

Practical Considerations in the Diagnosis of Mild Chronic Traumatic Encephalopathy and Distinction From Age-Related Tau Astrogliopathy

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To the Editor:

In volume 78, No. 7, July 2019 of the *Journal of Neuropathology and Experimental Neurology*, Iverson, Luoto, Karhunen, and Castellani report mild changes of chronic traumatic encephalopathy (CTE) in 6 of 8 men who were autopsied as part of the Tampere Sudden Death Study in Tampere, Finland (1). The men were middle-aged or older at the time of death, range 56–82 years, mean 71. Through a family health survey, none were determined to have a history of contact or collision sports participation, although 2 had a history of traumatic brain injury (TBI) documented in their medical records. Neuropathological examination performed by a single neuropathologist (R.J.C.) found that 6 of the 8 cases (75%) had “sparse” “pathognomonic lesions” of CTE defined as “p-tau in neurons, astrocytes, and cell processes around small blood vessels in an irregular pattern at the depths of the cortical sulci.” The authors presented representative images of the “pathognomonic CTE lesion” in their cases as their Figure 1 (1), as well as other diagnostic features of CTE as their Figures 2 and 3 (1). The authors concluded that 5 of 6 cases with no known history of brain trauma appeared to meet consensus criteria for CTE (2), and

suggested that the study “adds to the emerging literature indicating that CTE pathology is present in people not known to have experienced multiple concussions or subconcussive blows to the head.”

We respectfully disagree with their conclusions and, for the reasons outlined below, believe the authors have mistaken nonspecific hyperphosphorylated tau (p-tau) pathology and/or aging-related tau astrogliopathy (ARTAG) (3–7) for diagnostic CTE pathology (1).

The images provided for Case 1 (their Figure 1) show subpial astrocytic p-tau pathology at the sulcal depth with scattered sparse neurofibrillary tangles (NFTs) and neurites in the deeper cortical layers. Subpial astrocytic p-tau, which often involves thorn-shaped astrocytes or TSA, is a form of ARTAG (3–6). Subpial p-tau pathology may be found in CTE as a supportive feature, but in isolation, it is nondiagnostic for CTE (2). The images provided for Cases 2, 3, 6, and 7 show a sparse distribution of p-tau pathology in the form of neurites and sparse NFTs in brain regions containing a blood vessel; however, in the supplied images, there is no accentuation of p-tau pathology around the vessel or focal vasculocentricity of the neurites, as occurs in CTE. Instead, the p-tau

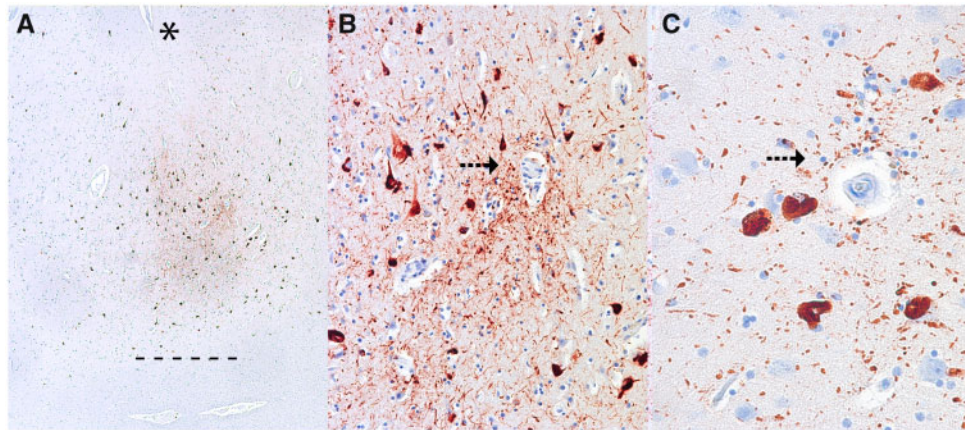


FIGURE 1 Representative images of the pathognomonic perivascular lesion of chronic traumatic encephalopathy. Ten- μ m paraffin-embedded tissue sections immunostained for phosphorylated tau (AT8) (Pierce Endogen). **(A)** Shows several perivascular clusters of p-tau-positive NFTs and neurites at the depths of the sulcus. Magnification: $\times 40$. The depth of the sulcus is indicated with an asterisk (*), the junction between gray and white matter is demarcated as a series of short lines (-). **(B, C)** There is markedly increased density of dotlike p-tau immunoreactive neurites surrounding the vessel wall (arrows) and the surrounding NFTs show clear vasulocentricity. Magnifications: **B**, $\times 200$, **C**, $\times 400$.

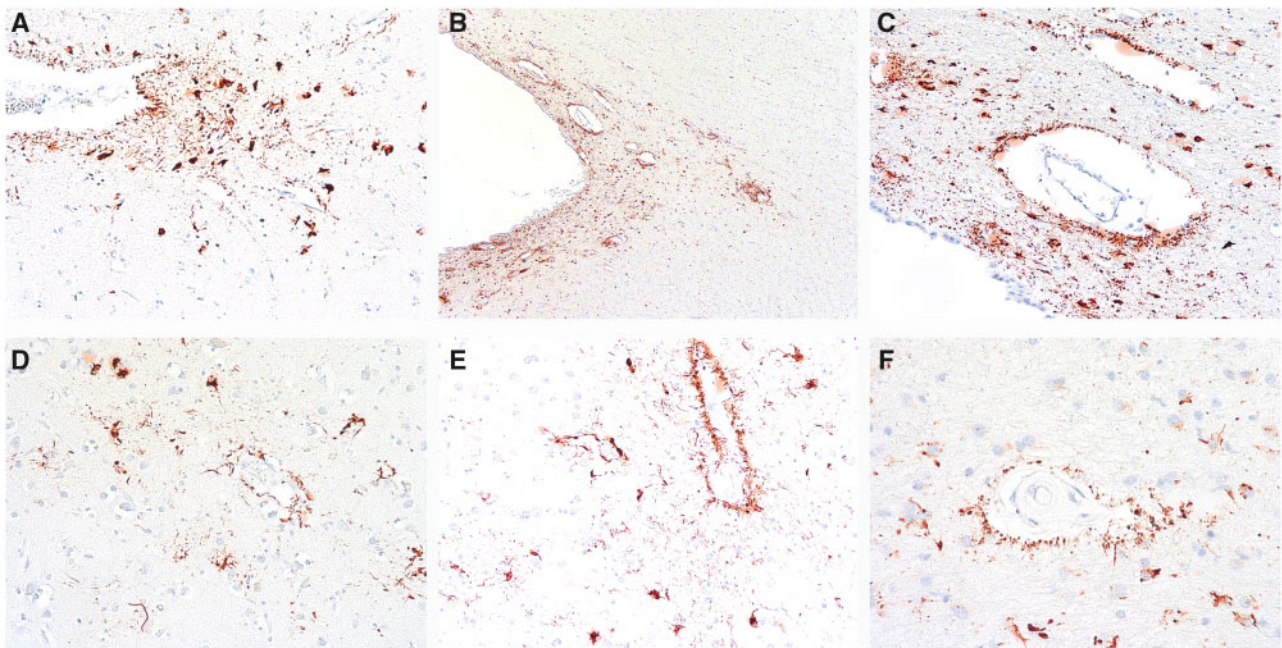


FIGURE 2 Representative images of ARTAG that might be mistaken for CTE. Ten- μ m paraffin-embedded tissue sections immunostained for phosphorylated tau (AT8) (Pierce Endogen). **(A, B)** P-tau-immunoreactive thorn-shaped astrocytes found at glial limitans at the depths of the sulcus are features of ARTAG that may be found in CTE, but are not diagnostic for CTE. Magnifications: **A**, $\times 200$, **B**, $\times 100$. **(C)** Perivascular clusters of p-tau positive astrocytes surrounding thin-walled vessel in the superficial regions of the sulcal depths also represent ARTAG. Magnification: $\times 200$. **(D-F)** Common forms of perivascular p-tau-immunoreactive astrocytic pathology (ARTAG) in white matter. Magnification: $\times 200$.

pathology appears diffusely distributed throughout the fields of view. The first 2 images for Case 5 show strictly subpial TSA p-tau pathology, a supportive, but nondiagnostic feature of CTE; the third image shows diffusely distributed NFTs and neurites in a field of view containing a blood vessel, but there is no focal localization to the region around the vessel. None of these images meet minimum criterion for CTE.

Images for Cases 4 and 8 were not supplied but were said to not have p-tau pathology at the sulcal depths suggesting that the diagnosis of CTE was made on the presence of still other, nondiagnostic features. The authors observed tau immunoreactivities (presented in their Figures 2–4), which they interpreted as supportive feature lesions. Indeed, Figure 2 shows examples of p-tau pathology in superficial laminae of Cases 3

and 5, a nonspecific feature of several tauopathies; a supportive, yet nondiagnostic feature of CTE. Their Figure 3 shows prominent “granular-fuzzy” astrocytic p-tau pathology in the amygdala of Cases 3 and 7, this pathology is characteristic of ARTAG and is not a feature of CTE (3–7). For reference on what constitutes the pathognomonic lesion of CTE in cases with a low burden of pathology, we enclose several representative images of mild CTE pathology (Figure 1). We also include several representative images of ARTAG pathology that might be confused for CTE (Figure 2).

Prior to wide recognition of ARTAG as an age-related p-tau pathology (3–5), there was some ambiguity in early publications as to whether astrocytic p-tau pathology in subpial regions, temporal lobe white matter, and brainstem was a feature of CTE (8–11). By 2016, with the publication of the NINDS criteria for CTE, it became clear that clusters of p-tau-immunoreactive astrocytes in the subpial region at the depths of the cortical sulci, white matter of the frontal and temporal cortex, basal ganglia, lateral, and medial brainstem in isolation were not pathognomonic for CTE, but were part of the spectrum of pathology collectively known as ARTAG (2).

Further evidence that the p-tau pathology shown by Iverson and colleagues in their small case series represents non-CTE-specific p-tau pathology or aging-related astrocytic p-tau pathology of ARTAG, comes from a recent large study conducted by Forrest and colleagues. Forrest and colleagues assessed the frontal, temporal, and parietal cortices, the regions most involved in mild CTE, of 310 aged participants in a European community-based population for the presence of CTE and ARTAG (7). Of the 310, none satisfied current diagnostic criteria for CTE and 117 were diagnosed with ARTAG. Isolated p-tau pathologies occurring at the depths of cortical sulci were found in 25 cases (8%) (7), but none reached diagnostic criteria for CTE (2). These findings indicate that ARTAG is a common age-related pathology in community populations but CTE is not (7). Together with a further study, (12) these observations corroborated that isolated p-tau immunoreactivities suggestive of CTE pathology, in the correct context, could be interpreted only as one possible feature or component (7) of CTE pathology. Thus, without fitting all parts of the criteria verbatim (2), in particular, without *neuronal tau accumulation in a pathognomonic location*, these isolated features should not warrant the diagnosis of CTE. Currently, there is insufficient evidence to support the position that perivascular p-tau-immunoreactive astrocytes alone are diagnostic for CTE. If present in isolation, astrocytic p-tau most likely represents a distinct pathological entity, aging-related tau astroglial pathology (ARTAG) (3–7). Further studies are needed to clarify common pathogenic aspects of CTE-related astroglial tau accumulation and ARTAG seen in nontraumatic aging brains.

The misclassification of isolated ARTAG pathology as CTE by Iverson and colleagues is not compatible with the current criteria of CTE (2) and thus invalidates their conclusion that “the results of this study are striking in that 75% of our small case series met neuropathological criteria for CTE, but none of the men had a known history of participation in contact sports, collision sports, or multiple concussions.” We

hope that this clarification between the p-tau pathology of CTE, which currently is emphasized to include neuronal tau accumulation, and isolated ARTAG will prove useful in future studies involving the neuropathological diagnosis of mild CTE.

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CONFLICT OF INTEREST

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Authors' Reply: Age-Related Tau Aggregates Resemble Chronic Traumatic Encephalopathy Neuropathologic Change

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To the Editor:

A group of authors wrote a thoughtful methodological critique of our small case series describing men from the general population who appeared to have chronic traumatic encephalopathy (CTE) neuropathology (1). In our case series, we identified CTE neuropathology, aging-related tau astroglialopathy (ARTAG), and primary age-related tauopathy (PART) in some of these men. As seen in Table 4 of our article, of the postmortem tissue from 8 men that we studied, we reported that 6 had CTE neuropathology, 5 had ARTAG, and 4 had PART.

TERMINOLOGY: CTE NEUROPATHOLOGIC CHANGE

In their letter (2), McKee and colleagues used the terms CTE and CTE pathology interchangeably. A recent study has introduced and encouraged the terminology “CTE neuropathologic change” (3). It is not known if small amounts of CTE-like neuropathology cause, or are clearly associated with, clinical symptoms, and it is not known if small amounts of this pathology propagate or spread in a progressive manner. It is also important to differentiate small amounts of this pathology from a clinical syndrome. Therefore, in this response, we will use “CTE neuropathology” or “CTE neuropathologic change” to refer to the postmortem neuropathology identified

through immunohistochemistry, as described in our original article (1).

ARTAG PATHOLOGY HAS BEEN CONCEPTUALIZED AS CTE NEUROPATHOLOGIC CHANGE IN PRIOR STUDIES

Their letter is entitled: “Practical Considerations in the Diagnosis of Mild Chronic Traumatic Encephalopathy and Distinction from Age-related Tau Astroglialopathy” (2). The title of their critique is apropos because the content of our original article, their critique, and our response, all relate to small amounts of neuropathology in the human brain that have been attributed, or ascribed, to CTE. McKee et al raise 2 primary issues: (i) the distinction between ARTAG and CTE neuropathologic change; and (ii) the geographic relationship between phosphorylated tau (tau) aggregates and blood vessels. Regarding the first issue, in none of our cases identified as having CTE neuropathologic change was p-tau restricted to astrocytes—neuronal p-tau was present—and we did not consider ARTAG sufficient to satisfy the required criterion for CTE neuropathologic change.

ARTAG encompasses a spectrum of astroglial tau pathologies, and the frequency of this astrocytic pathology varies depending on the type: Subpial, subependymal, and perivascular types are believed to be more frequent, whereas