National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome

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Abstract

Objective: To develop evidence-informed, expert consensus research diagnostic criteria for Traumatic Encephalopathy Syndrome (TES), the clinical disorder associated with neuropathologically diagnosed Chronic Traumatic Encephalopathy (CTE).

Methods: A panel of 20 expert clinician-scientists in neurology, neuropsychology, psychiatry, neurosurgery, and physical medicine and rehabilitation, from 11 academic institutions, participated in a modified Delphi procedure to achieve consensus, initiated at the First NINDS Consensus Workshop to Define the Diagnostic Criteria for TES, April, 2019. Prior to consensus, panelists reviewed evidence from all published cases of CTE with neuropathological confirmation and they examined the predictive validity data on clinical features in relation to CTE pathology from a large clinicopathological study (n = 298).
Results: Consensus was achieved in 4 rounds of the Delphi procedure.

Diagnosis of TES requires: 1) substantial exposure to repetitive head impacts (RHI) from contact sports, military service, or other causes; 2) core clinical features of cognitive impairment (in episodic memory and/or executive functioning) and/or neurobehavioral dysregulation; 3) a progressive course; and 4) that the clinical features are not fully accounted for by any other neurologic, psychiatric, or medical conditions. For those meeting criteria for TES, functional dependence is graded on 5 levels, ranging from independent to severe dementia. A provisional level of certainty for CTE pathology is determined based on specific RHI exposure thresholds, core clinical features, functional status, and additional supportive features, including delayed onset, motor signs, and psychiatric features.

Conclusions: New consensus diagnostic criteria for TES were developed with a primary goal of facilitating future CTE research. These criteria will be revised as updated clinical and pathological information and in vivo biomarkers become available.
Introduction

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with exposure to repetitive head impacts (RHI), including those sustained in contact and collision sports. The diagnosis of CTE is confirmed only by neuropathological examination demonstrating a unique pattern of hyperphosphorylated tau (p-tau) deposition. Descriptions of the clinical features of CTE are based on retrospective reports about deceased individuals with neuropathologically diagnosed CTE and include nonspecific cognitive, neuropsychiatric, and motor impairments, progressing to functional dependence and dementia. Preliminary diagnostic schemas for the clinical syndrome associated with CTE neuropathology have recognized deficiencies. These include the 2014 research diagnostic criteria, termed traumatic encephalopathy syndrome (TES). There is a need for evidence-informed, expert consensus diagnostic criteria to facilitate research and help close important knowledge gaps on the epidemiology, risk factors, and course of CTE, as well as to enable clinical trials for treatment and prevention. The development of consensus diagnostic criteria for the clinical features of CTE is one of the aims of the Diagnostics, Imaging, and Genetics Network for the Objective Study and Evaluation of Chronic Traumatic Encephalopathy (DIAGNOSE CTE) Research Project, funded by the National Institute of Neurological Disorders and Stroke (NINDS; U01NS093334). In April 2019, the First NINDS Consensus Workshop to Define the Diagnostic Criteria for TES was held in Phoenix, Arizona, for a multidisciplinary panel of 20 clinician-scientists and 7 observers, initiating a
modified Delphi process to achieve consensus. This paper describes the methodology employed and the resulting NINDS Consensus Diagnostic Criteria for TES.

**Methods**

The previously proposed research diagnostic criteria for TES (table e-1, doi.org/10.5061/dryad.f1vhhmgvk), published in 2014, were used as a starting point and initial organizing structure for the development of new consensus criteria. The NINDS Consensus Diagnostic Criteria for TES were generated as a result of a multi-step process that included: (1) selecting expert consensus panelists; (2) selecting non-voting observers; (3) assessing reliability, sensitivity, and specificity of the 2014 TES criteria used in the DIAGNOSE CTE Research Project ("DIAGNOSE CTE") and in the NINDS-funded Understanding Neurologic Injury and Traumatic Encephalopathy (UNITE) study (U01NS086659, U54NS115266); (4) literature review of all reported cases with pathology consistent with CTE and descriptions of clinical features; (5) review of published and unpublished clinicopathological data from the UNITE study to examine predictive validity of clinical variables in relation to pathologically confirmed CTE; (6) training of the expert panelists, external to the DIAGNOSE CTE study team, who were less familiar with use of the 2014 TES criteria; (7) convening an in-person consensus workshop of the panelists and observers to present a review of CTE literature, clinicopathological correlation findings, and interrater reliability of the 2014 TES criteria used in the UNITE and DIAGNOSE CTE studies; (8)
obtaining consensus using a modified Delphi procedure, started during the in-person consensus workshop and continuing online for subsequent rounds; and (9) inviting comments from stakeholders, including representatives of interested professional organizations, foundations, patient/family advocacy groups, and industry (table e-2, doi.org/10.5061/dryad.f1vhmgyk).

Expert Consensus Panel and Observers
The expert consensus panel consisted of 20 clinician-scientists from 11 academic centers around the United States, representing a variety of disciplines (neurology, neuropsychology, neurosurgery, psychiatry, and physical medicine and rehabilitation) and areas of clinical and research expertise (traumatic brain injury [TBI], sports concussion, neurodegenerative disorders). (See Appendix 1) Fourteen of the 20 panelists were investigators in DIAGNOSE CTE. These panelists, the DIAGNOSE CTE leadership team, and NINDS Program Officials provided recommendations for additional panelists who were senior thought leaders not affiliated with DIAGNOSE CTE and who could provide diversity of expertise and perspectives. Seven individuals were selected and all agreed to participate. One of the seven had a last-minute conflict and was unable to attend the consensus workshop. The resulting 20 consensus panel members participated in the workshop and were voting participants in the modified Delphi consensus process. Each panel member participated in all rounds of the modified Delphi consensus.

The non-voting observers included three representatives from NINDS (including the institute Director and two Program Directors), as well as the lead
biostatistician, co-principal investigators, and External Advisory Board Chair for DIAGNOSE CTE. Their role was to provide guidance, criticism, and commentary on the goals, process, and emerging consensus diagnostic criteria during each of the modified Delphi rounds.

Reliability, Sensitivity, and Specificity of the 2014 Research Diagnostic Criteria for TES

The 2014 TES criteria were used in the UNITE and DIAGNOSE CTE projects to diagnose deceased and living study subjects, respectively. Diagnoses were adjudicated through multidisciplinary diagnostic consensus conferences for both studies. Interrater reliability, sensitivity, and specificity for the TES criteria were calculated. Interrater reliability was assessed with intraclass correlations to account for multiple raters with inconsistent participation.

Literature Review of Reported Cases of CTE

Two reviewers from the DIAGNOSE CTE research team who were not on the expert consensus panel (MLM, EMF) screened abstracts (n=513) obtained from a PubMed search employing relevant search terms and by cross-referencing bibliographies of CTE literature reviews, using defined inclusion and exclusion criteria to identify all reported cases with descriptions of clinical features and neuropathology available at the time of the search, January 15, 2019. The search yielded 40 articles between 1957 and 2019, with information on 229 cases (tables e-3 – e-4, doi.org/10.5061/dryad.f1vhhmgvk).
Predictive Validity of Pathologically Diagnosed CTE from UNITE Study

Clinicopathological Data

The UNITE project relies on donations to a brain bank and retrospective review of clinical histories from detailed, systematized interviews of informants. The vast majority of donors had contact sport exposure, mostly American football. Data from 298 brain donors in the UNITE study were analyzed with respect to a number of predictor variables including: source of exposure; years of contact sport exposure; cognitive, behavioral, mood, motor and other clinical features; course; age of symptom onset; and multivariable prediction models. Outcome variables were the presence or absence of neuropathological diagnosis of CTE (using the NINDS/National Institute of Biomedical Imaging and Bioengineering [NIBIB] diagnostic criteria), with or without evidence of other neurodegenerative disorders, and categorized according to CTE stage (I–IV, increasing with severity). Analyses were based on a subset of the full UNITE sample available at the time. The results of these data analyses are beyond the scope of this paper and will be reported in a separate publication.

Hands-on Experience with 2014 Research Diagnostic Criteria for TES

Mock diagnostic sessions with the 2014 TES criteria, using three representative cases, were conducted with the external panelists prior to the NINDS consensus workshop to familiarize them with the criteria and the nature of their use in the research setting.
NINDS Consensus Workshop

On April 15, 2019, the First NINDS Consensus Workshop to Define the Diagnostic Criteria for TES was convened in Phoenix, Arizona. The primary aim of the workshop was to begin the process to develop evidence-informed, expert consensus diagnostic criteria for TES. We identified two primary goals at the start of the consensus workshop: (1) to improve upon previously proposed research diagnostic criteria for TES by maintaining adequate sensitivity and increasing the specificity for underlying CTE pathology, defined by the NINDS and NIBIB consensus criteria\(^5\); and (2) to develop a criteria structure amenable to future updates, without the need for complete reorganization.

Panel members agreed that biomarker development for CTE was not sufficiently mature to be included in the criteria at this time. Instead, the criteria would be based solely on clinical information, using RHI exposure history, symptom profiles, and clinical course specific to pathologically confirmed cases of CTE. It was agreed that the TES criteria will be revised in future NINDS consensus workshops based on updated research on biomarkers, neuropathology, clinical features, and reliability and validity of the new criteria.

A summary of evidence gathered prior to the meeting was provided to the panel and observers, consisting of: (1) data on interrater reliability using the 2014 TES criteria\(^7\); (2) the literature review of all reported cases with clinical information and descriptions of pathology consistent with CTE; and (3) predictive validity using unpublished data from the UNITE study. All published literature, data extraction
summaries, and unpublished analyses were made available to the panel and observers.

The panel discussed and agreed on the following parameters of a modified Delphi procedure to obtain consensus: all voting and commentary would be anonymous; a threshold of ≥ 80% agreement would be required for consensus on each diagnostic component; and there would be a limit of 4 rounds to achieve consensus.

**Modified Delphi Consensus Process**

The modified Delphi process follows an iterative procedure commonly used to achieve expert group consensus in medical science and other fields using rounds of voting, with summary of comments from each participant provided anonymously to all participants. It is a useful means of employing expert opinion when available evidence is incomplete.16

The first round of the modified Delphi process occurred at the NINDS consensus workshop. Three subsequent rounds were performed online. Following each round, panelist voting results and comments from each of the panelists and observers were provided to all participants anonymously. These were then used to restructure and revise the criteria by the lead organizers (DK, RS). The revised criteria were further reviewed and edited by a core subcommittee of panelists (DD, CB, JM) before distributing to the full panel for the next round. All panelists and observers were blinded to the identities of the respondents, except the
project manager (MM) who was not a voting panelist and who maintained the anonymity throughout the entire process, including publication of this report.

Results

Summary of Data Presented at the NINDS Consensus Workshop

Interrater reliability, sensitivity, and specificity of the 2014 research diagnostic criteria for TES

The 2014 research diagnostic criteria for TES had high interrater reliability when used in the UNITE and DIAGNOSE CTE studies. Intraclass correlation for UNITE was 0.77 (n=293 donors; n=12 raters) and for DIAGNOSE CTE, 0.93 (n=153 participants; n=16 raters), suggesting good agreement for both studies. The 2014 criteria were evaluated with respect to sensitivity and specificity in predicting a pathological diagnosis of CTE in the UNITE study (CTE, n = 224; no CTE, n = 74). Sensitivity was high (97.32); specificity was low (20.27). Similar results were found when limiting the sample to only those with “pure” CTE (i.e., pathology meeting CTE criteria without evidence of other neurodegenerative disease diagnoses) or no neurodegenerative pathologies (“pure” CTE, n = 135; no CTE, n = 40); sensitivity was 97.04 and specificity was 22.50. Although a diagnosis of TES was highly predictive of a pathological diagnosis of CTE, the confidence intervals were notably wide (CTE vs. no CTE, OR = 10.65, 95% CI: 3.32-34.17; “pure” CTE vs. no CTE: OR = 11.00, 95% CI: 2.76-43.81).
Given the high sensitivity and low specificity of the 2014 TES criteria, the panel concluded that the new consensus TES criteria should be structured to provide a greater level of specificity in diagnosing individuals with underlying CTE pathology.

**Literature review of RHI exposure of pathologically confirmed CTE**

At the time of this review, the majority of cases with neuropathology consistent with CTE described in the literature involved American football players (73.4%) and boxers (15.7%). There are substantially fewer cases in the literature related to other causes of RHI, including military veterans exposed to blast and other injuries, other contact and collision sports exposure, and victims of domestic violence (table e-5, doi.org/10.5061/dryad.f1vhhmgvk). There is a strong relationship of exposure to RHI as defined by the years of contact and collision sport participation with both the presence and severity of CTE pathology.\(^4\),\(^17\),\(^18\) A recent study that carefully adjusted for brain bank selection bias, found that the odds of having CTE doubled for every 2.6 years of football played, and deceased football players diagnosed with CTE were 1/10 as likely to have played fewer than 4.5 years and were 10 times more likely to have played greater than 14.5 years.\(^1\) A threshold of 11 years of play maximized the sensitivity and specificity of predicting a pathological diagnosis of CTE.

Data supporting a definitive association between CTE and TBI -- mild to severe, single or multiple -- independent of exposure to RHI are limited. There are a small number of autopsy cases of CTE or “CTE-like” pathology reported in
individuals without a history of RHI. However, history of RHI is often incomplete and the accuracy of the pathological diagnosis in some cases may have been compromised. For instance, low levels of tau—even at the depths of the cerebral sulci—due to other conditions, such as age related tau astrogliopathy (ARTAG) or primary age-related tauopathy (PART), have been misidentified as CTE. In contrast, a study from a large neurodegenerative disease brain bank found that nearly one third of cases with a history of contact sport participation (predominantly amateur football) had evidence of CTE (7/21 at stages III to IV); none (0/198) without a contact sports exposure history had evidence of CTE, including 33 individuals with a history of a single TBI.

Literature review of clinical features of pathologically confirmed CTE

Cognitive Features: The literature review indicated that cognitive features are among the most common clinical problems identified in the histories of individuals diagnosed with CTE at autopsy. The cognitive domains most affected (reported in more than 60% of the cases) are episodic memory, attention, and executive functioning, but other domains, such as language and visuospatial functions, may also be affected (table e-1, doi.org/10.5061/dryad.f1vhhmgvk).

Dementia was identified in more than half the cases.

Behavioral Features: Severe behavioral dysregulation problems were identified in more than 40% of the cases of autopsy identified CTE, including violent, impulsive, or explosive behavior. Other descriptions of abnormal behavior
included socially inappropriate behavior, aggression, rage, “short fuse,” and lack of behavioral control. (table e-7, doi.org/10.5061/dryad.f1vhhmgvk).

*Mood/Affect and Other Psychiatric Features:* Changes in mood and affect, anxiety symptoms, and paranoid delusions, were frequently reported in histories obtained from individuals with pathologically diagnosed CTE. The most common features (in at least 30% of individual cases), were depression, anxiety, hopelessness, and apathy (table e-8, doi.org/10.5061/dryad.f1vhhmgvk). The panel considered the high base rate of anxiety and mood disorders in the general population in interpreting these data.

*Clinical Course:* The natural history of clinical problems was characterized by progressive decline in the vast majority (95%) of cases (n=200; table e-9, doi.org/10.5061/dryad.f1vhhmgvk).

*Motor Features:* Motor problems were identified in a large proportion of cases. The most common problems involved gait and balance (51%). Dysarthria (23.5%) and signs of parkinsonism (up to 28%) were also reported (table e-10, doi.org/10.5061/dryad.f1vhhmgvk).

**Predictive validity analyses from the UNITE study**

The following summarizes several key findings that informed the consensus process. The number of years of contact and collision sport exposure (in particular, American football) was strongly associated with a pathological diagnosis of CTE. Of the clinical variables, cognitive dysfunction, particularly in
the domains of attention, episodic memory, executive function, and language, was significantly associated with CTE. Diagnosis of dementia, based on the Functional Activities Questionnaire\(^2^8\) (score ≥ 9) was also significantly related to a pathological diagnosis of CTE. The panelists considered the possible selection biases and confounds associated with the UNITE study design in interpreting the predictive validity data.

**NINDS Consensus Diagnostic Criteria for TES**

None of the components of the 2014 research diagnostic criteria for TES\(^7\) were retained in their original form after the first round of voting. Based on initial discussion and on the first round of voting, the criteria were divided into six sections to be voted upon separately. Consensus was reached after four rounds of the modified Delphi process. There was some variability in the final percentage of agreement for each of the six approved sections achieved by round four, with 80% approval for two of the six sections, 85% for two of the sections, and 90% for two of the sections. There were no panelists who disapproved of all sections; two panelists disapproved of three sections, though not the same sections.

There were a number of areas of concern raised by panelists over the course of the modified Delphi process that led to modifications necessary to reach consensus. These areas included: defining baseline functioning with respect to onset of clinical features; defining “delayed onset”; removing clinical features with high population base rates from the core clinical criteria; defining clinical impairment based on objective data, but when not available or inconclusive, relying on clinical judgement based on subjective reports; assuring qualifications
of clinicians reporting clinical features; accounting for biases introduced with the preponderance of data from American football clinicopathological studies; addressing the lack of data for exposure thresholds other than from male American football players; and proposing provisional levels of certainty given the limitations of available empirical data.

**Primary Criteria (Tables 1-4)**

Use of the NINDS Consensus Diagnostic Criteria for TES involves a stepwise process (see Figure 1). The primary criteria are divided into four parts: (1) **Substantial Exposure to Repetitive Head Impacts**; (2) **Core Clinical Features**; (3) **Not Fully Accounted for by Other Disorders**; and (4) **Level of Functional Dependence/Dementia**. Fulfilling the first three primary criteria is required for a diagnosis of TES. If these three criteria are met, the individual’s level of functioning is graded, including assessing for dementia. Tables 1-4 provides the specific wording of the consensus-approved criteria; the following provides a summary of each component.

**Substantial Exposure to Repetitive Head Impacts (Table 1)** refers to a history of multiple impacts to the head, with or without clinical symptoms or signs of concussion or TBI, including exposure to ‘high exposure’ contact or collision sports, military service involving exposure to repetitive blasts, or other sources, such as domestic violence, head banging, and vocational activities.

The majority of research in this area has been conducted with American football players. It is for this reason that the most specific criteria are provided for
individuals with that source of exposure. The inclusion of a minimum number of years for American football is based on initial existing data. The specific thresholds may be modified in the future as additional data are available. Specific thresholds for sources of exposure other than American football, and for women, are not yet known and will be provided in future modifications to these criteria. At this time, a single moderate-severe TBI does not meet TES exposure criteria; further research is required to assure that this is an appropriate exclusion.

*Core Clinical Features* (Table 2) requires cognitive impairment (involving episodic memory and/or executive functioning) or neurobehavioral dysregulation (including explosiveness, impulsivity, rage, violent outbursts, and emotional lability), or both, representing a change from baseline, and a progressive course, to meet TES criteria.

The *Not Fully Accounted for by Other Disorders* criterion (Table 3) excludes cognitive deficits or neurobehavioral dysregulation fully accounted for by pre-existing, established, or acquired neurodegenerative disorders or non-degenerative nervous system, medical, or psychiatric disorders and conditions. Comorbid diagnosis of another neurodegenerative disease, substance use disorder, posttraumatic stress disorder (PTSD), or mood or anxiety disorders does not exclude TES. The determination if other conditions more fully account for the core clinical features often may require extensive evaluation.

For those meeting criteria for TES, *Level of Functional Dependence and Dementia* (Table 4) is graded according to descriptions of the following levels:
independent, subtle/mild functional limitation, mild dementia, moderate dementia, or severe dementia.

Supportive Features and Provisional Levels of Certainty for CTE Pathology

(Tables 5 & 6)

As objective *in vivo* biomarkers are developed, refined, and validated for the detection of underlying neuropathological changes of CTE, it is anticipated that one or more of these biomarkers will be used in conjunction with the Primary Criteria for TES to increase diagnostic specificity. However, prior to the availability of validated diagnostic biomarkers, the current diagnostic schema provides criteria for Provisional Levels of Certainty for CTE Pathology, aimed at increasing the diagnostic specificity of the TES criteria. If an individual is found to meet criteria for a diagnosis of TES, these additional criteria can be used to provide a description of the level of certainty that there is underlying p-tau pathology meeting current neuropathological diagnostic criteria for CTE. This method of examining the relationship between antemortem clinical features and postmortem neuropathology to support levels of diagnostic certainty, as well as the terminology and corresponding weightings of sensitivity and specificity, has been used in criteria for diagnosis of other neurodegenerative diseases (e.g., progressive supranuclear palsy; PSP\textsuperscript{29, 30}).

Determination of Provisional Levels of Certainty for CTE Pathology (suggestive, possible, probable, definite) is based upon a stepwise assessment of source and level of RHI exposure, specific clinical features, and a set of supportive features
(see Figure 2). If an individual meets criteria for TES, and if they meet the Core Clinical Feature of Cognitive Impairment (but not Neurobehavioral Dysregulation without Cognitive Impairment), they are then assessed for the level of exposure to contact/collision sports. The preponderance of evidence used to formulate the current Provisional Levels of Certainty is from exposure to American football and, to a lesser extent, other contact/collision sports. Therefore, individuals without a history of playing contact/collision sports could only meet criteria for suggestive of CTE. If an individual is determined to have had substantial exposure to contact/collision sports, they are then assessed for the level of functional dependence/dementia (Table 4) and a set of Supportive Features (Table 5), including delayed onset, motor signs, and psychiatric features. Delayed onset refers to a clearly established, substantial (i.e., several years) period of stable functioning after the RHI exposure ends, before Core Clinical features become apparent. Motor signs include parkinsonism, other motor signs (e.g., dysarthria, ataxia, imbalance), or features of motor neuron disease. The inclusion of motor neuron disease as a Supportive Feature is based on preliminary research indicating an association between motor neuron disease and CTE neuropathology in a small number of individuals with a history of RHI exposure.\textsuperscript{31, 32}

**Discussion**

Here we present the first NINDS Consensus Diagnostic Criteria for TES for use in research settings, developed using a modified Delphi process, informed by
available evidence, employing an expert panel of 20 clinician-scientists representing a variety of disciplines and multiple institutions. The panel members and 7 observers initially convened at the First NINDS Consensus Workshop to Define the Diagnostic Criteria for TES. Following four rounds of reviewing, anonymous voting, and revising over the subsequent 8 months, a consensus was reached for four primary criteria for the diagnosis of TES as well as criteria for Supportive Features and Provisional Levels of Certainty for CTE Pathology.

Our approach in the development of these criteria is similar to the iterative process used in the development of diagnostic criteria for other neurodegenerative diseases. We began with the previously proposed 2014 research diagnostic criteria for TES. We then made substantial revisions based on current evidence and an expert consensus process, resulting in the current diagnostic criteria. No sections of the 2014 TES criteria were retained in original form, although some aspects of the general structure and nomenclature were carried into the new criteria. Our plan is to update these consensus diagnostic criteria for TES in future expert consensus efforts, incorporating new evidence into the consensus process, including findings from clinicopathological validation studies and in vivo diagnostic biomarker research.

At the April 2019 NINDS consensus workshop, panelists and observers agreed that a primary aim should be to improve specificity of the TES diagnostic criteria over the 2014 criteria in identifying cases of presumed CTE based on the current NINDS/NIBIB neuropathological criteria. This was further underscored through the early rounds of Delphi voting and commentary and was addressed through
the following modifications to the TES criteria: (1) requiring substantial exposure to RHI; (2) requiring a progressive course, reflecting the neurodegenerative nature of CTE; (3) clarifying the core clinical features to include only those with higher frequency in CTE but excluding those with high population base rates (e.g., depression, anxiety); and (4) requiring cognitive impairment (i.e., excluding neurobehavioral dysregulation without cognitive impairment) as a necessary criterion for possible and probable CTE, the higher levels of certainty for CTE pathology.

Psychiatric features such as anxiety, depression, apathy, and paranoia were not included as core features but reserved as supportive features that are used in determining levels of certainty for CTE pathology. Although these symptoms have been reported at a high frequency in published cases with confirmed CTE and commonly reported by next of kin of individuals with neuropathologically diagnosed CTE, the inclusion of these psychiatric problems as core clinical features in the previous TES criteria was problematic because of high population base rates and the potential for CTE false positive diagnoses.

In the current consensus TES criteria, the nonspecific mood and behavior features in the 2014 TES criteria have been replaced with a more specific syndrome of what the panelists termed, neurobehavioral dysregulation (i.e., poor regulation or control of emotions and/or behavior, including explosiveness, impulsivity, rage, violent outbursts, having a “short fuse,” emotional lability) as a core clinical feature (Table 2). Aspects of neurobehavioral dysregulation are often observed in primary psychiatric and neurodegenerative conditions, but the
specific features of neurobehavioral dysregulation, along with a progressive
course and a history of substantial RHI exposure, distinguishes neurobehavioral
dysregulation in TES from these other disorders. Although impulsivity is one of
the possible early features of behavioral variant frontotemporal dementia
(bvFTD), unlike in TES, the impulsivity in bvFTD is often part of an overall
picture of behavioral disinhibition, marked by the loss of social decorum, such as
using crude language, telling off color jokes, and being rude without
embarrassment. Moreover, the remaining diagnostic criteria for bvFTD are
distinct from those for TES. Mild behavioral impairment (MBI) is a diagnostic
construct in which later onset (age ≥ 50) behavior or personality changes are
viewed as early manifestations of neurodegenerative disease, depending on the
location and type of underlying neuropathology. Although neurobehavioral
dysregulation would be consistent with the MBI diagnostic features of “emotional
dysregulation” and “impulse dyscontrol,” individuals younger than age 50 or who
have dementia would not meet diagnostic criteria for MBI. Some features of
neurobehavioral dysregulation are also similar to those in idiopathic psychiatric
disorders such as intermittent explosive disorder and disruptive mood
dysregulation disorder. However, these can be distinguished from the
neurobehavioral dysregulation of TES since they are primarily disorders with
onset in childhood or adolescence that cannot be associated with other
conditions, such as brain injury or dementia, and are not progressive through
adulthood.
As with other diagnostic criteria for cognitive and neuropsychiatric disorders, these consensus criteria for TES include a requirement that the core clinical features cannot be fully accounted for by other pre-existing, established, or acquired non-degenerative nervous system, medical, or psychiatric disorders and conditions (Table 3). Also similar to other diagnostic schemas, our criteria state that a comorbid diagnosis of another neurodegenerative disease, substance use disorder, post-traumatic stress disorder (PTSD), mood or anxiety disorder, or a combination of these, does not exclude a TES diagnosis, unless they are determined to account for all core clinical features. This determination requires clinical judgment and is best made by experienced clinicians.

As stated earlier, a goal of these new criteria was to improve upon the specificity of 2014 criteria for the clinical presentation of CTE, while also assuring adequate sensitivity. Without accurate diagnostic biomarkers, it is difficult to achieve high specificity based on cognitive and neuropsychiatric features alone, especially when so many of these features are shared across multiple disorders. We have attempted to increase specificity of the clinical features of TES by requiring substantial RHI exposure (as defined in Table 1) and a progressive course (Table 2). It is indeed possible for an individual to meet TES criteria and meet criteria for a comorbid disease or disorder. For example, a 65-year-old former college football player (who played for 7 years) who developed progressive multi-domain cognitive impairment (with pronounced episodic memory deficits and executive dysfunction) at the age of 60, emotional lability at age 62, and is now
functionally dependent in most IADLs (although is engaged in some family and community activities), would meet diagnostic criteria for both TES with Mild Dementia and DSM-5 Major Neurocognitive Disorder Due to Possible Alzheimer’s Disease, with behavioral disturbance. However, if that same individual had a history of several family members with progressive cognitive decline in their early 60s (with postmortem diagnosis of AD in his mother) and he had an amyloid PET which clearly demonstrated elevated neuritic amyloid plaque deposition, a clinician could suspect that the AD fully accounts for the individual’s clinical features. Therefore, the patient in this example would not meet TES criteria because the profile can be fully accounted for by a diagnosis of Major Neurocognitive Disorder Due to Probable Alzheimer's Disease, with behavioral disturbance.

The levels of functional dependence and dementia included in these TES diagnostic criteria are based primarily on accepted and widely used descriptions, such as those for the CDR® Dementia Staging Instrument (CDR) or diagnostic criteria for all-cause dementia and mild cognitive impairment (MCI). Although our classification schema has face validity and closely follows the CDR, there is need for research examining the reliability and validity of our new rating.

These NINDS Consensus Diagnostic Criteria for TES will require future research to determine their interrater reliability and predictive validity. Longitudinal studies of individuals with diverse RHI exposure histories and clinical features who receive antemortem TES diagnoses and who, after death, receive postmortem neuropathological diagnoses are required. Well-designed longitudinal studies of
at-risk populations will help address some of the limitations in the presently available evidence, including the absence of information on incidence and prevalence of TES and CTE, and the ascertainment bias associated with brain bank studies using retrospective clinical information. Future research will need to incorporate any updates/revisions to CTE neuropathological diagnostic criteria.

These TES criteria are limited by the lack of existing clinicopathological data regarding risk for CTE pathology from RHI exposures other than tackle football, and to a lesser extent, boxing. Revisions to these criteria should incorporate findings from future research on risk from other contact and collision sports (e.g., ice hockey, soccer, rugby, mixed martial arts, professional wrestling, motocross, rodeo, bull riding, race car driving), military service, intimate partner and other domestic physical violence, head banging (e.g., by individuals with developmental disorders), and breaching (e.g., by first responders), as well as newer data on specific exposure risk thresholds for American football. It is possible that the clinical presentation of CTE may differ based on source of RHI exposure, gender, and other variables. At this time, the preponderance of research indicates that CTE pathology (based on the NINDS-NIBIB criteria) is found only in individuals with a history of repetitive mild brain trauma. However, there are observations of individuals who, following a history of a single moderate-to-severe TBI, demonstrate chronic or progressive cognitive and neuropsychiatric impairment. Recent research also indicates that, in individuals with TBI history, those who also have RHI exposure history have greater cognitive impairment and depression symptoms. Future
clinicopathological research should include a full range of injury exposure and severity to facilitate empirical investigation into the appropriateness of the current exclusion of a single (or more) moderate-severe TBI to meet criteria for TES.\textsuperscript{48}

It is unclear if tau pathology of CTE alone is responsible for the core clinical features of cognitive impairment and neurobehavioral dysregulation seen in individuals with a history of extensive RHI exposure.\textsuperscript{49} For example, it is not yet known if, and to what extent, the patchy areas of perivascular p-tau deposition at the depths of cerebral sulci seen in early stage CTE have direct clinical correlates. It is possible there are specific lesion loci that, through disconnections with distant cortical areas or deeper gray matter nuclei, result in specific clinical features. Additionally, p-tau involvement in specific brainstem nuclei (e.g., locus coeruleus) may result in specific early features. Even in later stage CTE, the relationship between the types and locations of p-tau lesions and cognitive and neuropsychiatric symptoms has not been elucidated. It is possible that some clinical features of TES may be unrelated to p-tau pathology and instead due to other consequences of brain trauma, such as white matter rarefaction\textsuperscript{50} or the long-term chronic or progressive inflammatory changes to subcortical and deep white matter.\textsuperscript{51} Moreover, neuropathological factors unrelated to RHI exposure (e.g., arteriosclerosis) as well as additional medical and psychosocial variables, such as sleep disorders, vascular risk factors, chronic pain, racial and associated inequities in social determinants of health, may contribute to the clinical features of TES in individuals with substantial RHI exposure, or modify the clinical presentation of CTE pathology. Similar to other neurodegenerative diseases, it is
also likely that some individuals with CTE pathology, especially earlier stage pathology, may not have any meaningful clinical symptoms.

The Provisional Levels of Certainty for CTE Pathology are stratified based on the relative degrees of sensitivity and specificity and, therefore, could provide guidance for selection of participants for different types of research studies. For example, Suggestive of CTE is weighted toward high sensitivity and low specificity and would be appropriate for studies focusing on early identification and longitudinal evaluation of individuals at risk for developing Possible or Probable CTE. Possible CTE balances sensitivity and specificity and would be appropriate for descriptive epidemiologic studies. Probable CTE is weighted toward high specificity but low sensitivity and would be appropriate for targeted therapeutic trials and diagnostic biomarker studies for which the exclusion of non-CTE participants is important.

Although there have been preliminary reports of potential fluid\textsuperscript{52-54} and neuroimaging biomarkers\textsuperscript{49, 55-58} of CTE pathology, they are limited by small sample sizes, a restricted range of symptom severity, a focus on former professional football players, small or no control groups, low specificity, and most importantly, the lack of postmortem validation. Potential \textit{diagnostic} biomarkers for CTE tau pathology include: tau PET imaging with radiotracers that specifically bind to CTE tau isoforms; and CSF and/or blood analytes for p-tau\textsubscript{181} or p-tau\textsubscript{217}, other CTE tau species, or proteomic (or other -omic) profile signatures of CTE, and others. There are additional potential \textit{supportive} fluid and imaging biomarkers that may have higher sensitivity-to-specificity ratios that could be
used as screening biomarkers. These include functional MRI measures of network connectivity, magnetic resonance spectroscopy measures of neurochemical metabolism, structural MRI (e.g., cortical thinning, volumetrics, evidence of cavum septum pellucidum), and CSF or plasma measures of neurodegeneration (e.g., total tau, neurofilament light chain protein). Further research on individual biomarkers and combinations of biomarkers should improve the accuracy of diagnosis of TES associated with underlying CTE pathology.

A diagnosis of TES (a clinical syndrome) is not intended as a diagnosis of CTE (a neuropathological diagnosis). Despite the previous lack of expert consensus or validated diagnostic criteria for the clinical diagnosis of CTE, a recent survey study of former NFL players found that 108 (out of 3913) respondents reported having been given a diagnosis of “CTE” by a clinician. Authors of that study cautioned that receiving a premortem CTE diagnosis could produce a nocebo effect, leading to additional mental health difficulties, as well as a reduction in the diagnostic evaluation and intervention for treatable conditions. These NINDS Consensus Diagnostic Criteria for TES are meant primarily for research purposes, and should be used cautiously in clinical and medico-legal settings, avoiding equivalence with a diagnosis of CTE, and using appropriate care when communicating a diagnosis of TES. Moreover, the Provisional Levels of Certainty for CTE Pathology described herein are intended for research purposes only. We strongly discourage disclosure of individual Levels of Certainty to participants or their healthcare providers.
With additional clinicopathological research, including longitudinal studies with antemortem clinical evaluations and postmortem neuropathological examination, and the development and validation of *in vivo* diagnostic biomarkers for underlying CTE pathology, we anticipate revising these consensus diagnostic criteria for TES; application of these criteria may then be appropriate for clinical diagnosis. For now, however, it is important for clinicians, researchers, and the public to be appropriately educated that a diagnosis of CTE cannot yet be confirmed during life and that it is imperative for individuals at presumed risk for CTE be properly evaluated for potentially treatable conditions and for relevant comorbidities that may exacerbate or accelerate neurodegeneration.\(^{59-60}\)

**Conclusions**

Consensus diagnostic criteria for TES were developed through a modified Delphi process involving a multidisciplinary panel of experts. The criteria are meant for use in research settings to facilitate investigations into the clinical features associated with CTE pathology and to fill other knowledge gaps, including the development of biomarkers for antemortem diagnosis of CTE. The Primary TES criteria favor diagnostic sensitivity over specificity with regard to predicting CTE neuropathology. To improve specificity, consensus diagnostic criteria for Provisional Levels of Certainty for underlying CTE pathology were developed. The levels of certainty (i.e., suggestive, possible, probable, definite) are based on exposure thresholds, core and supportive features, and level of functional dependence. As objective *in vivo* biomarkers are developed and validated for the
specific detection of underlying CTE neuropathology, it is anticipated that these
criteria will be revised to maximize overall clinical diagnostic accuracy.
References


23. McKee AC, Stein TD, Crary JF, Bieniek KF, Cantu RC, Kovacs GG. Practical considerations in the diagnosis of mild chronic traumatic


Figure Legends

Figure 1. Stepwise Process for Utilizing the NINDS Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome. The first step is to determine if the individual meets criteria for Substantial Exposure to Repetitive Head Impacts (Table 1). If yes, Core Clinical Features (Table 2) are determined and, if criteria are met, those features must be Not Fully Accounted for by Other Disorders (Table 3). If yes, then the TES criteria are met and the final step is to Determine Level of Functional Dependence/Dementia (Table 4).
Figure 2. Flow Diagram for Determining Provisional Levels of Certainty for CTE Pathology for Research Purposes. Specific criteria are provided in Tables 1-6. These Provisional Criteria are not meant for clinical diagnostic purposes. Rather, they are meant for research settings by providing a description of the level of certainty (i.e., diagnostic specificity) that an individual’s clinical features are due to underlying p-tau pathology meeting current neuropathological diagnostic criteria for CTE.
Tables

Table 1. Primary Diagnostic Criteria for TES: I. Substantial Exposure to Repetitive Head Impacts

- History of substantial exposure to repetitive impacts to the head is required. These impacts may or may not have been associated with clinical symptoms or signs of concussion or traumatic brain injury (TBI). Individuals should be screened for multiple possible sources of exposure over a lifetime. Examples of sources of substantial exposure to repetitive head impacts include:

- **Involvement in ‘high exposure’ contact or collision sports** such as (but not limited to) boxing, American (tackle) football, ice hockey, soccer, rugby, professional wrestling, mixed martial arts, and some other sports with high risk of exposure to repetitive head impacts (e.g., motocross, bull riding).

  For American football, a minimum of 5 years of organized play is required. This minimum should include ≥ 2 years at the high school level or beyond. [The inclusion of level of play (i.e., high school) is based on clinical judgment, with limited evidence. Nearly all of the participants in a published study establishing the
5-year threshold played at least high school level football\textsuperscript{1}

*Exposure risk thresholds for other contact or collision sports, or combinations of contact/collision sports, have not yet been established but should be a substantial number of years (e.g., \( \geq 5 \) years) at a level of play involving routine repetitive head impacts.*

**Military service** involving repetitive head impacts, including (but not limited to) combat exposure to multiple blast and other explosions, non-combat exposure to explosions (including breacher training – blasting and forced opening of locked doors), or multiple blows to the head over an extended period of time (e.g., pugil stick training - repeated blows with a padded military training weapon).

*Exposure risk thresholds for military service have not yet been established.*

**Other sources** involving multiple head impacts over an extended period of time, including (but not limited to) domestic violence (or intimate partner violence), head banging, and vocational activities such as breaching locked doors and other barriers by first responders.

*Exposure risk thresholds for other sources have not yet been established.*
**Table 2. Primary Diagnostic Criteria for TES: II. Core Clinical Features**

Cognitive Impairment or Neurobehavioral Dysregulation, or both, is required to meet TES criteria. A Progressive Course is also required to meet TES criteria.

<table>
<thead>
<tr>
<th>Cognitive Impairment (all 4 are required)</th>
</tr>
</thead>
<tbody>
<tr>
<td>As reported by self or informant, or by clinician’s report.</td>
</tr>
<tr>
<td>Representing a significant decline from baseline functioning. The determination of “baseline” level of functioning may be challenging and require clinical judgment in cases where decline may have begun during the period of repetitive head impact exposure.</td>
</tr>
<tr>
<td>With deficits in episodic memory and/or executive functioning (additional domains may be impaired in addition to these).</td>
</tr>
<tr>
<td>Substantiated by impaired performance on formal neuropsychological testing (if available), as defined by performance at a level of at least 1.5 standard deviations below appropriate norms, accounting for the individual’s estimated premorbid functioning. If formal neuropsychological testing is not available, there should be substantial evidence of impairment below expected norms and/or a person’s estimated baseline in episodic memory and/or executive functioning on a standardized mental status examination (e.g., MoCA, MMSE) by a clinician experienced in the</td>
</tr>
</tbody>
</table>

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Neurobehavioral Dysregulation (all 3 are required)

As reported by self or informant, or by clinician’s report.

Representing a significant change from baseline functioning. The determination of “baseline” level of functioning may require clinical judgment in cases where change may have begun during the period of repetitive head impact exposure.

With symptoms and/or observed behaviors representing poor regulation or control of emotions and/or behavior, including (but not limited to) explosiveness, impulsivity, rage, violent outbursts, having a “short fuse” (exceeding what might be described as periodic episodes of minor irritability), or emotional lability (often reported as “mood swings”), preferably substantiated by standardized measures that demonstrate clinical impairment in these domains. In most cases standardized measures of neurobehavioral dysregulation will not be available but there should be substantial evidence of change from a person’s baseline. These symptoms and/or observed behaviors do not appear to represent a transient response to life events, e.g., divorce, death of loved one, financial problems.

Progressive Course

There is evidence of progressive worsening of these clinical
features over a period of at least 1 year in the absence of continued exposure to repetitive head impacts or TBI. The evidence should be supported by serial standardized testing (if available) or clear history supporting a change in functioning over time (e.g., clinician reports, job performance evaluations, or self- or informant-report).
Table 3. Primary Diagnostic Criteria for TES: III. Not Fully Accounted for by Other Disorders

**Other Disorders**

<table>
<thead>
<tr>
<th><strong>The pattern of the cognitive deficits</strong> is not fully accounted for by other pre-existing, established, or acquired non-degenerative nervous system, medical, or psychiatric disorders and conditions.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The Core Clinical Feature of Neurobehavioral Dysregulation</strong>, if present, is not fully accounted for by other pre-existing, established, or acquired non-degenerative nervous system, medical, or psychiatric disorders and conditions.</td>
</tr>
<tr>
<td><strong>Comorbid diagnosis of another neurodegenerative disease</strong> does not exclude a TES diagnosis. However, TES may be excluded if, based on clinical judgment, the clinical features and any available biomarkers are fully accounted for by another neurodegenerative disorder.</td>
</tr>
<tr>
<td><strong>Comorbid diagnosis of substance use disorder, posttraumatic stress disorder (PTSD), mood or anxiety disorders</strong>, or a combination of these, can be present and do not exclude a TES diagnosis, unless they are determined to account for all Core Clinical Features.</td>
</tr>
</tbody>
</table>
Table 4. Primary Diagnostic Criteria for TES: IV. Level of Functional Dependence/Dementia

The level of functional dependence should be based on the impact of Cognitive Impairment and/or Neurobehavioral Dysregulation and not on physical limitations or medical illness. Information is obtained from self-report, informant, and/or clinical records. Functional dependence levels (other than Independent) should represent a change from previous baseline functioning.

**Independent**

Independent at usual level in job, household responsibilities, or family, social, and community roles. Able to engage in hobbies and intellectual activities at usual levels; fully independent instrumental and basic activities of daily living (ADLs).

**Subtle/Mild Functional Limitation**

Slightly reduced performance in job, household responsibilities, or family, social and community roles; slight problems in hobbies and intellectual interests reported; mostly independent but may be more challenged in some instrumental ADLs (e.g., managing money [e.g., paying bills, completing taxes], cleaning and maintaining the house, preparing meals, shopping for groceries and necessities, transportation within the community [e.g., driving, using public transportation], medication management, using the telephone [mobile or landline]) and fully
independent in basic ADLs (personal hygiene and grooming [e.g., brushing/combing/styling hair], toilet hygiene [e.g., getting to the toilet, cleaning oneself, and getting back up], bathing/showering, dressing, self-feeding, functional mobility [e.g., ability to walk, get in and out of bed, get into and out of a chair]).

**Mild Dementia**

Definite impairment of instrumental ADLs; may be engaged in some home, family, social, and community activities; more difficult activities abandoned; needs cues for some basic ADLs.

**Moderate Dementia**

Not independent but can be taken to some functions outside the home; only simple chores preserved; very restricted interests; needs assistance with basic ADLs.

**Severe Dementia**

Cannot participate in functions outside the home; no significant function in home; impaired basic ADLs; not independent with self-care; frequently incontinent.
Table 5. Supportive Features used in Determining Provisional Levels of Certainty for CTE Pathology.

The following three Supportive Features are used in determining the Provisional Levels of Certainty for CTE Pathology (Table 6). These features are frequently present in individuals with underlying CTE pathology, but have insufficient predictive value to qualify as Core Clinical Features.

**Delayed Onset**

Core Clinical features begin following a clearly established period of stable functioning after the repetitive head impact exposure ends. (A minimum time period of stability before onset and progression of symptoms has not been established but should be substantial [i.e., years] to suggest a history consistent with a degenerative disorder rather than problems associated with traumatic brain injury or other preexisting conditions.)

**Motor Signs**

*Parkinsonism*: bradykinesia, rigidity, rest tremor, parkinsonian gait disorder; these motor signs should not be more consistent with the clinical features of non-parkinsonian neurologic conditions or primary orthopedic problems.

*Other Motor Signs*: dysarthria, ataxia, imbalance; these motor signs should not be more consistent with the clinical features of other neurologic conditions or primary orthopedic problems.

*Motor Neuron Disease*: weakness, dysphagia, other lower motor
neuron signs (fasciculations, muscle atrophy), other upper motor neuron signs (spasticity, hyperreflexia, extensor plantar response, spastic dysarthria); a diagnosis of Amyotrophic Lateral Sclerosis (ALS) would meet this criterion but is not necessary.

**Psychiatric Features**

These supportive Psychiatric Features have not been accounted for by “Neurobehavioral Dysregulation” described in the Core Clinical Features. They may occur individually or in combination, should represent a clear change from baseline, and should be persistent (i.e., months to years) or progressive. These features can be based on self- or informant report, a history of treatment, or clinician’s report. The supportive Psychiatric Features include:

**Anxiety**: pervasive worries, excessive fears, agitation, or obsessive or compulsive behavior (or both); a formal diagnosis of anxiety disorder would meet this criterion but is not necessary. If available, scores on an established, validated anxiety scale should indicate a moderate level of anxiety or higher.

**Apathy**: loss of interest in usual activities, loss of motivation or drive. If available, scores on an established, validated apathy scale should indicate a moderate level of apathy or higher.

**Depression**: feeling overly sad, dysphoric, or hopeless, with or without a history of suicidal thoughts or attempts; a formal
diagnosis of major depressive disorder or persistent depressive disorder would meet this criterion but is not necessary. These symptoms should not be a time-limited reaction to an event (e.g., death of family member, illness, trauma). If available, scores on an established, validated depression scale should indicate a moderate level of depression or higher.

**Paranoia:** delusional beliefs of suspicion, persecution or unwarranted jealousy; a formal diagnosis of a psychotic disorder would meet this criterion but is not necessary. If available, scores on an established, validated paranoia scale should indicate a moderate level of paranoia or higher.
### Suggestive of CTE

Meets TES Criteria but does not meet additional criteria for Possible, Probable, or Definite CTE below. (*Highest sensitivity and lowest specificity*). Suggestive of CTE pathology but does not cross the threshold for Possible or Probable CTE.

### Possible CTE

Meets TES Criteria and must meet first two criteria and a minimum of 2 of remaining 5 criteria (*Balance of sensitivity and specificity.*)

**Required for Possible CTE:**

- *Substantial exposure to a contact/collision sport:*
  - Exposure to American football ≥5 years (including at least 2 years at high school or beyond the high school level**); or other contact/collision sport (e.g., boxing) to an equivalent extent.***

- Cognitive impairment as defined in Table 2

- Plus a minimum of 2 of the following 5 criteria:
  - Delayed onset (as defined in Table 5)
  - Motor signs (as defined in Table 5), not most likely accounted for by other etiology
One or more psychiatric features (as defined in Table 5)

Neurobehavioral dysregulation (as defined in Table 2)

Severity of Functional Dependence = Subtle/Mild

Functional Limitation or worse (as defined in Table 4)

**Probable CTE**

Meets TES criteria and must meet first two criteria below and a minimum of 3 of the remaining 5 criteria (meeting all 5 of remaining criteria supports a high level of certainty of CTE pathology). *(Higher specificity but lower sensitivity.)*

**Required for Probable CTE:**

*Extensive exposure to a contact/collision sport:*

Exposure to American football ≥11 years (including at least some at college level**); or boxing or other sports with high level exposure to repetitive head impacts to an equivalent extent***

Cognitive impairment as defined in Table 2

Plus a minimum of 3 of the following 5 Criteria:

Delayed onset (as defined in Table 5)

Motor signs (as defined in Table 5), not most likely accounted for by other etiology

One or more psychiatric features (as defined in Table 5)
Neurobehavioral dysregulation (as defined in Table 2)

Severity of Functional Dependence = Mild Dementia or worse (as defined in Table 4)

Definite CTE with TES

Meets TES criteria as well as CTE, confirmed by postmortem neuropathological diagnosis based on current NINDS criteria for neuropathological diagnosis of CTE. This is the gold standard for defining CTE disease entity.

*These Levels of Certainty for underlying CTE pathology are based on reviews of the literature and on current analysis of clinicopathological data from the UNITE Study (U01-NS086659, McKee, PI\textsuperscript{14}) and are likely to be refined in the future. For example, specific levels of exposure are based on data from American football players whose brains have been examined postmortem.\textsuperscript{1}

**The inclusion of level of play (i.e., high school and college) is based largely on clinical judgment but is supported by limited evidence. Nearly all of the participants in the single study establishing the 5-year threshold played at least high school level football. In the single study used to establish the 11-year threshold, nearly all of the participants who played for 11 or more years played at least college level football.\textsuperscript{1}

***As more data are obtained from other possible sources of exposure and as these criteria are validated with other exposure groups (e.g., other contact/collision sports, military, other), the specific amount of exposure associated with risk for CTE pathology will be updated.
## Appendices

### Appendix 1. Authors

<table>
<thead>
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