The science and questions surrounding chronic traumatic encephalopathy

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Recently, the pathobiology, causes, associated factors, incidence and prevalence, and natural history of chronic traumatic encephalopathy (CTE) have been debated. Data from retrospective case series and high-profile media reports have fueled public fear and affected the medical community’s understanding of the role of sports-related traumatic brain injury (TBI) in the development of CTE. There are a number of limitations posed by the current evidence that can lead to confusion within the public and scientific community. In this paper, the authors address common questions surrounding the science of CTE and propose future research directions.

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KEY WORDS chronic traumatic encephalopathy; concussion; subconcussion; diagnosis; treatment; research directions; controversies

Consensus Statement from the International Conference on Concussion in Sport, which was held in Zurich in 2012, published the following concern:

…the interpretation of causation in the modern CTE case studies should proceed cautiously. It was also recognized that it is important to address the fears of parents/athletes from media pressure related to the possibility of CTE.33

To better assess our scientific understanding of CTE, we reviewed the scientific literature on the long-term effects of sports-related TBI and CTE. We use this information to assess the answers to the most pertinent questions and discuss research opportunities to address the questions that remain unanswered.

CTE-Related Science and Questions
Does the Presence of Cerebral Tau Protein Equal a Diagnosis of CTE?

A common misconception is that the presence of tau protein in the brain leads to a diagnosis of CTE.16
Tau Biology

Tau protein is a microtubule-associated protein that is found within the central nervous system in healthy individuals who have not experienced head trauma.2,3 Normally, tau stabilizes intracellular microtubules and exists primarily in a soluble state. Hyperphosphorylation of tau renders it insoluble and precipitates aggregation into neurofibrillary tangles (NFTs). The insoluble NFTs alter neuronal cytoplasmic function and interfere with axonal transport, ultimately leading to cell death. NFTs (and therefore tau protein) have been linked to various tauopathies, including CTE, Alzheimer’s disease, Parkinson’s disease, frontal-lobe lobar degeneration (FTLD), and progressive supranuclear palsy.27 as well as opiate abuse.1,4 NFTs are also commonly found in the aging brain and often have no direct correlation with functional deficits.14 The activity of phosphatases (which dephosphorylate phosphorylated tau) changes with age and temperature, thus affecting the amount of phosphorylated tau found in brain specimens in an age-dependent manner.17

CTE and Tau

CTE can only be diagnosed at autopsy by histological analysis. Previously, there was no consensus as to what constitutes CTE (Table 1, Figs. 1–4). McKee and colleagues have proposed 4 stages of CTE based on postmortem analyses of donated brains from athletes and military personnel.35 Each stage (I–IV) involves a progressive increase in the regions affected with the presence of hyperphosphorylated tau (p-tau; ranging from involvement of the frontal lobe only to involvement of all cortical lobes, the diencephalon, the brainstem, and the cerebellum). Alternatively, Omalu and colleagues have proposed 4 phenotypes of CTE.39 The phenotypes are not characterized by any clear progression from one to another but are distinct in their differences with respect to distribution of NFTs, neuritic threads (NTs), and amyloid plaques. A review of the criteria proposed by both groups has been performed.26 Davis and colleagues have challenged the CTE criteria and staging proposed by McKee and colleagues and have presented an alternative interpretation. They interpret Stage I and II CTE to represent normal aging and Stages III and IV to represent a form of FTLD, concluding that Stage I and II CTE to represent normal aging and have presented an alternative interpretation. They in-
### TABLE 1. Comparison of the proposed definitions of CTE

<table>
<thead>
<tr>
<th>Feature</th>
<th>Classic CTE</th>
<th>Omalu et al.</th>
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<th>NIH Consensus Statement*</th>
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</thead>
<tbody>
<tr>
<td>Pathological findings of CTE</td>
<td>Cerebral atrophy, neuronal loss, gliosis, and argyrophilic NFTs;12,35</td>
<td>i) &quot;Multifocal/diffuse tauopathy (may be accompanied by low-grade multifocal white matter rarefaction, microglial activation, parenchymal histiocytes)&quot;;35 i) &quot;topographically distributed NFTs/NTs (+/- diffuse amyloid plaques)&quot;;39 ii) &quot;absence of classic/neuritic amyloid plaques&quot;;39 iii) &quot;absence of pathognomonic histomorphology of other tauopathies&quot;;39</td>
<td>i) &quot;Perivascular foci of p-tau immunoreactive ATs/NFTs&quot;;35 ii) &quot;irregular cortical distribution of p-tau immunoreactive NFTs/ATs, predilection for the depths of cerebral sulci&quot;;35 iii) &quot;clusters of subpial/periventricular ATs (cerebral cortex, diencephalon, basal ganglia and brainstem)&quot;;35 iv) &quot;NFTs in the cerebral cortex (preferentially in the superficial layers)&quot;;35</td>
<td>p-tau–related pathologies: i) &quot;Abnormal p-tau immunoreactive pretangles and NFTs preferentially affecting superficial layers (layers II–III), in contrast to layers III and V as in AD&quot;;12 ii) &quot;in the hippocampus, pretangles, NFTs or extracellular tangles preferentially affecting CA2 and pretangles and prominent proximal dendritic swellings in CA4. These regional p-tau pathologies differ from the preferential involvement of CA1 and subiculum found in AD&quot;;12 iii) &quot;abnormal p-tau immunoreactive neuronal and astrocytic aggregates in subcortical nuclei, including the mammillary bodies and other hypothalamic nuclei, amygdala, nucleus accumbens, thalamus, midbrain tegmentum, and isodendritic core (nucleus basalis of Meynert, raphe nuclei, substantia nigra and locus coeruleus)&quot;;12 iv) &quot;p-tau immunoreactive thorny astrocytes at the glial limitans most commonly found in the subpial and periventricular regions&quot;;12 v) &quot;p-tau immunoreactive large grain-like and dot-like structures (in addition to some threadlike neurites)&quot;12 Non-p-tau–related pathologies: i) &quot;macroscopic features: disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and contusions or other signs of previous traumatic injury&quot;;12 ii) &quot;TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex and amygdala&quot;12 Pathognomonic: &quot;p-tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci&quot;12</td>
</tr>
</tbody>
</table>
Sixty-three cases involved football players and 69 cases involved boxers. Thirty-six of the football players played professionally (National Football League [NFL] and Canadian Football League). Of the remaining cases, 5 involved hockey players, 5 involved veterans, 3 involved wrestlers, 1 involved a soccer player, and 6 were listed as miscellaneous (physical abuse, head banging, circus clown, epilepsy).

Estimating Incidence and Prevalence

There are approximately 18,000 former NFL players. Approximately 3 to 4 million athletes (at all levels) play football every year. Moreover, these numbers pale in comparison with the total number of athletes that play contact sports or sports that involve repetitive head contact (e.g., hockey, boxing, lacrosse, soccer, equestrian sports). The Centers for Disease Control and Prevention (CDC) data on the annual number of sports-related TBIs in children provides a very conservative denominator for the calculation of the incidence of long-term adverse effects such as CTE (Table 2). These data must be taken in the context of the historical total number of reported cases of CTE (n = 153, in the scientific literature and media) and raise the critical question of the true incidence and prevalence of CTE in athletes involved in contact sports.

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**TABLE 1. Comparison of the proposed definitions of CTE**

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<th>NIH Consensus Statement*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classification system</strong></td>
<td>NA</td>
<td>Phenotype 1: “a combination of sparse to frequent NFTs and NTs in the cerebral cortex and brainstem, +/- NFTs and NTs in the subcortical nuclei/basal ganglia, no NFTs and NTs in the cerebellum, no diffuse amyloid plaques in the cerebral cortex”39</td>
<td>Stage I: “perivascular p-tau NFTs in focal epicenters at the depths of the sulci in the superior, superior lateral or inferior frontal cortex”35</td>
<td>Not discussed</td>
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<td></td>
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<td>Phenotype 2: similar to Phenotype 1, except for “sparse to frequent diffuse amyloid plaques in the cerebral cortex”39</td>
<td>Stage II: “NFTs in superficial cortical layers (adjacent to the focal epicenters), nucleus basalis of Meynert, locus ceruleus”35</td>
<td></td>
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<td></td>
<td></td>
<td>Phenotype 3: “a combination of moderate to frequent NFTs and NTs in brainstem nuclei (brainstem predominant), none to sparse NFTs and NTs in the cerebral cortex and subcortical nuclei/basal ganglia, no NFTs and NTs in the cerebellum, no diffuse amyloid plaques in the cerebral cortex”39</td>
<td>Stage III: “dense p-tau in medial temporal lobe structures (hippocampus, entorhinal cortex, amygdala), widespread regions of the frontal, septal, temporal, parietal and insular cortices, diencephalon, brainstem and spinal cord. Macroscopic: mild cerebral atrophy, septal abnormalities, ventricular dilation, sharply concave contour of the third ventricle, locus ceruleus and substantia nigra depigmentation”35</td>
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<td>Phenotype 4: “a combination of none to sparse (several) NFTs and NTs in the cerebral cortex, brainstem, subcortical nuclei/basal ganglia (incipient); no NFTs and NTs in the cerebellum; no diffuse amyloid plaques in the cerebral cortex”39</td>
<td>Stage IV: “p-tau pathology involved widespread regions of the neuraxis including white matter, prominent neuronal loss, cerebral cortex gliosis, hippocampal sclerosis. Further cerebral, medial temporal lobe, hypothalamic, thalamic and mamillary body atrophy, septal abnormalities, ventricular dilation and pallor of the substantia nigra and locus ceruleus”35</td>
<td></td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>Progression of clinical symptoms in 3 stages39</td>
<td>No progression noted</td>
<td>Progresses slowly over decades from Stage I to IV</td>
<td>Not discussed</td>
</tr>
<tr>
<td><strong>Pathological example</strong></td>
<td>See Fig. 1</td>
<td>See Fig. 2</td>
<td>See Fig. 3</td>
<td>See Fig. 4</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease; AT = astrocytic tangle; CTE = chronic traumatic encephalopathy; NA = not applicable; NFT = neurofibrillary tangle; p-tau = hyperphosphorylated tau.

Future Work

 Attempts have been made to characterize the antemortem clinical features of individuals with CTE through retrospective recall on the part of family members and friends of the deceased individuals with CTE. Consequently, these descriptions and findings are limited by recall bias. Additionally, considerable overlap exists between the symptoms (as reported by the family of the deceased) in published cases, symptoms in the general population of individuals without neurodegenerative disease or a history of head trauma (e.g., depression), and symptoms found in other neurodegenerative diseases, including Alzheimer’s disease, Parkinson’s disease, FTLD, and progressive supranuclear palsy.30 Given the number of asymptomatic individuals documented to have CTE (McKee et al.35 note that 11% of those found to have CTE by pathological examination were asymptomatic), the clinical relevance of the histopathological findings must be further defined.

 The media descriptions of CTE in football players represent reporting bias and the availability cascade.49 Moreover, when families have donated the brains of former football players for histopathological examination, the donations have frequently been made in relationship to be-
TABLE 2. Estimated annual number of TBIs presenting to US emergency departments for the top 5 most common nonfatal sports-related TBIs in persons 19 years or younger during 2001–2009*

<table>
<thead>
<tr>
<th>Activity</th>
<th>No. of TBIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicycling</td>
<td>26,212</td>
</tr>
<tr>
<td>Football</td>
<td>25,376</td>
</tr>
<tr>
<td>Playground</td>
<td>16,706</td>
</tr>
<tr>
<td>Basketball</td>
<td>13,987</td>
</tr>
<tr>
<td>Soccer</td>
<td>10,436</td>
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</table>

* Data obtained from Gilchrist et al.19

havioral changes that the former players exhibited prior to death, which may represent a selection bias. It is unclear to what extent the behavioral changes contributed toward the athletes’ deaths or whether the behavioral changes were the direct or indirect results of previous exposures to head injury. While there is no doubt that football players sustain mild head trauma over the course of their careers,11,15,42, the actual significance of the cumulative effects of the trauma on their lives has yet to be established.

The only way to definitively answer the critical questions surrounding etiology, incidence and prevalence, and clinical features associated with CTE is to conduct a prospective longitudinal clinicopathological study of athletes (with variable exposure levels to head contact) and nonathletes (with variable levels of head injury). Furthermore, it will be critical for multiple centers to have access to pathological specimens for evaluation and review.

Does Repetitive Brain Impact in Football Lead to Clinical Features of CTE?

Claims have been made to suggest that repetitive brain impacts in sports are the precursor to the clinical features seen in CTE.38

Available Studies

Studies linking repetitive brain impact and the development of cognitive impairment and depression in later life consist of retrospective survey analyses.21,22 A retrospective cohort study with a median follow-up of 50 years has found no increased risk of dementia, Parkinson’s disease, or amyotrophic lateral sclerosis among 438 men who played high school football between 1946 and 1956 compared with 140 non–football-playing male classmates.43 While these observational studies can demonstrate correlation, they cannot answer the critical question of causation. In comparison with the general population, athletes lead quite different lives, and their playing careers tend to be relatively short and intense, peaking early. Additional factors such as genetics, sex, age when collision sports were started, the use of performance-enhancing drugs, and substance abuse need to be taken into account in identifying the problems athletes face in later years after their sporting careers are over.

Recently reported work demonstrated that there was an association between playing football before the age of 12 and cognitive impairment in later life among NFL players.50 This study examined 42 retired NFL players and tested cognitive function using a variety of neuropsychological measures. It was, however, limited by the inclusion of subjects with learning disabilities in the younger age group, the lack of quantification of actual head impacts incurred, and the lack of assessment for possible malingering.29 There has also been some debate regarding the statistical methods employed.

Future Work

Until we better understand the long-term effects of mild head injury in sport, the combination of medical management of sports-related TBI and a conservative approach that minimizes traumatic injury to the athlete’s brain will be important. The optimal management strategy for sports-related TBI is a major research question,33 and it remains to be seen whether the proper management of sports-related TBI will protect against long-term sequelae. It is also important to acknowledge, diagnose, and treat pathological personality changes and depression in all individuals, regardless of etiology. Only a prospective study that records clinical findings and impact of exposure in the antemortem period with histopathological correlation will be able to answer the question of clinical correlation of head impact (concussion or subconcussive injury) and clinical features associated with CTE (Table 3).

Do Cumulative Subconcussive blows Predispose to CTE?

Subconcussive Episodes

The concept of concussion is controversial. The definition and diagnosis of a concussion is often subjective, as it typically involves functional rather than structural deficits.33 Subconcussive impacts are caused by head impact below the threshold that would cause a concussion. The subjective nature of concussion and subconcussions and the lack of measurable and reproducible thresholds are challenges, especially when it comes to identifying suitable patients for research studies.

Previous Work

McKee and colleagues reported that in the cohort of individuals with pathologically diagnosed CTE, 16% had no known history of concussions.51 This led them to conclude that the impacts from subconcussions were sufficient to cause CTE. An alternative explanation would be that concussion and CTE development may not be consistently correlated (i.e., not all concussions cause CTE). The majority of the evidence base for the putative role of subconcussions in long-term impairment has come from studies in rodents over the last 15 years.4 In humans, accelerometers have been placed inside helmets for proxy measurement of head impacts. The evidence has been conflicting, with wide ranges of concussion thresholds being postulated. Technological limitations, including those in contemporary devices that measure rotational acceleration, have resulted in discordance between the forces measured by the helmet and the actual effect on the subjects.4,23,32 This could of course be interpreted as the helmets functioning as they were intended and absorbing the force of impacts.
TABLE 3. Clinical features associated with CTE*

<table>
<thead>
<tr>
<th>Clinical Features</th>
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<tbody>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Mood disorders</td>
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<tr>
<td>Depression</td>
</tr>
<tr>
<td>Anxiety/ agitation</td>
</tr>
<tr>
<td>Suicidal</td>
</tr>
<tr>
<td>Apathy</td>
</tr>
<tr>
<td>Hopelessness</td>
</tr>
<tr>
<td>Manic behavior/mania</td>
</tr>
</tbody>
</table>

Behavioral disorders

- Impulsivity
- Aggression
- Disinhibition
- Paranoia
- Socially inappropriate

Cognitive disorders

- Memory impairment
- Executive dysfunction
- Attention and concentration difficulties
- Language impairment
- Visuospatial difficulties

* Based on Maroon et al.30 and Iverson et al.36

Future Work

The thresholds of head impacts that would qualify as causing concussions and subconcussions will need to be quantified. Bench models may be helpful initially, but it is not always possible to translate the results into effects in humans.35 The use of accelerometers to noninvasively measure head impacts represents the best strategy available currently.35 The technology will need to be refined to enable accurate and reproducible linear and rotational force measurements. Collaboration with engineers will be crucial in this work.

Do Clinical Findings Correlate With Pathological Features of CTE, and Is CTE a Progressive Disorder?

Previous Work

CTE has frequently been described as a progressive neurological disorder.36 This description has been based on the finding that older brains appear to have a greater amount of associated tauopathy. McKee and colleagues defined CTE as “…a progressive tauopathy that occurs as a consequence of repetitive mild traumatic brain injury.”35 However, they also acknowledged that “Although the data suggest that CTE pathology is progressive, it remains to be determined whether some individuals are relatively resilient with static or even reversible pathology.”35

Their work was based on a selected cohort of retrospectively identified brains of deceased athletes and military personnel. The cohort was separated into stages based on the amount of brain regions with p-tau. An inference was made that a person with Stage IV CTE would have previously been at Stages III, II, and I prior to death. Sampling at a single time point (after death) provides insufficient evidence to ascribe the findings to progressive disease.

Future Work

To definitively determine whether CTE is correlated with clinical findings and whether it is a progressive disorder, longitudinal studies with multiple time point sampling are necessary. These findings should also be correlated with normal tau accumulation in nontraumatized brains from older individuals to assess the impact of normal aging on tau accumulation. Further, antemortem markers to assess diagnosis and assess for CTE progression are critical. These methods will permit clinical assessment of CTE and its progressive or reversible features. To begin to define biomarkers for antemortem diagnosis, studies have examined the potential utility of imaging techniques and biomarkers with the aim of developing methods to predict structural and functional deficits after TBI. For example, preliminary data from a recent study indicated that [F-18]-FDDNP, which selectively binds to tau and amyloid-β, seemed to show a distinct pattern of imaging in PET coregistered with MRI in former professional athletes with symptoms suspicious for early CTE (Fig. 5).37 Further work is required, but this suggests that in vivo imaging may be able to indicate neurodegenerative changes through functional imaging. [F-18]-AV-1451 (also known as [F-18]-T807) is another radiotracer that binds to tau and amyloid-β that has recently been used to study an NFL player with cognitive decline and features suggestive of Alzheimer’s disease.38 However, the absence of amyloid-β as evidenced by [F-18]-Florbetapir PET imaging ruled out Alzheimer’s disease. Although the [F-18]-AV-1451 localization in this patient was not typical of CTE, the authors concluded that the overall clinical findings and the involvement of the hippocampi in [F-18]-AV-1451 retention supported a diagnosis of CTE. This case report was also limited by the lack of pathological correlation. Other PET imaging biomarkers for tau protein have been studied primarily in the context of Alzheimer’s disease but not specifically in the context of CTE. These include [F-18]-THK5105, [F-18]-THK5117, and [C-11]-PBB3.32 Large-scale clinical trials are currently underway to validate these tracers as tau tracers. In general, the suboptimal sensitivity and specificity of tau imaging biomarkers can be explained by the complex characteristics of tau proteins—they are intracellular, exist in 6 isoforms, and undergo many different posttranslational modifications. Tracers for p-tau often also bind to amyloid-β due to the shared β-pleated sheet structures common to both p-tau and amyloid-β, requiring a high ratio of p-tau to amyloid-β selectivity in order for a tracer to be useful in the detection of CTE in vivo.

Conclusions

While sports-related TBI can have lasting consequences, there is a paucity of evidence on the long-term sequelae and their pathophysiology. It is premature to conclude that playing contact sports will lead to CTE. The potential risks involved in playing such sports need to be balanced against the potential benefits for the individuals.
It is crucial to base clinical decisions on an objective review of the current evidence. Large-scale longitudinal studies are needed to further our knowledge on sports-related TBI (Table 4).

References


41. Ramage SN, Anthony IC, Carnie FW, Busuttil A, Robertson


Disclosures

Dr. Batjer reports being co-chair of the NFL Head, Neck and Spine Committee and co-chair of the Texas Institute for Brain Injury and Repair. Dr. Lonser reports being a member of the NFL Head, Neck and Spine Committee. Dr. Bailes reports being a member of the NFL Players’ Association Mackey White Committee and the NCAA Concussion Task Force and chairman of the Pop Warner Football Medical Advisory Committee.

Author Contributions

Conception and design: all authors. Acquisition of data: Ban, Lonser. Analysis and interpretation of data: all authors. Drafting the article: Ban, Lonser. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ban. Study supervision: Batjer, Lonser.

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