The long road to in vivo diagnosis of chronic traumatic encephalopathy

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This scientific commentary refers to ‘Symptoms of traumatic encephalopathy syndrome are common in the United States general population’, by Iverson and Gardner (https://doi.org/10.1093/braincomms/fcab001).

Chronic traumatic encephalopathy (CTE) is a tauopathy that has been associated with repetitive head injury (RHI) and can be diagnosed only by post-mortem neuropathological examination. CTE is of tremendous public health concern: its proposed aetiologies [traumatic brain injury (TBI), contact sport participation, military service, domestic violence] are common, and its reported consequences [a progressive neurodegenerative disease termed traumatic encephalopathy syndrome (TES)] are devastating. As such, the quest to identify criteria for diagnosis during life has unfolded with great urgency alongside the development and refinement (Bieniek et al., 2021) of consensus neuropathological criteria for CTE.

In the current issue of Brain Communications, Iverson and Gardner (2021) examine the prevalence of symptoms that comprise the Montenigro et al. (2014) research diagnostic criteria for TES in a nationally representative sample of adults in the USA. This is the third in a series of studies from this team that apply TES criteria to the National Comorbidity Survey Replication data, and the first to include women. The authors demonstrate the high potential for inaccurate diagnosis of TES in adults, particularly those who report other mental health conditions that may have no relationship with prior head trauma or CTE neuropathology. In their very liberal application of these criteria to the National Comorbidity Survey Replication data, the authors use empirical satire to illustrate the absurdity of allowing psychosocial problems as multi-determined as substance use disorder, bankruptcy or divorce to satisfy criteria for a purported neurological disease. They report that about 6–12% of the US population, and up to almost 90% of those in some clinical samples, report symptoms of TES (Iverson and Gardner, 2021) based on the Montenigro criteria (Montenigro et al., 2014).

One might argue that this study does little more than demonstrate that the criteria are too broad—which we already knew. A phased approach to in vivo diagnosis, in which intentionally broad criteria are refined through further study, is precisely what Montenigro et al. (2014) prescribed. However, this study has taken on a challenge that few others have: they have begun the much-needed work of examining published TES criteria in unselected samples.

The process of applying diagnostic criteria to existing data is far from straightforward: it requires multiple subjective decisions about which reasonable people will disagree. All published TES diagnostic systems were based on retrospectively reported qualitative descriptions of individuals who were presumed or later found to have CTE neuropathology. These informants’ observations were then translated into diagnostic algorithms. To evaluate these criteria in research studies, decisions must be made about how to operationalize each criterion using...
available data. It is therefore the investigators’ discretion that determines the cut-points on psychometric scales, or the responses to single items, which are sufficient to meet a given criterion. These decisions will differ across each study, as will the reported rates of TES.

There is an inherent obstacle to validating diagnostic criteria when the external criterion, the gold standard, is unknowable until death. A central assumption underlying the proposed TES diagnostic criteria is that TES is caused by CTE neuropathology. The developers of these criteria did not intend to simply name a constellation of co-occurring clinical symptoms of diverse aetiologies, they set out to characterize the observable clinical manifestations of an underlying pathological process. The goal in refining these criteria is to isolate the core clinical features of the neurological disease that results from an accumulation of CTE pathognomonic lesions, if a pure clinical correlate of this pathology in fact exists. The presence and contribution of other pathologies that commonly co-occur with the pathognomonic lesions of CTE have therefore been largely disregarded in the development of current TES criteria to date. To further complicate matters, we are chasing a moving target: as CTE criteria have evolved to become more stringent, many of the cases upon which TES criteria were based would no longer qualify for a CTE diagnosis. The implications of recent modifications to CTE diagnostic criteria (Bieniek et al., 2021) for ongoing efforts to define TES cannot be understated. These challenges are not unique to CTE or TES; it is well known that the relationship of clinical symptoms with post-mortem pathology is complex even in the most extensively characterized neurodegenerative diseases (Power et al., 2018). The nature and strength of the association between clinical features of post-traumatic neurodegeneration and CTE neuropathology remain to be seen.

If TES represents the clinical expression of CTE neuropathology (irrespective of head trauma exposure), studies that have applied CTE diagnostic criteria to various autopsy cohorts can help inform expected TES rates across samples. Few studies have applied CTE criteria to samples unselected for head trauma exposure [reporting rates from 0 (Forrest et al., 2019) to 35% (Noy et al., 2016)], or even to groups with RHI other than former American football players (in whom up to 87% had CTE neuropathology; Mez et al., 2017). Multiple pathological processes in addition to CTE lesions were described in many cases, and some studies (e.g. Noy et al., 2016) report CTE in cases with single TBI and in those with no documented head trauma. Few cases of CTE have been reported in women, which stands in stark contrast to the TES symptom rates reported in women with chronic pain and mood disorder (Iverson and Gardner, 2021). Each of these post-mortem studies used different selection criteria and applied different sampling methods and CTE diagnostic criteria, and rates of CTE vary accordingly. Application of the revised CTE diagnostic criteria (Bieniek et al., 2021) to diverse autopsy cohorts will provide much-needed guidance about the rates of isolated CTE and CTE concurrent with other pathologies in high-risk and unselected samples.

Another important assumption is that CTE, and therefore TES, results from RHI. Rates of TES could therefore be no higher, and in fact must be considerably lower, than the rates of exposure in a given sample. Evidence suggests that 10% of US adults served in the military (United States Census Bureau, 2007), 73% played sports of some type (NPR et al., 2015) and 50–92% of the ~30% of women who experienced intimate partner violence sustain single TBI and/or RHI (Esopenko et al., 2021). Rates of TBI and RHI are particularly high in other subgroups, such as those who are homeless, involved in the criminal justice system or seeking treatment for substance abuse (Dams-O’Connor et al., 2014). Montenigro suggested four mild TBIs, two moderate-severe TBIs and/or repetitive subconcussive trauma (Montenigro et al., 2014) as a minimum exposure threshold for TES diagnosis; population estimates suggest more than 20% of non-institutionalized adults have sustained at least one TBI with loss of consciousness, and 8% have sustained two or more TBIs with loss of consciousness (Yi et al., 2018). We know, though dominating narratives invite us to forget, that most people who have sustained a TBI, played sports or served in the military, will not experience symptoms characterized by progressive decline, and therefore would not meet criteria for TES. Ultimately, it will be important to determine whether and with what frequency the same constellation of clinical symptoms associated with RHI-related neuropathology (i.e. TES) are found in those with single TBI or in unexposed individuals, with or without CTE neuropathology. As we await the maturation of prospective TBI studies with autopsy endpoints (Edlow et al., 2018), this work can and should be conducted in existing clinical datasets. Absent information about head trauma exposure in the National Comorbidity Survey Replication, the current study (Iverson and Gardner, 2021) is not able to compare the rates of TES across exposure subgroups and controls. Given the centrality of the questions pertaining to the role of head trauma in both CTE and TES, future studies investigating TES should be conducted in datasets that contain detailed information about lifetime TBI and RHI exposure.

Iverson and Gardner (2021) clearly demonstrate that TES rates will vary considerably depending on the data available and how the criteria are interpreted and applied. The same is true for CTE neuropathology, as those criteria continue to be refined. The assumptions underlying and motivating our ongoing efforts to define TES, together with the challenges to those assumptions, reflect the current state of knowledge in a rapidly evolving field. The scientific community should therefore be encouraged to publish detailed methods and results of studies applying TES criteria in research datasets with...
unprecedented transparency. Minimum methodological reporting requirements for TES studies include a clear description of how the sample was recruited, selected and retained, in addition to a detailed description of exactly how TES criteria were applied: the specific measures, items and responses that were required to meet each criterion. Researchers should share their rationale for these thoughtful decisions, present results based on multiple interpretations of the criteria, and whenever possible present findings in samples stratified by clinical subgroups, exposure patterns, and by sex. Scientific journals should be encouraged to publish novel findings, and their replications, with equal alacrity as criteria are examined and refined across diverse cohorts and datasets. Iverson and Gardner (2021) have provided a blueprint for the level of transparency required to facilitate replication and comparison. Those who question the methods or conclusions of their paper should be encouraged to contribute to this important body of work, just as they have.

The current paper will undoubtedly inform the lens through which the scientific community receives the empirically informed, consensus-based research diagnostic criteria for TES that will be introduced in early 2021. The National Institutes of Health/National Institute of Neurological Disorders and Stroke supported a consensus workshop to define research diagnostic criteria for TES, defined as the clinical disorder associated with neuropathologically diagnosed CTE. The revised research consensus criteria for TES are the result of the brave inclusion of experts with widely divergent perspectives on how and whether TES diagnostic criteria should be developed. Concerns similar to those raised by Iverson and Gardner (2021) posed a major obstacle to consensus development, but a Delphi process ultimately facilitated the formation of carefully revised TES research criteria. Until the risk of misdiagnosis illustrated by Iverson and Gardner (2021) can be substantially reduced, it is entirely premature to diagnose individual patients with a potentially devastating neurodegenerative disease about which so little is known. That said, our sincere hope is that the new consensus-based TES criteria will be widely tested and further improved to permit accurate in vivo diagnosis and development of disease-modifying therapies. Achieving this goal will require interdisciplinary collaboration, data sharing and open discourse that prioritizes the advancement of science—the ultimate goal of which is to benefit the millions of individuals across the world who are living with chronic symptoms of brain injury.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed.

Competing interests

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