Clinical and neuropsychological profile of patients with dementia and chronic traumatic encephalopathy

Christian LoBue, Jeff Schaffert, C Munro Cullum, Matthew E Peters, Nyaz Didehiani, John Hart, Charles L White

ABSTRACT

Objective To determine whether subjects with chronic traumatic encephalopathy (CTE) and dementia have distinct clinical features compared to subjects with pathologically confirmed Alzheimer’s disease (AD).

Methods Among 339 subjects assessed for CTE in the National Alzheimer’s Coordinating Center dataset, 6 subjects with CTE and 25 subjects with AD neuropathologic change matched for age (±5 years) and sex were identified. All subjects had a clinical diagnosis of dementia. Neuropsychological examination, neuropsychological testing and emotional/behavioural data were compared between CTE and AD subjects at the time of dementia diagnosis and last clinical visit near death.

Results A history of traumatic brain injury with loss of consciousness (LOC) was reported in one CTE and one AD subject; information about injuries without LOC or multiple injuries was unavailable. CTE and AD subjects did not differ significantly at the time of diagnosis or last visit on the Unified Parkinson’s Disease Rating Scale—Motor Exam, global measures of cognitive functioning (Mini-Mental State Exam and Clinical Dementia Rating Scale), emotional/behaviour symptoms as assessed with the Neuropsychiatric Inventory questionnaire or across neuropsychological measures. All CTE participants had co-occurring neuropathologic processes, including AD and most had TAR DNA-binding protein 43 (TDP-43) neuropathology.

Conclusions CTE pathology was rare in a large multicentre national dataset, and when present, was accompanied by AD and TDP-43 pathologies. CTE was not associated with a different clinical presentation from AD or with greater cognitive impairment or neurobehavioral symptoms. These findings suggest that CTE may not have a distinct clinical profile when other neuropathologic processes are coexistent with CTE pathology.

INTRODUCTION

Chronic traumatic encephalopathy (CTE) is a neuropathologic condition often reported to be associated with repetitive head injuries. The identification of CTE requires a single collection of hyperphosphorylated tau in neurons, astrocytes or cell processes around small blood vessels at the depths of sulci within the brain. While the neuropathologic features of CTE have been defined, the clinical manifestations of CTE are not well understood. Impulsivity, depression/suicidality, substance misuse, anxiety, anger, gait instability, motor slowness and cognitive changes have been reported in CTE subjects using postmortem interviews with informants, although these are nonspecific symptoms that are seen in many other conditions. Retrospective interviews are subject to recall bias, with potential for inaccurate reporting of symptoms, and depression and substance use disorders can occur for many reasons, possibly related to genetic predisposition, adverse life events and/or health problems unrelated to brain injuries. Many cases identified with CTE also show neuropathologic lesions that meet criteria for alternative neurodegenerative diseases, including Alzheimer’s disease (AD), Lewy body disease and frontotemporal lobar degeneration (FTLD), but when present with CTE, oftentimes CTE becomes the primary diagnosis/classification. Whether cases with CTE have a clinical phenotype that may be distinguished from other neurodegenerative diseases is unknown given the absence of prospective clinical studies during life. The aim of this study was to explore the clinical and neuropsychological characteristics of subjects later diagnosed as having CTE at autopsy and to compare the clinical features of subjects with CTE to those with AD from a large multicentre national database.

METHODS

Data were obtained from the National Alzheimer’s Coordinating Center (NACC). Since 2005, NACC has been collecting a Uniform Data Set (UDS) from all Alzheimer’s Disease Research Centers (ADRC) across the US, including detailed sociodemographic information, medical history (see online supplementary eMethods), neurological examination findings, neuropsychological test results and psychiatric symptoms on individuals with normal cognition, mild cognitive impairment and dementia. Information about traumatic brain injury (TBI) with loss of consciousness (LOC) is documented as absent, recent/active (occurring within 1 year of visit or currently requiring treatment) or remote/inactive (occurring > 1 year of visit and not currently receiving treatment); data about TBI without LOC or multiple injuries were unavailable for subjects in the dataset. For each ADRC visit, a multidisciplinary team or a single clinician determines a clinical diagnosis based on established guidelines. NACC has been collecting neuropathology data on AD, Lewy body disease (LBD), FTLD and other neurodegenerative conditions from participants autopsied at ADRCs since 2002 into a Neuropathology Data...
The UDS clinical data can be paired with neuropathological information on individual subjects to capture comprehensive clinical symptoms in autopsy-confirmed cases. NACC launched neuropathological data collection procedures for CTE in 2014. Research using the NACC dataset has been approved by the University of Washington IRB.

Study population
A cohort of subjects with CTE was identified by selecting participants who received a neuropathological diagnosis of CTE using previously defined criteria (see online supplementary eMethods). For a comparison group, patients who had a clinical diagnosis of dementia during ADRC visits, an absence of CTE pathology at autopsy and significant AD pathology reflecting a neuropathologic diagnosis of AD by NIA-AA criteria were selected (see online supplementary eMethods). AD subjects were matched to CTE subjects on sex and age (±5 years).

Neuropathological evaluation
ADRC neuropathologists used well-established diagnostic criteria to identify a variety of pathologic conditions at autopsy in addition to CTE and AD. These neuropathologic conditions included other tauopathies (eg, FTLD), synucleinopathy (eg, LBD), cerebral amyloid angiopathy and vascular brain injury (see online supplementary eTable 1 for full listing). The frequency of these pathologic conditions was examined in order to account for their presence and potential influence on the clinical and neuropsychological profiles.

Neuropsychological evaluation
A brief neuropsychological battery assessing attention, memory, language and executive functioning was completed (see box 1). Standardised scores were calculated based on a regression algorithm previously created in NACC subjects and were further defined as being within normal limits (t-scores ≥40), mildly impaired (t-scores 30–39), moderately impaired (t-scores 21–29) and severely impaired (t-scores ≤20). The frequency of scores falling into each category of functioning was examined in order to compare the level and pattern of cognitive function between CTE and AD subjects.

Psychiatric assessment
A psychiatric symptom data included a history of depression (coded as consulting a clinician, being prescribed medication or receiving a diagnosis related to depressed mood), a depressive symptoms scale (Geriatric Depression Scale-Short Form), history of pseudobulbar affect, history of substance use disorder and the Neuropsychiatric Inventory Questionnaire (NPI-Q) assessing presence/absence of 12 neurobehavioral symptoms (see online supplementary eMethods).

Statistical analysis
The CTE and AD groups were compared on sociodemographic, medical history, neurological examination, neuropsychological evaluation and psychiatric variables using t-tests for continuous variables and χ² analyses for categorical variables. Because all of the cases with CTE received a clinical diagnosis of dementia, characteristics from the initial encounter when dementia was diagnosed for both CTE and AD subjects were examined first. Data from the last visit before death were then analysed to determine if patients with CTE and AD differed on clinical symptoms in the final stages of dementia. Assumptions for all tests were reviewed and statistical significance was defined as p<0.05, with no correction for multiple comparisons to reduce the chances of Type II error. All analyses were conducted using IBM SPSS Statistics V24 (IBM, Armonk, New York, USA, 2016).

RESULTS

Neuropathological findings
A total of 339 subjects were documented as having a presence or absence of CTE since NACC initiated this data collection in 2014. Only six subjects were identified with CTE lesions and all were male. Among other subjects examined for CTE, we identified 25 with autopsy-confirmed AD who matched CTE subjects on sex and age (±5 years). The neuropathologic characteristics for both groups are summarised in table 1. Concomitant pathologies were common in those with CTE and included: intermediate AD neuropathologic change (3), high AD neuropathologic change (3), atherosclerosis (6), cerebral amyloid angiopathy (5), TAR DNA-binding protein 43 (TDP-43) reactive inclusions (5) and hippocampal sclerosis (3). Extent of beta-amyloid plaques and neurofibrillary tangles was high in all cases with CTE, with 67% having a Thal Phase of 4 or 5% and 100% having a Braak NFT Stage≥IV with moderate/frequent CERAD plaque scores. TDP-43 was also frequent in the medial temporal lobe (5).

Cohort summary
Demographic characteristics for the CTE and AD subject groups can be found in table 2. Mean estimated age of dementia onset was 3.6 years earlier for the CTE subjects relative to the AD group, though this difference was not statistically significant (p=0.51). Age of dementia diagnosis was nearly equivalent.
A single patient with CTE had a remote history of stroke and another cardiac bypass, while an additional patient with CTE had seizures; frequency of reported history of TBI with LOC and all other major medical comorbidities did not significantly differ between the CTE and AD groups. One CTE participant and all other major medical comorbidities did not significantly differ between the CTE and AD groups. One CTE participant and all other major medical comorbidities did not significantly differ between the CTE and AD groups.

The number of approximate annual follow-up visits for cases with CTE ranged from 1 to 7 (67% having at least five visits) and 88% of AD cases had a similar number of clinical visits. Five of the six CTE subjects were clinically diagnosed with AD at all visits, while one CTE subject’s diagnosis fluctuated between AD and dementia with Lewy Bodies over time. Only one subject with CTE completed the UPDRS-motor examination and/or neuropsychological evaluation at the last clinical visit near death; the severity of cognitive/behavioural problems in the other five subjects precluded these studies at the last clinical visit. However, measures of dementia severity and emotional/behavioural symptoms were completed on all subjects at the last clinical visit. The mean age at death and years between the last clinical visit and death (CTE Mean=0.9 years; AD Mean=1.2, range 1–4 years for all) were similar for both CTE and AD groups.

### Table 1 Neuropathological characteristics among the CTE and AD groups

<table>
<thead>
<tr>
<th>AD neuropathological change</th>
<th>CTE</th>
<th>AD</th>
<th>P value</th>
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| Total # n %                 | Total # n %<br>Low | 6 0 0 | 0 0 0 |<0.001*<br>Intermediate | 6 3 50 | 25 0 0 | 0.41<br>High | 6 3 50 | 25 100 | 0.53<br>Cerebral amyloid angiopathy | 6 5 80 | 24 21 88 | 0.41<br>α-5 Lewy bodies | 6 1 25 | 13 15 0.53<br>Brainstem predominant | 0 0 0 | 1 4<br>Limbic | 0 0 0 | 3 12<br>Neocortical (diffuse) | 1 16.7 | 2 8<br>Amygdala predominant | 0 0 0 | 6 24<br>Offactory bulb | 0 0 0 | 1 4<br>MSA synucleinopathy | 6 0 0 25 0 0<br>FTLD-tau Pick’s disease | 6 1 16.7 | 25 0 0 0.04*<br>Corticobasal degeneration | 6 0 0 25 0 0<br>Progressive supranuclear palsy | 6 1 16.7 25 4 12 0.76<br>Argyrophilic grain disease | 1 16.7 25 14 56 0.08<br>FTLD-TDP-43 | 6 2 33.3 | 18 1 5.6 0.08<br>Amygdala | 6 5 4 80 | 16 5 31.3 0.06<br>Hippocampus | 4 1 5 75 12 5 41.7 0.25<br>Entorhinal temporal cortex | 6 1 83.3 17 4 23.5 0.01*<br>Neocortical | 3 3 100 | 11 2 18.2 0.009*<br>Priob disease | 6 0 0 25 0 0<br>Hippocampal sclerosis | 6 3 5 80 | 24 1 4.2 0.01*<br>Neoplasm | 6 0 0 25 0 0<br>Contusion-TBI | 6 1 16.7 25 0 0 0.04*<br>Arteriosclerosis | 6 6 17 | 1 2 0.26<br>Mild | 2 33.3 12 | 70.6<br>Severe | 2 33.3 | 3 17.6<br>***Difference between the groups statistically significant (p<.05).<br>AD, Alzheimer’s disease; CTE, chronic traumatic encephalopathy; FTLD, frontotemporal lobar degeneration; MSA, multiple system atrophy; α-5, alpha-synuclein; TBI, traumatic brain injury; TDP-43, TAR DNA binding protein 43; Total #, the total number of cases examined for pathology.

### Table 2 Demographic, medical and clinical characteristics at the time of dementia diagnosis

<table>
<thead>
<tr>
<th>CTE</th>
<th>AD</th>
<th>P value</th>
</tr>
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| Total # n % | Total # n %<br>Age of dementia onset | 6 69.2±11.0 | 25 72.8±7.3 0.59<br>Age of dementia diagnosis | 6 80.3±5.4 | 25 79.1±6.1 0.51<br>Age of death | 6 84.7±7.2 | 25 82.8±7.2 0.82<br>Education, years | 6 15.8±2.0 | 24 16.4±2.9 0.60<br>Sex, male, % | 6 100 | 25 100<br>Race, Caucasian, % | 6 83.3 | 25 92 0.10<br>Medical history<br>Diabetes, n (%) | 6 1 (25) | 24 3 (12) 0.79<br>Hypertension, n (%) | 6 1 (25) | 24 3 (12) 0.79<br>Hypercholesterolemia, n (%) | 6 1 (25) | 24 3 (12) 0.79<br>B12 deficiency, n (%) | 6 1 (25) | 24 3 (12) 0.79<br>Myocardial infarction, n (%) | 6 1 (25) | 24 3 (12) 0.79<br>Atrial fibrillation, n (%) | 6 1 (25) | 24 3 (12) 0.79<br>Cardiac bypass, n (%) | 6 1 (25) | 24 3 (12) 0.79<br>Heart failure, n (%) | 6 1 (25) | 24 3 (12) 0.79<br>Stroke, >1 year ago, n (%) | 6 1 (25) | 24 3 (12) 0.79<br>TBI with LOC, % | 6 23 | 100 0.04†<br>Within 1 year, n (%) | 0 (0) | 0 (0) 0.04†<br>≥1 year ago, n (%) | 1 (16.7) | 1 (16.7) 0.04†<br>Seizures, n (%) | 6 1 (16.7) | 24 0 (0) 0.04†<br>Emotional measures<br>GDS total score | 6 2.4±1.5 | 22 2.2±2.1 0.20<br>NPI total score | 6 4.5±4.3 | 25 5.9±6.2 0.80<br>Neuropsychological scores<br>Digit Span Forwards | 6 2.4±0.4 | 22 5.8±1.3 0.51<br>Digit Span Backwards | 6 2.4±0.4 | 22 5.8±1.3 0.51<br>Coding | 6 2.4±0.4 | 22 5.8±1.3 0.51<br>Trail Making Test Part A | 6 2.4±0.4 | 22 5.8±1.3 0.51<br>Trail Making Test Part B | 6 2.4±0.4 | 22 5.8±1.3 0.51<br>Semantic Fluency | 6 2.4±0.4 | 22 5.8±1.3 0.51<br>Boston Naming Test | 6 2.4±0.4 | 22 5.8±1.3 0.51<br>Logical Memory I | 6 2.4±0.4 | 22 5.8±1.3 0.51<br>Logical Memory II | 6 2.4±0.4 | 22 5.8±1.3 0.51<br>***Difference between the groups statistically significant (p<.05).†Statistically significant difference (p<.05), but results may be unstable given only 1 CTE case had the condition. Neuropsychological scores reflect raw scores. AD, Alzheimer’s disease; CDR, Clinical Dementia Rating Scale; CTE, chronic traumatic encephalopathy; GDS, Geriatric Depression Scale; LOC, loss of consciousness; M, mean; MMSE, Mini-Mental State Exam; NPI, Neuropsychiatric Inventory Questionnaire; SD, standard deviation; TBI, traumatic brain injury; Total #, the total number of cases examined for each factor; UPDRS, Unified Parkinson’s disease rating scale.

### Neurological examination findings

Dementia severity in patients with CTE at the time of dementia diagnosis, as measured with the CDR, was classified as questionable in 1, mild in 2, moderate in 2 and severe in 1. The AD subjects (Median=1.0) were mostly rated as having questionable (44%) and mild dementia (44%). Mini-Mental State Exam (MMSE) scores did not significantly differ between the CTE (Mean=23.0; SD=4.8) and AD groups (Mean=20.7; SD=6.7), but scores were slightly higher in those with CTE. Abnormal motor symptoms were common in both CTE (100%); Mean UPDRS Total=11.8; SD=12.4) and AD (69.6%); Mean UPDRS Total=8.7; SD=9.5), and the average total UPDRS scores for the motor examination did not significantly differ between them (p=0.54). A profile of the motor symptoms for patients with CTE and AD at initial presentation can be seen in figure 1. Among CTE cases, one had dysthria, two hypomimia,
two tremor, two rigidity, two slowness of movements and four stooped posture/postural instability. Similarly, in the AD sample, two had dysarthria, five hypomimia, two tremor, five rigidity, two slowness of movements and seven with stooped posture/postural instability. Overall frequency of each motor symptom did not differ between the CTE and AD groups at the time of dementia diagnosis.

At the last clinical visit, dementia severity was rated on the CDR as being mild in one, moderate in two and severe in three CTE subjects. Dementia severity in AD subjects at the last clinical visit was classified as questionable in 1, mild in 7, moderate in 10 and severe in 7.

Neuropsychological functioning

Neuropsychological performances at the time of dementia diagnosis were similar for subjects with CTE and AD on nearly all tasks, with the exception of a measure of processing speed (TMT A) and confrontation naming (BNT), where cases with CTE performed slightly better and in the mildly impaired range, though this was not statistically significant. In general, however, patients with CTE and AD showed a cognitive profile at initial presentation consisting of moderate impairments in episodic memory and mental flexibility, mild deficits in semantic verbal fluency and relatively more preserved attention and processing speed skills. Neuropsychological data at the last clinical visit near death was missing for five CTE subjects and thus we were not able to examine for differences in functioning between CTE and AD subjects.

Mood and behavioural functioning

Neuropsychiatric symptoms on the NPI at the time of dementia diagnosis were similar between the groups (p=0.61), though slightly lower for the CTE group (Mean=4.5; SD=4.3) compared to AD participants (Mean=5.8; SD=6.2). The profile of mood and behavioural symptoms for each group at initial presentation can be seen in figure 3. Anxiety and apathy were somewhat common for CTE cases (three cases each), but other psychiatric and behavioural symptoms were less frequent. For CTE cases, only one had delusions/hallucinations, two agitation, one disinhibition, two irritability, one remote history of alcohol use disorder and none had a history of depression (>2 years ago or within 2 years), pseudobulbar affect or an illicit substance use disorder. The profile of neuropsychiatric symptoms for patients with AD at the time of dementia diagnosis was analogous, with apathy (15 cases) and anxiety (10 cases) being common, in addition to irritability (10 cases). For the AD group, five had delusions, one hallucinations, nine agitation, four disinhibition, seven with history of depression, two elated mood, one recent alcohol use disorder and none with illicit substance use disorder or pseudobulbar affect.

At the last clinical visit, neuropsychiatric symptoms on the NPI continued to be similar (p=0.35) between CTE (Mean=7.3; SD=7.1) and AD groups (Mean=8.5; SD=7.4). Apathy and anxiety remained the most common symptoms for patients with CTE (5 cases and three cases, respectively), while few subjects had delusions (2), hallucinations (1), depression (1), agitation (1), disinhibition (1) and irritability (1). In the AD group, apathy (18), anxiety (13) and agitation (12) were prevalent at the last visit prior to death and although the frequency of other psychiatric and behavioural symptoms had increased following the initial presentation, these remained less common. Specifically, seven had delusions, four hallucinations, seven depression, two
scored better on some tests (processing speed and confrontation naming). Whereas impulsivity, depression, anger and substance misuse have been reported to be common for cases with CTE pathology, neuropsychiatric symptoms were similar between the CTE and AD groups at the time of dementia diagnosis as well as the very late stages. Also, a history of depression was absent in all of the cases with CTE pathology at the time of dementia diagnosis and only one had a history of substance misuse. Later in the course, only one case with CTE appeared to experience depression prior to death. Interestingly, the profile of neurological, neuropsychological and psychiatric features for the CTE group matched that seen in the AD subjects at the time of dementia diagnosis, and no differences were found in dementia severity or emotional/behavioural symptoms later on in the course. Taken together, these findings suggest that CTE pathology may not be associated with a clinical phenotype that is distinct from AD or meaningfully contribute to the clinical presentation when AD and other pathologic processes are coexistent.

CTE pathology has been classified into four stages based on the amount and location of hyperphosphorylated tau aggregates present. NACC does not have procedures to report the CTE pathology stage as proposed by McKee and colleagues, and thus we cannot determine whether mild, moderate or severe CTE pathology may have had implications on results in the present study. Nonetheless, cognitive, behavioural and mood symptoms have been reported to be common at all stages of CTE pathologic burden, occurring in ≥85% of former professional athletes with CTE pathology at mild (Stages I and II) as well as moderate-to-severe stages (Stages III and IV). Based on these findings, we would have expected to see worse cognitive and neuropsychiatric symptoms in our CTE cohort if CTE pathology has such clinical implications, even if all of the subjects had mild levels of pathology. Other neuropathologic syndromes linked to progressive cognitive decline have been found to have separate and additive effects on cognitive impairment. Lewy body pathology and TDP-43 inclusions, when present in individuals with AD, have been associated with greater cognitive impairment and dementia severity. On the other hand, our CTE cohort was obtained from ADRCs and is not representative of the former professional athletes from which CTE symptoms have been previously described. As such, the lack of an association between CTE and any clinical symptoms could be related to cohort differences. It seems reasonable, however, to assume that CTE pathology should be distinctly associated with cognitive/behavioural symptoms regardless of purported risk factors (eg, head trauma and so on), if meaningful. For instance, cognitive/behavioural symptoms tied to neuropathologic changes for Alzheimer’s disease and related conditions are not thought to differ based on what risk factors are present/absent (eg, environmental or medical), and it would appear reasonable to treat CTE the same. In fact, a recent investigation of former contact sports athletes having dementia found no differences in clinical presentation during life between those with and without co-occurring CTE using limited information obtained from medical records (eg, presence/absence of alcohol misuse history, motor abnormalities, age of cognitive decline), similar to the present findings. There is also increasing evidence showing that CTE pathology is not uniquely linked to TBI and occurs in individuals with alcohol/substance misuse, temporal lobe epilepsy, amyotrophic lateral sclerosis, and those with no known exposure to contact sports/TBI, providing support for studying CTE more broadly than in former athletes.

It is quite rare for individuals across all age ranges (20–100) to have a total absence of pathologic lesions related to AD and

**DISCUSSION**

CTE has received widespread media attention as being associated with neurodegenerative changes following repetitive head trauma, leading to an increasing number of individuals having concerns about developing a ‘CTE-related dementia’. While information about multiple head injuries for subjects with CTE is unknown in the NACC dataset, this is the first study to examine neurological, neuropsychological and emotional/behavioural characteristics of subjects with CTE pathology using standardised assessments during life. All of the patients with CTE pathology were clinically diagnosed with dementia, but 6/6 also had AD and many had TDP-43 lesions, revealing that mixed pathologies were involved. These findings are consistent with previous reports showing comorbid processes such as AD and TDP-43 pathology are found in many CTE cases. A major question about CTE is to what extent the pathology contributes to the clinical profile in a meaningful way when other pathologic processes are present. Abnormal motor symptoms were common at the time of dementia diagnosis in subjects with CTE and other concomitant pathologies as well as subjects with AD and did not differ in terms of severity among the two groups. Neuropsychological performances at the time of dementia diagnosis were not worse for subjects with CTE compared with the AD group, and subjects having CTE even related mood, seven disinhibition and nine irritability in the AD group.
other tauopathies at autopsy. Also, it is well known that individuals with some or a few pathologic lesions seen in AD and other types of neurodegenerative disorders do not manifest cognitive/behavioural problems, with a threshold of pathologic burden considered critical for attributing pathologic changes to symptomatology. Some have raised the question of whether a pathologic threshold must also be exceeded for CTE to be associated with any clinical symptoms. One possibility is that our CTE sample may have possessed only small amounts of CTE pathology and thus did not contribute to the clinical presentation. Because the pathologic burden or stage of CTE lesions is unknown in the present study, at the very least, this may be why we did not find differences in the neuropsychological or psychiatric presentation between the groups. Yet, it has been reported that deposition of beta-amyloid plaques is linked to greater CTE pathologic stages, with only 20% in the mild CTE stage (Stages II/III) shown to have neuritic plaques vs. 97% of those in the moderate-to-severe stages (Stages III/IV). Another possibility then is that our CTE sample, in which 100% of the subjects had significant neuritic beta-amyloid plaques, may actually have had more severe CTE pathologic changes. Therefore, the lack of an association between co-occurring CTE and other pathologic processes with any clinical features in this study may indicate that CTE might not have a clinical correlate or be masked by AD clinical features. Regardless of either possibility, findings from the present study cast doubt on assigning CTE as the primary neuropathologic diagnosis when other pathologic processes are present, raising important questions about specificity in diagnosing CTE neuropathologically. Future research is clearly needed to validate CTE pathologic diagnostic criteria and to establish whether co-occurring pathology should be given greater weight in the classification guidelines (similar to Lewy body disease).

A strength of our study is that this is the first to characterise the neurological, neuropsychological and psychiatric features of patients with CTE pathology using standardised assessments. Unlike previous CTE investigations, information was obtained from specialised dementia clinics without a reliance on retrospective family reports or medical records after death. However, this study does have limitations. First, NACC’s neuropathological criteria for CTE are not the same as those in the guidelines recently developed by the NINDS/NIBIB consensus panel. At the consensus conference, CTE criteria were operationalized to reduce overlap with other tauopathies. Although this may have implications for the results from the current study, NACC’s criteria are consistent with the CTE pathologic guidelines used by the neuropathologists involved in the consensus conference to actually identify cases with CTE. Also, the extent of CTE pathology is not coded in NACC, which prohibited examination of the potential influence of mild, moderate or severe levels on clinical characteristics. It is important to note, however, that a staging system for CTE was not adopted by the NINDS/NIBIB consensus panel, and thus it is unclear whether CTE lesions previously posited to reflect different stages or severities would be reliable/valid. Last, we had a limited sample size with CTE pathology that was accompanied by other pathologic processes, which may have resulted in a minimally representative sample and/or restricted power to identify some differences between our groups.

Overall, CTE pathology was rare and found in <2% of cases examined in a large multicentre national dementia dataset. A recent investigation of 1721 men within the Mayo Clinic’s neurodegenerative disorders brain bank also found the frequency of CTE lesions to be quite low (1.2%). Thus, CTE appears to be a rare neuropathologic condition. In the present study, while all individuals with CTE pathology had a clinical diagnosis of dementia, AD and TDP-43 pathologies were also present, and the clinical profile was similar to an AD comparison group. In fact, CTE was not associated with depression, irritability or substance use relative to those with AD, and neuropsychological functioning was similar. These findings call into question the validity and specificity of CTE neuropathologic criteria and indicate that classification should consider co-occurring pathology to understand CTE’s implications in future studies.
Cognitive neurology


