 11 former NFL players to 9 healthy, non-athlete controls[27]. The scans showed that the NFL players had increased [11C] DPA-713 binding, a marker of neuroinflammation, in regions susceptible to NFT deposition, including the medial temporal lobe and cortical structures. While changes specific to CTE could not be found due to the small sample size, a connection between structural changes in the brain and CTE was suggested. Both studies detected brain volume loss and cortical thinning through an MRI scan.

Gonzalez et al. used DTI to examine changes in white matter in the brain. This study involved 53 patients with a history of multiple concussions and cognitive symptoms; 27 patients reported a history of concussions from contact sports[22]. Out of 53 patients, 19 were females, and 34 were males. The results showed that the patients had significantly lower fractional anisotropy (FA) values in several brain regions than healthy controls. FA measures the directionality of diffusion along axon bundles, and lower FA values indicate disruption

of white matter structure[22]. The use of DTI in identifying white matter abnormalities in professional pugilists (boxers) with a history of repetitive head trauma was also investigated by Wilde et al[28]. They included 10 pugilists and 9 non-contact sport controls. The results emphasized that professional fighters had significantly lower FA values than control groups in white matter regions[28]. There was a correlation between an athlete's number of fights and the extent of their white matter abnormalities, suggesting that DTI may help monitor the progression of brain injury in professional fighters. According to these studies, DTI is a valuable tool for detecting white matter abnormalities to diagnose CTE, potentially identifying early markers of CTE in individuals with head trauma[22,28].

Peters et al. used resting-state fMRI to investigate changes in brain connectivity with 24 former NFL players and 21 control subjects[29]. A loss of anticorrelation was found between the left supramarginal gyrus (SMG) and bilateral thalami in NFL players versus the controls. Interestingly, loss of anticorrelation was also found between the right SMG and bilateral thalami[29]. While this study had several limitations, the loss of anticorrelation was interpreted as a possible weakening of function between either side of the SMG and thalamus. Researchers concluded that resting-state fMRI could be useful for identifying changes in brain connectivity associated with CTE. However, it was noted that it would be best if further studies of healthy individuals were conducted.

Given that standard MRI, DTI, and fMRI imaging have been used to identify structural and functional differences in the brains of individuals with a history of repetitive head injury, MRI can be considered a promising imaging method for in vivo detection of CTE. Lee et al. found that MRI imaging was more accurate than other imaging techniques used to detect brain abnormalities in individuals with a history of repetitive head trauma[30]. While DTI is valuable for examining white matter microstructure and connectivity, it is still unclear whether this imaging method is able to fully capture macrostructural changes and brain abnormalities specific to CTE[22]. The ability of DTI is useful in that it detects microstructural changes in white matter tracts and is sensitive to axonal damage and disruption of fiber tracts; however, DTI primarily focuses on white matter structures and thus has a limited use. Similarly, fMRI, while usually used with MRI to assess structural aspects of the brain, has its limitations for detecting CTE[29]. fMRI measures changes in blood flow and oxygenation levels in the brain, indirectly reflecting neural activity. However, this is done through activation maps showing brain activity patterns, while MRI is able to generate concrete images of brain structures[22,29]. In the future, fMRI may offer insights showing functional alterations accompanying the changes seen in CTE. However, currently, more can be confirmed about tau pathology in images generated by MRI than activation maps. MRI can reveal macrostructural changes, such as brain volume loss and cortical thinning, and is well-established in clinical practice[30]. The non-invasive nature of MRI and its practical suitability for diseases similar to CTE makes MRI a promising method for imaging diagnosis.

This table summarizes the diagnosis technique, sample size and main results of a selection of relevant state-of-the-art studies that examine the diagnosis of CTE in vivo. We assumed that NFL athletes are male unless stated otherwise. (Abbreviations: DTI, Diffusion Tensor Imaging; NFL, National Football League; MRI, Magnetic Resonance Imaging; CTE, Chronic Traumatic Encephalopathy; FA, Fractional Anisotropy; fMRI, Functional Magnetic Resonance Imaging; SMG, Supramarginal Gyrus)

Limitations and Promises

While many other studies have been conducted on diagnosing CTE in vivo, commonly cited studies are limited by methodological biases, pathological inconsistencies, insufficient data, and reliance on postmortem data33. Due to the current state of CTE diagnosis, getting a large sample size and an unbiased data set is complex. The small sample size limited many studies (86 participants at most). Similarly, primarily men were involved when the sex of the participants was given. Participants' history of other contact sports, activities or other underlying conditions besides concussions were not considered. However, the studies were able to draw a clear connection between the severity of concussions and their relationship to CTE-related features in a patient's MRI scan. A study that includes a more significant number of participants with diverse head injuries, backgrounds, and contact sports must be conducted to get a deeper understanding of CTE. People will understand if they are at risk of developing CTE and the expected brain changes related to its development.

While there is a need for further validation, the preliminary evidence suggests that CTE may be observable using in vivo medical imaging scale techniques such as MRI[18,22,27]. As more studies are conducted, the relationship between macro changes and observations in imaging will be solidified. This is important for researchers to understand CTE better, which will possibly help towards prevention in the future. Specifically, slowing the spreading of CTE in the brain can lessen the effects, given that it is currently incurable. Funding for CTE is growing, with many large corporations providing grants for researchers to find a way to diagnose CTE in vivo[31]. In 2015, the National Institutes of Health and the National Institute of Neurological Disorders and Stroke awarded researchers a $16 million grant. In 2016, the NFL joined and promised to pledge $100 million to neuroscience research to make football safer[32]. With the growing support of companies, awareness of the dangers of CTE will become more widespread, and researchers will be allowed to explore CTE[7].

Table 1 Relevant state-of-the-art studies exploring in vivo diagnosis of CTE

Study	Method of Diagnosis	Sample Size	Results
Diffusion Tensor Imaging Correlates of Concussion Related Cognitive Impairment[22]	Diffusion Tensor Imaging	53 total patients; median age of 55 years; 19 females; 34 males; 27 sports-related trauma; 14 motor-vehicle accident; 9 falls; 7 head impact; 1 physical abuse; 1 suicide attempt	Concussed patients have a lower value of organized white matter fibers, implying that the white matter structure is disrupted.
Neuroinflammation and brain atrophy in former National Football League players: An in vivo multimodal imaging pilot study[27]	Magnetic Resonance Imaging	11 former National Football League players; age >55 years; 7 Caucasian; 4 African American; 9 age comparable controls	Scans were able to detect significant atrophy of the right hippocampus and an increase in binding of [11C] DPA-713 to TSPO, a marker of brain injury and repair, in NFL players.
Structural Magnetic Resonance Imaging profiles and tau correlates of atrophy in autopsy-confirmed Chronic Traumatic Encephalopathy[18]	Structural Magnetic Resonance Imaging	55 autopsy-confirmed Chronic Traumatic Encephalopathy males; 31 normal-cognition controls; age >60 years	Patients with Chronic Traumatic Encephalopathy had reduced brain volume, cortical thinning, and greater white matter abnormalities compared with the control group.
Chronic Effects of Boxing: Diffusion Tensor Imaging and Cognitive Findings[28]	Diffusion Tensor Imaging	10 professional male pugilists (age 27-59 years); 9 males with no history of contact sports (age 26-57 years)	The pugilists had lower Fractional Anisotropy values in white matter regions. There is a correlation between the number of fights and the extent of white matter abnormalities.
Characterizing the Link Between Glial Activation and Changed Functional Connectivity in National Football League Players Using Multimodal Neuroimaging[29]	Resting-state Functional Magnetic Resonance Imaging	24 former National Football League players; 21 healthy controls; all male participants; median age National Football League players was 37.5 years; median age control was 29 years; 4.0 median number of concussions; 9.0 median years in National Football League	Functional Magnetic Resonance Imaging detected a loss of anticorrelation in the left and right supramarginal gyrus (SMG) and the thalamus.

All that can be done currently to stop the development of CTE is prevention. The fact that CTE is incurable makes it important to understand its prevention. As the characteristics of CTE are unknown, it is believed that the only way to lower the risk of getting CTE is to avoid repeated head injuries[7]. For example, wearing the correct protective equipment can be helpful if playing contact sports. Furthermore, ensuring head injuries are treated and checked on properly can help the prevention of CTE[31]. Since 2002, the NFL has made 42 rule changes to protect players through safer practice methods, education programs, and enforcing the NFL Game Day Concussion Protocol37. The protocol is reviewed annually and designed by a board of physicians and scientists to provide a checklist of the necessary steps that must be taken when someone has a concussion[33].

Conclusion

This review highlights the importance of diagnosing CTE in vivo and summarizes the state-of-the-art methods to diagnose this disease. An in vivo diagnosis method is important to establish an understanding of the characteristics of CTE to help towards early intervention and prevention of CTE in the future. Furthermore, it is crucial to develop imaging techniques to detect CTE at earlier stages to prevent it from perpetuating.

Preliminary results, including the studies in this manuscript, suggest significant differences between those with CTE symptoms and controls, including disrupted white matter structure, brain volume loss, cortical thinning, and decreased functional connectivity between the DMN and SN.

Most studies on CTE diagnosis have included small sample sizes, methodological biases, pathological inconsistencies, in-

sufficient data, and reliance on postmortem data34. Due to the current state of CTE diagnosis, getting a large sample size and an unbiased data set is difficult. A study that includes many participants, diverse backgrounds, various types of head injuries, and different contact sports played must be conducted to understand CTE better. This will allow people to understand their potential to develop CTE and the preventative measures that should be taken.

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Abbreviations

TBI – Traumatic Brain Injury
RHI – Repetitive Head Impacts
CTE – Chronic Traumatic Encephalopathy
NFL – National Football League
NFT – Neurofibrillary Tangle
CT – Computed Tomography
PET – Positron Emission Tomography
MRI – Magnetic Resonance Imaging
DTI – Diffusion Tensor Imaging
FA – Fractional Anisotropy
SMG – Supramarginal Gyrus

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