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ORIGINAL ARTICLE

Evaluation of the specificity of the central diagnostic criterion for chronic traumatic encephalopathy

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Abstract

Introduction Chronic traumatic encephalopathy (CTE) is a postmortem diagnosis. Consensus postmortem, but not antemortem, diagnostic criteria have been established. A key factor in these criteria is evidence of phosphorylated-tau (p-tau) around sulcal vessels in the cortex. However, this sign has been observed anecdotally in a diverse range of neurodegenerative diseases (NDD). We therefore hypothesise that this criterion may lack specificity.

Methods To test this, we assessed patients with NDD, but no documented history of brain trauma, for sulcal p-tau. Tissue was retrieved from Dublin Brain Bank (known NDD n = 17; control with no diagnosed NDD n = 6; CTE n = 1), and slides were prepared from three sites with a predilection for trauma: superior frontal gyrus, temporal pole, and superior temporal gyrus. We stained the resulting anonymised slides with both hemotoxylin and eosin (H&E) and p-tau. Three neuropathologists, blinded to the clinical history and neuropathological diagnosis in each instance, evaluated each case for sulcal p-tau. We calculated the interrater agreement, using Fleiss's kappa, and the specificity of this neuropathological sign.

Results Sulcal p-tau was highly specific to diagnosed CTE cases (specificity 0.98), with moderate interrater agreement ($\kappa = 0.45$).

Conclusion In conclusion, therefore, we observed sulcal p-tau to be a sign highly specific to CTE when compared with NDD cases in the absence of head trauma.

Keywords Chronic traumatic encephalopathy · Hyper-phosphorylated tau · Specificity · Sulcal vessel

Introduction

Chronic traumatic encephalopathy (CTE) has been described as a progressive neurodegenerative disorder associated with repetitive brain injury (RBI), characterised by accumulation of hyperphosphorylated-tau (p-tau) in the brain [1]. It has been linked with contact sports at both an amateur and professional level [2], and possible links have been proposed with exposure to military blast injury [3]. Although all neuropathologically confirmed cases of CTE have had exposure to RBI, RBI does not guarantee that a patient will develop CTE [4].

Consensus antemortem diagnostic criteria for the diagnosis of CTE have not yet been accepted, but repeated episodes of concussion are alleged to be linked to the subsequent development of CTE [5]. Whilst there seems to be no doubt that concussion is damaging [6], there is no direct causal link between concussion and CTE. Two recent studies on elite rugby and ice hockey players found no significant ill effects in the cohorts of patients, despite repeated episodes of concussion [7, 8]. A review of all published cases of CTE in 2015 found that the neuropathological and clinical findings overlapped with many common neurodegenerative diseases [9]. Furthermore, histological evidence of CTE has been observed in a large series of neurodegenerative diseases [10].

Since the diagnosis of CTE is based on neuropathology, it has been suggested that we should be more critical of the reliability and validity of neuropathological diagnosis [11]. A central diagnostic criterion for CTE is evidence of hyperphosphorylated-tau (p-tau) irregularly deposited in neurons and astroglia around cortical sulcal vessels [12]. The discriminative capacity of this sign was validated in 2015, as a NINDS/NIBIB panel study reported good agreement between members as to the presence of p-tau around sulcal

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vessels in CTE cases, marking a step towards a set of validated diagnostic criteria for CTE [13]. Our aim in this study was to ascertain whether p-tau desposition around sulcal vessels is specific for the neuropathological diagnosis of CTE.

Materials and methods

We evaluated brains from patients with a NDD or healthy controls, using cases stored in the Dublin Brain Bank. At the time of donation, an autopsy is conducted and a neuropathological diagnosis is made; cases are categorised by these final neuropathological diagnoses. Amongst the neurodegenerative conditions evaluated, we excluded any patients with either a history of head injury or epileptic seizure [14].

In each case, we prepared slides from three sites which have a predilection for traumatic injuries—the temporal pole, superior temporal gyrus, and superior frontal gyrus. We stained the resulting slides with both hemotoxylin and eosin (H&E) and p-tau (Innogen BR-003, Clone AT8). Staining for p-tau was performed on the Bond III system (dilution 1/2000, protocol F).

The prepared slides had no identifiable features, other than a study reference number, to prevent rater bias. Three consultant neuropathologists, trained through Royal College of Pathologists in Ireland, evaluated each anonymised slide and recorded whether they could detect p-tau around a sulcal vessel in each instance. Instructions were issued as per McKee et al. [13]. Evidence of foci of positive p-tau staining proximal to the adventitia of any visible sulcal vessel was considered a positive result, regardless of its presence or absence around other visible vessels.

To determine the level of agreement between raters, we calculated Fleiss's kappa using the 'IRR' package [15]. We calculated Fleiss's kappa, rather than the more commonly reported Cohen's kappa, as there were three raters, and this approach has been demonstrated to be more germane in such instances of multiple raters [16]. Subsequently, the specificity of this neuropathological sign was investigated using a 'confusion matrix', in the 'caret' package [17]. All statistical analyses were performed using the R software package version 3.4.3 [18].

Results

We studied 23 brains from the Dublin Brain Bank: 17 with a known NDD (Alzheimer's disease $n = 6$; diffuse Lewy body disease $n = 3$; motor neuron disease $n = 3$; fronto-temporal lobar degeneration $n = 4$; vascular dementia $n = 1$), five healthy controls, and one CTE case. Table 1 summarises the demographic and clinical details of the cases included.

We found the presence of hyperphosphorylated tau to be highly specific for CTE (specificity: 0.98) (Fig. 1). There was a moderate level of inter-rater agreement ($\kappa = 0.44$) on the presence of this neuropathological sign, despite the omission of a rater training period. There were no cases in either a neurodegenerative disorder or a healthy control in which all three raters concurred on the presence of p-tau around a sulcal vessel.

Inter-rater consensus varied to the greatest extent in cases of NDD (see Table 2). The three raters disagreed on: 29% of samples in the control group; 50% of samples from patients with Alzheimer's disease; 33% of samples from patients with vascular dementia. There was consensus between two raters on one slide from the CTE case, whilst the third rater differed on this slide alone, i.e. there was complete agreement in the other two slides amongst all three raters. We also observed complete agreement between raters in samples from patients with motor neuron disease, diffuse Lewy body disease, and fronto-temporal lobar degeneration.

Discussion

We observed that p-tau around a sulcal vessel is a neuropathological sign that is highly specific to chronic traumatic encephalopathy, supporting the use of this finding as a central diagnostic criterion. Furthermore, in contrast to anecdotal reports, and our initial hypothesis, we did not consistently observe this sign in other neurological conditions in the absence of head injury. This further emphasises the diagnostic utility of p-tau around a sulcal vessel in suspected cases of CTE.

Whilst one might argue that the finding of p-tau around a sulcal vessel has been clearly described by McKee et al. [13], many other studies assessing the validity of this diagnostic marker have compared patients with CTE to healthy controls [19, 20]. Therefore, we believe that our independent validation of the findings is of importance as a demonstration of the reproducibility of the findings, which may be absent in some studies [21].

The presence of p-tau around a sulcal vessel as a diagnostic marker for CTE has been clearly described by McKee et al. [13], as well as having been previously described by various independent groups in both human CTE patients and animal models [19, 22, 23]. However, as the NINDS/NIBIB consensus meeting represents the current 'gold standard' for neuropathological diagnostic criteria for CTE, we believe that our independent validation of these findings is of importance as a further demonstration of their reproducibility [21].

Although these findings support the use of p-tau as a diagnostic criterion for CTE, it may still be valuable to further investigate the anecdotal observations of sulcal p-tau in non-CTE patients. It may therefore be of interest to repeat the study in samples from patients who had both NDD and a history of head injury, especially those disorders which have been linked to head injury, such as motor neuron disease, Parkinson's disease, and Alzheimer's disease [24–27]. Similar findings

Table 1 Demographic composition of the neurological states represented in the study

Diagnosis	Number of cases	Mean age at death (± standard deviation)	Sex	History of head trauma recorded
Neurologically normal (control)	$n = 5$	66 ± 22.93	M = 4 F = 1	No
Diffuse Lewy body disease	$n = 3$	69.67 ± 6.65	M = 3 F = 0	No
Alzheimer's dementia	$n = 6$	70.67 ± 8.30	M = 4 F = 2	No
Motor neuron disease	$n = 3$	69.67 ± 4.92	M = 1 F = 2	No
Fronto-temporal lobar degeneration	$n = 4$	71.25 ± 7.15	M = 2 F = 2	No
Vascular dementia	$n = 1$	88 ± 0	M = 1 F = 0	No
Chronic traumatic encephalopathy	$n = 1$	58 ± 0	M = 1 F = 0	Yes

would corroborate the use of this sign as a diagnostic criterion for CTE; a correlation between head injury and sulcal p-tau would suggest that the sign may be linked with head trauma rather than with CTE specifically, particularly, as recent evidence suggests that it is the impact, rather than concussive injury, that leads to CTE [28]. As CTE presently lacks validated clinical diagnostic criteria, a precise understanding of the neuropathological signs is highly important for accurate postmortem diagnosis, which may in turn lead to refined diagnosis of this syndrome antemortem.

The specificity was calculated by taking the average of the three raters for each sample. Therefore, whilst this sign was found to be highly specific, it may be of note that this study achieved only moderate agreement between raters, and that inter-rater disagreement varied between different NDD. In developing further studies, it would be valuable to consider whether more precise instructions, or the inclusion of printed example cases for reference, would achieve greater agreement. It is noteworthy that this present study did not include a training period for the raters, in contrast to the study by McKee et al., which may account for the discrepancy in κ-values. Improved inter-rater agreement is essential if future studies are to investigate the sensitivity of sulcal p-tau as a sign of CTE.

One of the greatest difficulties in the management of CTE is that the diagnosis can only be confirmed at postmortem examination, even in cases where there is a high index of clinical suspicion. There is a clear need for the identification

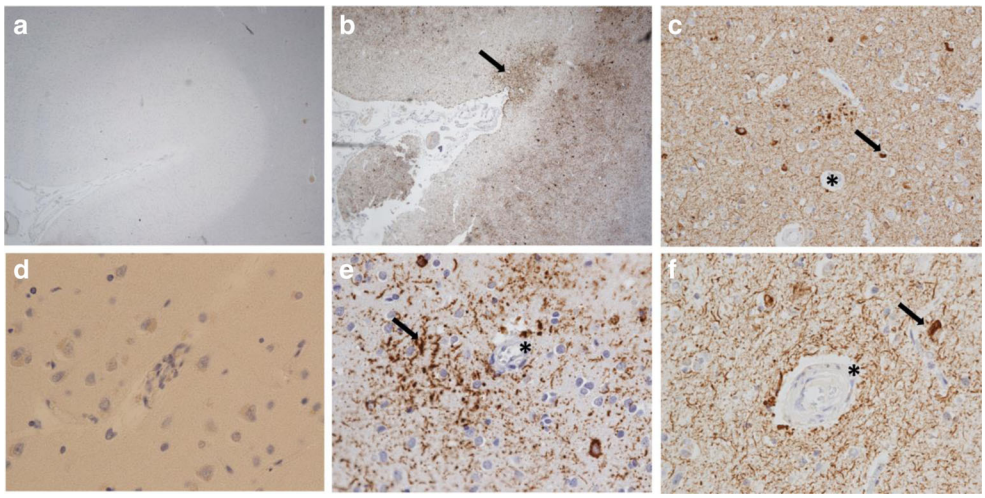

Fig. 1 Presence and absence of p-tau around vessels at depth of sulcus. **a** Neurologically healthy patient, low power. **b** Patient with CTE, low power. **c** Patient with disputed sulcal p-tau and AD, medium power. **d** Neurologically healthy patient, medium power. **e** Patient with CTE, high power, demonstrating that the observed phosphorylated *tau* is co-localised with a sulcal vessel. **f** Patient with disputed sulcal *tau* and AD, high power; in contrast to the CTE case, in image (**e**), the *tau* deposition is distant from the sulcal vessel and, therefore, does not fulfil the diagnostic criterion for a CTE diagnosis. Arrows indicate positive p-tau staining, whilst asterisks denote sulcal vessels. Low power images were taken at a magnification of × 4, whilst medium power images were taken at a magnification of × 10. All images taken from superior frontal gyrusggih

Table 2 Inter-rater consensus on sample evaluation for the presence of p-tau staining of neurons or glia around cortical sulcal vessels

		p-tau absent	p-tau present	p-tau disputed
Alzheimer's disease	Superior frontal cortex ($n = 5$)	2	0	4
$n = 6$	Temporal pole ($n = 6$)	3	0	2
	Superior temporal gyrus ($n = 6$)	4	0	1
Fronto-temporal lobar degeneration	Superior frontal cortex ($n = 4$)	4	0	0
$n = 4$	Temporal pole ($n = 4$)	4	0	0
	Superior frontal gyrus ($n = 2$)	2	0	0
Diffuse Lewy body disease	Superior frontal cortex ($n = 3$)	3	0	0
$n = 3$	Temporal pole ($n = 1$)	1	0	0
	Superior frontal gyrus ($n = 1$)	1	0	0
Motor neuron disease	Superior frontal cortex ($n = 3$)	3	0	0
$n = 3$	Temporal pole ($n = 3$)	3	0	0
	Superior frontal gyrus ($n = 3$)	3	0	0
Vascular dementia	Superior frontal cortex ($n = 1$)	0	0	1
$n = 1$	Temporal pole ($n = 1$)	1	0	0
	Superior frontal gyrus ($n = 1$)	1	0	0
Chronic traumatic encephalopathy	Superior frontal cortex ($n = 1$)	1	0	0
$n = 1$	Temporal pole ($n = 1$)	1	0	0
	Superior frontal gyrus ($n = 1$)	0	0	1
No neurological disorder	Superior frontal cortex ($n = 5$)	3	0	2
$n = 5$	Temporal pole ($n = 5$)	3	1	1
	Superior frontal gyrus ($n = 4$)	3	0	1

of neurological signs which could be detected in vivo. Early-stage PET scans for FDDNP, a tau-sensitive brain imaging ligand, suggest that this technique may be able to detect CTE in living individuals with varying degrees of symptomatology [29, 30]. Additionally, application of tract-based spatial statistics to the diffusion tensor has been used to report microstructural abnormalities in white matter tracts in athletes who have suffered concussion [31]. These data are in contrast to conventional MRI brain scans, which are typically normal following a concussive injury. A set of rigorous neuropathological diagnostic criteria would facilitate confirmation and refinement of these techniques over long-term studies, validating their clinical use and allowing for earlier, more confident diagnoses.

Certain limitations must be considered in interpretation of the results of this study. Firstly, certain tissue types are underrepresented. As the Dublin Brain Bank collection represents a sample of convenience—that is, those individuals who choose to donate their brain to medical research—it does not strictly reflect the incidence of neurological disorders in the general populations, and so, some conditions are poorly represented. After applying the exclusion criteria, this meant that some disorders (such as vascular dementia) were reduced to a single patient. For purposes of direct comparison, it would have been preferable to match for age and gender across different groups; however, the samples represented in the brain bank meant this was not possible for this study. This could be addressed in a future study, with different inclusion criteria, so that the relationship between head trauma and p-tau could be explored in a range of neurodegenerative diseases with appropriately matched comparisons. Secondly, for the above reasons, this present study included a single CTE case; a positive control group comprised of multiple CTE cases would have been more statistically powerful and would have facilitated an assessment of the sensitivity of this sign. Although the time it would take to accumulate such a cohort cannot reliably be predicted, it is hoped that growing public awareness of the neurological sequelae of head injuries may encourage patients and families to consider brain donation. Lastly, whilst factors such as a training period may have improved the inter-rater agreement, we must also consider that over longer-term studies, as more data are accrued, an automated approach through application of machine learning using an algorithm, such as a convolutional neural network may provide a higher level of agreement between centres, a prospect which could be explored through examination of electronic images recorded in cases of suspected CTE [32].

CTE remains difficult to diagnose antemortem. Therefore, accurate neuropathological diagnosis is a sine qua non to fully elucidate the aetiology of this condition. These data suggest that the central criterion of p-tau around a sulcal vessel is highly specific in the absence of head trauma; however,

further research is required to investigate the relationship between head trauma and sulcal p-tau, and to assess the sensitivity of this sign.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was conducted using human tissue sampled posthumously as part of the ongoing biobanking project at Dublin Brain Bank.

Informed consent Informed consent was obtained from the next-of-kin of all individual participants included in the study.

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