

Using the NINDS Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome on 4 Cohorts of Retired Contact Sport Athletes

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Background: A 2021 National Institute for Neurological Disorders and Stroke (NINDS) consensus panel proposed a set of clinical diagnostic criteria for traumatic encephalopathy syndrome (TES) and determined provisional levels of certainty for chronic traumatic encephalopathy (CTE) pathology based on neuropathological evidence. The panel suggested the criteria needed to be validated by clinical studies of living populations exposed to repetitive head impacts (RHIs).

Hypothesis: As the consensus criteria were developed solely from neuropathologically diagnosed cases of CTE, we hypothesized that they may not be readily applicable to the clinical impressions developed from the histories and examination findings of living patients whose neuropathology was unknown.

Study Design: We applied the consensus criteria to 4 groups of living retired contact sports athletes collected from previously published articles in the medical literature.

Level of Evidence: Level 4.

Methods: Clinical evidence from 4 groups of living retired athletes (boxers and American football players) with extensive RHI exposure was available. We used the NINDS consensus criteria to determine for each athlete whether or not they met the criteria for TES. For those who met the criteria, we determined their provisional level of certainty for CTE pathology.

Results: Among all 80 subjects, the prevalence of TES was 21.3% (17 of 80), the prevalence of possible CTE was 12.5% (10 of 80), and the prevalence of probable CTE was 2.5% (2 of 80). Among the 45 retired football players, the prevalence of TES was 24.4% (11 of 45) and the prevalence of possible CTE was 17.7% (8 of 45). None of the retired football players met the criteria for probable CTE. Among the 35 total retired boxers (from all 3 groups), the prevalence of TES was 17.1% (6 of 35), the prevalence of possible CTE was 5.7% (2 of 35), and the prevalence of probable CTE was 5.7% (2 of 35).

Conclusion: Applying the NINDS consensus criteria to this historical cohort of living retired athletes with extensive RHI exposure resulted in a relatively low prevalence of TES and possible/probable certainties of CTE pathology, which might suggest limitations on the sensitivity of the NINDS criteria.

Clinical Relevance: Physicians are often asked by retired contact sports athletes and their families to determine if their clinical picture is related to TES and/or CTE. Physicians may turn to the NINDS consensus criteria for guidance in making such determinations. The data presented here may assist physicians in evaluating the reliability and validity of using the consensus criteria in living subjects.

Keywords: Chronic traumatic encephalopathy (CTE); historical cohorts; repetitive head impact (RHI); traumatic encephalopathy syndrome (TES)

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The National Institute for Neurological Disorders and Stroke (NINDS) recently assembled a panel of 20 expert clinician-scientists charged with developing clinical guidelines for the diagnosis of traumatic encephalopathy syndrome (TES) and provisional levels of certainty of neuropathological chronic traumatic encephalopathy (CTE) in living contact sport athletes with significant exposure to repetitive head impacts (RHIs).⁴ The panelists reviewed evidence from all neuropathologically confirmed cases of CTE and a large clinicopathological study of clinical features in relation to CTE pathology. Using a modified Delphi procedure, the panel developed consensus diagnostic criteria for TES and, for those subjects meeting the TES criteria, criteria for determining a provisional level of certainty for CTE pathology. The authors stated “Although our classification schema has face validity and closely follows the CDR (clinical dementia rating) staging instrument, there is need for research examining the reliability and validity of our new rating.”⁴ The authors called for clinical studies of at-risk populations to help address some of the limitations of the presently available evidence, specifically the absence of information on incidence and prevalence of TES and CTE and the “ascertainment bias” of neuropathology studies utilizing “retrospective clinical information.”⁴ This present analysis of historical clinical cohorts of living subjects with significant exposure to repetitive head injuries in sport was undertaken to try to address these issues, specifically the concerns regarding ascertainment bias.

METHODS

We searched for previously reported clinical studies of living subjects with extensive exposure to sports-related repetitive head injury in which the clinical histories and examinations were performed by neurologists and neuropsychological testing was also utilized. We selected 3 studies in which enough detailed clinical information was available to allow for evaluation of the specific criteria needed for TES diagnosis under the NINDS consensus criteria.

The first study population for this analysis consisted of a convenience sample of 45 retired NFL players aged 30-60 years who underwent comprehensive neurological, neuropsychological and neuroradiological testing between 2007 and 2009 as part of a clinical study.³ We reviewed all the collected clinical neurological data on each subject, including contemporaneously prepared comprehensive neurological history and examination reports as well as the results of the mini-mental state examination (MMSE), results of Beck Depression Inventory and Patient Health Questionnaire-9, and the results of comprehensive written neuropsychological tests that were obtained and analyzed by neuropsychologists at the time.

The second study population for this analysis consisted of a group of 13 retired boxers who underwent clinical neurological history taking and examinations, electroencephalograms, written

neuropsychological tests, and CT scans of the head from 1981 to 1982 as part of a clinical study.¹

The third and fourth study populations were subsets of a group of 224 British retired professional boxers who fought between 1929 and 1955, and who underwent neurological examinations and written neuropsychological testing between 1967 and 1969 as part of a clinical study.⁶ Thirty-seven of the 224 were found to have abnormal physical neurological signs attributable to their careers in boxing. Detailed clinical results for 11 of these 37 subjects were presented in the published paper, and these 11 were the third group that was reviewed for this present analysis (referred to as group A in the rest of this paper). Eleven of the 224 were found to have abnormal neurological signs that the author of the paper attributed to neurological conditions not related to RHIs from boxing. Detailed clinical findings for all 11 of these subjects were presented in the published paper and these make up the fourth group that was reviewed for the present analysis (referred to as group B in the rest of this paper).

For every subject in each of the 4 groups, the clinical data were reviewed with the aim of determining whether or not the diagnostic criteria spelled out in the NINDS consensus were met.

We used the consensus criteria in listed order as a decision tree to determine for each subject whether or not he met the criteria for TES and, if so, his provisional level of certainty for CTE (Figure 1). If a subject met the criteria for TES: I, his results were then analyzed for TES: II criteria, and among those who met the criteria for TES: II, each was then analyzed for TES: III criteria. Subjects who met the criteria for TES: I-III were then analyzed for TES: IV criteria. Only the subjects who fulfilled all the criteria for a diagnosis of TES were then assessed for provisional levels of CTE certainty.

For full details of the TES and provisional CTE criteria, the reader is advised to consult the consensus paper.⁴ We will briefly summarize those criteria as used in this present analysis.

TES: I, substantial exposure to RHIs, ie, 5 or more years of organized tackle football play or participation in boxing or 30 or more boxing bouts.

TES: II (core clinical features), cognitive impairment or neurobehavioral dysregulation (NBD) or both, plus a progressive course. For cognitive impairment all 4 of the following: (1) self or informant report, (2) significant decline from baseline, (3) deficits in episodic memory and/or executive function, and (4) substantiated by impaired performance on formal neuropsychological testing, if available.

For NBD, all 3 of the following: (1) self or informant report, (2) significant change from baseline, and (3) symptoms and/or observed behaviors representing poor regulation or control of emotions and/or behavior (with a long list of examples of such

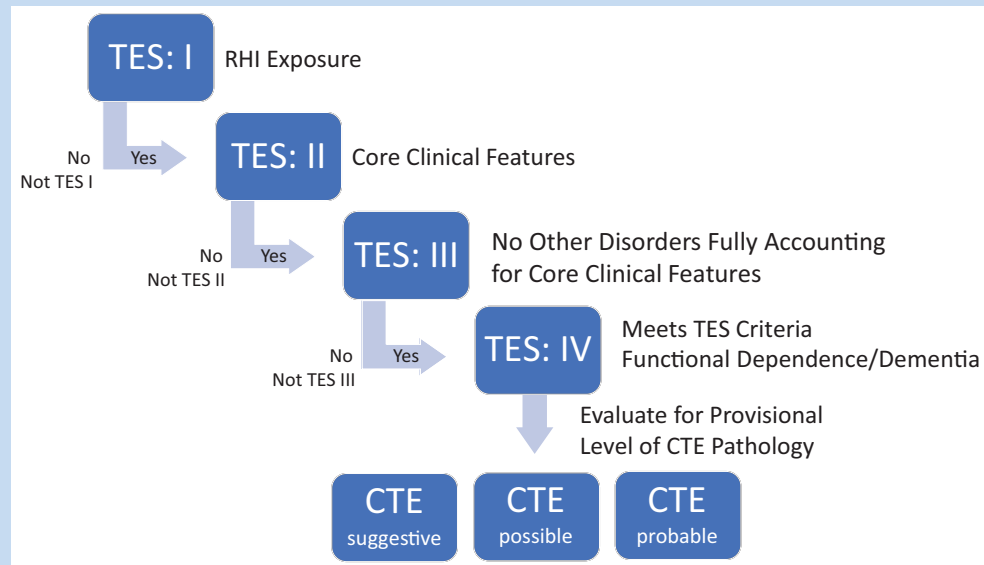


Figure 1. Decision tree for evaluating individuals for TES and provisional CTE. CTE, chronic traumatic encephalopathy; TES, traumatic encephalopathy syndrome.

symptoms and behaviors) not representing a transient response to life events.

TES: III, not fully accounted for by other disorders.

TES: IV, level of functional dependence/dementia (ie, independent, subtle/mild functional limitation, mild, moderate or severe dementia).

Provisional levels of certainty for CTE pathology: must first meet TES criteria. Three additional supportive features evaluated: (1) delayed onset, (2) motor signs on neurological examination, and (3) psychiatric features not accounted for by NBD (ie, anxiety, apathy, depression, paranoia).

Suggestive of CTE: meets criteria for TES but none of these additional features.

Possible CTE: meets TES criteria + 5 or more years exposure to RHI in football or boxing + cognitive impairment as defined in TES: II + at least 2 among the additional supportive features, NBD or subtle/mild functional limitation or worse.

Probable CTE: meets TES criteria + 11 or more years of exposure to RHI in football or boxing + cognitive impairment + at least 3 among the additional supportive features, NBD and dementia.

Standard Protocol Approvals, Registrations and Patient Consents

The 4 case samples analyzed involved previously published studies. For the retired football players, the publication of the research noted that the research methods were subjected to institutional review board review and approval at Wayne State University, including informed consent, methodologies, confidentiality, and statistical analysis.³ Details regarding the

recruitment process, exclusion criteria, informed consent, and authorization to disclose the results are provided in the published article.³ For the retired boxers 1984 cohort, the publication of the research noted that informed written consent was obtained from every participant.¹ For the retired boxers 1969 group, the publication of the research noted that the participants “allowed themselves to be interviewed and examined” after being “invited by letter” and, if necessary, “a personal visit by a social worker or fellow boxer to help in a research project into the medical aspects of boxing.”⁶

RESULTS

The main results are summarized in Table 1. Additional results are included here.

In the retired football players group, 6 of the 7 subjects with NBD also met the criteria for cognitive impairment; 6 of the 10 subjects with cognitive impairment also met the criteria for NBD. Six subjects had both NBD and cognitive impairment, 1 subject had NBD only and 4 subjects had only cognitive impairment. Thus, a total of 11 subjects exhibited the core clinical features (NBD and/or cognitive impairment) of TES: II.

In the 1969 ex-boxers group A, 1 of the 2 subjects who met the NBD criteria also met the cognitive impairment criteria. Thus, 5 subjects fulfilled the criteria for TES: II.

For the retired football players group, the mean number of total years of football play for the subgroup with TES was 17.5 years, for the subgroup with possible CTE it was 17.9 years, and for the entire group of 45 players it was 17.0 years. For the 1969 ex-boxers group A, the average number of total professional bouts was 149 for the 5 subjects who met the criteria for TES and 184 for the 6 subjects who did not meet the TES criteria.

Table 1. Summary of study samples

	Retired Football Players	Retired Boxers	Boxing Related	Not Boxing Related
Study Samples	2014	1984	1969	1969
Demographics				
Number	45	13	11	11
Age	30-60	27-60	35-60	35-64
Exposure	17.0 ^a	11.9 ^b	168.4 ^c	182.9 ^c
TES diagnostic criteria				
TES I	45	13	11	10
TES II				
NBD	7	0	2	0
Cognitive	10	0	4	1
Met criteria	11	0	5	1
TES III	11	13	11	1
TES IV				
Independent	5	13 ^d	0	0
Mild impairment	6	0	3	0
Dementia	0	3	2	1
CTE assessment				
Provisional CTE				
Delay	10	0	2	1
Motor	0	0	5	1
Psych	9	0	1	0
CTE				
Suggestive	3	0	2	0
Possible	8	0	2	0
Probable	0	0	1	1

CTE, chronic traumatic encephalopathy; NBD, neurobehavioral dysregulation; TES, traumatic encephalopathy syndrome.

^aAverage number of years of football.

^bAverage number of boxing years.

^cAverage number of professional bouts.

^dThirteen had abnormal neuropsychological testing.

Among the overall group of 80 subjects, the prevalence of TES was 21.3% (17 of 80), the prevalence of possible CTE was 12.5% (10 of 80), and the prevalence of probable CTE was 2.5% (2 of 80). Among the 45 retired football players, the prevalence of TES was 24.4% (11 of 45) and the prevalence of possible CTE was 17.7% (8 of 45). None of the retired football players met the

criteria for probable CTE. Among the 35 total retired boxers (from all 3 groups), the prevalence of TES was 17.1% (6 of 35), the prevalence of possible CTE was 5.7% (2 of 35), and the prevalence of probable CTE was 5.7% (2 of 35).

Regarding the 1984 ex-boxers' group,¹ we should explain how it was determined that none met the criteria for TES: II. The

criteria for both cognitive impairment and NBD indicated that symptoms be reported by self or other informant or clinician's report. None of the former boxers met this criterion. This may be explained by the selection criteria used for inclusion in the original study. To be included, the retired boxers had to have no history of neurological, psychiatric, or serious medical illness and needed to be actively working in the sport (as trainers, officials, managers, etc). Even though all 13 of the subjects exhibited deficits of recent memory and/or executive function documented by neuropsychological testing and/or neurologists' findings, none of the former boxers met the core clinical diagnostic criteria for TES: II because none had a self or other informant report of cognitive or NBD symptoms.

For that same group,¹ we should explain how we determined that all 13 were independent yet 3 had dementia. The inclusion criteria for the original clinical study meant that all 13 former boxers had to be independent in their daily lives. Despite this, 3 of the retired boxers were found to have mild dementia and 1 to have impaired recent memory on clinical mental status examination. In addition, all 13 former boxers had recent memory impairments on neuropsychological testing and 9 of the 13 had abnormal executive function on written neuropsychological testing. It should also be noted that none of these 13 retired boxers met the criteria for any level of CTE provisional diagnosis because none of them met the criteria for TES.

Classification of Evidence

The primary question was how the NINDS consensus criteria for TES could be applied to historical cohorts of living retired athletes with extensive exposure to RHIs. The level of evidence is 4. Applying the criteria to these groups provided a wider view of the reliability and validity of the consensus criteria. The strength of recommendation is C.

DISCUSSION

The neuropathological consequences of RHIs are important. Evaluating the clinical manifestations of that neuropathology in living patients presents a diagnostic challenge. The NINDS TES consensus criteria link the neuropathology to the clinical picture. These criteria were developed by working backwards from neuropathologically diagnosed cases of CTE to the clinical features gleaned from postmortem interviews with family members and, in some cases, review of medical records.¹ As the consensus authors indicate, there needs to be clinical information obtained from living subjects in order to determine the validity and reliability of criteria derived in such a manner. There also is a need for data obtained from clinical histories and examinations of groups of patients at high risk of RHI in order to look at the prevalence of these TES and "CTE" criteria in exposed subjects. We utilized data from 4 historical groups of living subjects who had significant exposure to RHI to gain insights into the usefulness of the TES diagnostic criteria in their evaluation.^{1,3,6}

Our results indicate a 21.3% prevalence of TES, a 12.5% prevalence of a provisional level of possible CTE, and a 2.5% prevalence of a provisional level of probable CTE in a group of

retired athletes with extensive exposure to RHI. There is a number of possible explanations for these findings. Clinical manifestations of exposure to RHIs could occur only infrequently. Alternatively, the consensus criteria may not be sensitive enough to detect the true prevalence of clinical manifestations of RHIs. It is also possible that the neuropathology of CTE and clinical manifestations of those neuropathological findings in living persons may only be weakly linked to each other. One must also consider the possibility that the 4 groups of retired athletes examined in this analysis are not representative of all retired boxers and football players.

To help distinguish between these possibilities, we should note that the consensus criteria place a heavy emphasis on cognitive and/or psychiatric dysfunction and less on the physical signs of neurological impairment that were noted in the 1969 ex-boxers.^{4,6} Also, as noted in the results, none of the 13 retired boxers reported on in the 1984 paper met the NINDS consensus criteria for TES, even though all 13 had neuropsychological test abnormalities indicating recent memory and/or executive function dysfunction, and 3 of these had organic mental syndromes on clinical mental status testing. They did not meet the NINDS consensus criteria because to do so requires that the subject and/or family complains of cognitive/memory/behavioral dysfunction and such complaints were denied in every case. As noted previously, this might be partially related to the manner in which subjects were recruited for the study; the authors specifically sought out subjects who had no neurological or psychiatric histories and who were still actively working in the boxing community. It may also be related to a phenomenon well known to clinical neurologists, that patients with organically based cognitive impairments are often unaware of these deficits.

The results from the retired boxers' groups versus the retired football players group are consistent with the idea that the NINDS consensus criteria are heavily weighted toward the "modern" CTE of football players as opposed to the "classic" CTE of boxers. Significant differences between the patterns of chronic brain damage seen in boxers versus football players have previously been documented.² It must also be remembered that the historical groups in this analysis represent different eras. The group of retired football players can be considered to represent modern era athletes that the consensus criteria were constructed to evaluate. However, it must be noted that these "modern era" retired football players are currently (in 2022) many years away from having last played, and in the interim there have been numerous changes in the rules, the protective equipment and the ways that the game is coached and played. This may limit the applicability of these present results when using the consensus criteria to evaluate more recently retired, current and future players. The retired boxers' groups include boxers who fought in the pre and post Second World War eras. Not only are the subjects of these studies from different eras but the neuropathological definition of CTE differs between these eras. As the NINDS consensus criteria for TES are derived directly from neuropathological studies using a 21st-century

definition of CTE, it should probably not come as a surprise that they lack sensitivity when applied to RHI-exposed athletes of previous eras. The retired boxers analyzed in this study all finished their careers more than 40 years ago. There have been a number of rules and equipment changes since that time and today's boxers have fewer bouts and shorter careers than in the past; this may limit the applicability of the present results if applied to recently retired, current, and future pugilists.

Although some have claimed that the prevalence of neuropathologically diagnosed CTE increases with longer duration of football exposure,⁵ the data presented here showed no clear relationship between total years of football play, total years of boxing or total number of professional bouts (proxies for exposure to RHI), and the presence of TES or possible or probable CTE. This indicates that, regardless of the neuropathology, the clinical picture that might suggest TES or CTE is related to many factors.

All of the retired football players as well as all the retired boxers from 1984 and group A from 1969 met the inclusion criterion for TES: III; that is, none of them had another medical, neurological, or psychiatric disorder that could fully account for their clinical picture. This is most likely due to a number of factors: (1) all of those subjects were 60 years old or younger, thus younger than the ages when degenerative neurological disorders, cardiovascular disorders, etc. become more prevalent; (2) the inclusion/exclusion criteria for the retired football players and the 1984 retired boxers studies resulted in cohorts without known major neurological, psychiatric, or medical conditions; and (3) the 1969 study specifically excluded from group A 11 other cases (group B) with evidence of neurological disease “whose lesions were adequately explicable on the basis of a diagnosis which bore no relation to their boxing careers.” Group B included 2 cases with stroke, 1 case with Parkinson's disease, 1 case with chronic catatonic schizophrenia, 1 case with chronic alcoholism, 2 cases with demyelinating disease, 1 case with cervical myelopathy presumably due to cervical spondylosis, 2 cases with epilepsy, and 1 case with “severe memory deficits without evidence of extensive lesions elsewhere” in the central nervous system.⁴ As noted in the results section (see Table 1), 1 of these cases met the consensus criteria for TES and probable CTE and the case diagnosed with Parkinson's disease, although not meeting the consensus criteria, might be considered by many modern neurologists to have chronic brain damage related to boxing RHIs. These 2 cases illustrate some of the difficulties that can arise when evaluating the TES: III criterion. The consensus criterion for TES: III indicates that in order to exclude a subject from TES consideration the other condition should “fully account” for the clinical picture. Using examples from the 1969 group B, many persons will have cognitive deficits after 1 or more strokes; if such patients also meet the TES: I and TES: II criteria, how can an observer determine with any certainty whether the strokes

“fully account” for the clinical picture? The same difficulties could also arise in persons with demyelinating disease, chronic alcoholism or epilepsy who have had RHI exposure. This suggests that the definition of the TES: III criterion may require further refinement.

Limitations

A major limitation of this analysis is the absence of neuropathological data on any of the cohort groups. Post-mortem analyses of these subjects would certainly add a great deal of important data to this study. This does not seem feasible for the ex-boxers from the 1969 study⁶ as they have likely died years ago. Some of the 1984 ex-boxer cohort¹ have died and some are still alive. Most of the retired football players cohort is still alive. A future post-mortem study of the neuropathology of these subjects would be very useful in determining the reliability and validity of the consensus criteria when applied to living retired athletes. Another limitation is that the cohort groups represented here played their sports under very different rules and with different protective gear than the modern athletes for whom the consensus criteria were developed.

CONCLUSION

The reliability and validity of the consensus clinical criteria depend on the evidence from which they are derived. The NINDS consensus criteria are based on neuropathological evidence. We evaluated clinical evidence from historical cohorts of living retired athletes with extensive RHI exposure as a means of providing a wider view of the reliability and validity of the NINDS consensus criteria. The results suggest that the consensus clinical criteria derived from posthumously obtained data in cases with CTE pathology may have limited usefulness when applied to living retired athletes.

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REFERENCES

1. Casson IR, Siegel O, Sham R, Campbell EA, Tarlau M, DiDomenico A. Brain damage in modern boxers. *JAMA*. 1984;251:2663-2667.
2. Casson IR, Viano DC. Long-term neurological consequences related to boxing and American football: a review of the literature. *J Alzheimer's Dis*. 2019;69:935-952.
3. Casson IR, Viano DC, Haacke EM, Kou Z, LeStrange DG. Is there chronic brain damage in retired NFL players? Neuroradiology, neuropsychology and neurology examinations of 45 retired players. *Sports Health*. 2014;6:384-395.
4. Katz DI, Bernick C, Dodick DW, et al. National Institute of Neurological Disorders and Stroke consensus diagnostic criteria for traumatic encephalopathy syndrome. *Neurology*. 2021;96:848-863.
5. Mez J, Daneshvar DH, Abdolmohammadi B, et al. Duration of American football play and chronic traumatic encephalopathy. *Ann Neurol*. 2020;87:116-131.
6. Roberts AH. *Brain Damage in Boxers*. London: Pitman Medical Scientific Publishing Co.; 1969.