Chronic Traumatic Encephalopathy-Like Abnormalities in a Routine Neuropathology Service

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Abstract
Chronic traumatic encephalopathy (CTE) has been described mainly in professional athletes and military personnel and is characterized by deposition of hyperphosphorylated tau at the depths of cortical sulci and around blood vessels. To assess CTE-like changes in a routine neuropathology service, we prospectively examined 111 brains (age 18–60 years). The presence of tau-immunoreactive deposits was staged using guidelines described by others and was correlated with the medical history. 72/111 cases were negative for any CTE-like changes were with any CTE-like changes were. Age was also a significant predictor; most cases (mean age 81 years), including 24% of Parkinson disease, 13% of non-demented controls >60 years age, 10% of Alzheimer disease, 7% of corticobasal degeneration, 4% of frontotemporal lobar degeneration, and 2% of multiple system atrophy (10). Other patterns of p-tau accumulation are well documented. In 138 brains from chronic epilepsy cases (age 15–96 years), p-tau-immunoreactive astrocytes were identified in cortical layer 1 and/or the periventricular region in 35% of cases, and less often at the depths of sulci (5.8%) or around white matter vessels (8%); these changes were more common in cases with prior head injury and correlated with advancing age (11). Similar abnormalities were reported in temporal lobe epilepsy resection specimens (12). Braak et al reported p-tau deposits in neurons with neurofibrillary tangles, particularly in the medial temporal lobe, as early as the second decade of life and becoming prevalent (albeit in small numbers of neurons) by the fourth decade; they considered this an early aging phenomenon; they did not comment on astroglial deposits (13). p-tau neurofibrillary tangles were reportedly more abundant in opiate drug abusers <40 years old (14) and in alcoholics (15).

Considering the attention CTE is receiving in the context of sports (4), and the possibility that CTE can occur in young individuals, it is important to know in what circumstances the histologic changes occur in the general population.
The main purpose of our study was to describe the occurrence of CTE-like pathological changes in brains of individuals <60 years age from a non-selected, community-based neuropathology referral base.

**MATERIALS AND METHODS**

This prospective study was performed at the Health Sciences Centre in Winnipeg, Manitoba, Canada. The study was performed in accordance with departmental tissue use guidelines and was approved for postmortem clinical record review and neuropathological examination by the Health Research Ethics Board at the University of Manitoba (reference number H2013:217). In Manitoba all medicolegal and almost all hospital/family permission autopsies are conducted within the 2 major teaching hospitals by a coordinated service of autopsy pathologists with forensic training. This includes approximately 1200 autopsies per year for a population of 1.3 million. Because the neuropathology service is integrated with the autopsy service, the decision to request a neuropathology consultation has a relatively low threshold.

Individuals 18–60 years presenting to the autopsy service between July 2013 and December 2015 were considered eligible if the entire brain was retained for neuropathological examination at the discretion of the forensic pathologist conducting the main autopsy. We chose to study cases <60 years age to avoid the complication of interpreting p-tau aggregates in the context of subclinical Alzheimer disease-type changes, which are common in older individuals (16). A few individuals with a clinical history and histological findings indicative of early onset Alzheimer disease (including 1 with Down syndrome) were excluded. In total, 111 brains were retained, which constitutes approximately 30% of total autopsies performed in the age range.

The brains were fixed in 10% buffered formalin for 10–14 days. The brains were sampled widely (typically 10–16 regions total) including the dorsolateral frontal, lateral frontal (at level of anterior basal nuclei), lateral frontal (at level of optic chiasm), hippocampus, and medial temporal including amygdala. Samples were dehydrated and embedded in standard 3 × 2 × 0.3 cm paraffin blocks, sectioned at 5 μm thicknesses, and stained with hematoxylin and eosin. p-tau immunostaining was performed during the first 6-month period of study using the rabbit polyclonal anti-tau [pSps199/202] antibody (44-768G, Invitrogen, ThermoFisher, Burlington, Ontario; dilution 1/5000), which detects tau phosphorylated at Ser199 + Ser202. We then switched to the AT8 mouse monoclonal antibody (MN1020, ThermoFisher; dilution 1/3000), which detects tau phosphorylated at Ser199 + Ser202 + Thr205. A 3-month overlap using both antibodies showed no significant differences in the patterns of labeling, although the polyclonal antibody rarely showed nonspecific nuclear labeling in what appeared to be normal neurons. Sections were pretreated with heat retrieval using an autoclave for 10 minutes in 10 mmol citrate buffer (pH 6.0); primary antibodies were detected using Dako EnVision + Dual Link System-HRP. p-tau immunostaining was performed on a minimum of three cortical regions (2 frontal and 1 temporal) although most cases had 4–6 regions immunostained. In cases judged to be stage 1 or greater, p-tau immunostains were also performed on the midbrain and pons.

Although our study began acquiring cases in 2013, summarization of the findings was done after consensus criteria for CTE-like p-tau-immunoreactive deposits were established by McKee et al (2). The specific changes were defined as abnormal perivascular accumulation of p-tau in neurons, astrocytes, and cell processes at the depths of cortical sulci in an irregular pattern. If present, they were staged as per the CTE stage outlined by McKee et al (1). McKee’s illustrations of half brain slices show p-tau-immunoreactive foci of ~3–4 mm diameter in stage 1; however, the minimum criteria for CTE have not been formally established (Ann McKee, personal communication, March 2016). For reasons that will be expanded upon in the Discussion, we subdivided the low abundance changes as follows: stage <1 was defined as 1 or 2 small foci (<200 μm), which could only be discerned at 10x objective magnification. Stage 1 had foci that were more numerous and larger. Stage 2 had multiple epicenters at the depths of the cerebral sulci and localized spread to the superficial layers of adjacent cortex (1); these could typically be discerned at 1.25× or 4× objective magnification. An experienced neuropathologist and the primary author examined all slides. Identification of CTE-like deposits had a near 100% concordance. Staging was reconciled through simultaneous viewing by all 3 authors. p-tau in neurofibrillary tangles alone or diffusely in the neuropil, typically in the hippocampal formation and/or medial temporal cortex, was not considered part of the CTE-specific pattern; however, these features were documented. We did not examine for the recently described dot-like pattern (17).

Additional histochemical stains on selected blocks included the modified phosphotungstic acid hematoxylin (mPTAH) method, which stains astrocytic processes in regions of chronic reactive change (18), and Perl’s Prussian blue method for hemosiderin. Additional immunohistochemical stains included detection of ubiquitin (mouse monoclonal Ub1, LSBio, Seattle, WA; diluted 1/70 000), β-amyloid (cleaved form, aa 17–24; mouse monoclonal clone 4G8, BioLegend, San Diego, CA, SIG39220-500; diluted 1/4000), human leukocyte antigen — DR (HLA-DR, mouse monoclonal CR3/43, Dako, Carpinteria, CA; diluted 1/100), vimentin (mouse monoclonal V9, Dako; diluted 1/5000), and αB crystallin (aBc) (rabbit polyclonal, Millipore, Billerica, MA, ABN185; diluted 1/2000). All antibody protocols used similar pretreatment and detection except the αBc antibody, which had a pH 9 pretreatment.

Clinical histories were summarized from the Medical Examiner reports of death. The centralized medical examiner death investigators in Manitoba have for decades specifically obtained detailed information about medical history, medications, and substance abuse both from medical chart review, (admission and emergency records), and from interviews with family members or acquaintances. This was done for all medical examiner cases. Eight cases were hospital deaths for which autopsies were requested by the physician or family; in these cases the authors conducted the entire history review. In all cases, the authors searched provincial imaging records for any imaging of the head or brain. This database includes almost all emergency computed tomography systems and all...
sites with MRI capability in the province and allows electronic access of records back to the mid-1990s. We also had access to complete hospital charts from the main trauma referral center (Health Sciences Centre), but not other sites. The following criteria were noted: age, sex, medical history details (particularly acute or remote head injury, history of violent lifestyle, drug or alcohol abuse, psychiatric disease, or neurological history), cause of death, and macroscopic and microscopic brain findings. Head injury history was subdivided into 3 grades: 0, no documented head injury; 1, 2 or fewer documented encounters with no structural abnormality on imaging; 2, 3 or more head injuries that prompted imaging of the head or a single injury that resulted in coma or structural brain damage such as contusion, or head injury requiring surgery for evacuation of hematoma. A more detailed medical chart review was performed by the authors (to supplement the initial medical examiner investigator review) in cases where the pathology showed CTE stages 1 or greater.

Pearson’s Chi square tests were performed to determine if there was a statistical association between CTE-like changes and age, sex, history of head injury, history of substance abuse including alcohol or other drugs, and history of psychiatric disease or neurologic symptoms. Statistical comparisons were made using JMP 12.1.0 software (SAS Institute Inc.). Specific tests are described in the “Results” section and table footnotes.

In addition to the prospective cases, we sought to determine if CTE cases similar to those referred for detailed study by McKee et al were encountered in our population. We retrospectively searched cases in the digitally archived autopsy database back to 1995 using a variety of whole text search phrases (ie neurofibrillary tangles, boxing, football, hockey, rugby, soccer, concussion, post-traumatic, post-traumatic stress disorder (PTSD), military, multiple head injuries, and others). The search yielded 13 cases of potential interest. The microscopic slides and paraffin blocks were retrieved. p-tau immunostaining was performed on sections from the parasagittal frontal and medial temporal brain regions (which were always present), as well as other cortical regions if they had been sampled. Staging and correlation were performed as described earlier.

**FIGURE 1.** Hyperphosphorylated tau (p-tau; using AT8 antibody) immunostain showing a single very small CTE-like perivascular focus considered to be stage <1.

**FIGURE 2.** Hyperphosphorylated tau (p-tau; using AT8 antibody) immunostain showing several CTE-like foci at depth of sulcus, in perivascular foci, and in the subpial region (arrows). This case was considered to be CTE stage 1.
<table>
<thead>
<tr>
<th>CTE stage (years)</th>
<th>Age</th>
<th>Medical history (2)</th>
<th>Alcohol and drug history</th>
<th>Cause of death</th>
<th>Brain abnormalities (2)</th>
<th>CTE-like features (hyperphosphorylated tau immunoreactivity) (2)</th>
<th>/-amyloid immunostainingb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 42</td>
<td>1</td>
<td>Traumatic brain injury (assault) 2 months prior to death</td>
<td>Chronic alcohol</td>
<td>Brain trauma (fall)</td>
<td>Chronic SDH and resolving ICH, recent EDH</td>
<td>3/5 slides with multiple small CTE-like foci in neocortex; NFT in medial temporal lobe; midbrain tiny perivascular foci along lateral aspect; locus cereuleus neurites and neurons</td>
<td>Nil</td>
</tr>
<tr>
<td>1 42</td>
<td>1</td>
<td>Memory and balance problems, smoker, took pain medications and anti-depressants</td>
<td>Chronic alcohol and solvent abuse</td>
<td>Brain trauma (pedestrian – motor vehicle)</td>
<td>Old contusion right temporal lobe, chronic neuron loss from hippocampus and cerebellum; acute contusions and brain swelling</td>
<td>4/4 slides with small CTE-like foci in neocortex; midbrain perivascular foci along lateral margin and periaqueductal; locus cereuleus neurites</td>
<td>Nil</td>
</tr>
<tr>
<td>1 48</td>
<td>1</td>
<td>Face and head trauma (bicycle—motor vehicle) 12 years prior to death and at least 2 assaults, DM, cardiomyopathy (? alcohol related)</td>
<td>Chronic alcohol</td>
<td>Cardiac</td>
<td>Old contusions bilateral inferior frontal</td>
<td>2/5 slides with multiple CTE-like foci in neocortex; 3/5 slides with scattered NFT (including medial temporal); midbrain neurites and neuron somata near midline and substantia nigra; pons - locus cereuleus neurons and sparse periventricular neurites</td>
<td>Nil</td>
</tr>
<tr>
<td>1 53</td>
<td>1</td>
<td>Neurosurgical removal of SDH 2 years prior to death, depression, schizoaffective disorder, hypertension</td>
<td>Unknown</td>
<td>Cardiac</td>
<td>Old SDH, SAH, laceration-contusions (inferior frontal and temporal)</td>
<td>5/5 slides multiple small CTE-like foci in neocortex; small subpial foci and scattered NFT (including medial temporal cortex near amygdala); midbrain neurites and neuron somata in substantia nigra and neurites around aqueduct; pons - locus cereuleus neurons and abundant periventricular neurites</td>
<td>Nil</td>
</tr>
<tr>
<td>1 60</td>
<td>1</td>
<td>Previous brain trauma with SDH, craniotomy, contusions (remote, but timing uncertain)</td>
<td>Chronic alcohol</td>
<td>Undetermined</td>
<td>Old SDH, contusions; recent small SDH; mild arteriosclerosis</td>
<td>5/5 slides multiple small CTE-like foci in neocortex; NFT in hippocampus</td>
<td>Nil</td>
</tr>
<tr>
<td>1 84</td>
<td>1</td>
<td>Professional wrestler (&gt;500 matches, retired ~30 years prior to death), hypertension, atrial fibrillation, hypothyroidism, multiple musculoskeletal injuries, depression, mild dementia/delirium with rare seizures beginning 2 months before death</td>
<td>Unknown</td>
<td>Sudden death (?) seizure</td>
<td>Slightly enlarged cerebral ventricles, moderate Alzheimer disease type changes (Braak NFT score 3-4/6, senile plaques moderate), small meningiomas on falx cerebri</td>
<td>11/19 slides with small CTE-like changes in neocortex; possibly stage 2 but difficult to be certain with background of Alzheimer type changes; scattered neurite deposits and neurons throughout midbrain and pons</td>
<td>Amyloid deposits abundant in neocortex and scattered in putamen</td>
</tr>
</tbody>
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(continued)
RESULTS

One hundred and eleven whole brains (88 male, 23 female) were included in the prospective study. We cannot exclude a referral bias as an explanation for the sex ratio. Among females, 7/23 had history of head injury and 16/22 (1 unknown) had a history of substance abuse; for males the ratios were 42/88 and 58/72, respectively (the substance abuse history was unknown for 14 males). Neither comparison was statistically significant (Pearson’s Chi square $p = 0.226$ and 0.432, respectively). Overall, alcohol was the most commonly documented psychoactive agent abused (>95%), with multi-drug abuse in a minority. The most common causes of death were injuries due to assaults or motor vehicle accidents, cardiac events, drug overdoses, and infections. Uncommon causes of death were sudden death in an epileptic, hanging, hypothermia, and malignancy.

Table 1 summarizes the age distributions, occurrences of head injury or substance abuse, and the association with CTE-like features. Brains from 72 individuals (64.9%) did not show any CTE-like changes. Among these, 25 had a history of head trauma and 38 had a history of chronic alcohol, drug, or solvent abuse. In cases that the etiology could be identified, head injuries were consequences of motor vehicle collisions, accidental falls, or assaults (or a combination of the latter 2 in many). Only one individual had explicitly been involved in sports; he was an 18-year-old male who played football and had suffered 2 concussions in the 2 years before his death. This group also included a 40-year-old man with history of military service and post-traumatic stress disorder but no specific head trauma events.

CTE-like p-tau-immunoreactive deposits were identified in 39 cases. Of the 34 stage $<1$ cases (31 male, 3 female) with minimal p-tau deposits (Fig. 1), 18 had previous head injuries and 25 had histories of alcohol or drug abuse. Three cases had what we considered stage 1 CTE-like changes (males age 42, 48, 53 years); 2 cases had stage 2 CTE-like changes (males age 47, 48 years) (Fig. 2). Details of these cases are presented in Table 2. In addition to the CTE-like deposits around blood vessels and in the neocortex, 19 cases (including all of the stage 1 and 2 cases) had labeling of neurofibrillary tangles and neuropil in the hippocampal formation and less often in the amygdala. We did not detect $\beta$ amyloid in any of the cases with CTE-like tau deposits (Table 2) (19).

The combined history of previous head injuries with history of drug or alcohol abuse was the strongest predictor of the presence of any CTE-like changes (Pearson’s Chi square $p = 0.0098$) (Fig. 3). Those with CTE-like changes were significantly older than those without (Fig. 4). Males were more likely than females to have any CTE-like changes (43% vs 15%, Pearson’s Chi square $p = 0.0075$). Splitting the head
injury and alcohol histories by sex reduced the likelihood differences among the males, but the historical factors remained strong among the females (Pearson’s Chi square p = 0.0175). Stratification of the severity of head trauma history showed that more severe cases were more likely to have CTE-like changes (Pearson’s Chi square p = 0.0212). Among the grade 0 head injury cases, 16/62 had minimal focal CTE-like changes (stage <1). Among grade 1 head injury cases, 12/34 had minimal focal CTE-like changes (stage <1) and there was 1 each of CTE stages 1 and 2. Among grade 2 head injury cases, 6/15 had CTE stage <1 and 3/15 had CTE stage 1 or 2. There was no significant relationship between the presence of any CTE-like change and the documentation of a psychiatric history (Pearson’s Chi square p = 0.2297).

Among the entire prospective study group, 13 cases had a history and physical evidence of recent (<7 days before death) brain trauma. Old contusions with focal atrophy and hemosiderin were identified in 9 cases, 8 of which also had some CTE-like foci. However, in none were the CTE-like p-tau deposits specifically associated with contusions. Old contusions only had p-tau immunoreactivity associated with ubiquitin and αB crystallin (αBc) immunoreactivity in granular eosinophilic bodies (Fig. 5). Recent contusions exhibited β-amyloid immunoreactivity in nearby damaged axons, vimentin immunoreactivity in reactive microglia and astrocytes, and αBc in reactive astrocytes; however, there was no immunoreactivity for p-tau. In comparison, p-tau deposits showed only occasional overlap with vimentin (in astrocyte processes), ubiquitin, or mPTAH (Fig. 6). p-tau did not colocalize with αBc (astrocytes in white matter), β-amyloid (lipofuscin only), HLA-DR (microglia), or hemosiderin.

Based on the search criteria of potential interest in the medical history (professional athlete, post concussion symptoms, multiple head injuries, etc.), 22 additional cases were selected for review (age range 27–84 years, median 46 years; 18 male, 4 female). These included some cases examined prior to the period of study (n = 13), and some examined concurrent with the study but outside of the designated age range (n = 9). One case encountered in this search was not available for review; the brain of a 58-year-old former professional football player had been sent to the McKee lab in Boston at the request of the family. Therefore, p-tau immunostains were performed on brain samples of 21 cases. No CTE-like changes were present in 12/21, minimal (stage <1) changes were present in 5/21, 3 cases (males age 42, 60, 84 years) had stage 1 CTE-like changes, and 1 case (male age 42 years) had stage 3 CTE changes (1). Details of these cases are presented in Table 2.
CTE is considered to be a neurodegenerative disease characterized by p-tau accumulation in characteristic brain locations and clinically associated with symptoms of irritability, impulsivity, aggression, depression, short-term memory loss, and heightened risk of suicide (1). To date, there are no generally accepted guidelines for the clinical diagnosis of CTE and it is currently only accurately diagnosed postmortem (2, 20). However, the link between p-tau aggregates in brain and the clinical syndrome is not fully established, and some authors have challenged the existence of the disease due to a lack of widely validated clinical or pathological criteria (9, 21–23). Furthermore, the pathogenesis of CTE remains unclear, although there are several postulated mechanisms (24). Traumatic shearing of axons might cause disassociation of tau from microtubules, misfolding, and accumulation of abnormally phosphorylated tau (3, 25). Abnormal exposure of the phosphatase-activating domain of the tau protein might lead to impairment of axonal transport (26). Endoplasmic reticulum stress might accompany the changes (27). There is limited evidence that the blood-brain barrier is disrupted in football players and in regions of dense perivascular p-tau accumulation (28, 29). However, other evidence for post-traumatic blood-brain barrier disruption suggests a distribution not concordant with CTE-like changes (30). Tau hyperphosphorylation may be a nonspecific response to damage; it also occurs in the context of hypoglycemia, hypoxia, stroke, and normal aging (21, 31).

We show here that approximately one-third of individuals <60 years age who undergo a medicolegal autopsy have very small CTE-like lesions in perivascular regions and at the depths of neocortical sulci. We found that there is a statistically significant association between CTE-like deposits and prior head injury and/or alcohol and drug abuse. We also identified several cases that fit the full definition of CTE (2), supporting the suggestion that this is a neuropathological diagnosis that is not exclusive to professional athletes and military veterans whose brains are examined in specialized referral laboratories (20). Neocortical p-tau deposits, which were not characterized in detail but were considered distinct from Alzheimer disease-type changes, were detected with the AT8 monoclonal antibody in 5% of individuals with a history of heavy alcohol consumption and 4% of controls age 25–77 years (32). A single traumatic brain episode 1–47 years prior to death was associated with a higher prevalence of neurofibrillary tangles in another study (33). Together these findings and ours support

**FIGURE 5.** Characterization of tissue at an old (estimated 2 years) contusion site. Immunostains and histochemical stains were performed on adjacent tissue sections. All are shown in the same location at the same magnification (200×). Old contusions are typically not associated with CTE-like p-tau immunoreactivity. The hemosiderin deposits (A, Perls’ Prussian blue method) are associated with granular eosinophilic bodies that are immunoreactive for p-tau (B), ubiquitin (C), and aBc (D).
the general proposition that head trauma is associated with the accumulation of p-tau in the brain. However, the direct causation by trauma is not fully established. For example, it is not clear why CTE-like deposits do not develop at sites of cerebral contusion. Perhaps viable neurons are required to deposit p-tau in the vicinity. The histological differences between chronic contusions and CTE-like sites make it unlikely that fluid markers such as aBc can be used to follow CTE-progression (34). We are also concerned that these tiny abnormalities might not have any specific clinical significance. We suggest that the

**FIGURE 6.** Characterization of tissue at depth of sulcus from a case with stage 2 CTE-like changes. Immunostains and histochemical stains were performed on adjacent tissue sections. All are shown in the same location at the same magnification (200×). Hyperphosphorylated tau (p-tau) is abundant in the neuropil around the blood vessels as well as in some neurons. There is no overall colocalization with other markers studied. αB crystallin (aBc) and modified phosphotungstic acid hematoxylin (mPTAH) label the chronic reactive astroglial processes. Some astrocytes are vimentin positive. Reactive microglia are HLA-DR positive. There is only minimal ubiquitin immunoreactivity.
consensus criteria for CTE diagnosis (2) should have a measurable lower limit to allow reporting of minimal abnormalities without making a disease diagnosis.

This study has several limitations. Brains retained for neuropathological examination were done at the discretion of the forensic pathologist conducting the main autopsy, almost certainly introducing a bias with respect to suspicious histories. Therefore, the real prevalence of CTE-like changes might be much lower. We were also limited by the available medical histories. While serious head injuries usually draw medical attention, minor head injuries associated with fights and falls are not all documented. Similarly, the magnitude and duration of substance abuse is extremely difficult to estimate. Although we are forced to rely on qualitative estimates, considering the methods of investigation used by the medical examiners we are reasonably confident that individuals with clinically or socially significant levels of substance abuse are usually identified. This study was started prior to publication of the consensus article on CTE diagnosis (2), therefore our sampling of brain regions was not optimal and the depth of our investigation was limited because we did not have dedicated grant funding. In general, we did p-tau immunostaining on the middle frontal gyrus, superior frontal gyrus, medial temporal cortex, and hippocampus, which corresponds fairly well to the consensus recommendations, and the consensus paper guided our final staging. However, in the absence of guidance concerning the size of p-tau deposits, we found it difficult to exactly utilize the staging scheme outlined by McKee et al (1).

It was based on thick sections (50 μm) from half brains. Immunostaining on thin sections (5 μm) from selected regions certainly underestimates the extent of p-tau deposits. More generally, we did not address general risk factors such as the apolipoprotein E genotype or mechanistic questions (35, 36).

In summary, we found that a significant proportion (35%) of the adult population <60 years old that undergoes a medicolegal autopsy have at least minimal CTE-like changes, which are usually (but not always) associated with histories of head injury and/or substance abuse. This broadens the susceptibility to CTE beyond athletes and military personnel toward the general population. This information does not, however, help to address the question whether CTE-like changes represent early features of a neurodegenerative disease. The absence of CTE-like changes at sites of contusion make hypotheses concerning blood-brain barrier opening, inflammation, and (iron-associated) oxidative changes less appealing as the initiators of the process. The significance of tiny p-tau deposits remains unclear, but the findings raise the possibility that CTE might represent a public health issue in vulnerable populations (eg those with chronic substance abuse).

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