The science and questions surrounding chronic traumatic encephalopathy

Vin Shen Ban, MBBChir, MRCS,¹ Christopher J. Madden, MD,¹ Julian E. Bailes, MD,²
H. Hunt Batjer, MD,¹ and Russell R. Lonser, MD³

¹Department of Neurological Surgery, University of Texas, Southwestern Medical Center, Dallas, Texas; ²Department of Neurological Surgery, NorthShore University HealthSystem, University of Chicago Pritzker School of Medicine, Evanston, Illinois; and ³Department of Neurological Surgery, The Ohio State University Wexner Medical Center, Columbus, Ohio

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.

<http://thejns.org/doi/abs/10.3171/2016.2.FOCUS15609>

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

CONCUSSION occurs most frequently during the routine activities of daily life, such as cycling, but it is the most common form of sports-related traumatic brain injury (TBI). Acute signs and symptoms related to concussion resolve within 10 days of injury in 90% to 95% of adult athletes²⁸ but may linger longer in concussed children and adolescents,^{3,20} and therapy is often required for persistent symptomatology.

Recently, media attention has surrounded the potential long-term effects of sports-related concussion (and subconcussive impacts), including chronic traumatic encephalopathy (CTE). Specifically, high-profile cases of athletes or former athletes who were thought to have suffered or died as a consequence of the cumulative nature of the head impacts they sustained during their careers have been highlighted in the media.^{6,7,13,25}

The increased media exposure related to CTE has underscored important questions surrounding the pathogenesis, incidence and prevalence, and natural history of CTE, but it has also led to common misperceptions due to lack of scientifically substantiated data. Specifically, the last

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

ABBREVIATIONS CTE = chronic traumatic encephalopathy; FTLT = frontotemporal lobar degeneration; NIH = National Institutes of Health; NFL = National Football League; NFT = neurofibrillary tangle; NT = neuritic thread; p-tau = hyperphosphorylated tau; TBI = traumatic brain injury.

SUBMITTED December 1, 2015. **ACCEPTED** February 5, 2016.

INCLUDE WHEN CITING DOI: 10.3171/2016.2.FOCUS15609.

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.³⁷ 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, frontotemporal lobar degeneration (FTLD), and progressive supranuclear palsy,²⁷ as well as opiate abuse.¹⁴¹ 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 colleagues¹⁷ 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 their review by stating that “there is insufficient evidence to establish a causal relationship between sports participation and the existence of modern CTE.”¹⁷

Current CTE Studies

In the published autopsy cases of athletes suspected to have had CTE over the past 11 years ($n = 85$), only 17 (20%) individuals were found to have the neuropathological findings fitting the individual authors' criteria of CTE with no coexisting neuropathology.¹⁸ Due to the retrospective nature of these case series (as well as all current published reports of CTE), reliable clinical correlation with the pathological findings was not possible and the high number of athletes included in the previous studies represents selection bias.

Future Work

Well-defined and uniform diagnostic criteria will need

to be developed to accurately assess and establish the diagnosis of CTE in the future. To establish a consistent pathological diagnosis of CTE, the National Institutes of Health (NIH) convened a Consensus Conference to define the neuropathological criteria for CTE diagnosis in early 2015.^{12,46} This group of experts found that

...the feature considered the most specific for CTE, and the one that distinguished the disorder from the other tauopathies, was the regional distribution of tau aggregates. In CTE, the tau lesion considered pathognomonic was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci.^{12,35}

While this consensus conference provided additional clarity to the pathological diagnosis of CTE (Table 1), the committee acknowledged that more work is required to determine the cause of CTE and its frequency.

Based on the NIH Consensus Committee's defined criteria for diagnosis of CTE, future systematic pathological studies of individuals at risk and those individuals not considered at risk are critical. As we do not know how frequently a tauopathy similar or consistent with CTE occurs (or does not occur) in nontraumatized individuals over a life span, large-scale assessment of brains of various ages is needed. Previously, Braak and colleagues examined brains from individuals ranging in age from 1 to 100 years and demonstrated that 99.6% had evidence of abnormally phosphorylated tau protein.⁸ In their group of 2332 brains, all brains from individuals older than 24 years had some degree of abnormally phosphorylated tau. These findings underscore the fact that individuals who have not suffered head trauma have tau deposits in their brains at death in age-associated amounts. Clearly, the findings consistent with normal aging need to be clarified with evolving histological and imaging platforms.

Will Nearly All Professional Football Players Develop CTE?

Current Media Reports

Recent media reports have indicated that CTE has been found in “96% of National Football League players” and “79% of all football players” that a single center has examined.^{9,10,24} One report stated that this finding

...supports past research suggesting that it's the repeat, more minor head trauma that occurs regularly in football that may pose the greatest risk to players, as opposed to just the sometimes violent collisions that cause concussions.¹⁰

Despite the data being described in the media, there do not appear to be published peer-reviewed scientific studies that support these claims.

Review of the CTE Case Reports

Recently, Maroon and colleagues performed a comprehensive and systematic review of all published cases of pathologically confirmed CTE ($n = 153$) since CTE was first described by Martland in 1928.^{30,31} McKee and colleagues were involved in the reporting of 113 (73.9%) of the 153 cases (although some of their cases have also been reported by others previously). The next largest cohort came from Omalu and colleagues, who reported on an additional 10 cases (6.5%).

TABLE 1. Comparison of the proposed definitions of CTE

Feature	Classic CTE	Omalu et al.	McKee et al.	NIH Consensus Statement*
Pathological findings of CTE	Cerebral atrophy, neuronal loss, gliosis, and argyrophilic NFTs; ^{12,35} cavum septum pellucidum, focal scarring of the cerebellum, loss of pigmented neurons in the substantia nigra ^{12,35}	i) "Multifocal/diffuse tauopathy (may be accompanied by low-grade multifocal white matter rarefaction, microglial activation, parenchymal histiocytes)"; ³⁹ ii) "topographically distributed NFTs/NTs (+/- diffuse amyloid plaques)"; ³⁹ iii) "absence of classic/neuritic amyloid plaques"; ³⁹ iv) "absence of pathognomonic histomorphology of other tauopathies" ³⁹ Pathognomonic: "sparse, moderate, or frequent band-shaped, flame-shaped, small globose, large globose NFTs accompanied by sparse, moderate, or frequent NTs" ³⁹	i) "Perivascular foci of p-tau immunoreactive ATs/NFTs"; ³⁵ ii) "irregular cortical distribution of p-tau immunoreactive NFTs/ATs, predilection for the depths of cerebral sulci"; ³⁵ iii) "clusters of subpial/periventricular ATs (cerebral cortex, diencephalon, basal ganglia and brainstem)"; ³⁵ iv) "NFTs in the cerebral cortex (preferentially in the superficial layers)" ³⁵	p-tau-related pathologies: i) "Abnormal p-tau immunoreactive pretangles and NFTs preferentially affecting superficial layers (layers II–III), in contrast to layers III and V as in AD"; ¹² ii) "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"; ¹² iii) "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)"; ¹² iv) "p-tau immunoreactive thorny astrocytes at the glial limitans most commonly found in the subpial and periventricular regions"; ¹² v) "p-tau immunoreactive large grain-like and dot-like structures (in addition to some threadlike neurites)" ¹² Non-p-tau-related pathologies: i) "macroscopic features: disproportionate dilatation of the third ventricle, septal abnormalities, mammillary body atrophy, and contusions or other signs of previous traumatic injury"; ¹² ii) "TDP-43 immunoreactive neuronal cytoplasmic inclusions and dot-like structures in the hippocampus, anteromedial temporal cortex and amygdala" ¹² Pathognomonic: "p-tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci" ¹²

CONTINUED ON PAGE 4 »

» CONTINUED FROM PAGE 3

TABLE 1. Comparison of the proposed definitions of CTE

Feature	Classic CTE	Omalu et al.	McKee et al.	NIH Consensus Statement*
Classification system	NA	<p>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</p> <p>Phenotype 2: similar to Phenotype 1, except for "sparse to frequent diffuse amyloid plaques in the cerebral cortex"³⁹</p> <p>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</p> <p>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</p>	<p>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</p> <p>Stage II: "NFTs in superficial cortical layers (adjacent to the focal epicenters), nucleus basalis of Meynert, locus ceruleus"³⁵</p> <p>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</p> <p>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 mammillary body atrophy, septal abnormalities, ventricular dilation and pallor of the substantia nigra and locus ceruleus"³⁵</p>	Not discussed
Progression	Progression of clinical symptoms in 3 stages ¹⁹	No progression noted	Progresses slowly over decades from Stage I to IV	Not discussed
Pathological example	See Fig. 1	See Fig. 2	See Fig. 3	See Fig. 4

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

* Quoted material is from Cairns et al: Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy. National Institute of Neurological Disease and Stroke, 2015. <http://www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm>. Public domain. Criteria defined in the Consensus Conference Report resemble those proposed earlier by McKee et al.³⁵

Sixty-three cases involved football players and 69 cases involved boxers.³⁰ Forty-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.² Approximately 3 to 4 million athletes (at all levels) play football every year. Moreover, these numbers pale in com-

parison 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.^{48,53}

FIG. 1. Diffuse β -protein deposition in the cortical layers without involvement of the white matter (wm). Formic acid pretreatment, original magnification $\times 20$. Reproduced from: The occult aftermath of boxing, Roberts GW, Allsop D, Bruton C, *J Neurol Neurosurg Psychiatry* 53:373–378, 1990, with permission from BMJ Publishing Group Ltd.

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, FTLT, and progressive supranuclear palsy.³⁰ Given the number of asymptomatic in-

FIG. 2. Tau-immunostained section of the temporal cortex with frequent band-shaped and flame-shaped NFTs and NTs. Original magnification $\times 400$. Reproduced from Omalu B, Bailes J, Hamilton RL, et al. Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. *Neurosurgery* 69:173–183, 2011, with permission from Wolters Kluwer Health.

FIG. 3. Perivascular astrocytic tangle and NFT accumulation at the depths of the cortical sulci. AT8 immunostain. Bar = 100 μ m. Reproduced from McKee AC, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain* 136:43–64, 2013 (Fig. 1Y). By permission of Oxford University Press on behalf of The Guarantors of Brain. The publication of this material under any Creative Commons of Open-Access license is prohibited and any forward reuse must have the express permission of journals.permissions@oup.com.

dividuals 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-

FIG. 4. Perivascular p-tau accumulation at the depths of the cortical sulci. Arrow indicates blood vessel. Reprinted from Cairns et al: Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy. National Institute of Neurological Disease and Stroke, 2015. <http://www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm>. Public domain. Criteria defined in the Consensus Conference Report resemble those proposed earlier by McKee et al.³⁵

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*

Activity	No. of TBIs
Bicycling	26,212
Football	25,376
Playground	16,706
Basketball	13,987
Soccer	10,436

* 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.⁴⁴ 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 play-

ers.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 subconcussion 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*

Clinical Features
Headache
Mood disorders
Depression
Anxiety/agitation
Suicidal
Apathy
Hopelessness
Manic behavior/mania
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.²⁶

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.⁴⁰ The use of accelerometers to noninvasively measure head impacts represents the best strategy available currently.⁴⁵ 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.³⁵ 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).^{5,47} 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.³⁶ 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]-PBB3.⁵² 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

FIG. 5. Left to right, brain FDDNP-PET scans of a healthy control, a former NFL player with clinically suspected CTE, and a patient with Alzheimer's disease (AD). Areas with the highest levels of tau aggregates appear red/yellow; medium, green; and lowest, blue. DVR = distribution volume ratio. Modified with permission from Barrio et al: *Proc Natl Acad Sci U S A* 112:E2039–E2047, 2015. Full description of the study can be found in that source.

TABLE 4. Unanswered questions about CTE and future research directions

Unanswered Questions	Future Research Directions
1. Differentiating between different tauopathies—is CTE just a variant of FTLT or normal aging?	Prospective identification of patients with clinically diagnosed tauopathies (AD, FTLT, etc.), including patients clinically suspected to have CTE. Longitudinal follow-up with standardized neuropsychological and clinical evaluation of symptoms. Postmortem examination of the patients' brains.
2. Does the degree of p-tau deposition in CTE correlate with clinical symptoms? Is there a cause and effect association?	
3. How does the accumulation of p-tau affect quality of life? How does it contribute to the cause of death?	
4. What are the other confounding factors (e.g., substance abuse, use of performance-enhancing drugs) that predispose to tau hyperphosphorylation found in athletes?	Prospective identification of patients with substance abuse (with a history of head impacts) and matched controls (without a history of head impacts). Postmortem examination of the patients' brains.
5. What causes the accumulation of p-tau in CTE? Is it progressive? Is it reversible? Can we slow or stop it?	Development of biomarkers and imaging techniques that correlate with the accumulation of p-tau. Development of methods to quantify head impacts. Postmortem examination of the patients' brains.
6. Can we detect CTE antemortem?	
7. What is the threshold of head impact that predisposes someone to the accumulation of p-tau? Is there an age difference for this threshold?	
8. Are there specific populations at risk due to genetic factors?	Prospective identification of populations from a young age. Longitudinal follow-up with genomic sequencing and postmortem examination of the patients' brains.
9. Why do some athletes develop accumulations of p-tau while others do not? Why don't all boxers have CTE?	
10. Why do people without prior history of head trauma develop accumulations of p-tau?	
11. What is the prevalence of the accumulation of p-tau in the general population?	

concerned.³⁴ 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

1. Anthony IC, Norrby KE, Dingwall T, Carnie FW, Millar T, Arango JC, et al: Predisposition to accelerated Alzheimer-related changes in the brains of human immunodeficiency virus negative opiate abusers. **Brain** 133:3685–3698, 2010

2. Associated Press: NFL, ex-players agree to \$765M settlement in concussions suit. **NFL.com**. (<http://www.nfl.com/news/story/0ap1000000235494/article/nfl-explayers-agree-to-765m-settlement-in-concussions-suit>) [Accessed February 17, 2016]

3. Babcock L, Byczkowski T, Wade SL, Ho M, Mookerjee S, Bazarian JJ: Predicting postconcussion syndrome after mild traumatic brain injury in children and adolescents who present to the emergency department. **JAMA Pediatr** 167:156–161, 2013

4. Bailes JE, Petraglia AL, Omalu BI, Nauman E, Talavage T: Role of subconcussion in repetitive mild traumatic brain injury. **J Neurosurg** 119:1235–1245, 2013

5. Barrio JR, Small GW, Wong KP, Huang SC, Liu J, Merrill DA, et al: In vivo characterization of chronic traumatic encephalopathy using [F-18]FDDNP PET brain imaging. *Proc Natl Acad Sci U S A* **112**:E2039–E2047, 2015
6. Belson K: Brain trauma to affect one in three players, N.F.L. agrees. *New York Times*. September 12, 2014. (<http://www.nytimes.com/2014/09/13/sports/football/actuarial-reports-in-nfl-concussion-deal-are-released.html>) [Accessed February 17, 2016]
7. Belson K: Frank Gifford had brain disease, his family announces. *New York Times*. November 25, 2015. (<http://www.nytimes.com/2015/11/26/sports/football/frank-gifford-had-cte-family-says.html>) [Accessed February 17, 2016]
8. Braak H, Thal DR, Ghebremedhin E, Del Tredici K: Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol* **70**:960–969, 2011
9. Breslow JM: 76 of 79 deceased NFL players found to have brain disease. *PBS Frontline*. (<http://www.pbs.org/wgbh/frontline/article/76-of-79-deceased-nfl-players-found-to-have-brain-disease/>) [Accessed February 17, 2016]
10. Breslow JM: New: 87 deceased NFL players test positive for brain disease. *PBS Frontline*. September 18, 2015. (<http://www.pbs.org/wgbh/frontline/article/new-87-deceased-nfl-players-test-positive-for-brain-disease/>) [Accessed February 17, 2016]
11. Broglio SP, Martini D, Kasper L, Eckner JT, Kutcher JS: Estimation of head impact exposure in high school football: implications for regulating contact practices. *Am J Sports Med* **41**:2877–2884, 2013
12. Cairns NJ, Dickson DW, Folkerth R, Keene CD, McKee A, Perl D, et al: Report from the First NIH Consensus Conference to Define the Neuropathological Criteria for the Diagnosis of Chronic Traumatic Encephalopathy. *NINDS.NIH.gov*. (<http://www.ninds.nih.gov/research/tbi/ReportFirstNIHConsensusConference.htm>) [Accessed February 17, 2016]
13. Carroll L: Borland retirement: is 24 too late to stop football brain damage? *NBC News*. March 18, 2015. (<http://www.nbcnews.com/health/health-news/borland-retirement-brain-damage-tk-n325866>) [Accessed February 17, 2016]
14. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, et al: Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol* **128**:755–766, 2014
15. Crisco JJ, Fiore R, Beckwith JG, Chu JJ, Brolinson PG, Duma S, et al: Frequency and location of head impact exposures in individual collegiate football players. *J Athl Train* **45**:549–559, 2010
16. CTE Awareness Foundation: **What causes CTE?** (<http://stopcte.org/what-is-cte/what-causes-cte/>) [Accessed February 17, 2016]
17. Davis GA, Castellani RJ, McCrory P: Neurodegeneration and sport. *Neurosurgery* **76**:643–656, 2015
18. Gardner A, Iverson GL, McCrory P: Chronic traumatic encephalopathy in sport: a systematic review. *Br J Sports Med* **48**:84–90, 2014
19. Gilchrist J, Thomas KE, Xu L, McGuire LC, Coronado V: Nonfatal traumatic brain injuries related to sports and recreation activities among persons aged ≤19 years—United States, 2001–2009. *MMWR Morb Mortal Wkly Rep* **60**:1337–1342, 2011
20. Gioia GA, Schneider JC, Vaughan CG, Isquith PK: Which symptom assessments and approaches are uniquely appropriate for paediatric concussion? *Br J Sports Med* **43** (Suppl 1):i13–i22, 2009
21. Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Cantu RC, Randolph C, et al: Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery* **57**:719–726, 2005
22. Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Harding HP Jr, Matthews A, et al: Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc* **39**:903–909, 2007
23. Guskiewicz KM, Mihalik JP, Shankar V, Marshall SW, Crowell DH, Oliaro SM, et al: Measurement of head impacts in collegiate football players: relationship between head impact biomechanics and acute clinical outcome after concussion. *Neurosurgery* **61**:1244–1253, 2007
24. Hanna J, Goldschmidt D, Flower K: 87 of 91 tested ex-NFL players had brain disease linked to head trauma. *CNN*. October 11, 2015. (<http://www.cnn.com/2015/09/18/health/nfl-brain-study-cte/>) [Accessed February 17, 2016]
25. Huffington Post: NFL brain injuries. *Huffington Post*. (<http://www.huffingtonpost.com/news/nfl-brain-injuries/>) [Accessed February 17, 2016]
26. Iverson GL, Gardner AJ, McCrory P, Zafonte R, Castellani RJ: A critical review of chronic traumatic encephalopathy. *Neurosci Biobehav Rev* **56**:276–293, 2015
27. Kovacs GG: Invited review: Neuropathology of tauopathies: principles and practice. *Neuropathol Appl Neurobiol* **41**:3–23, 2015
28. Makdissi M, Darby D, Maruff P, Ugoni A, Brukner P, McCrory PR: Natural history of concussion in sport: markers of severity and implications for management. *Am J Sports Med* **38**:464–471, 2010
29. Maroon JC, Bailes J, Collins M, Lovell M, Mathyssek C: Age of first exposure to football and later-life cognitive impairment in former NFL players. *Neurology* **85**:1007–1010, 2015 (Letter)
30. Maroon JC, Winkelman R, Bost J, Amos A, Mathyssek C, Miele V: Chronic traumatic encephalopathy in contact sports: a systematic review of all reported pathological cases. *PLoS One* **10**:e0117338, 2015
31. Martland H: Punch drunk. *JAMA* **91**:1103–1107, 1928
32. McCaffrey MA, Mihalik JP, Crowell DH, Shields EW, Guskiewicz KM: Measurement of head impacts in collegiate football players: clinical measures of concussion after high- and low-magnitude impacts. *Neurosurgery* **61**:1236–1243, 2007
33. McCrory P, Meeuwisse WH, Aubry M, Cantu B, Dvořák J, Echemendia RJ, et al: Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *J Am Coll Surg* **216**:e55–e71, 2013
34. McKee AC, Daneshvar DH, Alvarez VE, Stein TD: The neuropathology of sport. *Acta Neuropathol* **127**:29–51, 2014
35. McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH, et al: The spectrum of disease in chronic traumatic encephalopathy. *Brain* **136**:43–64, 2013
36. Mitsis EM, Riggio S, Kostakoglu L, Dickstein DL, Machac J, Delman B, et al: Tauopathy PET and amyloid PET in the diagnosis of chronic traumatic encephalopathies: studies of a retired NFL player and of a man with FTD and a severe head injury. *Transl Psychiatry* **4**:e441, 2014
37. Morris M, Maeda S, Vossel K, Mucke L: The many faces of tau. *Neuron* **70**:410–426, 2011
38. Neporent L: Youth sport injuries may lead to adult brain disease. *ABC News*. December 20, 2013. (<http://abcnews.go.com/Health/youth-sport-injuries-lead-adult-brain-disease/story?id=21239118>) [Accessed February 17, 2016]
39. Omalu B, Bailes J, Hamilton RL, Kambh MI, Hammers J, Case M, et al: Emerging histomorphologic phenotypes of chronic traumatic encephalopathy in American athletes. *Neurosurgery* **69**:173–183, 2011
40. Pellman EJ, Viano DC, Tucker AM, Casson IR, Waeckerle JF: Concussion in professional football: reconstruction of game impacts and injuries. *Neurosurgery* **53**:799–814, 2003
41. Ramage SN, Anthony IC, Carnie FW, Busuttill A, Robertson

- R, Bell JE: Hyperphosphorylated tau and amyloid precursor protein deposition is increased in the brains of young drug abusers. **Neuropathol Appl Neurobiol** 31:439–448, 2005
42. Reynolds BB, Patrie J, Henry EJ, Goodkin HP, Broshek DK, Wintermark M, et al: Practice type effects on head impact in collegiate football. **J Neurosurg** 124:501–510, 2015
43. Roberts GW, Allsop D, Bruton C: The occult aftermath of boxing. **J Neurol Neurosurg Psychiatry** 53:373–378, 1990
44. Savica R, Parisi JE, Wold LE, Josephs KA, Ahlskog JE: High school football and risk of neurodegeneration: a community-based study. **Mayo Clin Proc** 87:335–340, 2012
45. Schnebel B, Gwin JT, Anderson S, Gatlin R: In vivo study of head impacts in football: a comparison of National Collegiate Athletic Association Division I versus high school impacts. **Neurosurgery** 60:490–496, 2007
46. Shen H: Researchers seek definition of head-trauma disorder. **Nature** 518:466–467, 2015
47. Small GW, Kepe V, Siddarth P, Ercoli LM, Merrill DA, Donoghue N, et al: PET scanning of brain tau in retired national football league players: preliminary findings. **Am J Geriatr Psychiatry** 21:138–144, 2013
48. Solomon G, Sills AK: A retrospective view of concussion in American football, 1900–1959: What was suggested then we now know. **Phys Sportsmed** 43:247–252, 2015
49. Solomon GS, Sills A: Chronic traumatic encephalopathy and the availability cascade. **Phys Sportsmed** 42:26–31, 2014
50. Stamm JM, Bourlas AP, Baugh CM, Fritts NG, Daneshvar DH, Martin BM, et al: Age of first exposure to football and later-life cognitive impairment in former NFL players. **Neurology** 84:1114–1120, 2015
51. Stein TD, Alvarez VE, McKee AC: Concussion in chronic traumatic encephalopathy. **Curr Pain Headache Rep** 19:47, 2015
52. Sundman M, Doraiswamy PM, Morey RA: Neuroimaging assessment of early and late neurobiological sequelae of traumatic brain injury: implications for CTE. **Front Neurosci** 9:334, 2015
53. Tator CH: Chronic traumatic encephalopathy: how serious a sports problem is it? **Br J Sports Med** 48:81–83, 2014

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.

Correspondence

Vin Shen Ban, Department of Neurological Surgery, University of Texas, Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235-8855. email: vinshen.ban@cantab.net.