Tau Imaging in Head Injury

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KEYWORDS

• Tau • Chronic traumatic encephalopathy • PET • Neurodegeneration • Imaging • CTE

KEY POINTS

- Misfolded tau proteins underlie chronic traumatic encephalopathy (CTE) related to head trauma.
- Tau-PET radiotracers have shown superior specificity and selectivity.
- Tau-PET imaging of head trauma populations has shown elevated tau uptake related to CTE.

INTRODUCTION

Tau proteins play a significant role in a variety of degenerative neurologic conditions. Postmortem neuropathology studies of victims of repeat and severe head trauma have defined a unique spatial expression of neurologic tauopathies in these individuals known as chronic traumatic encephalopathy (CTE). Established and newly developed radiotracers are now being applied to head injury populations with the intent of diagnosis and disease monitoring. This review assesses the role of tau in head injury, the state of tau radiotracer development, and the potential clinical value of tau-PET as derived from head injury studies.

NEUROPATHOLOGY OF TAU PROTEINS IN HEAD INJURY

Tau protein expression is concentrated in the central nervous system (CNS).¹ Tau in the human brain is mostly contained in neurons, although minor expression has been observed in astrocytes and oligodendrocytes.² Tau proteins in intraneuronal

regions are concentrated within axons and minimal prevalence has been observed in somatodendritic regions, including the cellular membrane, nuclear membrane, and mitochondrial membrane.^{1,3} Although multiple functions of tau proteins have been characterized, the most common functions involve stabilizing microtubule (MT) structures, membrane binding, and axonal transport.⁴ Recent findings have also suggested that the interactions between MT and tau proteins are purposed to allow long labile domains so as to allow for dynamic growth and contractions.⁵

Nevertheless, the functions of tau are varied depending on the particular location of the tau proteins. In cytoskeletal regions, the binding of tau proteins to MTs either acts to directly stabilize MTs or create a bridge to link MTs and other cytoskeletal structures.³ Tau proteins are required for the proper formation of postsynaptic structures, dendritic spines, and terminals where tau proteins act as neurotrophic factors in neurogenesis.⁶ Certain domains of the tau protein have the capability of binding to the lipid bilayers in the cellular

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membrane, and although the purpose of such membrane associations is speculated, the prevalence of tau-membrane binding has been correlated with tau aggregation. Tau proteins exhibit similar binding processes, although the most characterized binding interaction has been those involving MTs.⁴ Tau proteins are natively unfolded, a paper-clip form of tau is present in the intracellular space as a result of intramolecular binding; otherwise, binding interactions with the MT structure alters the protein to expose the MT binding region of the tau proteins, which allows interactions between MT structures and the tau protein (Fig. 1).³

Tau proteins exist in 8 different conformations and 6 particular isoforms derived from alternative splicing of the MT-associated protein tau (MAPT) gene.^{3,7} Of the 6 isoforms, each is differentiated by the number of N-terminal inserts (0N, 1N, 2N) and the number of MT binding repeats in the C-terminal (3R, 4R).³ The ratio of isoforms varies over the developmental period and varies between regions of the human brain. For instance, the fetal brain expresses only 1 form of the tau isoform, whereas the fully developed brain confers all 6 isoforms. The 3R and 4R isoforms are equally expressed in the cerebral cortex of healthy adults⁸; otherwise, there is a notable discrepancy in the prevalence of N-terminal variants; for example, 0N, 1N, and 2N tau represent 40%, 50%, and 10% of the total CNS tau, respectively.⁹ With respect to the proportions of tau protein isoform,

there are significant differences between humans and other species.³ Once synthesized, tau proteins may undergo a variety of posttranslational modifications, including phosphorylation, glycation, acetylation, oxidation, polyamination, sumoylation, and ubiquitylation.³

Tau proteins are salient to the understanding of head injury. Head injuries, depending on the severity, can produce a series of complex and diverse neurophysiological consequences. The primary injury involves the immediate consequences of the physical insult, whereas secondary injury relates to a pathophysiological cascade. A common category of primary injuries is diffuse axonal injuries, which result from torsion and blunt forces. Specifically, external forces can harm the integrity of axonal structures such that axonal MT structures release previously bounded tau proteins into the parenchymal cerebrospinal fluid (CSF). Secondary injury has been associated with inflammatory pathways activation, neuronal metabolism and perfusion alteration, excitotoxicity, free radical generation, mitochondrial dysfunction, axonal degeneration, and neuronal dysfunction.¹⁰ Of note, secondary injury (eg, axonal degeneration) has been understood as the most contributory to the proliferation of tau proteins in the parenchymal space.

This relationship between free tau proteins as a result of head trauma has been examined by many studies in the context of fluid biomarkers. Following traumatic brain injuries (TBIs),

Fig. 1. Binding of tau to MTs. Tau associates with MTs primarily through the MT binding domain, comprising either 3 or 4 repeats. The N and C termini of tau are closely associated when tau is free in the cytoplasm, giving rise to the proposed “paper-clip” model of tau conformation. On binding to MTs, the terminal regions of tau become separated and the N terminus of tau projects away from the MT surface. (From Guo, T., W. Noble, and D.P. Hanger, Roles of tau protein in health and disease. *Acta neuropathologica*, 2017. 133(5): p. 665-704.; with permission.)

biomarkers can be assayed primarily in CSF or peripheral blood, although CSF is often preferred.¹¹ Several studies have thoroughly confirmed the association of several CSF biomarkers with axonal injury after mild (mTBI), moderate, and severe TBI (sTBI). More sensitive assays used by studies on sports-related mTBIs are associated with acute increases of tau in plasma where the concentration of tau correlated with the duration of postconcussive symptoms and the concentrations steadily declined during rehabilitation.¹² sTBI events have correlated with greater concentrations of tau in CSF samples where tau protein levels in ventricular CSF have directly related to TBI severity, lesion size, hypoxia, and clinical outcomes.¹³ In those with repeated injury (eg, boxers, contact sport athletes), elevated levels of tau in CSF samples were observed more than a week after the sporting event, where normalization of tau levels occurred 2 to 3 months from incident.¹³

Within the context of head injury, the most serious consequences of the accumulation of tau proteins are seen in unique neurologic tauopathies, namely CTE, in which tau aggregation is linked to subsequent neurodegenerative processes.¹⁴ Epidemiologic studies have linked TBI, single event and repeat, to the development of tauopathies.¹⁰ Although the etiology of tauopathies are somewhat speculative, the pathologic characterization of neurologic tauopathies is generally agreed on.¹⁵ Tauopathies are defined by the intraneuronal presence of tau aggregates termed neurofibrillary tangles (NFT), which are composed of multiple units of hyperphosphorylated MT-associated tau isoforms. The particular form of neurodegeneration leads to a unique distribution and identity of prions¹⁵ (**Figs. 2 and 3, Table 1**).^{16,17}

In most tauopathy cases, tau proteins are hyperphosphorylated to become unbound from MT

Fig. 2. Stages of CTE. In stage I CTE, p-tau pathology is found in discrete foci in the cerebral cortex, most commonly in the superior or lateral frontal cortices, typically around small vessels at the depths of sulci. In stage II CTE, there are multiple foci of p-tau at the depths of the cerebral sulci and there is localized spread of neurofibrillary pathology from these epicenters to the superficial layers of adjacent cortex. The medial temporal lobe is spared neurofibrillary p-tau pathology. In stage III CTE, p-tau pathology is widespread; the frontal, insular, temporal and parietal cortices show widespread neurofibrillary degeneration with greatest severity in the frontal and temporal lobes, concentrated at the depths of the sulci. Also, in stage III CTE, the amygdala, hippocampus, and entorhinal cortex show substantial neurofibrillary pathology that is found in earlier CTE stages. In stage IV CTE, there is widespread severe p-tau pathology affecting most regions of the cerebral cortex and the medial temporal lobe, sparing calcarine cortex in all but the most severe cases. All images, CP-13 immunostained 50 μ tissue sections. (From McKee, A.C., et al., The neuropathology of chronic traumatic encephalopathy. *Brain pathology*, 2015. 25(3): p. 350-364; with permission.)

Fig. 3. Microscopic changes in stage IV CTE. Whole-mount coronal sections in stage IV CTE show widespread p-tau pathology affecting most regions of the cerebral cortex and medial temporal lobe. Astrocytic tangles are prominent and there is marked neuronal loss in the cortex, amygdala, and hippocampus. There are also widespread pTDP-43 abnormalities. All images: 50 μ tissue sections, CP-13, or p-TDP-43 immunostain. (From McKee, A.C., et al., *The neuropathology of chronic traumatic encephalopathy*. Brain pathology, 2015. 25(3): p. 350-364; with permission.)

structures; these hyperphosphorylated proteins then accumulate within cells with MAPT mutations. However, changes in isoforms or phosphorylation patterns as a result of such mutations result in tau aggregation that is insoluble and harmful to neuronal function and axonal transport.¹⁸ Tau aggregates retain prion properties by way of seeding and spreading.¹⁹ Minimal exposure to tau seeds can further lead to misfolding and aggregation. This phenomenon is observed when tau proteins mislocalize into the soma and dendrites are transferred between the neurons.¹⁰ It has been observed that tau proteins can spread using the connectome network pattern and either spread preformed NFT or seed subsequent tau accumulation.¹⁰ Sparse tau aggregation generally develops naturally with age, however, and increased density and unique distributions of tau and other abnormal

protein aggregates (eg, beta-amyloid plaques) in the context of clinical dementia become indicative of neurodegenerative disease.¹⁵

Concerning TBI, NFTs can be observed within 6 hours of the event, and postmortem studies of those with single-event moderate to sTBI have shown higher levels of NFTs than in controls.¹⁰ It is further understood that the risk of CTE is directly related to the number and severity of TBI events.¹⁰ Interestingly, although the distribution of tau aggregates and, to a lesser extent, beta-amyloid plaques, is unique in CTE, there is not unique phosphorylation or a specific isoform that differentiates CTE from other neurodegenerative conditions.²⁰ Further, the ratio of tau proteins to beta-amyloid plaques is particularly elevated in CTE and is a unique characteristic of this neurodegenerative condition.

Table 1
Pathologic classification of chronic traumatic encephalopathy

Stage	Macroscopic Observations	Microscopic Observations
I	<ul style="list-style-type: none"> • Unremarkable 	<ul style="list-style-type: none"> • <i>Principal Characteristic:</i> One to 2 isolated perivascular focal epicenters of immunoreactive p-tau neurofibrillary tangles (NFT) and neurites (lesions) at the depths of the cerebral sulci in the parietal, frontal and temporal cortices • Beta-amyloid plaques are absent in subjects younger than 50 y • P-tau reactive microglia may exist
II	<ul style="list-style-type: none"> • Mild enlargement of lateral ventricles • Varying enlargement of the third ventricle • Pallor of the locus coeruleus and substantia nigra 	<ul style="list-style-type: none"> • <i>Principal Characteristic:</i> Multiple perivascular foci consisting of p-tau NFT, pre-tangles, and neurites are found in multiple cortices and the superficial cortical layers of surrounding regions such as the gyral crests and sulcal walls • Active microglia exist in the subcortical white matter with surrounding axonal swelling • Beta-amyloid plaques are absent in subjects younger than 50 y
III	<ul style="list-style-type: none"> • Decreased brain weight • Mild atrophy in the frontal and temporal lobes • Enlargement of the lateral and third ventricles • Potential cavum septum pellucidum, septal fenestration or perforation in some patients 	<ul style="list-style-type: none"> • <i>Principal Characteristic:</i> Multiple perivascular neurites, p-tau NFT, pre-tangles, and neurofibrillary lesions of degeneration in the amygdala, hippocampus, entorhinal cortex, and perirhinal cortex • Diminished myelinated nerve fibers, axonal dystrophy and axonal loss can be observed • Beta-amyloid plaques are rarely observed • TAR DNA-binding protein 43 (TDP-43) immunopositive neurites may exist in some cases
IV	<ul style="list-style-type: none"> • Decreased brain weight • Cerebral atrophy within the temporal, frontal, medial frontal lobes along with the anterior thalamus • Diffuse white matter and corpus callosum atrophy • Cavum septum, perforations, fenestration or absence of posterior septum in most patients 	<ul style="list-style-type: none"> • <i>Principal Characteristic:</i> Dense p-tau foci ubiquitously distributed in the cerebrum, diencephalon, and brainstem • Neuronal degeneration of the cortex, astrocytosis in the white matter, gliosis, loss of myelinated nerve fibers, axonal dystrophy, and TDP-43 immunopositive neurites are observed in most cases • Beta-amyloid plaques may be observed

From Ayubcha, C., et al., A critical review of radiotracers in the positron emission tomography imaging of traumatic brain injury: FDG, tau, and amyloid imaging in mild traumatic brain injury and chronic traumatic encephalopathy. European Journal of Nuclear Medicine and Molecular Imaging, 2020; with permission.

TAU RADIOTRACERS IN HEAD INJURY

The strong link between the presence of NFT and neurocognitive decline has strongly motivated the development of tau radiotracers that can assess the magnitude and localization of abnormal protein aggregates (Table 2).⁷ In the context of most tauopathies, tau radiotracers are required to cross plasma cell membranes and the blood-brain

barrier to reach intracellular tau proteins; tau NFT radiotracers must provide high selectivity given similar structures between NFT and β -amyloid aggregates; radiotracers must further account for the variation in NFT with respect to tertiary structures, posttranslational modifications, and isoforms.⁷ As such, there is a need for specificity and breadth when developing tau radiotracers.

Table 2
Tau radiotracers

Radiotracer	Description
[18F]FDDNP	Although one of the first radioligands developed for tau, this radioligand has low selectivity for tau. Uptake most often reflects amyloid and tau aggregates.
[18F]THK523	As a result of in vitro, ex vivo, and in vivo studies, this radiotracer has proven more selective for phosphorylated tau rather than β -amyloid. [18F]THK523 is mostly retention by white matter, which harms quantification. Imaging in non-Alzheimer's Disease (non-AD) tauopathies has not shown expected uptake patterns. Other THK compounds have presented a higher binding affinity for tau.
[18F]THK5351	[18F]THK5351 has faster kinetics and lower white matter binding compared with other [18F]THK derivatives. Off-target binding of all THK radiotracers was observed in the striatal regions and MAO-B sites. [18F]THK5351 has proven to have a lower binding affinity and higher increased off-target binding as compared with [18F]AV1451.
[18F]AV1451	[18F]AV1451, also known as [18F]T807 and flortaucipir, confers significantly lower white matter retention while indicating a higher binding affinity for tau as compared with beta-amyloid and other aggregates. Notable off-target binding of [18F]AV1451, likely due to iron and, in the basal ganglia, the substantia nigra, and the choroid plexus is observed.
[11C]PBB3	[11C]PBB3 has one of the highest affinities for neurofibrillary tangles (NFTs) as compared with other prions. Efficient blood-brain barrier penetration and minimal washout were noted. Limited white matter binding but retention in the venous sinuses were observed. This radiotracer can bind 3R and 4R tau isoforms in non-AD tauopathies. Nevertheless, the metabolite character and low half-life of the radiotracer can limit quantification.
Analogues of [11C]PBB3	New fluorinated PBB3 derivatives have attempted to overcome limitations in [11C] half-life, off-target binding in striatal regions, and limited dynamic range. Preliminary investigations have shown success in addressing these limiting characteristics.
[18F] Genentech tau probe 1	Preliminary research has shown that the Genentech tau probe 1 (GTP-1) has advantageous kinetics. Uptake has correlated with disease progression, severity, and differentiation between diseased patients and healthy controls.
[18F]RO6958948	[18F]RO6958948 is high-affinity tau with desirable kinetic characteristics (eg, rapid blood-brain barrier passage and minimal washout). Exploratory studies have shown tau accumulation in Braak-stage regions. [18F]RO6958948, [18F]AV1451, and [18F]THK535 demonstrated similar binding patterns for tau aggregates in AD, but none of the findings were remarkable in the context of non-AD tauopathies.
[18F]MK-6240	[18F]MK-6240 presents high specificity and selectivity for NFT along with sufficient pharmacokinetic properties. As of yet, no significant off-target binding has been observed but rapid washout has been noted.

Data from Hall, B., et al., In vivo tau PET imaging in dementia: pathophysiology, radiotracer quantification, and a systematic review of clinical findings. Ageing research reviews, 2017. 36: p. 50-63.

Interestingly, these challenges are less significant to the application of tau imaging in the context of head injury. Limitations in the concentration of tau proteins as compared with

beta-amyloid plaques have posed a significant challenge to tau imaging in dementias, but this is not the case in CTE. In CTE, the prevalence of tau is significantly greater than that of beta-

amyloid. As such, highly specific tau radiotracers can excel in binding to tau aggregates with less risk of off-site binding. In addition, there are higher concentrations of tau aggregates in perivascular space, which allows easier access of radiotracers to tau aggregates. As such, tau radiotracers in the context of CTE, as compared with other tauopathy dementias, are likely to perform well.

TAU PET IMAGING STUDIES IN HEAD INJURY

Using many of the noted radiotracers, many studies have applied tau PET to TBI populations. Most tau-PET imaging of individuals with single-event TBIs takes place long after the original insult, whereas most studies use patients with years of mTBI experiences through sports or military combat. Takahata and colleagues²¹ used [11C]PBB3-PET to assess tau patterns in 27

individuals with either repeat mTBI or sTBI as compared with 15 healthy control subjects. Increased uptake in the cerebrum and white matter correlated to psychosis and other neuropsychiatric symptoms.²¹ Gorggraptis and colleagues²² applied [18F]AV145-PET in 21 subjects with moderate to sTBI and 11 healthy control subjects; elevated whole brain and right occipital lobe uptake of [18F]AV145 were observed in the TBI group. Robinson and colleagues²³ observed increased white matter uptake of [18F]AV145 and notable uptake in the cerebellum, occipital lobe, inferior temporal lobe, and frontal lobe across 16 military veterans with a history of blast neurotrauma. However, no controls were used in this study as comparators.

Several studies have used National Football League (NFL) players as their study population, whereas most studies have aligned well with non-NFL populations with a few notable

Fig. 4. [18F]FDDNP-PET results for NFL players and a control. Coronal and transaxial [18F]FDDNP-PET scans of the retired NFL players include the following: NFL1: 59-year-old linebacker with mild cognitive impairment (MCI), who experienced momentary loss of consciousness after each of 2 concussions; NFL2: 64-year-old quarterback with age-consistent memory impairment, who experienced momentary loss of consciousness and 24-hour amnesia following 1 concussion; NFL3: 73-year-old guard with dementia and depression, who suffered brief loss of consciousness after 20 concussions, and a 12-hour coma following 1 concussion; NFL4: 50-year-old defensive lineman with MCI and depression, who suffered 2 concussions and loss consciousness for 10 minutes following one of them; NFL5: 45-year-old center with MCI, who suffered 10 concussions and complained of light sensitivity, irritability, and decreased concentration after the last two. The players' scans show consistently high signals in the amygdala and subcortical regions and a range of cortical binding from extensive to limited, whereas the control subject shows limited binding in these regions. Red and yellow areas indicate high [18F]FDDNP binding signals. (From Small, G.W., et al., PET scanning of brain tau in retired national football league players: preliminary findings. *The American Journal of Geriatric Psychiatry*, 2013. 21(2): p. 138–144; with permission.)

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exceptions. Dickstein and colleagues²⁴ examined one player with [18F]AV145-PET and found increased uptake in the gray matter–white junction along with the bilateral cingulate, occipital lobe, and orbitofrontal cortices, and temporal lobes. Mitsis and colleagues²⁵ observed increased [18F] AV1451 uptake in the 1 NFL player and 1 patient with sTBI in whom differential uptake patterns were observed. The NFL subject conferred higher uptake in the nigral and striatal regions, whereas the subcortical and hippocampal regions were more avid in the scans of the subject with sTBI.²⁵ Okonkwo and colleagues²⁶ also observed

elevated [18F]AV1451 uptake in 2 patients with TBI as compared with age–sex matched controls. Wooten and colleagues²⁷ assessed the [18F] AV1451-PET scans of 5 athletes, 2 veterans, and 1 vehicular accident patient as compared with 11 healthy subjects; regions with higher uptake in the TBI group were correlated with poor white matter function.

Larger studies with NFL players were performed by Barrio and colleagues²⁸ and Stern and colleagues²⁹ applied [18F] AV1451 to 16 NFL players and 31 healthy controls to find elevated uptake in the bilateral superior frontal,

Fig. 5. Involvement of amygdala and midbrain areas in concussion-based mTBI is supported by both mechanistic concept of injury (I) and by the results of neuropathological examinations in deceased retired American football players with premortem complaints of functional impairments (II and III). (I) Rotation of the brain in the sagittal plane during a concussion, associated with significant accelerations and deceleration, will have significant negative effect on the brain tissue in the midbrain and thalamus (green shaded area) and on the affected cortical areas (red area). Stretching, compression, and shearing of axons during such sudden brain movements are hypothesized to be the cause of axonal injury. Similarly, rotation in the coronal plane has been shown to lead to consistent damage to midbrain region tracts (27). (II) (A–D) show results of tau immunohistochemistry (IHC) and demonstrate that in the mTBI group areas of increased [18F]FDDNP signal in amygdala and dorsal midbrain coincide with presence of dense tau deposits in periaqueductal gray in dorsal midbrain (A, B) and in amygdala (C, D). (III) Amygdala and medial temporal lobe (MTL) areas are affected in the brains of retired professional American football players who died due to suicide (left; 45-year-old retired player) or due to natural causes (right; 80-year-old retired NFL player). Amygdala and MTL areas are the first areas with high density of tau deposits in the neocortex and remain one of the most affected cortical regions in most retired professional American football player cases. (From Barrio, J.R., et al., In vivo characterization of chronic traumatic encephalopathy using [F-18] FDDNP PET brain imaging. *Proceedings of the National Academy of Sciences*, 2015. 112(16): p. E2039–E2047; with permission.)

bilateral medial temporal, and left parietal regions. Barrio and colleagues²⁸ used [18F]FDDNP-PET to study uptake patterns among 14 NFL players and 28 healthy controls. Although [18F]FDDNP is bound to beta-amyloid and tau

aggregates, the limited prevalence of beta-amyloid in CTE implies that much of the unique uptake in these populations as compared with the control are likely driven by tau aggregate accumulation and not beta-amyloid deposition.²⁸

Fig. 6. [18F]FDDNP distribution volume ratios (DVR) parametric images showing patterns T1 to T4 of increased [18F]FDDNP signal observed in the mTBI group compared with cognitive control subjects (*left*). The T1 pattern shows involvement of 2 core areas that have consistently increased [18F]FDDNP signal in all 4 patterns: amygdala (limbic) and dorsal midbrain (subcortical). Patterns T2 to T4 are marked by increase of [18F]FDDNP signal in these 2 core regions and progressively larger number of subcortical, limbic, and cortical areas. Although more complex patterns (eg, T4) overlap with AD in the cortex, midbrain and amygdala signals are elevated above the levels in AD. An AD case is shown in the right column for comparison. (*Lower*) (A) is a 2-dimensional scatter plot showing [18F]FDDNP DVR values in 2 core areas consistently involved in CTE (subcortical structures [dorsal midbrain] and limbic structures [amygdala]), clearly demonstrating separation of mTBI and control (CTRL) groups. (B, C) demonstrate similar separation effect when dorsal midbrain is compared with cortical areas typically associated with CTE and its mood disorders, namely anterior cingulate gyrus (ACG) (B) and frontal lobe (C). Subjects with mTBI are represented by green circles, and CTRL subjects are represented by blue circles. (From Barrio, J.R., et al., In vivo characterization of chronic traumatic encephalopathy using [F-18] FDDNP PET brain imaging. Proceedings of the National Academy of Sciences, 2015. 112(16): p. E2039-E2047; with permission.)

Nevertheless, Barrio and colleagues²⁸ noted increased uptake in the amygdala, anterior cingulate gyrus, and frontal cortex in the NFL players. Chen and colleagues³⁰ used [18F]FDDN-PET in a study population of 7 military veterans, 15 retired players with mTBI histories, and 28 healthy controls; findings were consistent with Barrio and colleagues,²⁸ but it was noted that military personnel had limited uptake in the amygdala and striatum relative to the player population. Vasilevskaya and colleagues³¹ applied [18F]AV1451-PET to 38 former contact sport athletes. In this study, the presence of APOE4 alleles aligned with high cortical gray matter PET tau uptake such that the presence of APOE4 may incline individuals to accumulate tau aggregates more so than others³¹ (Fig. 4,³² Figs. 5 and 6,²⁸ Fig. 7³³).

Given that the present diagnosis of CTE is contingent on postmortem neuropathological examination, some of the most convincing tau-PET studies have attempted to confirm their imaging with postmortem analysis of the brain. Mantyh and colleagues³⁴ studied 1 former NFL player with [18F]AV1451-PET with subsequent postmortem analysis of the individual who was subsequently diagnosed with stage IV CTE, TDP 43 encephalopathy, and stage 3 Braak NFT. Uptake was most avid in degenerated and hypometabolic

regions in the frontotemporal region; this overlapped postmortem tau aggregates in the left fusiform, inferior temporal gyri, and juxtacortical frontal white matter. High uptake with minimal tau deposition was noted in the basal ganglia, thalamus, motor cortex, and calcarine cortex.³⁴ Omalu and colleagues³³ assessed the [18F]FDDNP-PET scan of 1 former NFL player and respective postmortem analysis to find that [18F]FDDNP-PET uptake correlated with tau deposition, most notably in the parasagittal and paraventricular regions of the brain and the brain stem. No correlation with amyloid or TDP-43 deposition was observed such that regions of the brain most involved in shearing and rotational forces were most linked to tau deposition; such deposition patterns would align with the unique patterns found in CTE.³³

Marquie and colleagues³⁵ did not perform any in vivo imaging, rather autoradiographic binding patterns of [18F]AV1451 were observed in 5 postmortem brains diagnosed with stage II through stage IV CTE. [18F]AV1451 binding observed in all NFT regions as confirmed by immunostaining and a limited signal was observed in white matter and other non-tangle-containing regions. Quantification of tau burden and tracer uptake was correlated.³⁵ Previously mentioned in vivo studies have

Fig. 7. Immunohistochemistry photomicrographs ($\times 400$) of parietal cortex, midbrain, amygdala, and hippocampus show the presence of tau neuropathological deposits in these regions. (Lower) Representative transaxial (2 sections), sagittal (middle), and coronal sections (right) of [18F]FDDNP-PET images with high signals in the periventricular subcortical regions, amygdala, and midbrain. Warmer colors (red and yellow) show areas with higher [18F]FDDNP binding signals. (From Omalu, B., et al., Postmortem autopsy-confirmation of antemortem [F-18]FDDNP-PET scans in a football player with chronic traumatic encephalopathy. *Neurosurgery*, 2018. 82(2): p. 237–246; with permission.)

not found such consistent binding patterns and strong correlations, which may be indicative of a difference between the ex vivo and in vivo environments.

SUMMARY

In reviewing this literature, there are several apparent takeaways. There are variations in the binding patterns between different tau radio-tracers. Nevertheless, there is consistently uptake in certain regions across studies; aberrant binding is expected given the variation in small studies and potential off-site radiotracer binding. However, the literature suggests that larger studies may be more consistent in finding uptake in regions where tau aggregates are normally observed in CTE populations. Overall, the evidence suggests that tau-PET imaging will continue to play a significant role in TBI and CTE. These studies have shown considerable promise in the imaging of tau and prospective larger studies may substantiate the use of a particular radiotracer in the assessment of long-term TBI ramifications and the diagnosis of CTE. In particular, there is a notable need for future studies that incorporate in vivo imaging and postmortem pathologic study.

CLINICS CARE POINTS

- Patients with a history of head trauma should be assessed for long-term sequelae associated with head injury.
- Tau deposition is associated with chronic ramifications of head trauma.
- Tau-PET has shown promise in assessing the progression of chronic symptoms and degenerative conditions associated with head trauma.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest.

DISCLOSURE

The authors have nothing to disclose.

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