# PATHOLOGY of CHRONIC TRAUMATIC ENCEPHALOPATHY 2017

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Over the last decade, there has been considerable interest in the potential long-term effects of repetitive impact injury that occurs in association with participation in contact sports and military service.[1-4] Case reports and case series have described athletes and military veterans who developed explosivity, loss of control, aggressive and violent behaviors, impaired attention, depression, executive dysfunction and memory disturbances associated with a progressive neurological deterioration, chronic traumatic encephalopathy (CTE). At the present time, CTE cannot be diagnosed during life, and is diagnosed with certainty only by neuropathological examination of brain tissue.

## NEUROPATHOLOGY OF CTE

### Gross Pathology

Grossly identifiable changes in the brain are unusual in early or mild CTE, if present in early disease, they are most often cavum septum pellucidum and mild enlargement of the frontal and temporal horns of the lateral ventricles. There may be prominent perivascular spaces in the white matter, particularly in the temporal lobe. In advanced CTE, macroscopic changes include a reduction in brain weight, gray and white matter atrophy (typically most severe in the frontal and anterior temporal lobes), medial temporal lobe atrophy, enlargement of the lateral and third ventricles, cavum septum pellucidum, septal fenestrations, atrophy of the thalamus, hypothalamus and mammillary bodies, thinning of the isthmus of the septum corpus callosum and depigmentation of the locus coeruleus and substantia nigra. Although grossly identifiable cerebellar abnormalities were described in the initial reports of CTE affecting boxers, macroscopic cerebellar abnormalities are rarely present in CTE associated with other sports or activities.[4]

### Microscopic pathology

In 2013, the clinical and pathological features of the largest cohort of 68 men with CTE were reported, including 50 football players, 5 hockey players, 8 boxers, 1 professional wrestler and 21 military veterans (18 of whom were also athletes) and 1 individual who engaged in self-injurious head banging behavior[4] and based on the pathological findings in that series, criteria for the neuropathological diagnosis of CTE were introduced.[4] In 2015, the National Institute of Neurological Disorders and Stroke (NINDS) and National Institute of Biomedical Imaging and Bioengineering  (NIBIB) convened a consensus panel of highly experienced neuropathologists to evaluate 25 cases of various tauopathies blinded to all clinical, demographic and gross neuropathological information to evaluate whether CTE could be reliably distinguished from other tauopathies using the preliminary diagnostic neuropathological criteria for CTE.[5] The tauopathies included examples of CTE, Alzheimer's disease, progressive supranuclear palsy, argyrophilic grain disease, corticobasal degeneration, primary age-related tauopathy (PART), and parkinsonism dementia complex of Guam (GPDC). All cases were processed uniformly by a single laboratory and the resulting slides were scanned into digital images that were provided to neuropathologists blinded to all other information, including the age, sex, clinical symptoms, sports or military history, and the gross neuropathological findings. The neuropathologists evaluated the cases independently and submitted their evaluations prior to a face-to-face meeting. The results indicated found that there was good agreement within the neuropathologists who reviewed the cases (Cohen's kappa: 0.67) and even better agreement between reviewers and the diagnosis of CTE (Cohen's kappa: 0.78). Furthermore, 91.4% of the total responses correctly identified CTE, which rose to 95.7% after the clinical information and gross neuropathological features were revealed. The panel further determined that there is a pathognomonic lesion of CTE that distinguishes it from all other neurodegenerative diseases, including aging and non-specific astrotauopathy (ARTAG) [6]. The pathognomonic lesion of CTE was defined as an accumulation of abnormal tau in neurons and astroglia distributed around small blood vessels at the depths of cortical sulci and in an irregular pattern. The panel also noted that there were p-tau immunoreactive dotlike neurites around the perivascular lesions. In addition, they found the TDP-43-immunoreactive inclusions in CTE were distinctive from other neurodegenerations and that the pattern of

hippocampal neurofibrillary degeneration was unlike the pattern found in AD. The group also defined supportive but non-specific features of CTE, recommended a minimum blocking and staining scheme for pathological evaluation and made recommendations for future study.[5]

## Staging of CTE pathology

In 2013, McKee and colleagues proposed a staging scheme of pathological progression of p-tau pathology in CTE.[4] The method of staging of p-tau pathology in tauopathies was adapted from the work of Braak and Braak who examined a series of 83 autopsy brains with Alzheimer's disease (AD) for neurofibrillary changes and found a characteristic distribution pattern of NFTs and neuropil threads that permitted the differentiation of AD into 6 stages.[7] This staging system forms the basis for the neuropathological diagnosis of AD used by all the National Institute on Aging,[8] and similar staging schemes are now in use for Aß plaques in AD,[9] and Lewy bodies in Parkinson's disease.[10] After examination of 68 cases of CTE, McKee and colleagues identified 4 pathological stages: stages I-IV.[4] In the earliest stage of CTE, stage I, p-tau NFTs and large dot-like and grain-like structures are found around small blood vessels as focal epicenters in the cortex. These perivascular foci have a tendency to be located at the sulcal depths of the frontal, temporal, parietal, insular and septal cortices and may be associated with astrocytic p-tau pathology in the subpial region. In stage II CTE, there are multiple ($\geq$ 3) perivascular foci and scattered NFTs in multiple regions of cortex, and NFTs in the locus coeruleus and nucleus basalis of Meynert. In stage III CTE, the perivascular lesions are larger and involve confluent areas, p-tau immunoreactive NFT and p-tau astrocytes are found centered around blood vessels at the sulcal depths, as well as in linear arrays in the superficial laminae of cortex. In Stage III CTE, NFTs are also found in the hippocampus, entorhinal cortex and amygdala – regions that are largely spared in CTE stages I and II. There are NFT in the substantia innominata, substantia nigra, dorsal and medial raphe and olfactory bulbs. Neurofibrillary degeneration in the hippocampus includes CA4 and CA2, as well as CA1. In CTE Stage IV, p-tau immunoreactive neurons and astrocytes are densely distributed throughout the cerebrum, thalamus, hypothalamus, mammillary bodies, basal ganglia, brainstem, cerebellar dentate nucleus and occasionally, spinal cord. There is often marked neuronal loss and gliosis of CA1 and the subiculum. Neuronal loss and astrocytosis may also be prominent in the frontal and temporal cortices, associated with microvacuolation of layer 2. Primary visual cortex is generally spared.

## Aß pathology in CTE

Unlike AD, CTE is a primary tauopathy. In other words, the tauopathy of CTE appears first in the progression of disease prior to the appearance of Aß plaques, and Aß plaques are not found in all individuals with CTE. Aß containing plaques, mostly as diffuse Aß plaques, are present in 52-65% of individuals with CTE; their presence is significantly associated with age and they are never found in early stage disease. Conversely, Aß deposits are a critical element of the diagnostic criteria for AD and are a prominent feature of AD even in early stages.[11] In CTE, Aß plaques are associated with accelerated tauopathy, Lewy body formation, dementia, Parkinsonism and inheritance of the ApoE4 allele.[12]

## CTE and other neurodegenerations

At the present time, CTE is a diagnosis that can only be made definitively upon neuropathological examination of the brain. Using the newly devised NINDS criteria, Bieniek et al reviewed the clinical records and brains of 1,721 cases donated to the Mayo Clinic Brain Bank over the past 18 years, and found 21 cases had evidence of CTE pathology – all in contact sport athletes (21/66).[13] No cases of CTE were found in 198 control brains without a history of brain trauma or in 33 cases with a history of a single traumatic brain injury. Of the 21 athletes with CTE pathology, 19 had participated in football or boxing, and many were multiple sport athletes including rugby, wrestling, basketball, and baseball. One athlete played only baseball, and another athlete only played basketball. Similarly, Ling and colleagues screened 268 cases of neurodegenerative diseases and controls and found CTE changes in 11.9%. Of the cases with CTE, 93.8% had a history of TBIs, 34% had participated in high-risk sports including rugby, soccer, cricket, lacrosse, judo and squash, and 18.8% were military veterans.[14] Recently CTE was found in 4 of 6 former soccer players who were demented.[15] All the athletes in the study had lengthy soccer careers (average 26 years).

**CTE with ALS**

Approximately ten percent of individuals with CTE develop a progressive motor neuron disease that is characterized by profound weakness, atrophy, spasticity and fasciculations and fulfills criteria for the clinical diagnosis of ALS.[4,16] In addition, a recent screen of ALS cases from the Mayo Clinic Jacksonville ALS brain bank and the Boston VA ALS bran bank found that 6/91 (6.6%) and 5/113 (4.4%) cases, respectively, had pathological features of CTE (all Caucasian males).[17] Most individuals with CTE and ALS present with symptoms of ALS and develop mild cognitive and behavioral symptoms several years after the onset of motor weakness and fasciculations. Individuals with motor neuron disease and CTE tend to die from respiratory failure at younger ages and in earlier stages of CTE (stage II-III) compared to CTE subjects without ALS. Approximately one third of CTE+ALS subjects present with depression, behavioral or cognitive changes related to CTE many years before developing ALS symptoms, and are diagnosed with CTE, grade III or IV, and ALS at autopsy. Subjects with CTE+ALS show more severe TDP-43 pathology than subjects with CTE alone. The marked accumulation of pTDP-43 aggregates in advanced stages of CTE, the partial immunohistochemical co-localization of p-tau with pTDP-43, and the development of ALS and FTLD in some individuals with CTE suggests that CTE and FTLD share some pathogenic mechanisms.[18,19]

**Can CTE pathology be explained by aging or Alzheimer's disease?**

Recently, there have been several reviews and commentaries that state there is no credible evidence that CTE exists and that the pathology of CTE represents the effects of aging, AD or a type of FTLD.[20-25] The findings of the NINDS consensus meeting are at odds with these statements as the panel was able to distinguish CTE from other tauopathies, including primary age-related tauopathy (PART), AD, argyrophilic grain disease, corticobasal degeneration and progressive supranuclear palsy, and GPDC. Furthermore, the p-tau pathology that develops with aging shares no microscopic features with CTE even in the mildest stages. CTE is characterized by perivascular lesions in the cerebral cortex, with an accentuation at depths of sulci. A similar pattern of p-tau pathology has never been described in aging or other neurodegenerations, including AD.

The question of inadequate controls is also cited as a failure of previous neuropathological investigations despite the fact that controls have been included and found to be negative for CTE in multiple studies. Geddes and colleagues reported the lack of the findings of CTE in 21 age matched subjects with no history of neurotrauma,[26] McKee and colleagues reported the lack of CTE in 18 age and gender matched control subjects[4] and Bieniek and colleagues reported the absence of CTE changes in 198 control cases from the Mayo Clinic Jacksonville brain bank without a history of brain trauma.[13]

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