Cerebellar Pathology of a Dual Clinical Diagnosis: Patients with Essential Tremor and Dystonia

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Abstract

Background: Clinical studies have implicated the cerebellum in the pathogenesis of essential tremor (ET), and recent postmortem studies have identified structural changes in the ET cerebellum. While the basal ganglia have traditionally been implicated in dystonia, cerebellar involvement has been suggested as well, and a recent study showed Purkinje cell (PC) loss. We conducted a detailed postmortem examination of the brain in four individuals with clinical diagnoses of ET and dystonia, and hypothesized that pathological changes in the cerebellum would be greater in these four ET cases than in published ET cases without dystonia.

Methods: After a complete neuropathological assessment, a standard parasagittal neocerebellar tissue block was harvested in each brain. One 7-μm thick section was stained with luxol fast blue/hematoxylin and eosin, and one section with the Bielschowsky method. We quantified PCs, torpedoes, heterotopic PCs, PC dendritic swellings, and basket cell changes.

Results: Two ET+dystonia cases had more microscopic changes in the cerebellum than published ET cases; the other two cases had similar changes to published ET cases.

Discussion: This is the first report that uses human autopsy tissue to study patients with both ET and dystonia. The findings were heterogeneous. Additional studies, with larger samples, are needed.

Keywords: Essential tremor, dystonia, cerebellum, Purkinje cells, neuropathology


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Editor: Julian Benito-Leon, Hospital “12 de Octubre”, Spain
Received: May 21, 2012 Accepted: June 1, 2012 Published: August 6, 2012
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Funding: This study was supported by R01 NS042859 (National Institutes of Health, Bethesda, MD) and by the Claire O’Neil Essential Tremor Research Fund (Columbia University).
Financial Disclosures: None.
Conflict of Interest: The authors report no conflict of interest.

Introduction

Essential tremor (ET) is the most common tremor disorder and among the most prevalent of neurological disorders in adults.¹ Kinetic tremor in the arms is characteristic of ET, although patients may also have cranial (neck, voice, jaw) tremors, and gait and balance issues.¹ ³ The cerebellum has been implicated in ET in clinical and neuroimaging studies.⁴ ⁶ Pathological changes have also been observed in recent postmortem studies of the brains of ET patients. ET patients have six to seven times more Purkinje cell (PC) axonal swellings (“torpedoes”) than controls.¹ Other significant pathological changes include an increase in PC dendritic swellings, an increase in heterotopic PCs, a reduction in the number of PCs (i.e., PC loss), and an unusually dense basket cell axonal plexus (“hairy baskets”) surrounding the PC soma.⁷ ¹⁰

Dystonia is a neurological syndrome characterized by simultaneous contractions of agonist and antagonist muscles, resulting in sustained postures, twisting movements or tremor.¹¹ Dystonic movements or postures may affect almost any part of the body, including the laryngeal muscles during speech (spasmodic dysphonia), the neck (torticollis), the periorbital muscles (blepharospasm), and the arms.¹¹ ¹³ Traditionally, dystonia has been attributed to dysfunction of the basal
ganglia. However, several other brain regions, including the cerebellum, have recently been posited to contribute to the pathophysiology of dystonia. There are a limited number of human autopsy studies of patients who had dystonia, and even fewer that have examined the cerebellum. None quantified PCs. More recently, a group of investigators described mild PC loss in the cerebellum in adult onset primary focal dystonia. This finding is similar to what has been observed in the brains of ET patients.

In the current study, four cases diagnosed during life with ET and dystonia were prospectively collected at the Essential Tremor Centralized Brain Repository (ETCBR) at Columbia University. We conducted a detailed postmortem examination of the brains of these four individuals, and hypothesized that pathological changes in the cerebellum would be greater in these ET+dystonia cases than in published ET cases without dystonia.

**Methods**

Each of these four ET+dystonia patients was enrolled as a participant in the ETCBR of the New York Brain Bank (NYBB) at Columbia University Medical Center (CUMC). The NYBB operates under approval of the institutional review board of CUMC.

Clinical ET diagnoses were carefully assigned using each of the following three sequential methods. First, cases were diagnosed clinically with ET by their treating physician (in three, this was a treating neurologist and in one, a general doctor). Second, cases were asked to complete a series of semi-structured clinical questionnaires, which were supplemented with additional medical information (from clinical records, treating physicians, family members). Each case also produced four standardized hand-drawn Archimedes spirals (two right and two left, each on a 8.5 x 11 inch sheet of paper). Based on these data, ET diagnoses were then confirmed by a senior neurologist specializing in movement disorders (E.D.L.) who used the following diagnostic criteria: 1) moderate or greater amplitude arm tremor (rating of 2 or higher) in at least one of the submitted Archimedes spirals (Figure 1), 2) no history of Parkinson’s disease (PD), and 3) no other etiology for tremor (i.e., medications). Third, ET cases then underwent a standardized, videotaped neurological examination.

The videotaped examination included several tests to elicitor postural tremor (sustained arm extension) and five tests to elicit kinetic tremor (e.g., writing, pouring, drawing Archimedes spirals). Each of these six tests was performed with each arm (12 tests total). Videotaped action tremor was rated by a senior neurologist specializing in movement disorders (E.D.L.) during each test using a scale from 0 (no tremor) to 3 (large amplitude tremor), resulting in a total tremor score (range 0–36). The videotape protocol also included assessment of neck, voice, and jaw tremors. The videotaped examination incorporated the motor portion of the Unified Parkinson’s Disease Rating Scale, including assessments of speech, facial expression, rest tremor, bradykinesia, posture, arising from a chair, and gait while walking and turning.

Each videotape was reviewed (E.D.L.) and the diagnosis of ET was confirmed in each case using published diagnostic criteria that required the presence of moderate or greater amplitude tremor on three or more tests.

Dystonia is defined as a disorder of sustained muscle contractions, often causing abnormal postures, or twisting and repetitive movements. In addition to dystonic postures or tremor during sustained arm extension, the videotape was assessed for the presence of spasmodic torticollis, voice tremor, and blepharospasm. Criteria for dystonia followed those recommended by Fahn. Spasmodic torticollis was defined as the presence of twisting or tilting movements of the neck, jerk-like or sustained neck deviation, often with mild hypertrophy of neck muscles. Voice tremor was assessed during sustained phonation, while reading a prepared paragraph, and during speech. If present, voice tremor was attributed to ET (tremor without voice breaks, strangled speech) or dystonia (tremor with voice breaks, strangled speech).

As previously described, all brains underwent a complete neuropathological assessment at the NYBB, which included the harvesting of standardized blocks from 18 brain regions. All brains had standardized measurements of brain weight (grams), postmortem interval (PMI, hours between death and the placement of the brain in a cold room or upon ice), Braak and Braak Alzheimer’s disease (AD) staging for neurofibrillary tangles, Braak PD staging, and the Consortium to Establish a Registry for AD ratings for neuritic plaques.

As described, a standard 3 x 20 x 25 mm parasagittal, formalin-fixed tissue block was harvested from the neocerebellum; the block included the cerebellar cortex, white matter, and dentate nucleus. For each of these four ET+dystonia cases, two sequential 7 μm thick paraffin sections were obtained. One was stained with luxol fast blue counterstained with hematoxylin and eosin (LH&E) and the other was stained with a Bielschowsky silver method. Torpedoes were counted throughout the entire LH&E and Bielschowsky-stained sections. Heterotopic PCs and PC dendritic swellings were counted throughout the entire LH&E section, and PCs were counted in 15 100 × fields (LH&E) and then averaged. A semiquantitative rating of the appearance of the basket cell plexus surrounding PC bodies throughout Bielschowsky preparations was carried out, as previously described. The following scale was used: 0 (few, or no discernible

**Figure 1. Archimedes Spirals Drawn by Case 4 First with the Right Hand (A) and then the Left Hand (B).** These spirals were each assigned a rating of 3 (large amplitude tremor).
processes); 1 (sparse number of processes); 2 (moderate number of processes); and 3 (dense tangle of processes). In some instances, the rater used intermediate values (0.5, 1.5, and 2.5). Counts in the four ET+dystonia brains were compared with published values from cerebellar ET brains collected through the ETCBR. Counts in the four ET+dystonia brains were compared with published values from cerebellar ET brains collected through the ETCBR.7,8,9,10

**Results**

All four cases had an ET diagnosis during life (three by their treating neurologists, one by a general doctor) based on the presence of moderate-to-severe and longstanding kinetic and postural arm tremor (in Figure 1, see example of spirals in case 4). None of the cases had been exposed to cerebellar toxic medications, and none had clinical dementia or deep brain stimulation surgery. Based on the review of the videotaped neurological examination (E.D.L.), the ET diagnosis was reconfirmed using published diagnostic criteria. Each case had moderate to severe, bilateral kinetic and postural tremor of the arms. Additionally, each case had mild torticollis that had not been self-reported or recognized or diagnosed by their treating physician (Table 1). On videotape, cases 2, 3, and 4 also had subtle dystonic posturing of one or both arms during arm extension, and case 3 also had spasmodic dysphonia with voice breaks on sustained phonation. In contrast to the features of ET, the dystonia was subtle, unreported, undiagnosed, and mild.

On postmortem examination, none of the ET+dystonia brains had brainstem or cortical Lewy bodies (Table 2). Case 2 had a 1.1 cm infarct in the external segment of the left globus pallidus. Case 3 had a 0.4 cm infarct in the lateral portion of the right putamen. The basal ganglia (caudate, putamen, globus

<table>
<thead>
<tr>
<th>Table 1. Clinical Features of ET+Dystonia Cases</th>
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<tbody>
<tr>
<td>Case 1</td>
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<tr>
<td>Age at death (years)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Age at ET Onset (years)</td>
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<tr>
<td>Duration of ET at death (years)</td>
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<tr>
<td>Heavy ethanol use</td>
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<tr>
<td>Exposure to cerebellar-toxic medication</td>
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<tr>
<td>Archimedes spiral ratings</td>
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<tr>
<td>Total tremor score</td>
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<tr>
<td>Other features of ET</td>
</tr>
<tr>
<td>ET medications</td>
</tr>
<tr>
<td>Severity of dystonia</td>
</tr>
<tr>
<td>Location of dystonic postures</td>
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<tr>
<td>Family history of tremor</td>
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Abbreviations: Cz, clonazepam; ET, essential tremor; JT, jaw tremor; PD, Parkinson’s disease; Prim, primidone; Prop, propranolol; R, right arm; L, left arm; VT, voice tremor.

^1Heavy ethanol use was defined as consumption of an average of four or more standard drinks (15 ml of absolute ethanol) per day for a man, or three or more per day for a woman, at any point in their lives.

^2Exposure to cerebellar-toxic medication was defined as lifetime exposure to medications that can produce cerebellar damage (e.g., lithium, diphenylhydantoin, chemotherapeutic agents).

^3Archimedes spirals were rated on a scale from 0 (no tremor) to 3 (large amplitude tremor), and included values of 0, 0.5, 1, 1.5, 2, and 3.

^4Total tremor score ranged from 0 (no tremor) to 36 (severe tremor).

^5Case 4 also had left vagus nerve stimulation surgery for tremor control.

^6Mild, irregular head tremor was also present.
pallidum, substantia nigra pars compacta) were otherwise normal in these two cases, and normal in cases 1 and 4.

In cases 1, 2, and 4, torpedo counts (on both LH&E and Bielschowsky-stained sections) were at the upper end or above that which has been reported and published in ET (Figure 2A,B). In cases 1 and 4, other counts (e.g., heterotopic PCs and PC dendritic swellings in case 1, and Basket plexus rating and PC dendritic swellings in case 4) were elevated as well (Figure 2). By contrast, most of the counts of cases 2 and 3 were well within the range of that which has been reported in ET (Figure 2A–F).

**Discussion**

Clinical studies have implicated the cerebellum in the pathogenesis of ET, and postmortem studies have identified structural changes in the ET cerebellum.4–10 While the basal ganglia have traditionally been implicated in dystonia, cerebellar involvement has been suggested as well,11 and a recent study showed PC loss.12 We conducted a detailed postmortem examination of the brain in four individuals with clinical diagnoses of ET and dystonia. Our findings for these four ET+dystonia cases were heterogeneous. Two ET+dystonia cases had more microscopic changes in the cerebellum than published ET cases; the other two cases had similar changes to published ET cases.7–10 Interestingly, the two cases (cases 1 and 4) with more microscopic changes in the cerebellum than published ET cases both had normal basal ganglia. Yet the other two cases (cases 2 and 3) each had a unilateral infarct in the basal ganglia. However, the clinical significance of these infarcts is not clear; indeed, in neither case could a unilateral lesion have accounted for their dystonic features, which were bilateral (Case 2) and widespread (torticollis, spasmodic dysphonia, left arm in Case 3).

To our knowledge, this is the first clinicopathological report on patients with both ET and dystonia. A recent study describes PC loss in adult onset primary focal dystonia.18 There are only a handful of postmortem studies conducted on dystonic human autopsy tissue, and only a few of these examine the cerebellum.12,13,15–17 None quantified PCs, torpedoes, or the microscopic changes we evaluated here. Thus, our contribution of four cases with both diagnoses seems to be unique. Yet additional studies, with larger samples, are still needed to explore the mechanistic basis of ET and dystonia.

Each case had moderate to severe, bilateral kinetic and postural tremor of the arms that was of long duration (25–67 years). In contrast to the signature feature of ET, the dystonia was subtle and mild. Indeed, the dystonia had not been self-reported or recognized or diagnosed by their treating physician. However, the presence of torsional neck movements on the videotaped neurological examination was unmistakably identified as spasmodic torticollis by a senior movement disorder neurologist and other features of dystonia were clearly present on examination in several cases. This raises the conceptual issue as to whether the dystonia seen on the examination of these four cases was a clinical sign that was merely a manifestation of longstanding ET (i.e., one disease), or if these patients had two neurological diseases (ET and dystonia). A third, albeit remote, possibility is that these patients had dystonia only (i.e., their “ET” was all merely dystonic tremor). However, because of the long duration (25+ years) of bilateral kinetic and postural arm tremor, the family

### Table 2. Neuropathological Features of ET+Dystonia Cases

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain weight (g)</td>
<td>1155.0</td>
<td>1127.2</td>
<td>1189.4</td>
</tr>
<tr>
<td>PMI cold (hours)</td>
<td>1.0</td>
<td>4.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Braak AD stage</td>
<td>1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Braak PD stage</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CERAD score</td>
<td>0</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Torpedoes (LH&amp;E)</td>
<td>19</td>
<td>21</td>
<td>3</td>
</tr>
<tr>
<td>Torpedoes (Bielschowsky)</td>
<td>56</td>
<td>33</td>
<td>14</td>
</tr>
<tr>
<td>PCs (LH&amp;E)</td>
<td>5.7</td>
<td>9.9</td>
<td>9.4</td>
</tr>
<tr>
<td>Dendritic Swellings (LH&amp;E)</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Heterotopic PCs (LH&amp;E)</td>
<td>7</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Basket cell plexus rating</td>
<td>2.0</td>
<td>1.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

**Abbreviations:** AD, Alzheimer’s disease; CERAD, Consortium to Establish a Registry for AD; LH&E, luxol fast blue counterstained with hematoxylin and eosin; PC, Purkinje cell; PD, Parkinson’s disease; PMI, postmortem interval.

1Purkinje cells were counted in 15 100× fields (LH&E) and then averaged.
We hypothesized that pathological changes in the cerebellum would be greater in these ET+dystonia cases than in published ET cases without dystonia; thus, control data were not directly relevant to our study hypothesis. These data have been published in several prior reports and are readily available; they were not reproduced here.

Future work on the pathogenesis of dystonia, and whether it involves the cerebellum, is important. Clinical, imaging, electrophysiological, and postmortem studies are critical for the evaluation of this area.

References


