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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Tau deposition in young adults with drug-resistant focal epilepsy

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Abstract

Objective: To evaluate the presence of tau deposition and pathologic features of chronic traumatic encephalopathy (CTE) in young adult patients treated with focal cortical resections for drug-resistant epilepsy.

Methods: Sixty consecutive patients who had undergone surgical treatment for drug-resistant focal epilepsy between 18 and 45 years of age were identified (2010-2017). Medical records were reviewed to determine clinical factors, including history of head trauma, age at seizure onset, age at surgical resection, seizure type(s) and frequency, imaging findings, and surgical outcome. All formalin-fixed, paraffin-embedded blocks from the surgical specimens from each subject were sectioned and stained with hematoxylin and eosin and antibodies to tau (Thermo Fisher Scientific Clone AT8), and examined blindly for tau pathology, including lesions characteristic of CTE.

Results: The median age at resection was 29.5 years (range = 19-45). A history of head trauma was reported in 19 patients. Although none of the patients had pathological findings characteristic of CTE, 23 patients (38%) demonstrated tau-immunoreactive lesions, including neurites, neurofibrillary pretangles, neurofibrillary tangles, subpial tau, and/or glial tau. In 4 of the 23 patients (7% of the cohort; 17% of those with tau pathology), substantial tau burden was identified. Three of these 4 patients had no significant history of head trauma; 1 patient had multiple sports-related concussions. No specific clinical factors correlated with the presence of tau pathology.

Significance: Tau-immunoreactive lesions were found in 38% of 60 patients who underwent a focal cortical resection for drug-resistant focal epilepsy. Diagnostic features of CTE were not detected in any patient; however, the pathological evaluation for CTE was limited to a surgical specimen. The prominent and excessive tau deposition in 23 patients (38%) is abnormal in this age group and warrants further investigation.

KEYWORDS
chronic traumatic encephalopathy, epilepsy surgery, neuropathology

1 | INTRODUCTION

Epilepsy poses a substantial global health care problem, with approximately 65 million patients affected worldwide.[1] The potential adverse effects of seizures include physical trauma with head injury, antiseizure medication toxicity, status epilepticus, sudden unexplained death in epilepsy, mood disorders, psychosocial debilitation, and memory loss. Cognitive abnormalities may develop in people with epilepsy and significantly impact their quality of life, especially in patients who are drug-resistant.[2] The pathophysiology of progressive cognitive impairment in selected patients is not well understood.[3]

Tau is a microtubule-associated protein that is involved in microtubule assembly and axonal transport.[4] Hyperphosphorylated tau is an important feature in several neurodegenerative disorders, including Alzheimer disease (AD), several of the frontotemporal dementias including Pick disease, progressive supranuclear palsy, and corticobasal degeneration, and chronic traumatic encephalopathy (CTE). CTE is a poorly understood progressive neurodegenerative disorder that develops following recurrent concussive and subconcussive head trauma.[5] In addition to dementia, patients with CTE may have significant psychiatric symptomatology including depression, suicidality, and substance abuse.[5] Similar psychiatric comorbidities may be found in patients with epilepsy.[6] Approximately one-third of patients with epilepsy experience significant mood or anxiety symptoms.[7] The diagnostic lesion of CTE is patchy, perivascular-predominant deposition of phosphorylated tau in neurons and astrocytes characteristically present in the sulcal depths.[5] CTE can only be diagnosed definitively by postmortem examination of the entire brain.[8] Previous studies have demonstrated an accumulation of tau in some patients with epilepsy.[9–12]

In this study, surgical specimens from focal cortical resections in younger patients aged 18-45 years with drug-resistant focal epilepsy were assessed for tau pathology. We hypothesized that tau pathology consistent with CTE may be identified in these patients, and evaluated the correlation between clinical symptoms and tau deposition.

Key Points

- Tau deposition was found in 38% of patients
- More young adults with tau deposition were identified in this series than were reported in an autopsy series of a similar age group
- Chronic traumatic encephalopathy was not confirmed in this series of limited surgical resections consisting of 60 patients with drug-resistant focal epilepsy

2 | MATERIALS AND METHODS

The study was reviewed and approved by the institutional review board. Sixty consecutive adult patients 18-45 years of age were identified from a surgical epilepsy database who had undergone focal cortical resection for drug-resistant focal epilepsy between 2010 and 2017 at Mayo Clinic in Rochester, Minnesota. Inclusion criteria were as follows: (1) age 18-45 years at the time of resection; and (2) no underlying pathological substrate (determined by neuroimaging, neuropathology, or both), for example, tumor or focal cortical dysplasia. Hippocampal sclerosis (HS) was not an exclusionary neuropathologic feature. Patients who had previous epilepsy surgery and those included in the pilot study were excluded.[9] All patients underwent a preoperative evaluation at our institution, including a comprehensive neurological history and examination, inpatient video-electroencephalographic monitoring, and epilepsy protocol for magnetic resonance imaging (MRI) of the head. Comprehensive neuropsychological studies including assessment of verbal and nonverbal memory, intelligence, verbal and perceptual abilities, and cognitive speed and flexibility were performed at Mayo Clinic in selected patients.

All formalin-fixed, paraffin-embedded blocks from each surgically resected specimen were resectioned and evaluated with hematoxylin and eosin and antibodies to tau (AT8 clone). Neuropathological evaluation (blinded to patient age, initial neuropathological diagnosis, clinical history, and contact sports exposure history) for tau pathology including the pathognomonic lesions for CTE was performed. Tau-immunoreactive lesions were categorized by pathology type and location (neurites, neurofibrillary pretangles [pre-NFTs], neurofibrillary tangles [NFTs], subpial tau, features of CTE) and cellular burden (rare neurites or single pre-NFT only, neurites with multiple pre-NFTs, NFTs, glial tau). Significant tau burden was defined as tau pathology reaching the threshold of "mild" or greater by institutional semiquantification grading criteria adapted from the Consortium to Establish a Registry for Alzheimer Disease recommendations.[13]

Medical records were reviewed to determine clinical factors including the duration of epilepsy, types of seizures, epilepsy risk factors, history of head trauma, involvement in contact sports, neuropsychological studies, and surgical outcome. Each patient's history and clinical evaluation were correlated with neuropathological findings.

Descriptive summaries were reported as mean and interquartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables. Associations

between the categorical variables were assessed using Fisher exact test. All tests were two-sided, and P values < 0.05 were considered statistically significant. Analysis was performed using SAS software version 9.4.

3 | RESULTS

3.1 | Clinical factors

Thirty-three of the 60 patients were men (55%). The median age of seizure onset was 16 years (IQR = 2-12.5) and median age at resection was 29.5 years (IQR = 23.5-39.5). The mean duration of epilepsy at the time of surgery was 15.7 years (IQR = 8.3-22.8). Focal impaired awareness seizures or focal aware seizures were present in 57 of 60 patients (95%) and focal seizures evolving into bilaterally convulsive seizures in 51 patients (85%) prior to surgery. A history of status epilepticus was present in 20 patients (33%).

The details of head trauma were determined exclusively from review of the neurological history in the Mayo Clinic electronic medical record. Head trauma was reported prior to surgical treatment for epilepsy in 19 of 60 patients (32%): mild head trauma/concussion without loss of consciousness in 12 patients and traumatic brain injury with loss of consciousness in 7 patients. Of these 7, 4 had mild injury with a short period of loss of consciousness, 1 had moderate injury with loss of consciousness lasting <1 day, and 2 had severe head trauma with an associated coma. Six patients had a history of playing contact sports, for example, football or wrestling.

MRI studies of the brain were obtained in all patients. Normal results were obtained in 15 patients. There were nonspecific white matter changes in 6 patients, HS in 31 patients, and other nonspecific findings in 8 patients. Preoperative neuropsychological testing was performed in 44 patients. The cognitive testing was normal in 9 patients. The neuropsychologist who conducted the study characterized the memory abnormality as mild in 30 patients and moderate in 4 patients. One patient had severe cognitive impairment. Postoperative neuropsychological testing was performed in 36 patients. The studies were normal in 11 patients and revealed mild or moderate deficits in 24 patients and 1 patient, respectively.

Patients were followed for a mean of 43.1 months (range = 1-238, IQR = 9-61.8). The surgical outcome on follow-up based on mean duration of 18.6 months after surgery (range = 0-82, IQR = 3-31) was Engel class I in 45 patients (75%), Engel class II in 5 patients (8.3%), Engel class III in 5 patients (8.3%), and Engel class IV in 5 patients (8.3%).[14]

3.2 | Pathology

The area of focal cortical resection in the 60 patients included the temporal lobe (n = 55), the frontal lobe (n = 4), and the parietal lobe (n = 1). The surgical pathologic findings revealed HS in 29 of the 55 patients who underwent a temporal lobe resection. Nonspecific subpial and subcortical gliosis was present in the surgical specimen in 59 of the 60

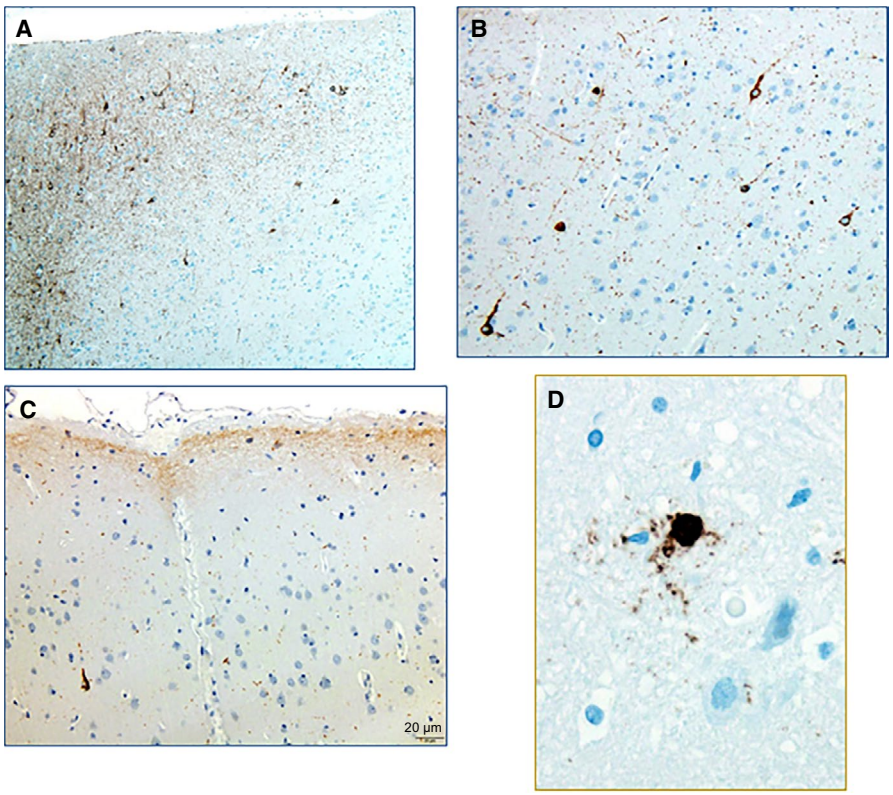

FIGURE 1 Tau pathology in the study cohort. A, A case with significant tau burden. B, Neurites and neurofibrillary tangles in this patient (see A). C, D, Additional patterns of tau in the cohort included nonspecific bandlike subpial tau (C) and glial tau (D) deposition

patients. In 1 patient, no significant pathologic findings were identified.

The blinded neuropathology review of the 60 focal cortical resections showed tau-immunoreactive lesions including neurites, pre-NFTs, NFTs, subpial tau, and white matter glial tau in 23 patients (38%; Figure 1). Four of the 23 patients (7% of the cohort; 17% of those with tau pathology) had a significant tau burden (Figure 1A,B).[13] Of these, 3 were 41-45 years of age and had no significant history of head trauma; a fourth had multiple sports-related concussions. However, none of the 60 patients demonstrated findings considered diagnostic of CTE. The 23 patients identified with tau-immunoreactive lesions included temporal lobe resections (n = 21) and frontal lobe resections (n = 2; $P = .64$, Fisher exact test). Tau deposition was neocortical in 16 (69.6%) of the 23 patients. The localization could not be adequately determined in 7 patients (ie, medial temporal, neocortical, or both) because of the excised surgical specimens available for pathologic interpretation. Tau deposition was more common in males, but this difference was not statistically significant ($P = .055$, odds ratio = 2.87). The median duration of epilepsy was 10 years for the 23 patients with tau deposition versus 14 years for those without ($P = .22$). Abnormalities on preoperative and postoperative neuropsychological testing did not correlate with tau deposition ($P = .43$, .57). There were no clinical factors that correlated with tau deposition. Neither patient with a history of severe head trauma had tau pathology.

4 | DISCUSSION

Tau deposition was found in a significant percentage (38%) of our cohort, although no pathologic lesions were

TABLE 1 Relevant studies on tau pathology in patients with epilepsy and healthy controls

Article	N	Age range (median)	Pathology type	Epilepsy patients	Summary of findings
Braak & Del Tredici 2011[15]	42	4-29 y (19.8 y)	Autopsy	No	No cases had neocortical phosphorylated tau deposition, with 4 cases having no tau deposition. Sixteen cases had tau deposition in the temporal lobe, particularly in transentorhinal region. Nineteen cases had subtle pretangle tau deposition in the coeruleus/subcoeruleus.
Braak et al 2011[16]	2332	1-100 y	Autopsy	No	Deposition of phosphorylated tau increased with age, and first appeared in subcortical areas. Patients younger than 40 years very rarely displayed deposition of tau in the neocortex.
Thom et al 2011[11]	138	15-96 y (56.5 y)	Autopsy	Yes	Cases with chronic, partially responsive, or drug-resistant epilepsy cases were included. Braak staging was done, and showed 31% stage 0, 36% stage I/II, 31% stage III/IV, and 2% stage V/VI. There was a significant increase in Braak stages III-IV in patients aged 40-65 years.
Tai et al 2016[10]	33	50-65 y	Surgical: temporal lobe resection	Yes	All patients had intractable temporal lobe epilepsy. Lesions pathognomonic for CTE were not present in any cases. However, 94% had hyperphosphorylated tau pathology. More extensive tau pathology correlated with greater decline in verbal learning, recall, and graded naming test scores >1 year after temporal lobe resection.
Puvenna et al 2016[12]	19	4 mo-58 y (27.6 y)	Surgical: temporal lobe resection	Yes	In a comparison between CTE on autopsy (n = 6) and temporal lobe resections for epilepsy (n = 19), immunoreactive phosphorylated tau was found in both groups without a significant staining intensity difference between the groups. High molecular weight tangle-associated tau was found in CTE, whereas low molecular weight tau was found in epilepsy patients.
Jones et al 2018[9]	10	23-43 y (32.5 y)	Surgical: focal cortical resection	Yes	Tau-immunoreactive lesions suggestive of CTE were found in a frontal lobe resection of 1 patient with intractable epilepsy.

Abbreviation: CTE, chronic traumatic encephalopathy.

determined to be diagnostic of CTE. These findings may represent the presence of a novel tauopathy in people with drug-resistant focal epilepsy, undersampling given the limited nature of epilepsy surgical resections relative to autopsy, or an increase in nonspecific tau pathology in young patients with medically refractory epilepsy. Tau deposition has previously been evaluated in people with epilepsy and healthy controls (Table 1). Importantly, the present study demonstrates that tau deposition may be found in younger patients with drug-resistant focal epilepsy than previously reported (50-65 years of age).[10] Significant tau deposition is uncommon in healthy controls in a similar age group.[15] One autopsy study evaluated for the presence of tau-positive "intraneuronal and extracellular protein aggregates associated with Alzheimer disease" in 42 patients between 4 and 29 years of age.[15] None demonstrated neocortical tau, 16 of 42 had medial temporal lobe tau, and the remaining had subcortical lesions, largely confined to the locus coeruleus.[15] Four of the 42 patients had no tau lesions.[15] The presence of neocortical tau deposition in the present study was significantly increased compared to the autopsy study ($P < .0001$).[15] A subsequent larger autopsy study had similar findings.[16] Pretangle tau pathology was limited to the brainstem and medial temporal lobe structures in individuals younger than 30 years; a very low percentage of individuals between 31 and 40 years of age showed tau advancement into the neocortex.[16] Our study further raises the question of tau deposition playing a role in cognitive decline in epilepsy, as it is a common pathologic feature of several neurodegenerative disorders including AD and CTE. It previously has been hypothesized that intractable epilepsy may be a neurodegenerative tauopathy.[17] In a previous pilot study of young patients who had undergone epilepsy surgery, 1 patient (10%) demonstrated tau pathology consistent with CTE.[9] The remaining 9 patients had no abnormal tau deposition.[9]

In a prior study of 33 patients between the ages of 50 and 65 years with temporal lobe epilepsy and HS, 94% of patients had deposition of hyperphosphorylated tau.[10] In that study, increasing levels of tau corresponded with decreasing scores in verbal learning, recall, and graded naming test scores, supporting that tau deposition may play a role in cognitive decline.[10] In a postmortem study of 138 patients at a mean age of 56.5 years (range = 15-96) with chronic focal and generalized epilepsy, Braak staging was done and showed 36% stage I/II, 31% stage III/IV, and 2% stage V/VI.[11] Higher Braak staging correlated with advanced age and was more frequently identified in patients with focal epilepsy in comparison to patients with generalized epilepsy ($P < .01$).[11] In a comparison study between 6 patients with CTE with a history of repetitive traumatic brain injury and 19 patients with temporal lobe epilepsy who had undergone resections, there were similar patterns and expressions of phosphorylated tau in the two groups.[12] Tau deposition in this study was not related to age.[12]

Tau may be associated with increased epileptogenicity, as there is evidence to indicate its involvement in network synchronization and hyperexcitability.[18] In a transgenic mouse model of epilepsy, reduction in tau led to reduced seizure frequency in addition to increased survival.[18] In addition, there is an increase in seizures in all age groups in patients with AD.[19] Seizure reduction in AD can improve cognitive function. A reduction in tau deposition may be neuroprotective and may have implications for therapeutics in the future.[20]

There are several limitations to the present study that need to be considered. The pathological diagnosis of CTE requires extensive postmortem neuropathological examination of numerous cortical and subcortical regions.[16] Clinical factors that are relevant in these 60 patients including a history of head injuries and contact sports engagement were thoroughly extracted through a retrospective review of medical records. There was not pre- and postoperative neuropsychological testing in all patients. Therefore, an analysis of tau burden in regard to changes in cognition over time could not be reliably calculated.

This study supports the previously reported findings of tau pathology in patients with drug-resistant epilepsy. The younger age of our patient cohort may explain the lower proportion of patients with tauopathy compared to previous studies.[10,11] Additional investigation is needed to explore the potential role of tau in epileptogenesis or whether it occurs as a consequence of seizure activity or part of a heretofore unclarified neurodegenerative process developing in parallel with drug-resistant epilepsy over time. The relationship between tau deposition and cognitive decline in individuals with drug-resistant focal epilepsy remains to be determined, and the clinical importance of this pathological finding is unknown. Potentially, the outcome of investigations of tauopathy in people with epilepsy may improve the understanding of the underlying pathophysiology of seizures and cognitive impairment and yield the development of novel therapeutics.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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