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Cerebellar Pathology in Childhood-Onset vs. Adult-Onset Essential Tremor

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Abstract

Although the incidence of ET increases with advancing age, the disease may begin at any age, including childhood. The question arises as to whether childhood-onset ET cases manifest the same sets of pathological changes in the cerebellum as those whose onset is during adult life. We quantified a broad range of postmortem features (Purkinje cell [PC] counts, PC axonal torpedoes, a host of associated axonal changes [PC axonal recurrent collateral count, PC thickened axonal profile count, PC axonal branching count], heterotopic PCs, and basket cell rating) in 60 ET cases (11 childhood-onset and 49 adult-onset) and 30 controls. Compared to controls, childhood-onset ET cases had lower PC counts, higher torpedo counts, higher heterotopic PC counts, higher basket cell plexus rating, and marginally higher PC axonal recurrent collateral counts. The median PC thickened axonal profile count and median PC axonal branching count were two to five times higher in childhood-onset ET than controls, but the differences did not reach statistical significance. Childhood-onset and adult-onset ET had similar PC counts, torpedo counts, heterotopic PC counts, basket cell plexus rating, PC axonal recurrent collateral counts, PC thickened axonal profile count and PC axonal branching count. In conclusion, we found that childhood-onset and adult-onset ET shared similar pathological changes in the cerebellum. The

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Conflicts of Interest

The authors had no conflicts of interest. Each of the authors participated in a substantive manner with the research and in the preparation of the manuscript and approved the final manuscript.

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data suggest that pathological changes we have observed in the cerebellum in ET are a part of the pathophysiological cascade of events in both forms of the disease and that both groups seem to reach the same pathological endpoints at a similar age of death.

Keywords

essential tremor; cerebellum; neurodegenerative; Purkinje cell; pathology; childhood-onset

Introduction

Essential tremor (ET) is one of the most common movement disorders as well as the most common tremor disorder [1; 2]. Despite its high prevalence, disease mechanisms are not completely understood [3; 4]. Clinical [5; 6; 7; 8; 9] and neuroimaging [3; 10; 11; 12] studies suggest that the cerebellum plays an important role in the generation of tremor in ET. Furthermore, in recent years we have observed a constellation of pathological changes in the ET cerebellum, present mainly in the cerebellar cortex and involving the Purkinje cell (PC) and its neighboring neuronal populations, and distinguishing ET from control brains. These changes include an increase in the number of torpedoes and associated PC axonal pathologies [13; 14], an increase in heterotopic PCs [15], and abnormal basket cell axons with a dense and tangled appearance (“hairiness”) surrounding the PC soma and elongated processes extending past the PC axon initial segment [16; 17]. In addition to these changes we have reported PC loss [13; 18], a finding that has been variably reproduced [19; 20; 21]. These pathological changes support the concept that the cerebellum is of mechanistic importance in ET [4; 22; 23]. They also support the concept that ET may be a neurodegenerative disease [4; 22; 23; 24].

Although the incidence of ET increases with advancing age [25], the disease may begin at any age. Indeed, ET cases may arise during childhood [26; 27; 28; 29; 30], with one study reporting that 5.3% of cases began prior to age 20 years [25]. Studies indicate that the familial form of ET is enriched for earlier onset cases, many of which arise during childhood [29; 31; 32].

With the notion that ET could be degenerative [4; 22; 23; 24], the question arises as to whether childhood-onset cases, whose disease duration is generally very long, are also degenerative. Whether they manifest the same sets of pathological changes as those whose onset is during adult life has yet to be examined. We capitalized on a large, prospectively-assembled collection of ET brains, including both childhood-onset and adult-onset forms, to investigate whether the postmortem changes in the cerebellum differ between childhood-onset and adult-onset cases.

Methods

Brain repository, study subjects, sample size

ET brains were from the Essential Tremor Centralized Brain Repository (ETCBBR), a joint effort between investigators at Yale and Columbia Universities [33; 34]. ET diagnoses were all carefully assigned using three sequential methods, as described at length [14]. Briefly, the

clinical diagnosis of ET was initially assigned by treating neurologists, and then confirmed by an ETCBR study neurologist (EDL) using clinical questionnaires, review of medical records and examination of Archimedes spirals. Third, a detailed, videotaped, neurological examination was performed, and published diagnostic criteria applied, as described [35]. A total tremor score (range = 0 – 36) was assigned to each ET case based on the severity of postural and kinetic tremor (pouring, drinking, using spoon, drawing spirals, finger-nose-finger) on videotaped examination [33; 34]. None of the ET cases had a history of (1) traumatic brain injury, (2) exposure to medications known to cause cerebellar damage, or (3) heavy ethanol use, as previously defined [33; 34; 36].

Childhood-onset ET was defined as ET whose age of onset was less than or equal to 18 years of age [26].

Most of the control brains were obtained from the New York Brain Bank (NYBB) (n = 21) and were from individuals followed at the Alzheimer disease (AD) Research Center or the Washington Heights Inwood Columbia Aging Project at Columbia University [33; 34]. They had been followed prospectively with serial neurological examinations, and were clinically free of AD, ET, Parkinson's disease (PD), Lewy body dementia, or progressive supranuclear palsy (PSP). Nine control brains were from Harvard Brain Tissue Resource Center (McLean Hospital, Belmont, MA) [33; 34]. During life, all cases and controls signed informed consent approved by these University Ethics Boards.

These analyses were performed on a sample of 90 brains comprising a 2:1 age-match of 60 ET cases and 30 controls [33; 34]. We performed a power analysis that utilized data from our previous publications on PC counts [13] and torpedo counts [7]. Our sample (11 childhood-onset ET cases, 49 adult-onset ET cases, and 30 controls) was powered at > 80% to detect differences between study groups (childhood-onset ET vs. controls, childhood-onset ET vs. adult-onset ET) of the magnitudes previously detected.

Neuropathological assessment

All ET and control brains had a complete neuropathological assessment at the NYBB and Harvard Brain Bank [33; 34]. Each brain had a standardized measurement of brain weight (grams), postmortem interval (PMI, hours between death and placement of brain in a cold room or upon ice), Braak and Braak AD staging for neurofibrillary tangles [37; 38], and Consortium to Establish a Registry for AD (CERAD) ratings for neuritic plaques [39]. We did not include any ET cases with either Lewy body pathology (α -synuclein staining) or PSP pathology [40].

Characterization of cerebellar pathology

A standard 3 × 20 × 25 mm parasagittal, formalin-fixed, tissue block was harvested from the neocerebellum; this block included cerebellar cortex, white matter and dentate nucleus [33; 34]. A senior neuropathologist (P.L.F.), blinded to clinical information, counted torpedoes and heterotopic PCs (i.e., a PC whose cell body was completely surrounded by the molecular layer and that did not contact the granule layer) throughout a single Luxol fast blue Hematoxylin & Eosin (LH&E) stained 7- μ m thick section from this block [15]. PCs

were counted and averaged from 15 microscopic fields at 100x magnification (LH&E) [33; 34].

We have previously shown that examination of a single, standard section provides an adequate representation of the pathology within that sample block. Using a systematic uniform random (SUR) sampling approach, one of every five sections obtained from a series of 40 collected paraffin sections from the standard cerebellar block was stained with LH&E. We determined that there was little variation in torpedo and PC counts among sampled sections within this block in 11 ET and 9 control brains. The agreement between these counts was very high (for torpedo counts, intraclass correlation coefficient = 0.96, $p < 0.001$; for PC counts, intraclass correlation coefficient = 0.94, $p < 0.001$).

In addition, a single 7- μ m thick paraffin section was stained by modified Bielschowsky silver technique and a semi-quantitative basket cell plexus rating scale was applied: 0 (few, or no discernible processes); 1 (sparse number of processes); 2 (moderate number of processes); and 3 (dense tangle of processes). In some instances, as described, the rater used intermediate values (0.5, 1.5, and 2.5) [17; 33; 34].

Calbindin_{D28k} immunohistochemistry was performed in free-floating 100 μ m thick, formalin-fixed vibratome sections of cerebellar cortex to visualize PC axonal morphology. The sections were heated at 37°C for 10 min in 20 μ g/ml Proteinase K (Roche Applied Science) in 10 mM Tris, 0.1 mM EDTA, pH 8, followed by 1% hydrogen peroxide in PBS for 30 min and serum blocking solution (10% normal goat serum, 1% IgG-free bovine serum albumin [Jackson ImmunoResearch], 1% Triton^{TM}X-100, in PBS) for 1 hour. Rabbit polyclonal anti-calbindin D28k (1:1000, Swant) was applied overnight at 4°C in antibody diluent (1% IgG-free bovine serum albumin, 1% Triton^{TM}X-100 in PBS). Secondary antibody (1:200, 2 hours, biotin-SP goat-anti-rabbit [Fisher Scientific]), followed by streptavidin-horseradish peroxidase (1:200, 1 h, AbD Serotec, for biotinylated antibodies) was developed with 3,3'-diaminobenzidine chromogen solution (Dako). PC axonal morphology in 10 randomly-selected 100X images from three sections was quantified in each brain: axon recurrent collaterals (an axon with at least a 90° turn back towards the PC layer from its initial trajectory), thickened PC axonal profiles (an axon with at least double the width of other apparently normal axons), and PC axonal branching (any PC axon with at least one branch point; multiple bifurcations on the same axon were not separately counted). The raw counts of Purkinje cell axonal features were normalized to the total length of the Purkinje cell layer length [14; 33; 34].

Statistical analyses

We first compared clinical and pathological characteristics between ET cases and controls (Table 1), but our main analyses were to compare childhood-onset ET to controls and then childhood-onset ET to adult-onset ET (Table 2). Clinical characteristics such as gender were compared using chi-square tests. Age at death, total tremor score, and PC counts were normally distributed (Kolmogorov-Smirnov test p values > 0.05); thus, we compared groups using Student's t tests. Age of tremor onset, duration of tremor, torpedo counts, heterotopic PC counts, basket cell plexus rating, PC axonal recurrent collateral counts, PC thickened axon counts, and PC axonal branching counts were not normally distributed (Kolmogorov-

Smirnov test p values < 0.05). Therefore, we used Mann-Whitney tests. Data were analyzed in SPSS (version 24).

Results

The 60 ET cases and 30 controls were similar in age at death and gender (Table 1). When compared with controls, ET cases had lower PC counts, more torpedoes, more heterotopic PCs, a higher basket cell plexus rating, an increase in PC axonal collaterals, an increase in PC thickened axonal profiles, and an increase in PC axonal branching (Table 1).

We compared the clinical characteristics of cases with childhood-onset ET to controls (Table 2). There were no differences in age at death or gender (Table 2). Childhood-onset ET cases had lower PC counts, higher torpedo counts, higher heterotopic PC counts, higher basket cell plexus rating, and marginally higher ($p = 0.059$) PC axonal recurrent collateral counts than controls (Table 2). The median PC thickened axonal profile count and median PC axonal branching count were two to five times higher in childhood-onset ET than controls, but the differences did not reach statistical significance in this small sample (Table 2).

We compared the clinical characteristics of cases with childhood-onset ET to cases with adult-onset ET (Table 2). There were no differences in age at death or gender (Table 2). As expected, childhood-onset ET cases had a younger mean age of tremor onset and a longer duration of tremor than adult-onset ET cases. The two groups did not differ with respect to total tremor score. The two groups were similar in terms of PC counts, torpedo counts, heterotopic PC counts, basket cell plexus rating, PC axonal recurrent collateral counts, PC thickened axonal profile count and PC axonal branching count (Table 2, Figure 1).

Discussion

We investigated whether postmortem changes in the cerebellum differ in childhood-onset vs. adult-onset ET. To our knowledge, this specific issue has not been addressed in the literature in prior analyses. We found that childhood-onset and adult-onset ET shared similar pathological changes in cerebellum. The data suggest that pathological changes we have observed in the cerebellum in ET are a part of the pathophysiological cascade of events in both forms of the disease. The data also suggest that both groups seem to reach the same pathological endpoints at a similar age of death.

Is it possible that a disease can begin in childhood, and then continue with a slow form of degeneration over 50 – 70 years into adulthood? There are certainly several examples of this in the cerebellar degenerations. For example, some forms of SCA, such as SCA13, SCA14 and SCA28 [41; 42; 43; 44], begin in childhood and/or early adult life, progress very slowly and may be associated with a normal lifespan. In some (e.g., SCA13), the disease, which begins in childhood, is even considered degenerative yet non-progressive [41; 42].

Clinically, while childhood-onset ET cases are more often familial than adult-onset cases [32], there have been no consistently reported clinical differences between childhood-onset and adult-onset ET cases. Hence, it is possible that postmortem features are overall similar as well. It is also possible that the postmortem changes we have observed are non-specific

cellular changes rather than disease-specific molecular changes that are more proximate to the underlying cause of ET. It may be that the differences between childhood-onset and adult-onset ET will eventually become more apparent on a molecular level, once the molecular bases for ET are better explored.

One may ask, in other neurodegenerative disease, how juvenile and adult-onset cases compare with one another in terms of postmortem features. In Huntington's disease, a number of postmortem features are more likely to occur in individuals with juvenile-onset than adult-onset disease, including the presence of greater diffuse atrophy, the presence of severe atrophy of the internal segment of the globus pallidum, and the blurring of the striatal gradient of severity of neuronal loss and reactive gliosis (e.g., the relative preservation of the nucleus accumbens is no longer visible or identifiable) [45]. Individuals with juvenile-onset Parkinson's disease have been classified into three groups: (1) cases whose pathological features do not differ from those with adult-onset disease, (2) cases with more severe neuronal degeneration with more widespread Lewy bodies, and (3) familial cases with deficient or absent melanin in the substantia nigra, in the presence of nigral Lewy bodies [46]. However, other patterns exist - other familial juvenile Parkinson's disease cases do not have Lewy bodies [47]. In summary, some juvenile onset Parkinson's disease cases seem to exhibit postmortem changes that differ from adult-onset Parkinson's disease cases whereas others do not.

This study should be interpreted within the context of several potential limitations. First, we did not directly compare pathological features in other relevant brain areas that are connected to the cerebellar cortex as part of functional-physiological loops (e.g., thalamus, inferior olivary nucleus). Nonetheless, we have not observed any changes in these brain regions in ET to date. With specific regards to the inferior olivary nucleus, in our study comparing a range of microscopic changes in this brain region in ET cases and controls, there were no differences [48]. Second, we did not employ stereological methods for PC counts; nonetheless, we have previously validated PC counting with a random sampling approach [19]. Third, age of onset was based on self-report. Prior studies have indicated that age of tremor onset is reliably reported by ET patients [49]. Indeed, the test-retest reliability for reported age of onset in ET, r , was 0.91, and among individuals with younger age of onset it was even higher, with $r = 0.99$ [49]. In 75% of cases, the difference in reported ages was ± 5 years. Fourth, the number of childhood-onset cases was small; nonetheless, we were able to detect significant differences between childhood-onset ET and controls for most postmortem features, even with this small sample. Finally, future studies comparing molecular markers would be of value and could be more sensitive; at the moment, however, none have been identified for ET.

Our study had several strengths. First, we investigated a carefully-diagnosed ET cohort. Second, we studied a broad range of postmortem features. Third, our sample included not only comparison of ET groups but a control group as well.

Conclusions

In conclusion, we found that childhood-onset and adult-onset ET shared similar pathological changes in the cerebellum. The data suggest that pathological changes we have observed in the cerebellum in ET are a part of the pathophysiological cascade of events in both forms of the disease and that both groups seem to reach the same pathological endpoints at a similar age of death.

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Highlights

- Little is known about the underlying pathology of childhood onset ET
- Do childhood- and adult-onset ET share the same degenerative cerebellar pathology?
- We quantified a range of postmortem changes in childhood- and adult-onset ET cases
- In all measures, both forms of this disease shared similar cerebellar pathology
- Childhood- and adult-onset ET both exhibit degenerative changes in the cerebellum

Figure 1.

(**A–D**) Childhood-Onset essential tremor (ET) cases, (**E–H**) Adult-Onset ET cases, (**I–L**) Controls.

A,E. Purkinje cell (PC) axonal torpedo (arrow) in ET cases, Luxol fast blue Hematoxylin & Eosin (LH&E) x 400. No torpedo is seen in the control (**I**).

B,F. Heterotopic PC (arrow) mislocalized in the molecular layer, LH&E x200. A heterotopic PC is not visualized in the control (**J**).

C,G. Dense tangle of processes (basket plexus), Bielschowsky x200. No dense tangle is seen in the control (**K**).

D,H. Calbindin PC axonal branching (arrows) and recurrent collaterals (carets), x200. The axons appear normal in the control (**L**).

Table 1

Clinical and pathological features of controls and ET cases

Variables	Controls	ET cases	<i>p</i> -value
<i>n</i>	30	60	
Age at death (years)	85.2 ± 5.7	86.0 ± 6.6	0.57 ^a
Age of tremor onset (years)	NA	44.0 ± 21.6 Median = 47.5	NA
Duration of tremor (years)	NA	42.0 ± 21.5 Median = 39.0	NA
Gender			0.23 ^b
Male	15 (50.0%)	22 (36.7%)	
Female	15 (50.0%)	38 (63.3%)	
Total tremor scores	NA	24.9 ± 6.4	NA
Purkinje cell counts ^I	10.52 ± 1.49	8.82 ± 1.48	<0.001 ^a
Torpedo counts	3.90 ± 3.28 Median = 3.00	15.38 ± 15.02 Median = 12.00	<0.001 ^c
Heterotopic Purkinje cell counts	6.23 ± 11.45 Median = 2.00	7.65 ± 9.14 Median = 4.50	0.020 ^c
Basket cell plexus rating	1.57 ± 0.61 Median = 1.50	2.00 ± 0.78 Median = 2.00	0.004 ^c
Purkinje cell axonal recurrent collateral counts	1.01 ± 1.16 Median = 0.60	1.88 ± 1.53 Median = 1.42	0.006 ^c
Purkinje cell thickened axonal profile counts	0.96 ± 1.60 Median = 0.55	1.76 ± 2.32 Median = 1.09	0.017 ^c
Purkinje cell axonal branching counts	0.09 ± 0.10 Median = 0.07	0.37 ± 0.40 Median = 0.27	<0.001 ^c

Values represent mean ± standard deviation or number (percentage), and for variables with non-normal distribution, the median is reported as well.

^I Mean number of Purkinje Cell Counts (PCs) per 100x microscopic field, among 15 sampled fields.

^aIndependent samples t-test

^bChi-square test

^cIndependent samples Mann-Whitney U test

NA = not applicable.

Table 2

Clinical and pathological features of ET cases grouped by age of onset

Variables	Controls		ET		Childhood-Onset ET vs. Controls	Childhood-Onset ET vs. Adult-Onset ET
			Childhood-Onset ET	Adult-Onset ET		
<i>n</i>	30	11	49			
Age at death (years)	85.2 ± 5.7	84.0 ± 9.4	86.5 ± 5.9	0.61 ^a		0.26 ^a
Age of tremor onset (years)	NA	12.1 ± 3.9 Median = 13.0	51.2 ± 16.9 Median = 55.0	NA		<0.001 ^c
Duration of tremor (years)	NA	71.9 ± 10.2 Median = 74.0	35.3 ± 17.2 Median = 32.0	NA		<0.001 ^c
Gender						
Male	15 (50.0%)	4 (36.4%)	18 (36.7%)	0.44 ^b		1.00 ^d
Female	15 (15.0%)	7 (63.6%)	31 (63.3%)			
Total tremor scores	NA	23.4 ± 5.6	25.3 ± 6.6	NA		0.45 ^a
Purkinje cell counts	10.52 ± 1.49	8.99 ± 1.22	8.62 ± 1.98	0.004 ^a		0.55 ^a
Torpedo counts	3.90 ± 3.28 Median = 3.00	18.73 ± 22.71 Median = 13.00	14.63 ± 12.92 Median = 9.00	<0.001 ^c		0.78 ^c
Heterotopic Purkinje cell counts	6.23 ± 11.45 Median = 2.00	10.45 ± 13.94 Median = 6.00	7.02 ± 7.74 Median = 4.00	0.04 ^c		0.45 ^c
Basket cell plexus rating	1.57 ± 0.61 Median = 1.50	2.10 ± 0.58 Median = 2.00	1.98 ± 0.82 Median = 2.00	0.03 ^c		0.80 ^c
Purkinje cell axonal recurrent collateral counts	1.01 ± 1.16 Median = 0.60	1.66 ± 1.14 Median = 1.28	1.94 ± 1.63 Median = 1.51	0.059 ^c		0.78 ^c
Purkinje cell thickened axonal profile counts	0.96 ± 1.60 Median = 0.55	1.08 ± 0.82 Median = 0.99	1.94 ± 2.56 Median = 1.09	0.24 ^c		0.49 ^c
Purkinje cell axonal branching counts	0.09 ± 0.10 Median = 0.07	0.30 ± 0.27 Median = 0.34	0.39 ± 0.43 Median = 0.27	0.14 ^c		0.64 ^c

Values represent mean ± standard deviation or number (percentage), and for variables with non-normal distribution, the median is reported as well.

Mean number of Purkinje Cell Counts (PCs) per 100x microscopic field, among 15 sampled fields.

^aStudent's *t* test^bChi-square test^cIndependent samples Mann-Whitney U test

Fisher's exact test
 p

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