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Review Article

Traumatic encephalopathy: Review and provisional research diagnostic criteria

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Abstract.
OBJECTIVES: To determine the frequency of neurobehavioral signs and symptoms reported in every published case of traumatic encephalopathy with a view toward the development of clinical diagnostic criteria with predictive validity.
INTRODUCTION: Cases of persistent or progressive neurological or neurobehavioral change following exposure to one or more head injuries have been reported since 1928. This condition is often referred to as traumatic encephalopathy (TE). To date, however, no diagnostic criteria have been advanced or accepted for the clinical diagnosis of TE. Provisional research diagnostic criteria are required not only for meaningful diagnosis but also to facilitate research to determine the epidemiology, etiology, course, prognosis, imaging and biomarkers, neuropathological features and potentially effective treatments of TE.
METHODS: All 436 published cases of TE in all languages were reviewed. All symptoms and signs reported in these cases were classified and enumerated.
RESULTS: Ninety-seven cases met inclusion criteria based on sufficient documentation of the history and neurobehavioral examination. Provisional research diagnostic criteria for clinically probable and clinically possible TE were developed based on the most frequently reported clinical features.
CONCLUSION: The provisional diagnostic criteria for TE presented here are the first published criteria for this condition based upon a systematic analysis of its clinical characteristics. This is the first a step toward scientifically derived consensus criteria, which are essential to accelerate progress in the investigation of this important condition.

Keywords: Concussion, chronic traumatic encephalopathy, traumatic brain injury, boxing, football

1. The concept of traumatic encephalopathy

Traumatic encephalopathy (TE) has been reported using various nomenclature since Martland's report titled *Punch Drunk* in 1928 (Martland, 1928). For the next 50 years, the TE literature focused on the risk of brain damage among boxers. Reflecting that bias, Millspaugh (1937) introduced the term *dementia pugilistica* in 1937. This phrase gained backing with advances in the study of boxer's brains (Bradenburg & Hallervorden, 1945; Roberts, 1988; Rudelli, Strom, Welch, & Ambler, 1982) Other authorities have described a similar or perhaps identical disorder with other names. Parker (1934) may have been the first to publish a peer-reviewed paper referring to *traumatic encephalopathy* (TE) of pugilists. Similar terminology was employed by Grahmann and Ule (1957) ("traumatischen Boxer-Encephalopathie"), and by La Cava (1963) ("Boxer's Encephalopathy"). Critchley (1937), noting the striking tendency for gradual worsening in some cases, initially proposed the phrase *chronic progressive traumatic encephalopathy*. Critchley (1949) and Johnson (1969), noting that some cases did not progress, later proposed dropping the qualifier *progressive* and calling this condition *chronic traumatic encephalopathy* (CTE). Critchley's term CTE

has recently become popular in the literature, despite many reports suggesting that the course is more often progressive, not persistent, static, or "chronic" (e.g., Jordan, 1995; Haglund & Bergstrand, 1990; McCrory, 2002; McKee et al., 2009; Mendez, 1995). For this reason, Victoroff and Baron (2012) suggested that the label CTE misleadingly implies a particular, infrequently observed clinical course. It may be more inclusive and accurate to employ Parker's original terminology, traumatic encephalopathy (TE).

TE is typically described as a persistent or progressive alteration in neurological or neurobehavioral status that follows exposure to head injury, traumatic brain injury, or concussion. Alterations in the primary neurological examination, such as dysarthria, tremor, or gait ataxia, are often combined with alterations in behavior, including memory loss, depression, or aggression (Critchley, 1937; Grahmann & Ule, 1957; Martland, 1928; McKee et al., 2009). Most reported cases involve exposure to recurrent injuries, although some evidence suggests that a single injury may also generate this condition (McCrory, Zazryn, & Cameron, 2007; McKee et al., 2009; Rudelli, Strom, Welch, & Ambler, 1982). Moreover, since this condition has been reported in athletes whose sports involve many collisions or head blows but in whom there is no explicit history of concussion, it has been proposed that multiple subconcussive injuries can similarly harm the brain (e.g., Guskiewicz et al., 2007; McKee et al., 2009; Miller, Adamson, Pink, & Sweet, 2007; Shaw, 2002).

Neuropathological studies of TE cases have reported a variety of changes in the brainstem and cerebrum, including frequent cavum septum pellucidum, loss of neurons in the substantia nigra, locus coeruleus, and dorsal raphe, loss of Purkinje cells, and deposition of abnormal proteins typically associated with neurodegeneration, especially a patchy distribution of neocortical hyperphosphorylated 4 R/3 R tau-positive neocortical neurofibrillary tangles (NFTs) and neuropil threads, often peri-vascular and often found in the depths of sulci, typically out of proportion to diffuse (and less often neuritic) β-amyloid plaques (Corsellis, Bruton, & Freeman-Browne, 1973; Geddes, Vowles, Robinson, & Sutcliffe, 1996; Geddes, Vowles, Nicoll, & Revesz, 1999; Hof et al., 1992; Lampert & Hardman, 1984; Tokuda, Ikeda, Yanagisaw, Ihara, & Glenner, 1991). One recent report raises the possibility that trauma may also activate transactive response DNA binding protein 43 to produce a motor neuron disease (McKee et al., 2010). A putative medical narrative has emerged: exposure to repetitive concussions can cause a clinical disorder, traumatic encephalopathy (TE), which may progress to tauopathic dementia (McKee et al., 2009; Schmidt, Zhukareva, Newell, Lee, & Trojanowski, 2001).

85 years have thus passed since the first clinical description of this putative condition. Yet to date, no clinical diagnostic criteria have been adopted. Like Alzheimer's disease prior to the publication of the NINCDS-ADRDA Work Group criteria of 1984 (McKhann et al., 1984), TE has been diagnosed for decades without reference to published standards. Absent criteria for the diagnosis of clinically possible or probable TE, it is not possible for neurologists to make this diagnosis reliably, to assess the incidence, prevalence, risk factors, etiology, neuroimaging, biomarkers, or neuropathological correlates of this condition, or to design and conduct clinical trials for promising interventions. In short, diagnostic criteria are required to test hypotheses regarding TE.

In an effort to define the traumatic exposure predictors, clinical symptoms, and neurological/behavioral signs that might comprise TE, a review was conducted of all published cases that have been attributed to TE or to a synonymous condition (e.g., dementia pugilistica). This review identified all pertinent positive symptoms and signs that have been reported in cases that have been accepted in the peer-reviewed literature as exemplary of this condition. Provisional research diagnostic criteria for clinically possible and probable TE were developed based on the results of this review. The hypothesis was then tested that the proposed criteria accurately identify the subset of published cases in which (a) a medical history, a neurological examination, and a behavioral examination were all reported and (b) neuropathological examination of the whole brain ruled out most alternative diagnoses.

2. Method

A search was conducted using Ovid MEDLINE (1950–July 2010), Ovid OLDMEDLINE 1947–1965) and PsycINFO. Search terms included dementia pugilistica (KW), traumatic encephalopathy, (brain injuries (KW) or brain injury.mp or traumatic brain injury.mp or Craniocerebral trauma (KW) or head injury.mp or Brain concussion (KW) or concussion.mp) + encephalopathy, (brain injuries (KW) or brain injury.mp or traumatic brain injury.mp or Craniocerebral trauma (KW) or head injury.mp or Brain concussion (KW) or concussion.mp) + (boxing

Table 1
Sources and cases in alphabetical order by first author

Report no.	Source	Cases reported (n)	Reports meeting inclusion criteria [identification numbers]
1	Aotsuka, et al., 1990	1	1
2	Areza-Fegyveres et al., 2007	1	1
3	Bouras, Hof, Guntern, & Morrison, 1990*	1	1
4	Brandenburg & Halloverden, 1954	1	1
5	Casson, Sham, Campbell, Tarlau, & DiDomenico, 1982	4	0
6	Casson et al., 1984	1	0
7	Constantinides & Tissot, 1967*	1	1
8	Cordero Jr. & de Oliviera, 2001	1	1
9	Corsellis, Bruton, & Freeman-Browne, 1973	15	10 [Cases No. 1–4, 6–10, 13]
10	Courville, 1962	1	0
11	Critchley, 1949	7	6 [Cases B, C, D, E, F, G]
12	Critchley, 1957**	11	6 [Cases No. 2, 3, 8–11]
13	Drachman & Newell, 1999	1	1
14	Geddes, Vowles, Robinson, & Sutcliffe, 1996	1	0
15	Geddes, Vowles, Nicoll, & Revesz, 1999	5	0
16	Grahmann & Ule, 1957	4	4 [Cases No. 1–4]
17	Harvey & Newsome Davis, 1974	1	1
18	Hof, Knabe, Bovier, & Bouras, 1991	1	0
19	Hof et al., 1992	2	2 [Cases No. 2, 3]
20	Hof, Delacourte, & Bouras, 1992	6	0
21	Jedlinski, Gatarski, & Szymusik, 1970	60	0
22	Johnson, 1969	17	3 [Cases No. 1, 6, 10]
23	Jordan, 1995	1	0
24	Jordan et al., 1997	12	2 [Cases No. 5, 29]
25	Kaste et al., 1982	14	1 [Case No. 1]
26	Martland, 1928	1	1 [Case No. 2]
27	Mawdsley & Ferguson, 1963	10	9 [Cases No. 2–10]
28	McKee et al., 2009	3	3 [Cases No. A–C]
29	McKee et al., 2010	3	3 [Cases No., 1–3]
30	Neuberger, Sinton, & Denst, 1959	2	2 [Cases No. 1, 2]
31	Nowak, Smith, & Reyes, 2009	1	0
32	Omalu et al., 2005	1	0
33	Omalu et al., 2006	1	1
34	Parker, 1934	3	3 [Cases No. 1–III]
35	Payne, 1968	6	3 [Cases No. 2–4]
36	Raevuori-Nallinmaa, 1951	2	2 [Cases No. 1, 2]
37	Roberts, 1969	37	11 fully described [Cases No. 1–11]; 26 less fully described [7 cases similar to #7; 7 similar to #8; 5 similar to #9; 4 similar to #10; 3 similar to #11]
38	Roberts, Allsop, & Bruten, 1990	1	0
39	Rodriguez, Ferrillo, Montano, Rosadini, & Sannita, 1983	1	0
40	Ross, Cole, Thompson, & Kim, 1983	40	0
41	Schmidt, Zhukareva, Newell, Lee, & Trojanowski, 2001	2	0
42	Sercl & Jaros, 1962	148	0
43	Spillane, 1962[e28]	5	4 [Cases No. 1–3, 5]
44	Williams & Tannenberg, 1996[e29]	1	0
	Totals	436	109 (including all of Roberts's cases); 83 (including Roberts's best described cases)

*The same case is reported by Constantinides & Tissot, 1967; Bouras, Hof, Guntern, & Morrison, 1990 and Hof et al., 1992. **Critchley's 1949 report includes cases he also reported in 1957. 1957 cases No. 1 and 5–7 are entered only once and listed among the 1949 reports.

or football or martial arts or karate or soccer or sports), and (boxing or football or martial arts or karate or soccer or sports) + encephalopathy. All abstracts were reviewed. Articles that discussed persistent or progressive neurological or neurobehavioral changes after one or more traumatic head or brain injuries or concussions were read. Bibliographies of all articles were searched, and all relevant articles in all languages were obtained, translated, and reviewed.

151 articles and four books were reviewed. Of these, 60 articles and three books were determined to be reviews, 50 articles were scientific reports summarizing

neurological, behavioral, laboratory, neuroimaging, or neuropathological findings in populations thought to have been exposed to repetitive head injury (e.g., boxers or football players), and 42 articles and 1 book reported cases of persons exposed to one or more traumatic brain injuries or concussions followed by the development of persistent or progressive neurological or neurobehavioral dysfunction.

Table 1 lists the 43 identified articles and one book, which together report 438 cases.

The completeness of these reports varies. The following criteria were used to select case reports for enumeration of symptoms and signs:

1. Reports document probable exposure to one or more head injuries, traumatic brain injuries, concussions, or multiple subconcussive injuries, with or without documented episodes of loss of consciousness.
2. Reports document onset of persistent or progressive neurological or neurobehavioral symptoms *and* objective signs, both post-dating the traumatic exposure.
3. Cases were excluded (a) in which an acute focal brain injury (e.g., subdural hematoma) was followed by immediate neurological deterioration, then by coma, death, or recovery, (b) in which a premorbid medical condition, e.g., infarct, autism, or progressive supranuclear palsy, was considered possibly to have contributed to the observed neurological condition (e.g., Hof et al., 1992; Hof, Delacourte, & Bouras, 1992; Nowak, Smith, & Reyes, 2009), or (c) that summed symptoms or signs in a population without identifying which cases exhibited which features (Jedlinski, Gatarski, & Szymusik, 1970; Ross, Cole, Thompson, & Kim, 1983; Sercl & Jaros, 1962).
4. Roberts's (1969) case reports received special treatment. His 1969 book was included despite the fact that it was not peer-reviewed because it is the seminal treatise in this field. Roberts provides 11 complete, individual case reports. An additional 26 cases are described in less detail, although sufficient information is provided to characterize individuals by symptoms and signs. The enumeration of clinical features distinguished between the totals including Roberts's best-described 11 cases versus all 37 of his case reports.

As shown in Table 1, 25 articles and one book reporting 97 cases the met inclusion criteria – if one includes *all* those reported by Roberts (1969) – or 82 if one includes only the best-described of Roberts's case reports.

3. Results

92 of 97 cases were boxers, four were professional American football players, and one was a practitioner of karate. The gender was male in all case reports that specified gender. Descriptive statistics regarding sporting careers versus onset of symptoms are presented in Table 2.

Thirty-nine reports included information regarding the occurrence, or lack thereof, of knock-outs (KOs) or episodes of loss of consciousness (LOCs). A specific number of KOs or LOCs was reported in 27 cases. Among these, the mean number of episodes was 6.37 (range 0–60; SD = 14.42). Concussions were not reported in any of the boxing cases. Among the football cases, the number of concussions was reported as from "3 to 4" to "many."

Age of symptom onset was reported in 44/97 (45.4%) of cases. The mean onset was 36.64 years (range 19–60; SD = 11.79). The timing of symptom onset with respect to athletic career was reported only in the best-described 82 cases. Onset occurred during or at the end of the

Table 2
Demographics and career statistics

Statistic	*n*	*M* (range)	SD
Age at start of career	54	14.67 (9–21)	2.61
Age at end of career	53	30.51 (22–45)	5.42
Duration of career	51	15.45 (5–32)	6.07
Cases with delayed onset of symptoms	20	36.64 y (19–60) *M* = 14.2 years after end of career (2–42)	10.52
Age at diagnosis	56	45.38 (20–69) *M* = 15.3 years after end of career	8.04
Age at death	11	61.0 (45–80)	11.61
Estimated number of bouts	38	326.37 (60–1500)	273.68

Table 3
Symptoms and signs of TE

Clinical feature	Symptom including the most complete of Roberts's cases $N=82$ [%]	Symptom including all of Roberts's cases $n=97$ [%]	Sign including the most complete of Roberts's cases $N=82$ [%]	Sign including all of Roberts's cases = 97 [%]
Somatic complaints				
Headache	19 [23.2%]	19 [19.6%]		
Dizziness	3 [3.7%]	3 [3.1%]		
Diplopia	3 [3.7%]	3 [3.1%]		
Cranial nerves				
Gaze paresis			9 [11.0%]	9 [9.3%]
Nystagmus			12 [14.6%]	12 [12.4%]
Hearing loss	1 [1.2%]	2 [2.1%]	0	0
Tinnitus (Sx)	1 [1.2%]	1 [1.0%]		
Dysarthria	9 [11.0%]	9 [9.3%]	44 [53.7%]	70 [72.2%]
Dysphagia	5 [6.1%]	5 [5.2%]		
Slurred speech	22 [26.8%]	25 [25.8]	20 [24.4%]	32 [33.0]
Masked face			22 [26.8%]	34 [35.1%]
Titibation			6 [7.3%]	6 [6.2%]
Frontal release signs			3 [3.7%]	3 [3.1%]
Pseudobulbar affect			3 [3.7%]	3 [3.1%]
Motor				
Weakness	2 [2.4%]	2 [1.8%]	7 [8.5%]	7 [7.2%]
Muscle atrophy			2 [2.4%]	2 [2.1%]
Spasticity			7 [8.5%]	14 [14.4%]
Rigidity/stiffness	3 [3.7%]	3 [2.8%]	13 [15.9%]	13 [13.4%]
Hypertonia			9 [11.0%]	14 [13.4%]
Hemiparesis			9 [11.0%]	9 [9.3%]
Paraparesis			0	0
Drags leg (Sx)	7 [8.5]	7 [7.2%]		
Increased DTRs			29 [35.4%]	36 [37.1%]
+Babinsky reflex			18 [22.0%]	18 [18.6%]
Motor slowing	4 [4.9%]	4 [4.1%]	7 [8.5%]	7 [7.2%]
Clumsy	5 [6.1%]	5 [5.2%]	8 [9.8%]	20 [20.6%]
Tremor NOS	10 [12.2%]	10 [10.3%]	17 [20.7%]	17 [17.5%]
Tremor/rest	2 [2.4%]	2 [2.1%]	7 [8.5%]	7 [7.2%]
Tremor/intention			4 [4.9%]	4 [4.1%]
Ataxia NOS			3 [3.7%]	3 [3.1%]
Limb ataxia or dysdiadokokinesis			25 [30.5%]	25 [25.8%]
Unsteadiness NOS	7 [8.5%]	7 [7.2%]	7 [8.5%]	7 [7.2%]
Unsteady stance	3 [3.7%]	3 [3.1%]	6 [7.3%]	6 [6.2%]
Unsteady gait	4 [4.9%]	4 [4.1%]	15 [18.3%]	15 [15.5%]
Disequilibrium/Unsteadiness NOS	9 [11.0%]	21 [21.6%]	7 [8.5%]	7 [7.2%]
Imbalance	3 [3.7%]	3 [3.1%]	1 [1.2%]	1 [1.0%]
Falls	10 [12.2%]	10 [10.3%]		
Ataxic gait	3 [3.7%]	3 [3.1%]	16 [19.5%]	24 [24.7%]
Spastic gait			2 [2.4%]	2 [2.1%]
Staggering gait			9 [11.0%]	9 [9.3%]
Slow gait	1 [1.2%]	1 [1.0%]	4 [4.9%]	4 [4.1%]
Shuffling gait	2 [2.4%]	2 [2.1%]	8 [9.8%]	8 [8.2%]
Wide based gait			3 [3.7%]	3 [3.1%]
Behavior/cognitive				
Cognitive disorder NOS	3 [3.7%]	3 [3.1%]	9 [11.0%]	9 [9.3%]
Memory loss	32 [39.0%]	32 [33.0%]	47 [51.3%]	47 [48.4%]
Mental slowing	4 [4.9%]	4 [4.1%]	18 [22.0%]	19 [19.6%]
Disorientation	2 [2.4%]	2 [2.1%]	6 [7.3%]	6 [6.2%]
Visuo-spatial dysfunction/"Gets lost"	5 [6.1%]	5 [5.2%]	8 [9.8%]	8 [8.2%]
Inattention	2 [2.4%]	2 [2.1%]	1 [1.2%]	1 [1.0%]
Decreased concentration	6 [7.3%]	6 [6.2%]	4 [4.9%]	4 [4.1%]

Table 3
(*Continued*)

Clinical feature	Symptom including the most complete of Roberts's cases $N = 82$ [%]	Symptom including all of Roberts's cases $n = 97$ [%]	Sign including the most complete of Roberts's cases $N = 82$ [%]	Sign including all of Roberts's cases = 97 [%]
"Dementia"	6 [7.3%]	6 [6.2%]	13 [15.9%]	16 [16.5%]
Dysphasia			3 [3.7%]	3 [3.1%]
Dyspraxia	1 [1.2%]	1 [1.0%]	5 [6.1%]	5 [5.2%]
Hypomimia			4 [4.9%]	4 [4.1%]
Executive dysfunction (sign only)			4 [4.9%]	4 [4.1%]
Behavior/Non-cognitive				
Depression	10 [12.2%]	10 [10.3%]	12 [14.6%]	12 [12.4%]
Suicidal behavior	1 [1.2%]	1 [1.0%]		
Anxiety	6 [7.3%]	6 [6.2%]	3 [3.7%]	3 [3.1%]
Apathy	3 [3.7%]	4 [4.1%]	5 [6.1%]	7 [7.2%]
Euphoria	3 [3.7%]	3 [3.1%]	7 [8.5%]	7 [7.2%]
Hypomania	0	0	0	0
Mood lability	7 [8.5%]	7 [7.2%]	3 [3.7%]	3 [3.1%]
Lethargy	2 [2.4%]	2 [2.1%]		
Paranoia	6 [7.3%]	6 [6.2%]	7 [8.5%]	7 [7.2%]
Paranoid delusions	1 [1.2%]	2 [2.1%]	2 [2.4%]	3 [3.1%]
Jealous delusions	4 [4.9%]	4 [4.1%]	3 [3.7%]	3 [3.1%]
Persecutory delusions	0	0	1 [1.2%]	1 [1.0%]
Grandiose delusions	0	0	1 [1.2%]	1 [1.0%]
Hallucinations NOS	1 [1.2%]	1 [1.0%]		
Visual hallucinations	0	0	0	0
Auditory hallucinations	1 [1.2%]	1 [1.0%]	0	0
Disinhibition/Socially inappropriate behavior	3 [3.7%]	3 [3.1%]	2 [2.4%]	2 [2.1%]
Impulsivity	3 [3.7%]	3 [3.1%]	2 [2.4%]	2 [2.1%]
Irritability	9 [11.0%]	9 [9.3%]	4 [4.9%]	4 [4.1%]
Anger/Temper	4 [4.9%]	4 [4.1%]	2 [2.4%]	2 [2.1%]
Agitation NOS	3 [3.7%]	3 [23.1%]	4 [4.9%]	4 [4.1%]
Aggression NOS	4 [4.9%]	4 [4.1%]	3 [3.7%]	3 [3.1%]
Violence	13 [15.9%]	13 [13.4%]	3 [3.7%]	3 [3.1%]
Aggressive or violent outbursts	12 [14.6%]	13 [13.4%]	0	0
Childish	2 [2.4%]	2 [2.1%]	3 [3.7%]	3 [3.1%]
ETOH abuse or dependence	8 [9.8%]	9 [9.3%]		
ETOH sensitivity	13 [15.9%]	13 [13.4%]		
Hypersexuality	2 [2.4%]	2 [2.1%]	0	0
Epilepsy	7 [8.5%]	7 [7.2%]		
R/O Epilepsy	2 [2.4%]	2 [2.1%]		

athletic career in 36/82 (44.0%). Onset was delayed after the exposure in 21/82 (25.6%). In 20 of those cases the time could be calculated from the end of the sporting career to symptom onset: mean delay was 14.2 years (range 2–42; SD = 10.52). Even though 44% presented with symptoms during or at the end of their careers, the mean delay between symptom onset and diagnosis was 15.3 years. The course was described as *progressive* in 47/82 (57.3%), *persistent* or static without progression in 10/82 (12.2%), and *improving* in 3/82 (3.7%) of the best-described cases.

Table 3 reports the enumeration of symptoms and signs for all the selected cases. Some clinical descriptors in the case reports were recorded as symptoms, others as signs. For example, "headache" or "dizziness" were always reported as symptoms, while "gaze paresis" or "executive dysfunction" were always reported as signs. There are several exceptions. For instance, "slurred speech," "unsteady gait," or "memory loss" were reported in some cases as symptoms, in others as signs, and in others as both. In so far as practicable, verbatim transcription was employed. For example, different original reports employ the terms "spasticity," "rigidity," or "hypertonia". In the interests of fidelity, the table separately enumerates the occurrence of each term, understanding that these clinicians are perhaps

describing similar or identical signs. When the language in the original report was ambiguous, the suffix "not otherwise specified" (NOS) was added. For example, cases described as "mentally off," "mentally deficient," "confused," or "muddled" were all recorded as exhibiting "cognitive disorder NOS".

To facilitate practical analysis, several categories were collapsed. Combining symptoms and signs of "slurred speech" or "dysarthria," speech disturbance was reported in 84/97 (86.6%) of cases. Combining the symptoms and signs "tremor NOS," "resting tremor" or "intention tremor," 30/97 (30.9%) of cases exhibited tremor. Combining the symptoms of signs of "spasticity," "rigidity", or "hypertonia," 39/97 (40.2%) of cases exhibited increased muscle tone. Combining the symptoms and signs of "incoordination" "clumsy," "ataxia NOS," or "limb ataxia/dysdiadochokinesis," 45/97 (46.4%) of cases exhibited incoordination. Combining the symptoms and signs of "unsteady gait," "ataxic gait," "spastic gait," "staggering," "slow gait," "shuffling gait," and "wide based gait," 39/97 (40.2%) exhibited gait disturbance.

Memory loss was by far the most frequently reported cognitive problem. Combining symptoms and signs of "memory loss," "cognitive disorder NOS," "mental slowing," "disorientation," "visuospatial dysfunction," "dysphasia," or "dementia," 70/97 (72.2%) of cases exhibited cognitive dysfunction. Anger/aggression was the most commonly reported behavioral disturbance. "Aggressive or violent outbursts," which refers to sudden transient episodes of aggression (and may meet DSM-IV-TR criteria for Intermittent Explosive Disorder) (American Psychiatric Association, 2004), was reported in 13/97 (13.4%) of cases. Combining the symptoms or signs "anger," "aggression NOS," "violence" and "aggressive or violent outbursts," (excluding cases reported only to exhibit irritability or agitation) 32/97 (33.0%) of cases exhibited anger/aggression. Mood disturbance was the second most commonly reported behavioral problem. 19/97 (19.6%) of cases reported depression either as a symptom or a sign. Combining "depression," "euphoria," "mood lability," or "suicide attempts," 28/97 (28.9%) of cases reported mood disturbance. Combining "paranoia," "paranoid delusions," "morbid jealousy," and "jealous delusions," or "hallucinations," 21/97 (21.6%) exhibited signs of thought disorder.

In summary, the most commonly reported features of the elementary neurological examination were nystagmus, masked face, speech disturbance, increased tone, hyperreflexia, tremor, limb ataxia, and gait disturbance. The most commonly reported neurobehavioral features were cognitive impairment, aggression, mood disorder, paranoid thought disorder, and sensitivity to alcohol.

4. Provisional research diagnostic criteria

Provisional research diagnostic criteria for *clinically probable TE* and *clinically possible TE* were developed based on the frequency of clinical symptoms and signs reported in well-described TE case reports published between 1928 and 2010. Signs and symptoms were included that were reportedly present in at least 7% of cases, either in the best-described group of 82 or the well-described group of 97. Criteria for this neuropsychiatric disorder were written to be consistent with the template of the American Psychiatric Association's Diagnostic and Statistical Manuals (e.g., APA, 2004). The proposed provisional criteria are presented in Table 4.

5. Discussion

This review of all published case reports of TE in all languages was undertaken as a step toward consolidating the knowledge regarding the clinical presentation of this putative condition. The resulting enumeration indicates that headache, subjective changes in speech, altered gait, cognitive decline, mood changes, personality changes and sensitivity to alcohol are the most commonly reported symptoms in historical cases thought to represent TE, probably present in at least 15% of cases. Dysarthria, masked facies, hyperreflexia, tremor, pathological Babinsky reflex, tremor, limb ataxia, gait disturbance, and cognitive impairment are the signs most commonly observed by clinicians who regard their reports as exemplary of TE, probably present in at least 20% of cases. Most cases reported the onset of TE after exposure to multiple head injuries or concussions, although several reports described onset after a single head injury. A delay in onset after the last head trauma was common; among the subgroup whose onset was delayed, that delay typically exceeding a decade. On average, the delay from symptom onset to diagnosis exceeded 15 years. Most cases were *progressive* rather than persistent, static, or "chronic." A small proportion of cases exhibited improvement on follow-up. The provisional research diagnostic criteria that emerge from this review and enumeration are thought to represent the first scientifically based recommendations for the clinical diagnosis of TE.

Table 4
Provisional research diagnostic criteria for the diagnosis of clinically probable and clinically possible traumatic encephalopathy

A. Criterion: History	History of probable or definite exposure to one or more head injuries, traumatic brain injuries, concussions, or subconcussive brain injuries, with or without known loss of consciousness
B. Criterion: Symptoms	Onset of persistent or progressive neurological or neurobehavioral symptoms post-dating the traumatic exposure: a. Headache b. Speech changes (e.g., slurring, slowing) c. Tremor d. Deterioration in stance or gait, or falls e. Cognitive decline (e.g., memory loss, getting lost) f. Mood changes (e.g. depression, lability, or euphoria) g. Anxiety h. Paranoia i. Personality change (e.g., irritability, apathy, impulsivity, agitation, childishness, poor judgment) j. ETOH abuse or dependence k. ETOH sensitivity l. Anger or aggression (e.g., short fuse, uncharacteristic violence)
C. Criterion: Signs	Presence of objective neurological or behavioral signs: C1. Neurological signs: a. Nystagmus b. Dysarthria c. Reduced facial expression d. Hypertonia or rigidity e. Hyperreflexia f. Hemiparesis g. Tremor h. Limb ataxia (e.g., dysmetria or dysdiadokokinesis) i. Disorders of stance or gait (e.g., +Romberg, slowing, shuffling, ataxia, observed falls) C2. Neurobehavioral signs: a. Memory loss b. Other cognitive impairment (e.g., disorientation, mental slowing, confusion, visuospatial impairment, frank dementia) c. Mood disturbance (e.g., depression, lability, euphoria) d. Thought disorder (e.g., paranoia) e. Pathological personality traits (e.g., irritability, apathy, impulsivity, agitation, childishness) f. Anger or aggression
D. Criterion: Persistence	Persistence of both symptoms and signs for at least two years after the traumatic exposure
E. Criterion: No alternative diagnosis	No alternative medical or psychiatric disorder that might better account for the observed syndrome

1. The diagnosis of *clinically probable TE* requires meeting the A, D, and E criteria, as well as at least two symptoms (B criteria), and three signs (C criteria). The diagnosis of *clinically possible TE* requires meeting the A, D, and E criteria, as well as at least one symptom (B criteria), and two signs (C criteria). 2. Cases should be identified as either *acute onset* (no clear period of recovery in the 6–12 month post-concussive phase) or *delayed onset* (evidence of a functional decline after a history of recovery in the post-traumatic phase). 3. Cases should be identified as either *apparently persistent*, (signs and symptoms lasting more than 24 months), *apparently progressive*, (signs and symptoms for at least 2 years and unequivocally progressing), or *apparently improving*.

There are several limitations to this strategy. First, case report literature does not readily lend itself to quantitative analysis. Some otherwise interesting reports had to be excluded due to incomplete clinical information (e.g., Casson et al., 1984; Courville, 1962; Geddes, Vowles, Robinson, & Sutcliffe, 1996; Geddes, Vowles, Nicoll, & Revesz, 1999; Hof, Knabe, Bovier, & Bouras, 1991; Hof, Delacourte, & Bouras, 1992; Jordan, 1995). The evolving conceptualization of this condition and the quality of the reports varies too much to conclude that the proportion of published cases reporting a given feature – e.g., nystagmus – necessarily predicts the statistical likelihood that feature will occur in TE. It also seems likely that most clinicians did not entertain the possibility of an association between trauma and motor neuron disease. The 5.2–6.1% of cases with subjective dysphagia, the 7.2–8.5% of cases with objective weakness, and the 2.1–2.4% of cases with objective atrophy conceivably represent undetected cases of this suspected atypical presentation. Moreover, one faces the dilemma that the absence of data is not data supporting the absence of signs and symptoms. That is, some case reports fail to describe complaints often elicited from traumatic brain injury patients on

a modern review of systems, and/or fail to document cranial nerve findings, motor status, and cognitive or non-cognitive behavioral disorders often found on examinations of such patients. This lack of history and examination data cannot be interpreted as evidence that those persons did not complain of, for example, dizziness, tinnitus, sleep disorder, anxiety, or suicidality; nor can they be interpreted as evidence that a comprehensive neurological examination would have failed to find, for example, saccadic break-up of smooth pursuit eye movements, diminished gag reflex, fasciculations, or impulsivity. The quality of the reported evaluations has profound implications for the diagnostic validity of the proposed provisional research criteria. Clinicians seeking to determine whether patients fulfill such criteria will presumably perform complete examinations. The proposed provisional criteria are merely a starting point. As more evaluations of presumed TE cases are published by independent scholars at different centers – and once sufficient consensus has been achieved to begin clinic-pathological correlation studies – the signs and symptoms with the greatest predictive validity for the diagnosis of clinically possible, clinically probably, and pathologically definite TE will gradually evolve.

A related limitation is the emphasis, in many historical cases, on the primary neurological examination. Neuropsychiatric features frequently reported in the modern TBI literature – such as executive dysfunction, disinhibition, impulsivity, personality change, apathy, sleep disorder, anxiety, and post traumatic stress disorder (PTSD) (e.g., Ashman, Gordon, Cantor, & Hibbard, 2006; Kim et al., 2007; Rogers & Read, 2007; Vaishnavi, Rao, & Fann, 2009) – were infrequently reported in these historical reports. For example, the author has examined a number of retired National Football Players who meet these criteria for persistent or progressive TE. In addition to the behavioral problems noted above, I have noted a very high prevalence of a sleep disorder associated with vigorous physical activity or acting out of dreams (possibly a REM sleep disorder), and a surprisingly high prevalence of suicidal ideation. It is possible that the training and disciplinary orientation of the clinicians who have published most of these reports decreased the likelihood of detecting such co-morbid neuropsychiatric conditions. The fact that some features modern clinicians associate with TBI have been infrequently reported in the published cases of TE may be due to (a) reporting bias related to the disciplinary training and clinical orientation of the authors, (b) lack of resources to conduct comprehensive evaluations at some reporting centers, including neuropsychological testing or psychiatric assessment, (c) evolution in the understanding of TBI, such that the clinical community is becoming more attuned to neuropsychiatric manifestations, and, (d) the unresolved nosology of brain injury.

This latter factor represents a third challenge to the development of diagnostic criteria. At present, the neurological literature describes a suite of conceptually overlapping conditions, syndromes, or disorders, including concussion, repetitive concussion, mild traumatic brain injury (mTBI), post-concussion syndrome (PCS), TE, persistent sequelae of TBI, and post traumatic dementia. These disorders are addressed in parallel literatures that emphasize different aspects of this spectrum of post-traumatic neurobehavioral dysfunction. Many of the clinical traits of TE identified in this review are also reported in persistent PCS. The present state of the science of post-traumatic neurological dysfunction does not reveal a definitive pathophysiological difference between TE and persistent PCS. A question yet to be resolved is what operational definition should distinguish the boundaries of TE. A splitter might urge that, whether due to injury variables, innate differences in persons who are injured, or gene-environment interactions, a subset of mTBI cases exhibit an elevated risk of persistence or progression, and only such cases should be called TE. One might propose that some TBIs – whether single or recurrent, with or without loss of consciousness – precipitate a neurodegenerative cascade and others do not. Ultimately, TE may be the clinico-physiopathological explanation for the miserable minority who suffer persistent and often progressive effects. A lumper might counter that *every* brain is different after mTBI, and that observed clinical differences are a matter of type and degree within the broad spectrum of post-traumatic neurobehavioral change, all of which might reasonably be called TE.

One potential advantage of employing Parker's original term, *traumatic encephalopathy*, may be to encourage a paradigm shift toward a coherent understanding of these overlapping entities. From the moment of impact to death, victims of brain injury may exhibit neurological and psychiatric changes. TE is a useful umbrella. Seven-year-old Pop Warner football players who suffer a momentary alteration in awareness, 14-year-old hockey players knocked out for five minutes, and claiming no sequelae after a week, 22-year-old college soccer players whose heads have collided with those of others several times, and note a

diminution in their grade point averages, 30-year-old victims of motor vehicle accidents who remain in a fog eight months after the evacuation of a small subdural hematoma, and 41-year-old professional boxers or football players who were never aware of any symptoms from their multiple subconcussive injuries but who, a decade after retiring, develop early onset dementia, might all be said to suffer from an encephalopathy due to trauma. It remains to be seen whether the consensus that eventually emerges declares that all these clinical phenomena belong to a common pathophysiological spectrum, or that there are meaningfully dissociable conditions.

One acknowledges the complication of an evolving nosology. One acknowledges the fact that a given symptom or signs has been reported in a large proportion of peer-reviewed case reports cannot be regarded as evidence that symptom or sign is pathognomonic of TE. Yet a preliminary attempt such as this to enumerate the symptoms or signs most frequently reported as pertinent positives in a systematic review of published cases is a necessary first step in the development of research diagnostic criteria.

A fourth limitation of this strategy for the development of clinical diagnostic criteria – by far the greatest barrier – is the lack of gold standard neuropathological criteria for TE. Absent such a standard, one can identify cases in which there is no obvious alternative diagnosis (e.g., infarction, neoplasm, or neuroinfection), but one cannot assume that the manifold neuropathological findings published as exemplary of TE all represent a unitary diagnostic entity.

Reports of an association between cases of presumptive TE and neocortical tau suggests that, in some cases and due to yet-to-be-identified genetic risk, environmental risk, and pathophysiological processes, one of more brain injuries may initiate a cascade of events culminating in a biologically distinct progressive neurodegenerative process (e.g., Allsop, Haga, Bruton, Ishii, & Roberts, 1990; Corsellis, Bruton, & Freeman-Browne, 1973; Geddes, Vowles, Robinson, & Sutcliffe, 1996; Geddes, Vowles, Nicoll, & Revesz, 1999; Hof et al., 1992; McKee et al, 2009; Roberts, 1988; Schmidt, Zhukareva, Newell, Lee, & Trojanowski, 2001; Tokuda, Ikeda, Yanagisaw, Ihara, & Glenner, 1991). Yet the frequent observation of hyperphosphorylated tau must be balanced against other frequently observed pathological findings, including cavum septum pellucidum, substantia nigral and Purkinje cell loss, cerebrovascular changes, and deposition of amyloid-β protein – primarily in diffuse rather than in neurotic plaques – in approximately 40% of cases (Bradenburg & Hallervorden, 1954; Corsellis, Bruton, & Freeman-Browne, 1973; Geddes, Vowles, Robinson, & Sutcliffe, 1996; Geddes, Vowles, Nicoll, & Revesz, 1999; Hof et al., 1992; Lampert & Hardman, 1984; McKee et al, 2009; Schmidt, Zhukareva, Newell, Lee, & Trojanowski, 2001; Tokuda, Ikeda, Yanagisaw, Ihara, & Glenner, 1991). Pending further research, it may be premature to assume that valid neuropathological criteria for a distinct entity have been identified. Given the diversity of precipitating injuries, clinical presentations, courses, and pathological findings, it remains to be seen whether TE is best classified as a unitary environmentally-precipitated neurodegenerative tauopathy.

Thus, the neurobehavioral community faces the same Catch-22 addressed by investigators of Alzheimer's disease in decades past: until neuropathologists reach a consensus on caseness – what macro- or microscopic and/or immunocytochemical criteria distinguish TE from not-TE – it will not be possible to determine the predictive validity of clinical signs and symptoms. Yet until clinicians reach a consensus regarding caseness – what combination of history, subjective complaints, and atypicalities on objective examination or testing should be regarding as inside versus outside the spectrum of TE – neuropathologists can only speculate that the cases they elect to label TE are diagnosable in life. One predicts an iterative process (and a certain amount of academic drama) in which dialogue between clinicians and pathologists will eventually achieve a common understanding of what is and what is not TE, and whether meaningfully distinct variants occur. Simply put, until *definite* TE can be diagnosed, the sensitivity, specificity, and predictive validity of diagnostic criteria for clinically *probable* and *possible* TE cannot be tested and such criteria will remain provisional.

A fifth limitation arises from the unresolved question whether TE necessarily requires exposure to multiple brain injuries. TE is often discussed as if it were invariably a consequence of repetitive or recurrent head trauma (Courville, 1962; Geddes, Vowles, Nicoll, & Revesz, 1999; McCrory, Zazryn, & Cameron, 2007; McKee et al., 2009; Rabadi & Jordan, 2001). In fact, several lines of evidence support the notion that repetitive mild injuries produce unique neurobiological effects. Animal studies show that when the brain is recovering from one impulsive injury, viscoelastic changes, ion shifts, and transient neurometabolic crises make axons and cell bodies more vulnerable to damage from a second injury, and that repetitive

injuries produce more lasting cognitive effects than single injuries (Friess et al., 2009; Uryu et al., 2002; Yoshiyama et al., 2005). However, no *a priori* logic dictates that multiple small injuries need produce different persistent brain effects than one large injury, and, although rodent percussion research indeed suggests the additive or synergistic effect of repetitive injuries, no persuasive preclinical neurobiological evidence to date demonstrates that repetitive injuries produce a clinical or pathological condition that cannot be produced by single injuries. Moreover, many animal models of repetitive brain injury do not appear to parallel the experience of contact athletes, who may suffer one concussion in childhood and three over the course of the next twenty-five years, and then exhibit symptoms a decade later.

Nor can most animals studies examine subtle changes that might only have functional significance for humans. For example, rodent experiments will fail to detect persistent changes in verbal memory, executive function, or mood.

Preclinical studies of repetitive brain injury are usually designed to test a very different part of the temporal sequence, for instance, determining whether a window of vulnerability to second impact occurs during the period of measurably reduced cerebral blood flow or glucose metabolic rate – about three to ten days (e.g., Longhi et al., 2005). Moreover, as Roberts et al. (1991) stated, "Previous reports suggested that both repetitive head trauma and a single injury can be associated with the presence of diffuse beta A4 amyloid protein plaques in long-term survivors." The same paper reported that extensive deposition of amyloid-β can occur within days of injury. Other reports have been published in which TE has apparently resulted from a single bout of boxing (e.g., Critchley, 1937; Kremer, Russell, & Ge, 1947) and in which progressive neurodegeneration has followed a single TBI (Rudelli, Strom, Welch, & Ambler, 1982). Therefore, at this early stage in the evolution of diagnostic criteria, it seems prudent to include cases in which neurological and behavioral problems persist or progress after single injuries.

It is not important that the provisional research diagnostic criteria proposed here gain broad acceptance. It is, however important that *some* operational clinical criteria gain acceptance, or (a) no two clinicians diagnosing TE will necessarily be referring to comparable cases, (b) little progress can be made in determining the correlation between what pathologists call TE and the various syndromes clinicians encounter, and, (c) more important than nosological debates or even advancement in understanding of the molecular pathology of neurodegeneration – one does not have a scientific basis for advising the hundreds of millions of people who participate in contact sports.

While American football is the most common cause of concussion among U.S. athletes, the game that North Americans call soccer probably creates a much greater global risk, since an estimated 100 million people play. Whatever the sport, players, coaches, athletic trainers, and parents are routinely confronted with decisions regarding (a) whether to play (primary prevention) or "return to play" (RTP) (secondary prevention). Should seven year olds ever play tackle football? Should headgear be obligatory in high-school soccer? For how long should a given person who suffers a concussion avoid participating in the game that caused that concussion?

Numerous RTP guidelines have been advanced by various well-meaning groups, such as the Consensus Statement on Concussion in Sport from the 3rd International Conference on Concussion in Sport (McCrory et al., 2009), or the American Academy of Neurology (Quality Standards Subcommittee of the American Academy of Neurology; 1997; American Academy of Neurology, 2010). The proposals for type of assessment, testing protocol, period of rest, and readiness to return are derived by inference from preclinical investigations and from a very small body of human concussion research with short-term follow-up. In terms of mitigating the risk of persistent or progressive TE (that is, a post-concussion syndrome present more than two years after the last concussion), no prospective longitudinal controlled study comparing RTP protocols has ever demonstrated either that one such protocol is better than another or, in fact, that any protocol is better than no protocol. Moreover, most of the proposed periods of rest before return to play are expressed in days or weeks, or tied to a "neurological examination." Evidence suggests that amateur boxers, even without specific histories of concussion, exhibit elevated neuron specific enolase two months after their last bout (Zetterberg, Tanriverdi, Unluhizarci, Selcuklu, Kelestimur, & Blennow, 2009). Moreover, persons who suffer a concussion yet exhibit normal cognitive performance have been shown to have impaired cerebral efficiency a year later, detectible with cognitive testing monitored with functional magnetic resonance imaging (Chen, Johnston, Frey, Petrides, Worsley, & Ptitoa, 2004). Thus, after a concussion, many people may have both persistent brain damage and persistent vulnerability to repeat injury, neither of which is detectible by the most rig-

orous combined neurological and neuropsychological examination. The persistence and progression of this disease may be occult. If so, what is the value of current RTP testing protocols? Indeed, given the accumulating evidence that repetitive injuries have an insidious effect on the brain, inapparent to the athlete and to those who examine him in the days, months and years following injury, return to play is perhaps better conceptualized as return to risk. Clinical diagnostic criteria for TE are an essential first step toward conducting the required studies required to generate evidence-based rationale for return to risk, non-return, or primary prevention, because, for the first time, investigators will have a outcome variable – the presence or absence of a diagnosable clinical condition.

Provisional research diagnostic criteria for TE should allow clinicians to focus on this significant subset of TBI victims, and hopefully accelerate the understanding of this important condition.

Declaration of interest

The author is one of six U.S. neurologists to whom the National Football League refers patients in the NFL Neurological Care Program. This program is unfunded. Otherwise, the author has no interest in any enterprise related to the subject matter of this paper.

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