



## Short communication

## Alzheimer's-related changes in non-demented essential tremor patients vs. controls: Links between tau and tremor?



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## ABSTRACT

**Background:** In addition to tremor, patients with essential tremor (ET) may exhibit non-motor features, including a range of cognitive deficits. Several prospective, population-based epidemiological studies have reported an association between ET and incident dementia, especially Alzheimer's disease (AD). Moreover, in a brain repository-based study, a larger than expected proportion of ET patients also developed pathological changes characteristic of progressive supranuclear palsy, further suggesting a link between ET and tau pathology.

**Methods:** We selected a group of ET patients that were free of dementia clinically and without AD on postmortem examination. Our hypothesis was that neuronal tauopathic burden would be higher in the brains of these ET patients compared to controls. We compared Braak stage for neuronal tangles and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores for neuritic plaques in the two groups. **Results:** The two groups were similar in age ( $82.6 \pm 6.0$  vs.  $80.4 \pm 8.1$ ,  $p = 0.22$ ). The 40 ET patients had a higher Braak neurofibrillary stage than 32 controls (means:  $2.2 \pm 1.2$  vs.  $1.2 \pm 1.1$ ; medians: 2.0 vs. 1.0,  $p < 0.001$ ). Meanwhile, CERAD scores for neuritic plaques were similar in patients and controls (means:  $0.6 \pm 0.9$  vs.  $0.5 \pm 0.6$ ; medians: 0.0 vs. 0.0,  $p = 0.83$ ).

**Conclusion:** While ET itself is not a tauopathy (i.e., a neurodegenerative disorder among whose main features are accumulation of hyperphosphorylated tau protein), ET may predispose individuals to accumulate more widespread cellular tau aggregates, and thus tau could play a central role in the cognitive impairment that can accompany ET.

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## 1. Introduction

In addition to motor features, essential tremor (ET) patients may exhibit a range of cognitive deficits that are in excess of those seen in age-matched control subjects [1]. Several prospective, population-based epidemiological studies have reported an association between ET and incident dementia, especially Alzheimer's disease (AD) [2]. Moreover, a brain repository-based study reported the development of pathological changes characteristic of progressive supranuclear palsy (PSP) in a larger than expected

proportion of ET patients, further suggesting the presence of links between ET and tau burden [3].

To further explore links between ET and Alzheimer's type pathological changes, and especially tau burden, we compared Braak neurofibrillary tangle stage [4] and Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [5] scores for neuritic plaques in non-demented ET patients and controls. Our hypothesis was that neuronal tangle burden rather than neuritic plaque burden would be increased in non-demented ET patients compared to controls.

## 2. Methods

## 2.1. Subjects

This study was conducted at the Essential Tremor Centralized Brain Repository (ETCBR), Columbia University Medical Center. The ETCBR is a centralized repository for the prospective collection of brains from ET patients in the United States. Participants signed informed consent approved by the CUMC Internal Review Board.

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ET diagnoses were carefully assigned using three sequential methods, as described [6]. Every six months, patients completed a follow-up telephone questionnaire, which included a series of screening questions for Parkinson's disease (PD) and dystonia. A follow-up videotaped neurological examination was performed if any screening question was positive for PD or dystonia, or if hand-drawn spirals showed signs of micrographia.

The ET patients underwent a brief cognitive assessment upon enrollment and every six months, which consisted of a short version of the Telephone Interview for Cognitive Status (TICS) (range = 0–9) performed at both times [7] and the Mini-Mental Status Examination (MMSE) performed upon enrollment (range = 0–30) [8]. Furthermore, the patients were asked to self-report a diagnosis of dementia. Clinical dementia was defined as any self-report of dementia or a Mini-Mental Status score < 25 [9]. Between 2003 and mid-2013, 112 ET patients died and their brains were prospectively collected.

Sixty-seven available normal elderly control brains from the New York Brain Bank, mainly derived from the Alzheimer's Disease Research Center at CUMC and the Washington Heights Inwood Columbia Aging Project, did not have clinical diagnoses of dementia, AD, ET, or PD, and were without neuropathological diagnoses of neurodegenerative disease. Controls underwent detailed cognitive assessments by neuropsychological testers, including an extensive neuropsychological battery and either the MMSE and/or the Short Blessed Test [10] every 12–18 months.

## 2.2. Tissue processing

The New York Brain Bank operates under approval of the Institutional Review Board of CUMC. All brains were well-characterized including standardized, complete neuropathological assessment and determination of any pathological findings in paraffin embedded tissue sections (see [nybb.hs.columbia.edu](http://nybb.hs.columbia.edu)). This consisted of a comprehensive neuropathological histologic evaluation with Luxol Fast Blue-Hematoxylin Eosin (LH&E), modified Bielschowsky, and immunohistochemical staining for hyperphosphorylated tau (AT8) (1:200, Thermo Scientific, Rockford, IL) (including hippocampus, globus pallidus, putamen, caudate nucleus, amygdala, thalamus, subthalamic nucleus, mesencephalon with red nucleus, pons, medulla oblongata, cerebellum with dentate nucleus, and cerebral cortex), beta-amyloid (1:400, Biocare Medical, Concord, CA) (including cerebral cortex, hippocampal formation, caudate nucleus, putamen, and thalamus) and alpha-synuclein (1:40, Leica, Buffalo Grove, IL) (including cerebral cortex, hippocampal formation, globus pallidus, putamen, amygdala, midbrain with substantia nigra, pons with the locus ceruleus, medulla with the dorsal vagal nucleus, and olfactory bulbs). A CERAD score for neuritic plaques [5] and Braak stage for neurofibrillary tangles [4] was assigned to each brain. AD (low, intermediate, high-likelihood) was defined using NIA-Reagan criteria [11]. Postmortem interval (PMI) was the number of hours between death and placement of brain in a cold room or upon ice.

## 2.3. Final sample

From the 112 ET brains, we excluded 28 with additional clinical diagnoses other than/in addition to ET (2 with dystonia, 1 with AD) or the presence of definite pathological findings that do not occur in brains from patients with pure ET ( $n = 25$  with either PD, PSP, or corticobasal degeneration). Additionally, we excluded 3 with a pathological diagnosis of intermediate or high-likelihood AD, and 13 with a missing cognitive assessment. We were able to age-match a final sample of 40 ET patients with 32 controls who had complete clinical and pathological data.

## 2.4. Statistical analyses

Analyses were performed using SPSS (version 21.0). Clinical characteristics of ET patients and controls were compared using Student's *t*-tests and chi-square tests. Since Braak stage and CERAD scores were not normally distributed, a non-parametric test (Mann–Whitney test) was used when comparing stages/scores in patients vs. controls. We also reported Braak stage and CERAD score as categorical variables, comparing the proportions with each stage/score in patients vs. controls using a chi-square test or Fischer's exact test. Spearman's correlation coefficients were used to test for a correlation between Braak stage and CERAD scores. We also performed several secondary analyses. First, we excluded 4 additional ET patients with diagnoses of low-likelihood AD on postmortem examination, to further ensure that the study sample was AD-free. Second, to reduce the effects of potential selection bias caused by the different cognitive assessments between patients and controls, we repeated our main analysis including only the top quartile of patients and controls based on their most recent TICS and the Short Blessed test scores. To assess the independent association of Braak stage and CERAD score with diagnosis (ET patient vs. control), a logistic regression model was performed in which the ET patient–control status was the outcome variable, and Braak stage and CERAD score were the independent variables, adjusting for age and education.

## 3. Results

None of the selected 40 ET patients or 32 controls had clinical dementia or pathological changes that met the criteria of AD. Patients and controls were similar in age, gender and brain weight; PMIs in controls were longer than in patients (Table 1). None had Lewy bodies.

ET brains had a higher Braak stage than control brains (means:  $2.2 \pm 1.2$  vs.  $1.2 \pm 1.1$ ; medians: 2.0 vs. 1.0,  $p < 0.001$ ) (Table 1). We also treated Braak stage for neuronal tangles as a categorical variable, and compared the proportion at each stage in patients vs. controls; the patient–control difference remained robust ( $p = 0.018$ , Table 1, Fig. 1a). CERAD scores in ET patients and controls were similar (means:  $0.6 \pm 0.9$  vs.  $0.5 \pm 0.6$ ; medians: 0.0 vs. 0.0,  $p = 0.83$ ) (Table 1). The overall proportion at each CERAD stage (zero, A, B, C) was also similar in patients vs. controls ( $p = 0.40$ , Table 1, Fig. 1b).

Although we had already excluded patients and controls with postmortem diagnoses of intermediate or high-likelihood AD, we also performed an analysis in which we excluded 4 additional ET patients with postmortem diagnoses of low-likelihood AD. The patient–control difference in Braak stage persisted (means:  $2.0 \pm 1.1$  vs.  $1.2 \pm 1.1$ ; medians: 2.0 vs. 1.0,  $p = 0.002$ ) and CERAD scores again remained similar (means:  $0.5 \pm 0.6$  vs.  $0.4 \pm 0.8$ ; medians: 0.0 vs. 0.0,  $p = 0.36$ ). We also repeated the analysis, including only the top quartile of patients and controls based on their most recent cognitive screen (Short Blessed Test or MMS), and results were similar (mean Braak stages:  $2.1 \pm 1.1$  vs.  $1.2 \pm 0.8$ ; medians: 2.0 vs. 1.0,  $p = 0.009$ , and mean CERAD scores:  $0.5 \pm 0.7$  vs.  $0.6 \pm 0.9$ ; median scores: 0.0 vs. 0.0,  $p = 0.99$ ).

Overall, Braak stage and CERAD scores were correlated with one another (Spearman's  $r = 0.46$ ,  $p < 0.001$ ).

We assessed the role of potential confounders. In our controls, Braak stage was not associated with Short Blessed Test scores

**Table 1**  
Clinical and pathological characteristics in ET patients and controls.

	ET ( $n = 40$ )	Controls ( $n = 32$ )	<i>p</i> Value
<i>Clinical</i>			
Age in years	$82.6 \pm 6.0$	$80.4 \pm 8.1$	0.22 <sup>a</sup>
Education (years)	$14.3 \pm 2.7$	$15.7 \pm 3.5$	0.13 <sup>a</sup>
Female gender	23 (57.5)	15 (46.9)	0.37 <sup>b</sup>
Age of tremor onset (years)	$39.3 \pm 20.9$	Not applicable	Not applicable
Tremor duration (years)	$41.9 \pm 21.4$	Not applicable	Not applicable
<i>Brain pathology</i>			
PMI (h)	$3.5 \pm 3.7$	$8.7 \pm 9.9$	0.008 <sup>a</sup>
Brain weight (g)	$1223 \pm 162$	$1215 \pm 128$	0.82 <sup>a</sup>
Braak stage			
Mean	$2.2 \pm 1.2$	$1.2 \pm 1.1$	
Median	2.0	1.0	<0.001 <sup>c</sup>
0	3 (7.5)	10 (31.3)	0.018 <sup>d</sup>
1	8 (20.0)	11 (34.4)	
2	15 (37.5)	8 (25.0)	
3	9 (22.5)	2 (6.3)	
4	4 (10.0)	1 (3.1)	
5	1 (2.5)	0 (0)	
6	0 (0)	0 (0)	
CERAD score			
Mean	$0.6 \pm 0.9$	$0.5 \pm 0.6$	
Median	0.0	0.0	0.83 <sup>c</sup>
0	25 (62.5)	18 (56.3)	0.40 <sup>d</sup>
1	10 (25.0)	12 (37.5)	
2	2 (5.0)	2 (6.3)	
3	3 (7.5)	0 (0)	

Values are mean  $\pm$  standard deviation or numbers (percentage). Abbreviations: CERAD, Consortium to Establish a Registry for AD; PMI, postmortem interval.

<sup>a</sup> Student's *t* test, Subjects were matched on age.

<sup>b</sup> Chi-square test.

<sup>c</sup> Mann–Whitney test.

<sup>d</sup> Fisher's exact test.

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