THE NEUROPATHOLOGICAL DIAGNOSIS OF CHRONIC TRAUMATIC ENCEPHALOPATHY (CTE): NEXT STEPS

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Acronyms List

Aβ	amyloid-beta
AD	Alzheimer's disease
ADRC	Alzheimer's Disease Research Centers
ALS	amyotrophic lateral sclerosis
ARTAG	aging-related tau astrogliopathy
BBB	blood–brain barrier
BU	Boston University
CDE	common data elements
CLF	Concussion Legacy Foundation
CTE	chronic traumatic encephalopathy
DoD	Department of Defense
FY	fiscal year
mTBI	mild traumatic brain injury
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
PD	Parkinson's disease
p-tau	phosphorylated-tau
TBI	traumatic brain injury
USU	Uniform Services University
VA	U.S. Department of Veterans Affairs

Executive Summary

The National Institute of Neurological Disorders and Stroke (NINDS) hosted the 2015 and 2017 Neuropathological CTE Diagnosis Consensus Conferences that focused upon defining the CTE pathognomonic lesion and severity rating, respectively. Ultimately, this research investment aims to guide future prevention strategies that might include imaging and biomarkers for at-risk individuals and populations. The goals of the 2019 NINDS-hosted CTE conference were to assess the current state of neuropathological CTE diagnosis from multiple perspectives; to discuss scientific needs across diagnostic domains; to address challenges related to sensitivity and specificity, progression, severity, and prevalence—toward prioritizing neuropathology research goals. The meeting included five sessions, followed by a summary of next steps articulated by meeting attendees. See Appendixes A and B for the meeting agenda and participants list, respectively.

Session I: State of the Evidence

The 2015 CTE Diagnosis Consensus Conference defined the single pathognomonic criterion for CTE as "an accumulation of abnormal phosphorylated-tau (p-tau) in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci" as well as provided additional supporting features to define CTE. One current concern amid the CTE research community is a perceived lack of clarity about the role of non-neuronal cells in CTE p-tau neuropathology, because there have been many reports of astrocyte involvement and shallow (subpial) lesions, both of which may represent other neurodegenerative conditions or multiple, comorbid tauopathies.

Session II: Sensitivity and Specificity

Developing a set of gold-standard neuropathological criteria for CTE remains a work in progress, because of difficulties distinguishing CTE from other tauopathies. Methods for brain sampling, tissue preparation and analysis; and data collection and sharing must be standardized. Additional practical questions to refine CTE neuropathological criteria include determining appropriate study cohorts and ensuring accurate identification of occult past neurotrauma.

Session III: Progression and Severity

At the second consensus conference in Boston in November 2016 that reviewed (blinded) 19 CTE cases, there was least agreement among staging mild CTE cases. For CTE, the presence of the pathognomic lesion indicates that a pathological process is under way, but other information (age, exposure type, and dose) likely translate to appearance of clinical symptoms—including but not limited to behavioral changes and psychiatric conditions. Understanding these processes is critical for development of a severity index for future use in living individuals.

Session IV: Prevalence

Many challenges restrict progress in assessing CTE prevalence, including selection bias (autopsy, individual vs population cohorts), exposure, and disease latency. Potential solutions include

more clearly defined CTE diagnostic procedures, statistical tools to counter selection bias, and evaluation of additional (including nonclinical) cohorts.

Session V: Brain Donations and Brain Banking

Analyses of the CTE disease trajectory requires additional samples, especially from younger cases. Through various types of creative outreach, many individuals and groups are working to expand the number of brains available for future research on CTE and other conditions. Defining and accessing control brains is a difficult challenge—in large part because there is not clear agreement on what a "control" brain is. Brain-donation efforts will be most useful through more extensive and standardized donor phenotyping.

Next Steps

Both near-term and long-term strategies are needed to align current CTE research with evidence to date, as well as to further understand links between CTE neuropathology and clinical manifestations. Attendees agreed on an immediate need for the original authors of the 2015 CTE consensus criteria to issue an emphasis/clarification that neuronal, not glial, p-tau is the necessary, defining component of the pathognomic CTE lesion. Longer-term actions include (1) addressing reproducibility concerns through replication studies and specific technical criteria; (2) conducting CTE studies in additional cohorts, potentially including existing population-based cohorts representing a range of physiological and pathological phenotypes; (3) assessing roles and contributions of additional brain regions and components (e.g., white-matter abnormalities, neuroinflammation, glial cells, blood-brain barrier) in CTE neuropathology and clinical manifestations; and (4) employing a range of technologies to study tau isoforms and other suspected proteins involved in neurodegenerative/dementia-related proteinopathies. These actions should be accompanied by a public consensus conference including a broad range of institutions (and samples) to refine/define standard procedures and nomenclature and to decide the best quantitative and qualitative measures for CTE data collection (including common data elements). Soliciting broader input from the neurological research community about CTE research priorities, applications, and participants (scientific, advocacy, and subjects/cases) will pave the way for aggregate data analyses, which may achieve sufficient statistical power for assessing prevalence and risk in varied populations, along with the ultimate development of a CTE severity index.

Meeting Summary

The NINDS Perspective on CTE

Walter Koroshetz, MD, National Institute of Neurological Disorders and Stroke/NIH

Traumatic brain injury (TBI) is a major health problem with long-term effects including those caused by mild TBI (mTBI). This area of biomedical research has received steadily growing support from the National Institutes of Health (NIH) and other federal agencies including the Department of Defense (DoD). The total NIH expenditures on TBI have roughly doubled in the last 10 years. In fiscal year 2018 (FY18), the National Institute of Neurological Disorders and Stroke (NINDS) funded more than 219 extramural TBI grants spanning both basic and clinical studies. Further, NINDS has funded an increasing number of projects exploring mTBI and repetitive head injuries. Research has demonstrated that the brains of individuals with TBI show various histological phenotypes in addition to the condition's hallmark diffuse axonal injury. Scientific reports dating back decades show that TBI and/or exposure to repeated head impacts is also a potential risk factor for multiple forms of dementia and neurodegeneration. A recent study of more than 350,000 Veterans showed that even mTBI without loss of consciousness increased risk of a dementia diagnosis.

Recommendations from the 2019 Alzheimer's Disease and Related Diseases (ADRD) Summit included recognizing TBI-related dementia as an Emerging Topic and encouraging further study of links between TBI and ADRD neuropathologies and clinical symptoms. This research investment would be leveraged through several resources and would establish common data elements (CDEs) to facilitate data sharing and further discovery. NINDS has previously funded CTE research through various mechanisms and hosted the 2015 and 2017 Neuropathological CTE Diagnosis Consensus Conferences that focused upon defining the CTE pathognomonic lesion and its severity rating, respectively. In addition to illuminating the features and processes of CTE, these efforts aimed to guide prevention strategies that might include imaging and biomarkers, in particular for the benefit of current and future youth participants in contact sports. The goals of the 2019 CTE meeting are to assess the current state of neuropathological CTE diagnosis from multiple perspectives; to discuss scientific needs across diagnostic domains; and to address challenges related to sensitivity and specificity, , severity, and prevalence, prioritizing neuropathology research goals.

SESSION 1: STATE OF EVIDENCE IN CTE NEUROPATHOLOGY

CTE as a Tauopathy

Ann McKee, MD, Boston University & Veterans Administration

Dementia pugilistica, or "punch-drunk syndrome," was first reported in 1928 but it wasn't until decades later that it was studied histologically. It is considered the earliest description of what is today termed CTE. Early reports preceded the advent of immunohistochemistry and used silver staining to illustrate the presence of neurofibrillary tangles in the brains of 15 deceased former boxers. Additional studies (e.g., in 1991 and 1999) correlated repetitive head injury with

neurofibrillary tangles similar to those seen with CTE and noted histological features distinct from Alzheimer's disease (AD), including the absence of amyloid-beta (Aβ) and suspected damage to blood vessels or perivascular elements in the brain. The first associations of CTE and (American) football described CTE as a neuropathologically distinct, slowly progressive tauopathy with a clear environmental etiology.

A 2013 study analyzing postmortem brains of individuals with a range of repetitive head injuries demonstrated that CTE follows a predictable progression of hyperphosphorylated tau (p-tau) abnormalities throughout the nervous system. This work proposed criteria for the pathological diagnosis of CTE as well as a four-stage scheme for the pathological severity of CTE. Further, the study determined that CTE stage significantly correlates with age at death and duration of exposure to football.

In 2015, NIH hosted a consensus meeting to further define and refine these criteria. The group defined the single pathognomonic criterion for CTE as "an accumulation of abnormal p-tau in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci" and provided additional supporting features to define CTE. Subsequent work that analyzed postmortem brains of a mixture of contact athletes and non-athletes affirmed these criteria and concluded that contact sports are the greatest risk factor for CTE. This was quantified in a 2019 study showing that the odds of developing CTE doubled for every 2.6 years of football played.

CTE dementia appears to develop from multiple sources, including white-matter rarefaction and p-tau accumulation as well as independent factors such as arteriolosclerosis. Current research is evaluating CTE in young individuals (under age 34 at time of death), and results suggest that perivascular p-tau CTE lesions are most common in deep cortical neurons amid white-matter perivascular hemosiderin-laden macrophages. Because repetitive head injury is linked to chronic activation of microglia, neuroinflammation may be an important diagnostic or therapeutic target for CTE. Finally, as with most neurodegenerative diseases, comorbid neurodegeneration in CTE is age-related, as demonstrated by appearance of Lewy body pathology, Aβ, and parkinsonism.

The Spectrum of Pathology in CTE

Willie Stewart, MD, PhD, University of Glasgow

TBI is associated with long-term neuropathological changes like those seen with neurodegenerative disease and CTE. This includes accumulation of p-tau but also variable levels of Aβ and TDP-43, as well as axonal degeneration, neuroinflammation, neuronal loss, and white-matter degradation. CTE p-tau phenotypes appear to mimic those of aging and AD (e.g., cerebral amyloid angiopathy), and recent evidence suggests that specific sulcal CTE pathology is astroglial, contradicting previous data. Severe and repeated TBI is linked to dementia, as is head injury in individuals with genetic loci associated with AD. While associations of TBI with various neurodegenerative diseases are well accepted, assigning a CTE diagnosis remains challenging without unambiguous clinical criteria and associated diagnostic codes. The currently unclear

correspondence between neuropathology and clinical symptoms, especially dementia, is evident in studies showing variation in CTE comorbidity and dementia onset by type of contact sport. The observed spectrum of mixed neuropathologies and clinical phenotypes is increasingly typical of many neurodegenerative diseases and their progression over time. For example, disruption of the blood–brain barrier (BBB) is a feature of various neurologic disorders, including dementias. Evidence shows widespread BBB disruption after TBI as well as coincidence with p-tau lesions in CTE, suggesting a vascular contribution to post-concussion events and CTE risk. The varied components and descriptions of CTE (both neuropathological and clinical) have resulted in public and scientific confusion about the cause(s) of CTE. One strategy to clarify some of this information is a the proposed polyproteinopathy classification scheme entitled TBI-Related NeuroDegeneration, or TReND, which reflects exposure, neuropathological features, and clinical outcomes for related neurodegenerative disorders.

CTE in Military Personnel

Daniel Perl, MD, Uniformed Services University (USU)

TBI is common among military personnel – both before and during military service. An estimated 80 percent of all TBIs experienced by active duty Service members are impact in nature and occur off the battlefield (including participation in contact sports). Service members also frequently experience blast-wave exposure from weaponry such as improvised explosive devices as well as repeated low-level blast exposures from training exercises and military operations (e.g., breeching). These exposures lead to a diverse array of physical, cognitive, and behavioral/emotional post-blast symptoms that appear immediately after exposure but can persist over time. Neuropathological evaluation of brain specimens from deceased Service members between ages 18-70 at time of death (obtained from the USU Center for Neuroscience and Regenerative Medicine Brain Tissue Repository) estimated the prevalence of CTE and CTE-related p-tau immunoreactive lesions using a standard and expanded protocol. Although it did not increase the sensitivity for making a CTE diagnosis, the expanded protocol did reveal a greater percentage of cases with focal subpial p-tau lesions (focal aggregates of subpial intracellular and neuropil p-tau at the depth of cortical sulci that do not satisfy criteria for the CTE pathognomonic lesion). This CTE neuropathology was not apparent until ages 40-49 at time of death and is rare (2 of 100 cases—both of which coincided with a history of prior participation in American football). Appearance of the newly described subpial intracellular and neuropil p-tau was more prevalent in (and limited to) brains from individuals who died at age 45 or older. The nature of these subpial lesions remains unclear: they may represent precursors of CTE, early aging-related tau astrogliopathy (ARTAG), or incidental findings.

Thematic Summary of Moderated Panel Discussion on CTE State of the Evidence

Moderator: Thomas Montine, MD, PhD, Stanford University

Panelists: Stephen Gentleman, PhD, Imperial College, London; Ann McKee, MD, Boston University and Veterans Administration; Daniel Perl, MD, USU; and Willie Stewart, MD, PhD, University of Glasgow

What is the single most important gap for establishing definitive CTE neuropathological diagnostic criteria?

One significant topic of concern among the CTE research community is a perceived lack of clarity about the role of non-neuronal cells in CTE p-tau neuropathology, because there have been many reports of astrocyte involvement and shallow (subpial) lesions (which may represent ARTAG and not CTE). While the current CTE consensus criteria have provided a useful starting point for research, varied reports (and different sampling procedures) have generated confusion. One important issue is age—the current CTE pathognomonic criteria were generated by analyses of advanced cases. Because the standard neuropathological view is via autopsy, within-subject temporal progression of disease cannot be evaluated. A selection bias for contact-sport athletes has also made it difficult to understand CTE prevalence in the "general" population. Disparate (or no) CTE neuropathology in military Service members who died relatively young and individuals from other populations raises questions about the sensitivity and specificity of the current CTE criteria. Additional questions surround description and identification of neuropathology that leads to clinical symptoms similar or overlapping to those seen in CTE.

What is the minimal neuropathological signature of CTE, and how does it relate to clinical symptoms?

In most chronic diseases, anatomical lesions precede clinical symptoms—often by many years or even decades. However, "back-diagnosing" from end-stage pathology may incorrectly assume spatiotemporal progression of disease without solid evidence to support specific pathways. Thus, for any neurodegenerative disease, pathology and clinical course must remain distinct concepts until biomarkers have been identified and thoroughly validated. Moreover, lesions may be proxies for various sources of injury or disease. It is worth noting that the odds ratio for dementia from "high" CTE lesions is much lower than the odds ratio for dementia for AD (1.6 compared to 8, respectively). Several recent studies hint at the involvement of white matter, neuroinflammation, and microvascular changes (including disruption of the BBB) in the development of CTE neuropathology—along with dose of exposure. Techniques such as myelin Black-Gold II staining, diffusion tensor magnetic resonance imaging, and Fourier transform analyses of samples offer opportunities to interpret data more deeply and dynamically. Experimental approaches that combine analyses of additional proteins known to be involved in neurodegeneration in samples from individuals of different ages will begin to dissect patterns specific to certain tauopathies—and guide understanding of the pathological and clinical features of co-morbid conditions. Age of onset of CTE is another unresolved issue about pathology-clinical associations. Behavioral correlates are often difficult to study (and

understand) based upon lack of mechanistic knowledge about how many neuropsychiatric conditions develop; however, animal studies are starting to reveal some hints.

How can exposure be correlated with neuropathology and symptoms?
The postmortem brains of military personnel exhibit unusual CTE-like lesions, and it remains unclear how to identify and quantify the many types of brain injury experienced throughout life (e.g., on and off the battlefield). The observed latency of CTE may preclude its identification in individuals who died before its currently observable p-tau neuropathology. In addition, more granular measurements (e.g., synaptic activity, BBB integrity) may deepen understanding of molecular and biochemical processes. One unanswered question is, "How do the neuropathological findings from postmortem brains of American football players differ from those of individuals who played other contact sports, such as hockey or wrestling?" Answering this question is complicated by the existence of various brain banks and the use of different procedures to process tissue (e.g., "expanded" sampling protocols). Although one goal is to diagnose CTE early, in living individuals, concerns remain about stigma and behavioral health issues that might accompany this diagnosis.

SESSION 2: SENSITIVITY AND SPECIFICITY

Overview of Definitions and Methodological Challenges

C. Dirk Keene, MD, PhD, University of Washington

By definition, a neuropathological diagnosis is driven by evidence of tissue affected by disease and typically does not incorporate clinical phenotype or function. Developing a set of gold-standard neuropathological criteria for CTE requires consideration of both sensitivity and specificity: ensuring reporting of all true positives and no false positives, respectively. Beyond accurate diagnostic value, such criteria are essential for estimating prevalence, correlating clinical phenotypes with pathologic tissue features, and ultimately developing sensitive and specific biomarkers.

The NINDS/NIBIB [National Institute of Biomedical Imaging and Bioengineering] CTE/TBI Neuropathology Working Group was convened in 2015 to develop neuropathological criteria for the diagnosis of CTE based upon a blinded review of 25 cases and described the pathognomonic CTE lesion as "perivascular accumulation of p-tau aggregates in neurons, astrocytes, and cell processes in an irregular spatial pattern in the cerebral cortex and found preferentially at the depths of the sulci." This work provided standardized criteria for clinicians and researchers to further characterize CTE and test hypotheses and prompted development of neuropathological CDEs for CTE; however, additional CTE pathologies (and p-tau variants) merit further study. Doing so is important to differentiate CTE from ARTAG, primary age-related tauopathy (PART), and other age-related tau processes); to differentiate CTE from co-morbid pathologies (e.g., AD, TDP-43); and to better understand heterogeneity in the presentation of CTE. To date, p-tau has been the primary focus for CTE neuropathology, but many other neurological disorders exhibit tau abnormalities, including AD, PART, ARTAG, and Parkinson's disease (PD). Practical questions to guide ongoing efforts to refine CTE neuropathological

criteria include determining appropriate study cohorts and ensuring identification of occult past neurotrauma. Beyond professional athletes, potential at-risk individuals for study include military personnel and population-based cohorts such as the Framingham Brain Donation Program, the Memory and Aging Project, and the Religious Orders Study. Sampling methods should also be standardized for brain regions and tissue preparation and analyses, and attention should be paid to potential confounding variables such as medication use, aging, and exposure to other types of neurotrauma.

Thematic Summary of Moderated Panel Discussion: Sensitivity and Specificity of Diagnosing CTE

Moderator: Julie Schneider, MD, Rush Medical College

Panelists: C. Dirk Keene, MD, PhD, University of Washington; Julia Kofler, MD, University of Pittsburgh; Amber Nolan, MD, PhD, University of California, San Francisco; and Thor Stein, MD, PhD, Boston University

Should additional neuropathological features be added to describe the current CTE pathognomonic lesion?

While neuronal p-tau remains an essential component of the pathognomonic lesion, research should continue to investigate additional contributors such as axonal injury, white-matter pathology, and other potential factors. One pressing issue is establishing and disseminating a standardized, bilateral sampling protocol, recognizing that continued investigation of a given sample may unearth heterogeneity of neural trauma without clear understanding of its cause. For many diseases, a signature lesion is defined by a single pathological feature, whereas CTE has four; thus, a more precise definition of each of these components is important. The NINDS-funded U54 projects are working on these issues as well as creating data-sharing standards and processes. An additional strategy may be to create a “suspicious CTE” diagnostic category for later analysis as evidence supports additional definitive neuropathological features. Establishing careful quantitative measures is important for CTE detection in early-stage cases, although adopting a “binary” approach remains challenging given the spectrum of changes and the potential involvement of additional proteins.

What is the best way to link neuropathological data with clinical features?

Many examples, such as prostate cancer, illustrate that pathological evidence alone does not correlate with disease manifestation. For CTE, the presence of a pathognomonic lesion indicates that a pathological process is under way, but other information (age, traumatic-exposure type, and dose) translates ultimately to appearance of clinical symptoms—including neurological effects, behavioral changes, and psychiatric conditions. Although age at death is an important parameter for diagnosing CTE, there does not appear to be a simple progression of symptoms as in AD and some other dementias. Diagnosing and staging CTE is further complicated by observations of multiple, comorbid tauopathies that appear with advanced age. Disagreement remains about how to constrain variables to refine the definition of the CTE pathognomonic lesion; however, there is general agreement that sensitivity and specificity must be addressed separately. One approach is to define very clear patterns in well-defined

subsets, then use strong statistical methods to draw connections between these patterns and clinical symptoms (each assessed independently). Another conundrum is the desire to develop preventive measures without knowing the true prevalence of CTE in broad (not at-risk) populations. Wider validation of existing CTE diagnostic criteria through expanded analyses of different exposures, age, and other variables may complicate interpretation based upon neuropathological samples collected with existing, circumscribed criteria.

SESSION 3: PROGRESSION AND SEVERITY

Preliminary Findings from the Second CTE Consensus Conference

Dennis Dickson, MD, Mayo Clinic

The second CTE consensus conference (held in Boston, November 2016, *manuscript in preparation*) aimed to further clarify CTE progression and severity through use of the standardized Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) CTE scoring sheet (decision tree). Of the 19 CTE cases reviewed (blinded), there was less agreement among neuropathologists on attempts to stage either mild cases or severe cases. While a key goal of this conference was to define CTE staging criteria, that effort was deferred based upon low inter-rater reliability. The sampling procedure used at this conference aligned closely with that established by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) but looked for distribution in frontal, temporal, parietal cortices; hippocampus and entorhinal cortex; amygdala; thalamus/mammillary body; and the cerebellar dentate nucleus. Re-sampling was performed in brains of high-risk subjects with no pathognomonic lesion. Lesions were analyzed by depth of sulcus, presence of perivascular and superficial cortical tau, and neuronal and glial p-tau. Analyses revealed significant other pathologies (ARTAG, PART, TDP-43, and others, such as the sex/male-specific condition hypothalamic perivascular neuritic dystrophy); many samples exhibited multiple tauopathies. At present, development of consensus CTE neuropathology remains a work in progress, because of difficulties in distinguishing CTE from ARTAG (in mild cases) and from other primary tauopathies, especially mixed tauopathies (in severe cases).

Thematic Summary of Moderated Panel Discussion: CTE Progression and Severity

Moderator: Gabor Kovacs, MD, PhD, University of Toronto

Panelists: John Crary, MD, PhD, Mount Sinai; Dennis Dickson, MD, Mayo Clinic; Ian Mackenzie, MD, University of British Columbia; and Douglas Smith, MD, University of Pennsylvania

Are there emerging mechanisms to guide staging criteria for CTE?

Investigations involving a European cohort of subjects (that did not include American football players) suggest additional neuropathological features for CTE, such as astroglial p-tau and multiproteinopathies (e.g., TDP-43 and others). Variant neuropathology in individuals exposed to blast injury also suggest different pathways of brain damage, and correlations with symptomology (and its timing) remain unclear. Observed distinctions in brain-region distribution of p-tau and other proteins point to the need for further exploration of the role(s) of different types of traumatic exposure in development of CTE and related tauopathies. These

studies may help define patterns of vulnerability as well as features of disease progression. Toward understanding pathological mechanisms, studies that assess structural changes over time will be important. Many dynamic neurodegenerative aspects of CTE remain unspecified in the absence of spatiotemporal data; however, understanding these processes is critical to the development of a severity index for future use in living individuals.

Can technology inform development of a CTE staging index?
Humans are complex organisms; physiological and pathological processes result from an array of influences, both intrinsic (e.g., genomic) and extrinsic (e.g., exposure to head injury). As has been the case for other neurodegenerative diseases, scientific investigation of CTE will likely require a multifaceted approach to tease apart the roles of contributory factors. These investigations will help inform development of CTE staging criteria. It should be noted that a lack of data tracking CTE over time currently limits progress toward developing a severity index, and at this time, use of "types" instead of stages may be prudent. There is some enthusiasm for employing data-science strategies such as artificial intelligence (e.g., machine learning) to assist with development of tissue analyses, especially given the large sample sizes required to attain sufficient statistical power to characterize CTE disease and its variance. However, a current lack of sample diversity (currently mostly brains from white males) may skew algorithms. The current reliance on specific histochemical methods limits detection to what can be observed with existing tools. For example, is it possible that CTE is a prion disease? New protein-capture techniques such as different antibodies or other approaches may enhance understanding of the potential role of p-tau isoforms and potentially other molecular contributors.

SESSION 4: PREVALENCE

Attempts to Begin Prevalence Estimates

Kevin Bieniek, PhD, University of Texas Health, San Antonio

Prevalence addresses a disease's distribution and determinants. It is clear from past consensus conferences that CTE is a distinct neurodegenerative tauopathy most often observed in individuals with a past history of repetitive TBI—but with variable severity, frequency, and latency. Potentially at-risk populations include contact-sports athletes with many years of play, military Service members and Veterans, as well as individuals who suffer domestic violence, self-injury, poorly controlled epilepsy, and other brain injury conditions or scenarios. Overall, neurodegenerative diseases affect millions of people in the United States and worldwide, at varying levels by condition, with AD being the largest affected group at close to 6 million individuals. TBI also exacts a large toll, accounting for about 2.5 million emergency department visits (87%), hospitalizations (11%), and deaths (2%) annually, according to the U.S. Centers for Disease Control and Prevention, and costing about $60 billion each year. Of note, the vast majority of TBI is considered "mild." Brain trauma has been associated with dementia – AD in particular.

Concussions from youth sports participation has become a societal concern as the CTE story continues to mature. Individuals who play sports in the United States include approximately 22

million youths (ages 6-12), 8 million high school students, 500,000 college students, and 13,500 professional athletes. Of these, wrestlers, ice hockey players, and football players experience the highest rates of concussion – and this number has risen sharply in recent years. Rates of neurodegenerative disease vary considerably by sport, with the highest prevalence in American football players – although these data have been difficult to parse based upon variable use of diagnostic criteria worldwide. Data from boxers illustrate that the appearance of dementia follows a dose-response relationship related to number of fights (and head trauma).

According to DoD estimates, 383,947 Service members were diagnosed with a TBI between 2000 and 2018; most was mTBI and in Army personnel. The U.S. Department of Veteran's Affairs (VA) estimates that as of 2019, 767,544 Veterans have dementia. Veterans with posttraumatic stress disorder or depression are twice as likely to develop dementia, and Veterans with TBI (even mTBI) are also at increased risk for dementia. Many challenges frustrate progress in assessing CTE prevalence, including selection bias (e.g., autopsy, individual versus population cohorts), exposure, and disease latency. Potential solutions to these challenges include more clearly defined CTE diagnostic procedures, statistical tools to counter selection bias, and evaluation of additional (including non-clinical) cohorts.

Thematic Summary of Moderated Panel Discussion: CTE Prevalence

Moderator: Marc Del Bigio, MD, PhD, University of Manitoba

Panelists: Kevin Bieniek, PhD, University of Texas Health, San Antonio; Rebecca Folkerth, MD, New York City Office of the Chief Medical Examiner; Matthew Frosch, MD, PhD, Massachusetts General Hospital, and Lea Grinberg, MD, PhD, University of California, San Francisco

What are confounding variables to consider when balancing specificity and sensitivity of CTE detection?

Several potential resources may expand the number of brains available for CTE analysis, but caution is warranted. Brain banks tend to skew toward dementia and older people, which may confound study and progression of CTE after head injury in relatively younger individuals. Medical examiners examine large numbers of brains routinely but do not have an infrastructure in place to support research activities, although parents of children who died from sudden infant death syndrome have successfully lobbied for research access to autopsy tissue, providing a possible model for research advocacy. Autopsy samples available to medical examiners, however, are often enriched with individuals who died from non-natural causes, including self-harm, violence, and substance abuse. Expanding the definition of head-injury exposure to include more types of contact sports may also be problematic toward efforts to refine the specificity of a CTE diagnosis. Sports differ markedly across the world, and they have evolved over time in ways that influence safety—and thus, risk. Use of TBI as an exposure is also difficult because it is still unclear how to quantitate TBI-induced head injury, including both intensity (e.g., mild, moderate, severe, and penetrating) and frequency (e.g., single versus repetitive). Use of technology also affects clarity of diagnosis; for example, brain-imaging results without corresponding autopsy control data may be imprecise.

Is it possible to determine CTE prevalence in the general population?
Odds ratios are a central tool for evaluating and communicating risk, but calculations of such an association for CTE and dementia remain much lower than for other neurodegenerative diseases, such as AD. Collection of more phenotypic information from brain donors than is currently obtained with questionnaires in common use (such as the Ohio State University Traumatic Brain Injury (TBI) Identification Method and the Brain Injury Screening Questionnaire) may help establish clearer links between pathology and symptoms by documenting injury and other exposures more thoroughly across an individual's lifetime. Responses to well-structured questionnaires of qualitative and quantitative information can then be mined by computer algorithms to generate additional data in an unbiased manner. The use of population-based cohorts increases the number of samples, and thus statistical power. However, populations differ markedly, and thus inter-population comparisons must be conducted and interpreted with caution. For example, because in Brazil autopsy is mandatory upon death, the Biobank for Aging Studies at the University of São Paulo in Brazil is a potential source for CTE analyses. However, the median age of brains in this bank is 72 years. Thus, such a resource may be more useful for investigating conditions known to be age-related, such as ARTAG. A major current limitation of population-based cohorts is the lack of diversity of brain samples. Efforts are under way to expand brain donation from women athletes, and head trauma from domestic violence may offer another avenue for data collection. Toward an ultimate goal of predicting risk in youth, collection of samples from younger brains should be a priority.

SESSION 5: BRAIN DONATIONS AND BRAIN BANKING

Current State of CTE Brain Banking and Donation/Acquisition

Christopher Nowinski, PhD, Concussion Legacy Foundation

The Concussion Legacy Foundation (CLF) is a non-profit organization dedicated to addressing sports concussions through education, policy, and research. In 2008, CLF partnered with Boston University (BU) and the VA to establish the VA-BU-CLF Brain Bank, which houses 70 percent of global CTE cases and discovered the first cases of CTE in athletes whose primary exposure was soccer, rugby, baseball, ice hockey, college football, and high-school football. It is currently a digital research registry for concussion and CTE-related studies and as of November 2019 contained 800 donated brains (the majority of which are from American football players). VA-BU-CLF Brain Bank staff carry pagers 24/7 and actively communicate with families of athletes (through a structured protocol) to request brain donations after death. In turn, CLF staff take great care to develop and nurture close relationships with donor families to respect their specific wishes related to donation. Donations to the VA-BU-CLF Brain Bank have significantly increased the numbers of CTE brains available for research.

The CLF's experience points to the high profile of sports media as creating an important partnership to accelerate brain donation and CTE research. Family cooperation and media coverage of donations has encouraged donation and CTE awareness toward developing prevention strategies against head injury–related neurodegenerative disease. Currently, most

donated brains are predominantly from white males, and efforts are under way to diversify this research resource. Recently, for example, three female Olympians have pledged to donate their brains to CTE research, and scientists have launched the Soccer, Head Impacts and Neurological Effects (SHINE) study that will follow 20 former high-level female soccer players (all at least age 40) to assess possible links between headers and CTE. Ongoing CLF collaborations include the Global Brain Bank, CLF Project Enlist, the Australian Sports Brain Bank, and the Biobank for Aging Studies at the University of São Paulo in Brazil.

A 2015 study reported that exposure to contact sports was the greatest risk factor for CTE pathology, although other etiologies are under investigation. For example, amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disorder with motor-neuron dysfunction and often cognitive decline. ALS is more common in males and military Veterans, and environmental factors (including TBI) are believed to play an important role in development of the disease. A 2018 study described ALS/CTE as a distinct clinical and pathological condition.

Thematic Summary of Moderated Panel Discussion: Brain Donations and Brain Banks

Moderator: Anna Taylor, PhD, National Institute of Neurological Disorders and Stroke/NIH

Panelists: Lili-Naz Hazrati, MD, PhD, Hospital for Sick Children, Toronto; Tish Hevel, The Brain Donor Project; and Christopher Nowinski, PhD, Concussion Legacy Foundation

What are effective strategies to increase the number of brain donations, especially those suspected to have CTE?

Many people do not appreciate the fact that being a designated organ donor does not include brain donation. Through various types of creative outreach, many individuals and groups are working hard to expand the number of brains available for future research on CTE and other neurological conditions. These efforts have targeted athletes and Veterans, including those without symptoms. Victims of domestic violence (both women and men) are another potential source. For example, about 2-3 percent of the brains in the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study have come from individuals who were exposed to domestic violence. An important component of effective outreach strategies has been to invite people to be a part of something larger by pre-consenting participants for future research.

Existing infrastructure such as the NIH Neurobiobank, the Alzheimer's Disease Research Centers (ADRCs), the Framingham Brain Donation Program, and similar European and Canadian resources comprise networks of centers to share samples and data, and these efforts are growing the evidence base. The ADRCs are trying to streamline these processes by digitizing slides for broader distribution. However, shipping brains and brain tissue, and sharing data, are complicated and expensive—as is the concomitant clinical work-up time and costs (which are not typically covered by third-party payers). Many investigators report their activities as a "labor of love" and largely uncompensated (and new, more extensive courier rules and costs [e.g., FedEx] further complicate these tasks). Moreover, resource centers in academic settings must align with institutional values that support not only research but also teaching and clinical

care—necessitating additional planning and resources. Outreach to obtain autopsy tissue from local hospitals may provide another outlet for sample collection.

How can research be enhanced to better understand CTE?

Reproducibility and replication are core features of scientific investigation. In the CTE research arena, several steps can be taken to ensure both. These include efforts to standardize tissue-processing protocols, clinical data capture, and nomenclature usage, as well as dedicated efforts to replicate existing data sets. Continued definition and refinement of CDEs will advance neuropathological methods beyond local/regional practices that currently vary across sites. The dynamic features of CTE remain obscure based on mostly static investigations (i.e., at one point in time) of autopsy tissues. Analyses of the CTE disease trajectory requires additional samples, especially from younger cases, as well as controls. Obtaining additional types of tissues may shed light on disease characteristics and symptom development and progression: currently, the VA-BU-CLF Brain Bank collects the spinal cord and eyes along with brain donations. Brain banks could expand outreach to acquire ancillary tissue for research. The VA-BU-CLF Brain Bank has established a system to receive and review requests (most are approved), and the facility limits the number of samples sent to individual researchers to leverage the value of tissue. Some organizations, such as Autism Brain Net, employ tissue-review committees consisting of people not conducting autism research to ensure unbiased distribution of samples for research. Opportunities for preclinical research in CTE are very limited, because tau pathology does not appear in preclinical models as it does in human samples. However, some injury models in rodents may permit mechanistic studies of brain injury, and structural analysis methods (e.g., cryoEM) can facilitate investigation of isoforms of tau and other proteins linked to CTE and other tauopathies.

What is a control brain for CTE research?

Defining and accessing control brains is another challenge—in large part because there is not clear agreement on what a "control" brain is. There is debate about what a "normal" life is in this respect because most individuals experience TBI during their lifetimes, and many never seek or report treatment. Moreover, individuals belong to multiple populations; for example, military personnel may also play contact sports. Information resulting from current brain donation efforts could be enriched through more extensive and standardized phenotyping of donors. Possible sources include brains from family members of affected individuals and various population-based cohorts—although such populations are internally heterogeneous according to normal human variation. Another possibility is hospital pathology departments that have archived records and samples linked to individuals' professions and that could scan across job types to obtain population-based samples. Acquiring more samples and different types of samples might be facilitated with NIH support, but there is a critical lack of a workforce pipeline in neuropathology. Some current structures, such as the ADRC supplement program, have been helpful to grow the trainee pool, but lack of financial incentives for clinical research remains a perennial challenge.

DISCUSSION AND PRIORITY SETTING

The development of multiple/parallel diagnostic criteria for CTE is likely to confuse both research and patient communities and slow progress. Beyond the 2019 and previous CTE conferences, NINDS has proposed to support future consensus meetings. Discussion about next steps generated a consensus view that both near-term and long-term strategies are needed to align current research with the evidence to date and to further understand links between CTE neuropathology and clinical manifestations. The latter requires adherence to standardized approaches for tissue preparation; sampling; and data collection, analyses, and reporting.

Near-term/immediate action:

- The original authors of the 2015 CTE consensus criteria should publish an emphasis/clarification that neuronal p-tau is the necessary component of the pathognomonic CTE lesion. Additional features, such as glial pathology, are insufficient in the absence of neural p-tau.

Longer-term actions include:

- Replicate studies used for defining CTE pathognomonic criteria with existing samples.
- Conduct CTE studies in additional cohorts, potentially including existing population-based cohorts that represent a range of physiological and pathological phenotypes.
- Optimize protein-capture techniques to enable fuller understanding of tau isoforms and a range of other suspected proteins involved in neurodegenerative/dementia-related proteinopathies.
- Continue research to assess roles and contributions of additional brain regions and components (e.g., white-matter abnormalities, neuroinflammation, glial cells) in CTE neuropathology and clinical manifestations.
- Solicit broader input from the neurological research community about CTE research priorities, applications, and participants (scientific, advocacy, and subjects/cases).
- Convene a public consensus conference including a broader range of institutions (and samples) to refine/define standard procedures and nomenclature and to decide the best quantitative and qualitative measures for CTE data collection (including CDEs). These include but are not limited to sampling depth and vascular proximity. When possible and appropriate, use unbiased, data-science methods.
- Simplify and clarify existing CDEs for CTE research.
- Decide, as a result of the above, how to consider “borderline” CTE cases, toward guiding more research on potential CTE comorbidities and a possible spectrum of CTE-like diseases associated with aging and various environmental exposures. Validation studies with co-morbidities and sample-age variation will be important to achieve this goal.
- Operationalize recommendations for practicing pathologists to guide field work and move toward generating CTE clinical codes for diagnosis, research, and reimbursement. These recommendations should specify technical criteria, including tissue preparation and staining components and protocols.

Anticipated results of the above steps include:

- The ability to conduct aggregate data analyses, which may achieve sufficient statistical power for assessing prevalence and risk in varied populations
- The knowledge necessary to define CTE staging criteria, and ultimately, a CTE severity index

Appendix A: Meeting Agenda

The Neuropathological Diagnosis of Chronic Traumatic Encephalopathy (CTE): Next Steps

John Edward Porter Neuroscience Research Center, NIH Main Campus
November 6-7, 2019

Day 1: November 6, 2019

08:00 am **Registration**

08:30 am **Welcome**
Patrick Bellgowan, PhD, National Institute of Neurological Disorders and Stroke/NIH

08:40 am **The NINDS Perspective on CTE**
Walter Koroshetz, MD, National Institute of Neurological Disorders and Stroke/NIH

09:00 am **Session 1: State of Evidence in CTE Neuropathology**
Goal: *Set the stage; what does the literature deach us about CTE neuropathology?*
30 min presentations and 45 min Panel Discussion

Perspectives on CTE:
- CTE as a Tauopathy
  Ann McKee, MD, Boston University & Veterans Administration
- The Spectrum of Pathology in CTE
  Willie Stewart, MD, PhD, University of Glasgow
- CTE in Military Personnel
  Daniel Perl, MD, Uniformed Services University

10:45 am **Break** (15 minutes)

11:00 am **Moderated Panel Discussion: Discussion of agreements, uncertainties, and disagreements (45 min)**
Moderator: Thomas Montine, MD, PhD, Stanford University
Panelists:
Stephen Gentleman, PhD, Imperial College, London
Ann McKee, MD, Boston University & Veterans Administration
Daniel Perl, MD, Uniformed Services University
Willie Stewart, MD, PhD, University of Glasgow

11:45 am **Lunch** (1 hour)

12:45 pm **Session 2: Sensitivity and Specificity**
Goal: *Discuss existing knowledge and outline needs for determining the sensitivity and specificity of CTE neuropathology.*
30 min presentation and 45 min Panel Discussion

Topic Presentation:
- Overview of Definitions and Methodological Challenges
  C. Dirk Keene, MD, PhD, University of Washington

Day 1 Agenda, continued

01:15 pm **Moderated Panel Discussion: Discussion of barriers, potential solutions, priorities, and approaches, e.g., overlap with other diagnostic criteria, premorbid TBI diagnosis, tissue sampling, etc. (45 min)**
Moderator: Julie Schneider, MD, Rush Medical College
Panelists:
C. Dirk Keene, MD, PhD, University of Washington
Julia Kofler, MD, University of Pittsburgh
Amber Nolan, MD, PhD, University of California, San Fransisco
Thor Stein, MD, PhD, Boston University

02:00 pm **Break** (15 minutes)

02:15 pm **Session 3: Progression and Severity**
Goal: *Prioritize necessary steps to determine and describe neuropathological progression of CTE (onset to latest stage).*
30 min presentation and 45 min Panel Discussion

Topic Presentation:
- Findings Regarding Progresion From 2nd Consensus Conference
  Dennis Dickson, MD, Mayo Clinic

02:45 pm **Moderated Panel Discussion: Discussion of lessons learned from the 2nd consensus conference, next steps, needs, definitions, priorities and approaches. (45 min)**
Moderator: Gabor Kovacs, MD, PhD, University of Toronto
Panelists:
John Crary, MD, PhD, Mount Sinai
Dennis Dickson, MD, Mayo Clinic
Ian Mackenzie, MD, University of British Columbia
Douglas Smith, MD, University of Pennsylvania

03:30 pm **Break** (15 minutes)

03:45 pm **Session 4: Prevalence**
Goal: *Determine readiness criteria and steps to assess prevalence of CTE neuropathology.*
30 min presentation and 45 min Panel Discussion

Topic Presentation:
- Attempts to Begin Prevalence Estimates
  Kevin Bieniek, PhD, University of Texas Health, San Antonio

04:15 pm **Moderated Panel Discussion: Discussion of effect of case selection bias on prevalence estimates, the accurate denominator for estimating prevalence, and other disease area brain banks that would be most relevant for estimating prevalence. (45 min)**
Moderator: Marc Del Bigio, MD, PhD, University of Manitoba
Panelists:
Kevin Bieniek, PhD, University of Texas Health, San Antonio
Rebecca Folkerth, MD, NYC Office of Chief Medical Examiner
Matthew Frosch, MD, PhD, Massachusetts General Hospital
Lea Grinberg, MD, PhD, University of California, San Fransisco

05:00 pm **Adjourn**

Day 2 Agenda

Day 2: November 7, 2019

08:30 am **Introduction to Day 2:** Structure and Goals

09:00 am **Session 5: Brain Donations and Brain Banking**

Goal: *Describe the need for increased brain donation and methods for obtaining appropriate donations. Describe current CTE-relevant brain banking, methods for increasing collaboration, common tissue catalogues, and development of common data elements, e.g., exposure measures and relevant procedural meaasures.*

30 min presentation and 45 min Panel Discussion

Topic Presentation:

- Current State of CTE Brain Banking and Donation/Acquisition
  Christopher Nowinski, PhD, Concussion Legacy Foundation

09:30 am **Moderated Panel Discussion: Discussion of effect of case selection bias on prevalence estimates, the accurate denominator for estimating prevalence, and other disease area brain banks that would be most relevant for estimating prevalence. (45 min)**

Moderator: Anna Taylor, PhD, National Institute of Neurological Disorders and Stroke/NIH

Panelists:

Lili-Naz Hazrati, MD, PhD, Hospital for Sick Children, Toronto
Tish Hevel, The Brain Donor Project
Christopher Nowinski, PhD, Concussion Legacy Foundation

10:15 am **Break** (30 min)

10:45 am **Session 6: Breakout Sessions: Discussion and Priority Setting (1.25 hours)**

Breakout 1 – Orange Skybox (Floor 1)
Breakout 2 – Blue Skybox (Floor 3)
Breakout 3 – Main Conference Room

12:00 pm **Break** (30 min)

12:30 pm **Working Lunch: Breakout Sessions Report Back on Setting Priorities for Next Steps**

01:30 pm **Summary & Closing**

Walter Koroshetz, MD, National Institute of Neurological Disorders and Stroke/NIH

02:00 pm **Adjourn**

Appendix B: Participants List

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