Clinical appraisal of chronic traumatic encephalopathy: current perspectives and future directions

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Purpose of review

There are currently no consensus-based clinical diagnostic criteria for chronic traumatic encephalopathy (CTE). This review provides an update on recent literature pertaining to clinically relevant procedures that – presently or in the future – may be useful for the in-vivo detection, characterization, and/or prediction of CTE.

Recent findings

Preliminary evidence about the clinical manifestations of CTE has been accumulating via post-mortem medical record review and interviews of friends or family members of individuals with neuropathologically documented CTE. This evidence suggests that CTE is manifested clinically by changes in cognition (especially memory and executive functioning, with dementia later in the disease course), mood (especially, depression, apathy, and suicidality), personality and behavior (especially poor impulse control and behavioral disinhibition), and movement (including parkinsonism and signs of motor neuron disease). At the present time, evidence regarding CTE has not been confirmed in a prospective study of a cohort at risk for CTE.

Summary

On the basis of recent research in the fields of dementia and traumatic brain injury, several in-vivo procedures (including neurological examination, neuropsychological assessment, neuroimaging techniques, and blood and cerebrospinal fluid biomarkers) each have the potential to contribute unique information about the manifestations of CTE, including clinical and preclinical stages. More research is needed to develop a set of consensus diagnostic criteria that provide a reliable and valid indicator of neuropathologically verified CTE. Until such criteria are developed, the clinical assessment of CTE should be informed by modern research that is of relevance to traumatic brain injury and neurodegenerative diseases.

Keywords

biomarkers, chronic traumatic encephalopathy, concussion, dementia, traumatic brain injury

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Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease that is thought to be caused by repeated exposure to brain trauma [1]. Over the past several decades, researchers have identified a specific pattern of neurodegenerative markers that distinguish CTE from other forms of neurodegeneration [1,2]. Although a clinical picture of CTE has been developed, there are no consensus-based criteria for diagnosing CTE clinically, due in part to the fact that individuals with a history of repeated brain injury have not been studied prospectively, until death, in such a manner that links clinical phenotypes with autopsy-confirmed CTE. Whereas such studies are currently underway, increased media attention may lead patients to seek medical attention (including diagnosis and treatment) for possible CTE, even though neither in-vivo diagnosis nor disease-specific treatments have been developed. The current manuscript is intended to provide a review of recent research pertaining to clinically based investigations and techniques that may be relevant for clinical and research evaluations of individuals at risk for CTE. We will review technologies that are currently part of a standard clinical evaluation for traumatic brain injury (TBI) or dementias such as Alzheimer's disease, as well as emerging technologies that are presently only available in research settings. We conclude by offering suggestions for evaluating patients at risk for CTE and for future research efforts that will eventually lead to the development of valid clinical diagnostic criteria for CTE.

Current assessment tools that may be of use in CTE include a neurologic examination, neuropsychological assessment (which encompasses evaluation of cognitive functioning, olfaction, mood, personality, and behavior), radiologic techniques, and blood and cerebrospinal fluid (CSF) biomarkers. It is important to emphasize that although it is believed to result from repeated concussive or subconcussive (i.e. asymptomatic) TBI, CTE is a neurodegenerative condition that is distinct from the immediate sequelae of TBI [1,3]. Therefore, it is likely that the clinical appraisal of CTE will be more akin to the approach used in Alzheimer's disease [4] than that used for TBI.

Neurologic effects

The neurologic examination is a cornerstone of a dementia workup. CTE is believed to cause signs and symptoms of neurological dysfunction that can affect balance, gaze, mental status, and movement, among other domains usually assessed by neurologists. In their review of 51 neuropathologically verified CTE cases, McKee *et al.* [1] found evidence of reported movement abnormalities in 21 (41%) of the 51 cases, including parkinsonism in 18 cases. Signs of parkinsonism in this sample included tremor, decreased facial movement, balance problems and falls, slowed movements, and rigidity. Other commonly reported motor difficulties included gait problems in 19 cases, most commonly staggered and ataxic. Speech changes (slowed, slurred, dysarthric) were common, reportedly occurring in 18 cases. Also reported were ocular abnormalities in 4 of 51 cases (8%), including ptosis and reduced upgaze [1].

CTE may also be associated with motor neuron disease. In a case series, our group [5•] found widespread transactive response DNA-binding protein of approximately 43 kDa (TDP-43) in the brains of 10 out of 12 individuals with a history of repeated mild TBI and pathologically confirmed CTE. In three of these cases, there was TDP-43 in the spinal cord and clinical evidence of motor neuron disease, including muscle weakness, atrophy, fasciculations, dysarthria, dysphagia, hyperactive deep tendon reflexes, and gait problems [5•]. On the basis of its association with CTE, this new form of motor neuron disease has subsequently been referred to as chronic traumatic encephalomyelopathy (CTEM).

Neuropsychological and neuropsychiatric effects

Neuropathololgical studies have shown that, in CTE, some of the most severely damaged regions of the brain include the medial structures of the limbic system (e.g. amygdala, hippocampal–entorhinal complex, basal forebrain, mammillary bodies), with scattered pathological changes throughout the majority of the cerebral cortex [1]. Continued degeneration of these areas can cause substantial cognitive impairment, which, in some individuals, may progress to clinical dementia. Below, we discuss some of the more specific cognitive and behavioral symptoms that may be seen in CTE.

Key points

- Because the neuropathological characteristics of chronic traumatic encephalopathy (CTE) are dissociable from other neurodegenerative diseases, it is likely that its clinical phenotype is also dissociable. However, more research is needed to accurately characterize the clinical phenotype of CTE.
- Clinical abnormalities caused by CTE pathology are likely to include mental status and cognitive impairments (especially memory and executive functioning), neuropsychiatric alterations (especially depression, apathy, poor impulse control, anger, and irritability), and impaired motor behavior (especially parkinsonism).
- Some of the most promising methods for the early detection, prediction, and characterization of CTE include blood and cerebrospinal fluid-based biomarkers, diffusion tensor imaging, susceptibility-weighted imaging, fMRI, magnetic resonance spectroscopy, and PET.

Memory

A recent meta-analysis of eight studies, which included a total of 614 participants with a history of repeated mild TBI, found evidence to suggest that a history of repeated TBI is associated with a decline in delayed recall for new information [6]. On the basis of a survey completed by a sample of retired National Football League (NFL) players, Guskiewicz *et al.* [7] reported a strong relationship between TBI history and memory complaints. More specifically, individuals with a history of at least three concussions were five times more likely than those with no concussions to have been diagnosed with mild cognitive impairment and three times more likely to report significant memory problems [7]. Retrospective reports provided by close friends or family members of individuals with neuropathologically documented CTE consistently describe a loss of short-term memory. For example, McKee *et al.* [1] reported that memory loss was reportedly observed in 32 of 51 (63%) of individuals with CTE. In addition, memory loss was also a symptom described in a subsequent single case report of CTE [8]. On the basis of neuropathological studies and clinical reports, it is believed that the memory loss caused by CTE may, in many cases, be similar to the memory loss experienced by individuals with Alzheimer's disease (i.e. rapid forgetting of newly learned information) [9]. Like Alzheimer's disease, CTE is associated with a high density of

hyperphosphorylated tau protein in the medial temporal lobe structures that subserve the encoding and storage of new information, including the hippocampus, entorhinal cortex, and parahippocampal gyrus [1]. Cognitive tests that require participants to learn and remember new information have been reportedly affected by a history of multiple concussions [10] and are likely to be negatively affected by CTE. Examples of such tests include list-learning tests [11–13], story learning tests [14], and tests of visual/nonverbal memory, all of which contain one or more immediate recall trials and a delayed recall trial.

Executive function

Executive functioning is an umbrella term used to describe many different, yet inter-related, cognitive abilities, all of which are responsible in some way for goal-directed behaviors [15]. On the basis of the meta-analytic study described in the preceding section, there is evidence to support the notion that repeated brain injury causes a decline in executive functioning [6]. In neuropathologically confirmed CTE, executive dysfunction may be common prior to death [16]. Poor insight, judgment, and disinhibition have been reported very commonly in individuals with CTE. Executive functioning is largely governed by the frontal lobes and the networks they form with other areas of the brain, such as the parietal lobes and limbic system. McKee *et al.* [1] described evidence for frontal and parietal lobe atrophy, neuronal loss, and neurofibrillary tangles in the majority of CTE cases. More recent evidence also suggests that visual working memory may be impaired in athletes with a history of at least three concussions [17•]. Neuropsychological tests that evaluate judgment and decision-making, impulse control [18], problem-solving and self-monitoring, working memory, and mental flexibility [11] may show sensitivity to the effects of CTE on executive functioning.

Attention, language, and visuospatial function

Meta-analysis found no effect of repeated TBI on attention or language fluency several months post-injury [6]. Retrospective reports from friends or family members of individuals with documented CTE indicate that eight of 51 cases were thought to have reduced concentration [1]. Although a small to medium effect of repeated TBI on visuospatial functioning has been found using meta-analysis, the size estimate of this effect is imprecise and therefore not statistically significant [6]. As described above, speech problems (e.g. dysarthria) appear to be somewhat common in later stages of CTE, but there is insufficient evidence to support the notion that language abilities are commonly affected by CTE.

Olfaction

Sense of smell is often affected by head trauma [19,20] due to the fact that the olfactory bulb is prone to damage caused by blunt force trauma to the head [21,22]. In CTE, there is also substantial neurofibrillary change in the olfactory bulb, which is distinct from the direct effects of head trauma, and more akin to the olfactory bulb pathology seen in other neurodegenerative conditions such as Alzheimer's disease and Parkinson's disease. A recent study reported that, compared to controls, boxers show impairments in olfactory threshold and odor identification [23•]. Therefore, olfactory assessment may be valuable in individuals with CTE.

Mood, personality, and behavior

Changes to mood, personality, and behavior are some of the most commonly reported manifestations of individuals with documented CTE [1,16] and have often been described in living individuals with a history of repeated TBI [24]. For example, in a review of the CTE literature from 1928 to 2009, McKee *et al.* [1] reported that personality or behavior changes were noted to have occurred in 33 of 51 (65%) of individuals with neuropathological evidence of CTE. These changes included aggression or violence in 23 (70%) of the 33 cases, confusion in 18 of the 33 (55%) cases, dysphoria in 16 (48%) cases, paranoia in 14 (42%) cases, irritability in 13 (39%) cases, agitation in 8 (24%) cases, apathy in 3 (9%) cases, and hypersexuality in one (3%) case.

Depression appears to be a common symptom in those with a history of head injury. For instance, retired NFL players with a history of at least three concussions were three times more likely than those with no concussions to have been diagnosed with depression [24]. Suicidality, possibly associated with the combination of mood change (from amygdala pathology) and impulse control deficits (from orbitofrontal pathology), has also been found to be common in CTE [1,16].

Radiologic effects

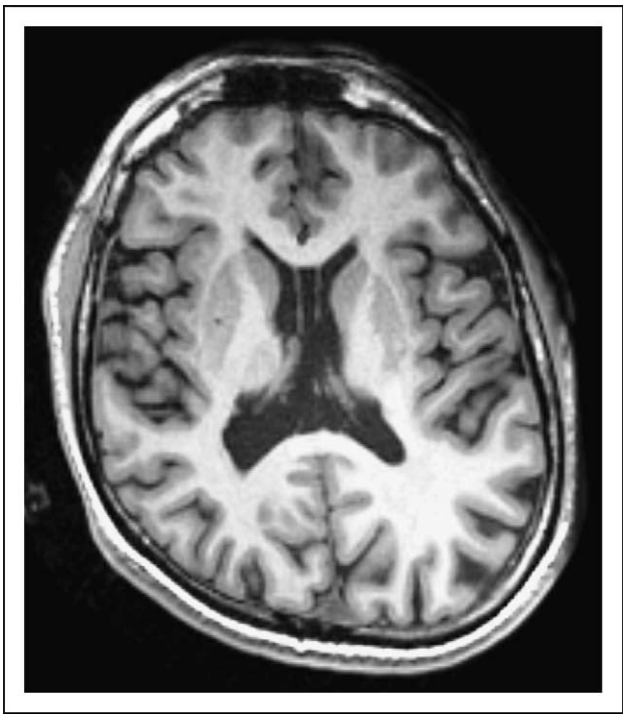
A variety of structural and functional neuroimaging and electrophysiological techniques may be beneficial in the diagnostic work-up of CTE. These will be reviewed below.

MRI

Neuropathological changes that are commonly observed in CTE may be amenable to detection using MRI techniques. For instance, whole brain atrophy has been reported as a common feature of CTE at autopsy in addition to cavum septum pellucidum with occasional fenestrations [1]; each of these features may be detected with MRI. Figure 1 depicts a 1.55 mm coronal T1 MRI scan showing substantial cavum septum pellucidum, taken from a middle-age male boxer with symptoms consistent with CTE.

Differences in blood oxygen level-dependent (BOLD) functional MRI (fMRI) have been found to be useful in

Figure 1 A 1.5 mm coronal T1 MRI slice showing a large cavum septum pellucidum visible within the lateral ventricles of the brain in a retired boxer



differentiating Alzheimer's disease from dementia with Lewy bodies [25] and frontotemporal dementia [26]. fMRI has been useful in providing insights into brain–behavior relationships in a number of neurodegenerative diseases [27], and thus holds promise for facilitating our understanding of these relationships in CTE. Already, fMRI has been used to demonstrate functional neurophysiologic alterations in concussed athletes, even in the absence of overt clinical symptoms [28••].

Susceptibility-weighted imaging

Susceptibility-weighted imaging (SWI) is sensitive to micro-hemorrhages that occur in the context of physical trauma to the central nervous system [29•]. This area of examination is particularly important given the frequent perivascular tau deposition observed in studies of CTE [1]. SWI has been shown to predict future outcomes after brain injury in children [30•], but its predictive validity has been more limited in adults [31]. Whereas SWI appears to be a promising tool that may be used to identify the long-term effects of repeated head injuries in older adults, more research is necessary to identify its clinical utility [32•].

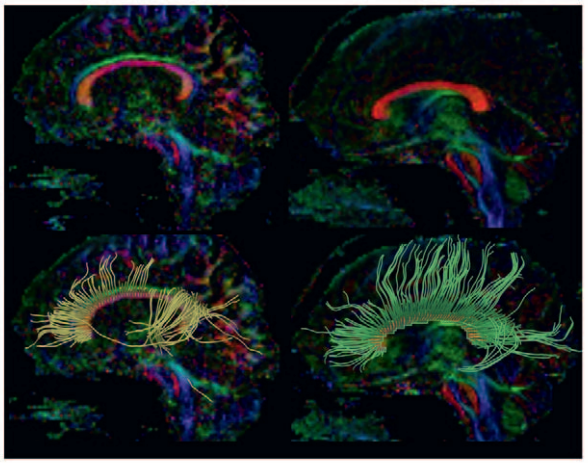
Diffusion tensor imaging

Diffusion tensor imaging (DTI) is sensitive to diffuse axonal injury, one of the signature injuries in TBI [29•,33]. DTI-based measures of mean diffusivity have been shown to increase following ischemia or brain trauma, reflecting either a partial redistribution of water from the extracellular to intracellular compartment or a reduction in the diffusivity of water in the cytosolic environment [34]. In experimental rat models of TBI, DTI has been shown to predict long-term outcomes [35]. In humans, DTI findings have supported a link between axonal injury and executive impairment after TBI [36]. Of interest here, we have preliminary data from five retired professional athletes (American football, boxing, and wrestling) suggesting a correlation between concussion history and DTI measures that reveal a thinning of callosal white matter integrity (Fig. 2; on the left is a symptomatic middle-aged retired football player, and on the right is a normal control matched for age). As with SWI, research on the usefulness of DTI in understanding CTE is in its early stages. However, this technology is quite promising and likely to lead to new findings, particularly given that TBI is difficult to discern on conventional MRI and computed tomography (CT) because these imaging modalities are not as sensitive to diffuse axonal injury as diffusion imaging measures. Thus, given that diffuse axonal injury characterizes mild TBI, imaging modalities that are sensitive to such injuries will likely play a key role in further delineating such abnormalities in CTE.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is a noninvasive method of measuring human brain chemistry *in vivo* using the same clinical MR scanners utilized for MRI. MRS studies have demonstrated alterations in brain metabolism with brain trauma, including decreased N-acetyl aspartate (NAA) indicating neuronal damage, increased choline (Cho) and lipid indicating membrane damage, and increased combined glutamate and glutamine (Glx) indicating excitotoxic effects of the brain injury [37–39]. Furthermore, these changes correlated with clinical outcome [40,41]. However, sports-related TBI are generally milder head injuries. To date, there are only a few studies that have focused specifically on sports-related TBI. Cimatti [42] found that NAA decreased in two of six adult athletes after head trauma. Henry *et al.* [43] showed a significant decrease in Glx and NAA in the primary motor cortex and NAA in the prefrontal cortex in 14 concussed compared with nonconcussed athletes (aged 20–25 years). Vagnozzi *et al.* [44] showed in 13 concussed athletes (aged 22–25 years) a decrease of 18.5% in NAA, with modest recovery at 15 days and full recovery at 30 days. Those with second concussive injuries took up to 45 days to fully recover NAA. These studies demonstrate that neurochemical effects are detectable with TBI, with recovery on the timescale of months. Only one study has demonstrated the long-term effects of repetitive head injury suffered by

Figure 2 Diffusion tensor imaging of the brain



The former athlete is on the left (top and bottom) and the healthy volunteer is on the right (top and bottom). The top view shows the directionality of the diffusion with red in the X-plane, blue in the Y-plane, and green in the Z-plane. Note the thinner red of the corpus callosum in athlete (top left). The bottom panel shows the corpus callosum fiber bundle created from streamline tractography. Note again the smaller fiber bundle in the athlete (bottom left) compared with the healthy volunteer. The shorter tracts are consistent with the thinning of the corpus callosum in the top panel.

professional athletes and likely related to CTE [45••]. In this pilot study, Lin *et al.* showed that changes in Cho and Glx were significantly increased when individuals with a history of repetitive head injury and CTE symptoms were compared with healthy, age-matched controls. In addition, the study showed that advanced spectroscopy methods, such as two-dimensional correlated spectroscopy, also showed changes in excitatory and inhibitory amino acids not normally measured by conventional 1D MRS.

Event-related potentials

Pioneering research that uses event-related potentials (ERPs) to study the long-term consequences of TBI has been conducted by a research team at the University of Montreal [17•]. A portion of this and related research focuses on the P300, a cognitive ERP with a distinct amplitude and latency, thought to be an index of brain processes elicited from tasks required in the maintenance of working memory [46,47] and proportional to the amount of attentional resources that are employed in a given task [48,49]. P300 latency increases and amplitude decreases as cognitive capability decreases in individuals with dementing illnesses [50–53]. Recently, De Beaumont *et al.* [10] have shown that P3a/P3b components of the P300 are delayed and attenuated in older athletes with concussions 30+ years earlier compared to older athletes without a history of concussion. In addition, these investigators found an association between multiple TBI and working memory difficulties that appears to be mediated by neurophysiological changes that can be detected using ERP [17•].

Positron emission tomography

Although modern PET ligands have been developed for Alzheimer's disease, these ligands have been developed to selectively bind to beta-amyloid (e.g. Pittsburgh compound B) or nonselectively to both beta-amyloid and tau [e.g. 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP)]. Because beta-amyloid is relatively sparse in CTE brains [1], ligands that selectively bind to tau are likely to be more useful for CTE [54••].

Single photon emission computed tomography

Although one recent publication reported group differences between retired NFL players and a control group on single photon emission computed tomography (SPECT) imaging [55], the study had significant methodological flaws limiting interpretation of results. Moreover, SPECT, a nonspecific measure of regional cerebral blood flow, would not be expected to have any specificity to the tau-based pathological changes associated with CTE.

Blood and cerebrospinal fluid biomarkers

Blood and CSF biomarkers have yielded promising results for the detection of neurodegenerative changes caused by Alzheimer's disease [56,57]. Because Alzheimer's disease and CTE have neuropathologic similarities, such as dense neurofibrillary tangles [1] (though it should be noted that the cortical distribution of these tau inclusions differ significantly between the two diseases), some of the biomarkers that are used in Alzheimer's disease research may also be useful for CTE. For instance, CSF tau and phosphorylated tau, and isoprostanes in plasma and CSF may have the potential to contribute to the prediction and diagnosis of CTE [58–61].

Conclusion

At the present time, clinical research into CTE is lacking, especially pertaining to the prospective study of its early detection and differential diagnosis from other neurodegenerative conditions. Clinical assessment tools that are of relevance to TBI and dementia are likely to be of use when evaluating individuals in whom CTE is suspected. Currently, a comprehensive neurologic examination, neuropsychological assessment (including measures of mood, behavior, olfaction, and personality, in addition to a focus on memory and executive functioning), and standard radiologic techniques (e.g. MRI) are widely available methods that may have some clinical benefit

in the assessment of CTE. In addition, there is also a host of emerging technologies (e.g. DTI, 18F-THK523 PET) that, with additional research, may prove far more informative and beneficial in the clinical appraisal of CTE.

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Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 653).

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