

CURRENT CLINICAL RESEARCH IN CHRONIC TRAUMATIC ENCEPHALOPATHY

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Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease characterized by deposition of an abnormal form of tau protein in a pattern that is unique from other diseases, including Alzheimer's disease. CTE has been found most often in professional contact sport athletes (e.g., boxers, football players) who have been subjected to repetitive head impacts. The clinical features of CTE are believed to include memory and other cognitive impairment (with eventual dementia), changes in mood (e.g., depression, apathy), behavioral regulation difficulties (e.g., impulsivity, rage), and in some cases, motor changes (e.g., parkinsonism). At this time, CTE can only be diagnosed after death through neuropathological examination of brain tissue. Dr. Ann McKee and colleagues, with funding from NINDS for the "Understanding Neurologic Injury in Traumatic Encephalopathy" (UNITE) Project, have made tremendous gains in the understanding and description of the neuropathological changes of CTE.

Although there has been a great deal of media attention to CTE, the scientific study of this disease is still in its early stages. Critical questions remain, such as: How common is CTE? Why do some people get it and others do not? What is the mechanism leading from repetitive head impacts to the brain disease and later life symptoms? What are the risk factors for CTE? How can we diagnose CTE during life? Can CTE be treated or even prevented?

Our group has been conducting preliminary clinical research in several key areas to address these questions. This presentation will provide an overview of findings of two studies:

- **LEGEND** (Longitudinal Examination to Gather Evidence of Neurodegenerative Disease), a longitudinal study of several hundred active and former athletes who undergo annual on-line and telephone-based assessments of cognition, mood, and behavior, as well as interviews to obtain detailed information about head impact exposure.
- **DETECT** (Diagnosing and Evaluating Traumatic Encephalopathy using Clinical Tests), a cross-sectional study funded by an NIH R01 grant (PI: Dr. Robert Stern), involving ~100 former NFL players and ~30 controls who underwent extensive evaluations, including: clinical examinations (neurological, motor, cognitive, mood, behavior); neuroimaging (MRI, DTI, fMRI, MRS); lumbar punctures; EEG, genetic, and experimental blood tests to detect tau. A subset of subjects also received PET imaging with tau (AV-1451) and amyloid (florbetapir) ligands, funded by a separate grant from Avid Radiopharmaceuticals.

Results pertaining to the following topics will be presented:

- **Exposure Risk:** Studies examining the relationship between repetitive head impact exposure variables and later –life neurological consequences.
- **Structural MRI:** Studies conducted in collaboration with colleagues at the Brigham and Women's Hospital (BWH; Drs. Shenton, Koerte), including volumetric measurement of key regions of interest, detection of cavum septi pellucidi, and white matter integrity with diffusion tensor imaging.
- **Magnetic Resonance Spectroscopy (MRS):** Studies conducted in collaboration with Dr. Alex Lin at BWH examining the measurement of biochemical metabolites as possible proxy biomarkers of CTE.
- **PET Tau Imaging:** Preliminary findings of the use of AV-1451 to detect paired helical filament (PHF) tau in former NFL players.
- **Fluid Biomarkers:** Studies of CSF proteins, as well as plasma total tau (using the Quanterix Simoa technology), and preliminary examination of plasma exosomal tau.

The presentation will also include a description of the **DIAGNOSE CTE Research Project** (Diagnostics, Imaging, And Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy), a multi-center, multi-disciplinary, 7-year, longitudinal study, funded by a U01 grant from NINDS. Co-Principal Investigators of the project are: Drs. Robert Stern (Boston University; Contact PI), Jeffrey Cummings (Cleveland Clinic), Eric Reiman (Banner Alzheimer's Institute), and Martha Shenton (Harvard). The aims of the project are the following:

1. To collect and analyze neuroimaging and fluid biomarkers for the detection of CTE during life.
2. To characterize the clinical presentation of CTE.
3. To examine the progression of CTE over a three year period.
4. To refine and validate diagnostic criteria for the clinical diagnosis of CTE.
5. To investigate genetic and head impact exposure risk factors for CTE.
6. To share project data with researchers across the country and abroad in order to expedite growth in our understanding and treatment of this disease.

Participants in the DIAGNOSE CTE Research Project are 240 men, ages 45-74, including former NFL players, former college football players, and asymptomatic controls who have never participated in contact sports or have had any brain injury. Data collection began in late 2016.

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