Reduced Purkinje Cell Number in Essential Tremor

A Postmortem Study

Jordan E. Axelrad, BS; Elan D. Louis, MD, MSc; Lawrence S. Honig, MD, PhD; Ingrid Flores, MS; G. Webster Ross, MD; Rajesh Pahwa, MD; Kelly E. Lyons, PhD; Phyllis L. Faust, MD, PhD; Jean Paul G. Vonsattel, MD

Background: Clinical and functional imaging evidence suggests that cerebellar dysfunction occurs in essential tremor (ET). In recent postmortem studies, we documented increased numbers of torpedoes (Purkinje cell axonal swellings) in ET patients without Lewy bodies. Purkinje cell loss, however, has never been rigorously assessed.

Objective: To quantitatively assess the number of Purkinje cells in brains of ET patients and similarly aged controls.

Methods: Postmortem cerebellar tissue was available in 14 ET cases (6 with Lewy bodies and 8 without Lewy bodies) and 11 controls. Calbindin immunohistochemistry was performed on paraffin sections of the cerebellum. Images were digitally recorded and blinded measurements of the number of Purkinje cells per millimeter of cell layer (linear density) were made.

Results: Purkinje cell linear density was inversely correlated with age ($r = -0.53$, $P = .006$) and number of torpedoes ($r = -0.42$, $P = .04$). Purkinje cell linear density differed by diagnosis (mean [SD], controls, 3.46 [1.27] cells/mm; ET cases with Lewy bodies, 3.33 [1.06] cells/mm; and ET cases without Lewy bodies, 2.14 [0.82] cells/mm; $P = .04$), with the most significant difference between ET cases without Lewy bodies and controls, where the reduction was 38.2% ($P = .04$). In an adjusted linear regression analysis that compared ET cases without Lewy bodies with controls, decreased linear density (outcome variable) was associated with ET ($\beta = .56$, $P = .03$).

Conclusions: We demonstrated a reduction in Purkinje cell number in the brains of patients with ET who do not have Lewy bodies. These data further support the view that the cerebellum is anatomically, as well as functionally, abnormal in these ET cases.

Arch Neurol. 2008;65(1):101-107

ESSENTIAL TREMOR (ET) IS A common and often progressive neurological disease, with a prevalence of approximately 4% among adults aged 40 years and older.1-3 There have been few postmortem ET studies.4-9 While these studies did not reveal consistent structural abnormalities, several noted mild to marked loss of Purkinje cells. However, as none of these were controlled studies (ie, there were no control brains for comparison), it was not clear whether this finding represented a normal age-related change.

Clinical and functional imaging evidence suggests that cerebellar dysfunction occurs in ET,10-13 and magnetic resonance spectroscopic imaging suggests that metabolic abnormalities occur; these abnormalities might represent neuronal loss.4 In several recent postmortem studies,14,15 we documented a marked increase in the number of Purkinje cell axonal swellings, torpedoes, in ET. In one ET case, the pathologic changes in the cerebellum were more manifest, with degenerative changes in the dentate nucleus.15 However, quantification of Purkinje cells was not rigorous in these earlier reports,14,15 thus it was not clear whether these torpedoes in the ET cerebellum were accompanied by Purkinje cell loss. To address this question, we quantitatively assessed cerebellar Purkinje cell numbers by measuring linear cell densities in ET patients’ brains and controls’ brains. This is the only study, to our knowledge, that has attempted to do so.

METHODS

PARTICIPANTS

This study was conducted at the Essential Tremor Centralized Brain Repository (ETCBR) at Columbia University, New York, New York. Postmortem tissue from the cerebellum was available in 14 ET cases (5 were not included in earlier reports14,15) and 11 control brains (1 was not included in earlier reports14,15). The ET cases included 5 archival and 9 prospectively collected cases. All brains were well characterized by the New York Brain Bank, Columbia University Medical Center, and underwent complete neuropathologic assessment (among other things, this included alpha-
The 9 prospectively collected ET cases were all recruited through International Essential Tremor Foundation newsletters. International Essential Tremor Foundation members who were interested in brain donation responded to these quarterly brain bank advertisements. Each patient had ET diagnosed by his or her treating neurologist. To reconfirm these diagnoses, members interested in brain donation were mailed standardized clinical questionnaires (which included screening questions for Parkinson disease and spinocerebellar ataxia and family history information) and written instructions to assist them in the preparation of a videotaped neurological examination. Based on the instructions, they prepared a 30-minute videotaped neurological examination, following the sequential instructions. The videotape included (1) a full tremor demonstration (assessments of postural arm tremor, rest tremor [while seated and while walking], kinetic tremor [while pouring, using a spoon, drinking, drawing a spiral, and performing the finger-nose-finger maneuver with each hand], head tremor, chin tremor, and voice tremor), (2) elicitation of parkinsonism with items from the motor portion of the Unified Parkinson Disease Rating Scale20 (facial expression and blink frequency while seated and facing the camera, speech, rest tremor in each limb evaluated while seated and while walking, rapid alternating movements [opening and closing each hand, pronating and supinating each hand, and foot taps], arising from a chair to a standing position, standing with arms at the sides, and walking for 60 seconds), and (3) an assessment of cerebellar signs with items taken from the International Cooperative Ataxia Rating Scale21 (as noted, speech, 3 types of rapid alternating movements, finger-nose-finger maneuver, drawing spirals with each hand, sitting, stance, and gait). Using these records, an ETCBR neurologist who specialized in movement disorders confirmed patients’ diagnoses after death using ETCBR diagnostic criteria, which were modeled after the criteria proposed in the Consensus Statement of the Movement Disorder Society.18

Ten of 11 control brains were obtained through the New York Brain Bank. These were individuals who had been enrolled as healthy elderly controls in the Alzheimer’s Disease Research Center or the Washington Heights Inwood Columbia Aging Project; they were followed up prospectively with serial neurological assessments, remaining free of a diagnosis of Alzheimer disease, ET, or Parkinson disease during life and not having significant neuropathologic changes on postmortem evaluation. These 10 controls were selected for this study based on their age (ie, they were frequency matched to ET participants based on age). One control brain was obtained from the Honolulu-Asia Aging Study as a match for the 2 cases from that study. This person had remained free of a neurological diagnosis during life.

Demographic and clinical information was collected on all cases and controls (from treating physicians and also directly from the patient in prospectively collected cases). Heavy ethanol use was defined as a man consuming a mean of 4 or more standard drinks (15 mL of absolute ethanol) per day or a woman consuming 3 or more standard drinks per day.22 Lifetime exposure to medications known to cause cerebellar damage (eg, lithium and diphenylhydantoin) was assessed.

**PROCESSING TISSUE**

Postmortem interval (PMI) was the number of hours between death and placement of the brain in a cold room or on ice. For the current analyses, the cerebellum was our primary region of interest because many studies have implicated its involvement in ET.10,15,21 A 3 × 20 × 25-mm parasagittal tissue block that came from the same region of the neocerebellum in cases and controls and included, in continuity, the cerebellar cortex, white matter, and dentate nucleus, was harvested from each brain and then immersion fixed in buffered formalin, 10%.15,13 Paraffin sections (7 µm) were stained with Luxol fast blue and hematoxylin and cosin for general tissue survey and quantification of torpedoes.

**IMMUNOHISTOCHEMISTRY**

Paraffin sections measuring 7 µm × 20 mm × 25 mm were placed on subbed glass slides. Calbindin immunoreactivity was evaluated using a primary mouse monoclonal antibody to calbindin D-28K (clone CG-955, Sigma-Aldrich Corp, St Louis, Missouri). Sections were deparaffinized, incubated in proteinase K, 0.1% (Sigma-Aldrich Corp), at room temperature for 10 minutes, washed, and then treated with hydrogen peroxide, 3%. All washes used phosphate-buffered saline. Secondary antibody treatment with antimouse IgG was visualized using avidin-biotin peroxidase complex (Vectastain Elite ABC; Vector Laboratories, Burlingame, California) with the chromogen 3,3-diaminobenzidine (DAB Substrate Kit, Vector Laboratories). For each brain, staining was also performed in the absence of primary antibody to be certain no nonspecific 3,3-diaminobenzidine reaction product was present.

**ASSESSMENT OF PURKINJE CELL LINEAR DENSITY AND TORPEDOES**

Sections were examined using a microscope with an × 4 objective. A color charged-coupled device video camera, a video capture card, and Videum 2.9.3a (Winnov, Santa Clara, California) Windows software were used to digitally record microscopic images. These were analyzed to quantify Purkinje cell synuclein–stained sections of the dorsal vagal nucleus, locus ceruleus, and substantia nigra pars compacta; New York Brain Bank Web site, http://nybb.hs.columbia.edu) and determination of any pathologic findings. Each brain was rated by Braak and Braak staging16 for Alzheimer neurofibrillary changes and by Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) staging2 for plaque pathology.

The 5 archival ET cases comprised 2 from the New York Brain Bank, 2 from the Honolulu-Asia Aging Study, and 1 from the University of Kansas Brain Bank. In 3 of the 5 archival ET cases, the treating neurologists, all of whom were neurologists specializing in movement disorders, had assigned the ET diagnoses while the patients were alive. The ETCBR neurologists obtained clinical records (office records from treating internists and neurologists) to acquire data about tremor type, distribution, severity, and duration; coexistence of other medical and neurological disorders; and medications. Using these records, an ETCBR neurologist who specialized in movement disorders confirmed their diagnoses post mortem using ETCBR diagnostic criteria, which were modeled after the diagnostic criteria for ET proposed in the Consensus Statement of the Movement Disorder Society.18 The ETCBR criteria were as follows: (1) bilateral action tremor of the arms for 5 or more years with a diagnosis of ET during life, (2) head tremor or moderate or severe action tremor of at least one hand (ie, tremor resulted in difficulty with 2 or more activities of daily living or required medication), and (3) action tremor was not the result of other movement disorders, hyperthyroidism, other medical conditions, or medications.14 During serial assessments, the 2 archival ET patients from the Honolulu-Asia Aging Study had repeatedly demonstrated moderate to severe bilateral hand tremor in the absence of parkinsonism and other etiologies but had not received a diagnosis of ET during their lives.

**ASSESSMENT OF PURKINJE CELL LINEAR DENSITY AND TORPEDOES**

Sections were examined using a microscope with an × 4 objective. A color charged-coupled device video camera, a video capture card, and Videum 2.9.3a (Winnov, Santa Clara, California) Windows software were used to digitally record microscopic images. These were analyzed to quantify Purkinje cell...
Table. Demographic, Clinical, and Pathologic Features of Essential Tremor (ET) Cases and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All ET Cases</th>
<th>ET Cases With Lewy Bodies</th>
<th>ET Cases Without Lewy Bodies</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>14</td>
<td>6</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
<td>88.0 (7.7)</td>
<td>89.0 (4.2)</td>
<td>87.3 (9.8)</td>
<td>84.6 (8.8)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>7 (50)</td>
<td>4 (66.7)</td>
<td>3 (37.5)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>White race, No. (%)</td>
<td>12 (85.7)</td>
<td>4 (66.7)</td>
<td>8 (100)</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td>Mean postmortem interval (SD), h</td>
<td>6.7 (3.4)</td>
<td>3.9 (3.1)</td>
<td>5.7 (3.3)</td>
<td>7.3 (3.3)</td>
</tr>
<tr>
<td>Mean brain weight (SD), g</td>
<td>1169.7 (335.8)</td>
<td>1241.9 (139.9)</td>
<td>1115.5 (434.5)</td>
<td>1238.1 (129.2)</td>
</tr>
<tr>
<td>History of heavy alcohol use, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated with a medication for ET, No. (%)</td>
<td>10 (74.1)a</td>
<td>5 (83.3)a</td>
<td>5 (62.5)b</td>
<td>0</td>
</tr>
<tr>
<td>Lifetime exposure to a medication known to cause cerebellar damage, No. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean duration of tremor (SD), y</td>
<td>27.9 (21.2)</td>
<td>26.0 (27.8)</td>
<td>29.1 (180)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Family history of ET, first-degree relative, No. (%)</td>
<td>6 (42.9)b</td>
<td>2 (33.3)c</td>
<td>4 (50.0)b</td>
<td>0</td>
</tr>
<tr>
<td>Family history of Parkinson disease, first-degree relative, No. (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean No. of torpedoes (SD)</td>
<td>8.2 (6.3)b</td>
<td>4.8 (4.8)</td>
<td>10.8 (6.3)a</td>
<td>1.2 (1.1)</td>
</tr>
<tr>
<td>Mean Purkinje cell linear density (SD), cells/mm</td>
<td>2.64 (1.09)</td>
<td>3.33 (1.06)</td>
<td>2.14 (0.82)c</td>
<td>3.46 (1.27)</td>
</tr>
</tbody>
</table>

a P < .01 compared with controls.
b P < .05 compared with controls.
c P < .001 compared with controls.

The 14 ET cases were similar to the 11 controls in terms of age, sex, race, PMI, and brain weight. None of the cases or controls had a history of heavy ethanol use or exposure to a medication known to cause cerebellar damage (Table). The mean number of torpedoes was 10 times higher in ET cases without Lewy bodies (mean [SD], 10.8 [6.3]) than in controls (1.2 [1.1]). One of the ET cases with Lewy bodies had Alzheimer disease (CERAD plaque score, C; Braak and Braak stage, V).

Purkinje cell linear density differed by diagnosis (mean [SD], controls, 3.46 [1.27] cells/mm [n=11]; ET cases with Lewy bodies, 3.33 [1.06] cells/mm [n=8]; and ET cases without Lewy bodies, 2.14 [0.82] cells/mm [n=6]; F=3.71; P=.04). In this analysis, there was a significant 38.2% difference (P=.04) between ET cases without Lewy bodies and controls (Figure 1 and Figure 2). Combining all 14 ET cases into one group, mean Purkinje cell linear density was 2.64 (SD, 1.09) cells/mm (ie, 23.3% of ET cases was also applied in the current analyses and all cases fell into 1 of these 2 categories.

Statistical analyses were performed using SPSS, version 13.0 (SPSS Inc, Chicago, Illinois). We used χ² tests, t tests, and analysis of variance to compare ET cases with controls in terms of age, sex, and other characteristics. Pearson coefficients (r) were used to assess correlations between continuous, normally distributed variables. Purkinje cell linear densities were compared among diagnostic groups using t tests and analysis of variance. In an unadjusted linear regression analysis, in which the dependent variable was Purkinje cell linear density, we compared diagnostic groups. This model was then adjusted for age, sex, and PMI. We also tested for a trend in Purkinje cell linear density using a similar linear regression model that included all 3 diagnostic groups (controls [reference group], ET cases with Lewy bodies, and ET cases without Lewy bodies). In some analyses, ET cases were stratified into those with 10 or more torpedoes vs those with fewer than 10.

**RESULTS**

In a previous study,14 ET cases demonstrated 2 patterns of pathologic changes: ET cases with Lewy bodies vs ET cases without Lewy bodies. As reported previously,14 these Lewy bodies were primarily found in the locus ceruleus. The number of cerebellar torpedoes was significantly increased in the ET cases without Lewy bodies.14 This pathologic subdivision of ET cases without Lewy bodies. As reported previously,14 these Lewy bodies were primarily found in the locus ceruleus. The number of cerebellar torpedoes was significantly increased in the ET cases without Lewy bodies.14 This pathologic subdivision

---

In a previous study, ET cases demonstrated 2 patterns of pathologic changes: ET cases with Lewy bodies vs ET cases without Lewy bodies. As reported previously, these Lewy bodies were primarily found in the locus ceruleus. The number of cerebellar torpedoes was significantly increased in the ET cases without Lewy bodies.

This pathologic subdivision of ET cases without Lewy bodies. As reported previously, these Lewy bodies were primarily found in the locus ceruleus. The number of cerebellar torpedoes was significantly increased in the ET cases without Lewy bodies.
lower than that of controls), with a P value for the case-control comparison that was of marginal significance (r = 1.72, P = .1).

In our sample of 14 ET cases and 11 controls, Purkinje cell linear density was inversely correlated with age (r = −0.53, P = .006); with every 1-year increase in age, Purkinje cell linear density declined by 0.08 cells/mm. Purkinje cell linear density was also inversely correlated with the number of torpedoes (r = −0.42, P = .04); with each 1-torpedo increase, Purkinje cell linear density declined by 0.08 cells/mm. Purkinje cell linear density did not correlate with PMI (r = 0.24, P = .33), CERAD plaque score (r = 0.60, P = .78), Braak and Braak stage (r = −0.32, P = .14), or brain weight (r = 0.34, P = .11), nor did it differ between men and women (neither in the total sample nor when stratified by diagnosis).

In an unadjusted linear regression analysis that compared ET cases without Lewy bodies (n = 8) with controls (n = 11), Purkinje cell linear density (outcome variable) was lower in ET cases without Lewy bodies than in controls (β = .66, P = .02). Adjusting in this model for age, sex, and PMI, the association remained significant (β = .56, P = .03). Adjusting for brain weight in the same model did not change the results either (β = .56, P = .03).

In an unadjusted linear regression analysis that included all participants (ie, a test for trend), Purkinje cell linear density (outcome variable) was associated with diagnosis (controls [reference group], ET cases with Lewy bodies, and ET cases without Lewy bodies; test for trend, β = .64, P = .02) After adjusting for age, sex, and PMI, this association remained significant (test for trend β = .56, P = .03). Starting with the same adjusted model and further adjusting for brain weight or for Braak and Braak stage and CERAD plaque score did not change the results. Removing the one ET case with Alzheimer disease did not change these results either.

We further stratified ET cases without Lewy bodies into those with 10 or more torpedoes (n = 3) vs those with fewer than 10 torpedoes (n = 5). Mean Purkinje cell linear density was 1.42 (SD, 0.41) cells/mm in ET cases with 10 or more torpedoes, which was 59.0% lower than that of controls (3.46 [SD, 1.27] cells/mm, P = .04). Mean Purkinje cell linear density was 2.57 (SD, 0.69) cells/mm in ET cases with fewer than 10 torpedoes. This was 25.7% lower (P = .43) than that of controls (Figure 3).

This study has sought to further elucidate the pathogenesis of ET. Converging clinical and neuroimaging data suggest the presence of cerebellar dysfunction in ET, and recent postmortem studies have shown the existence of microscopic changes (Purkinje cell swellings) in the cerebellum of most ET cases. The loss of Purkinje cells in the ET cerebellum rarely has been commented on. However, a quantitative comparison of the number of Purkinje cells in ET vs control brains has never been undertaken. Thus, the actual loss of Purkinje cells in a subset of ET brains has not been formally assessed. In this study, we demonstrated that ET patients without Lewy bodies had a significant reduction in the number of Purkinje cells compared with a similarly aged control group.

In the older literature, authors occasionally commented briefly on the presence of Purkinje cell loss in some of their ET cases. In one case, this loss was mild, whereas in 3 others it was more marked. In a more recent study, Rajput et al commented on the presence of mild Purkinje cell loss in 2 of their 20 ET cases. However, as mentioned, none of these studies performed a formal quantification of Purkinje cell number and none compared these ET case brains with control brains. Although we demonstrated a reduction in Purkinje cells in ET patients without Lewy bodies, the reduction was modest (approximately 40%), which is less than that which has been reported in patients with multiple system atrophy (60%-75% in postmortem studies).

We found that Purkinje cell linear density was inversely associated with age. With healthy aging, the loss of Purkinje cells has been estimated to be 2.5% to 5.0% per decade. This underscores the importance of the use of a healthy age-matched comparison group. It also lends validity to our method of assessing Purkinje cell linear density (ie, failure to demonstrate this association between age and Purkinje cell linear density would have raised concerns about the validity of our linear density data).

We also found an inverse correlation between linear density of Purkinje cells and the number of torpedoes. This further corroborates the validity of our measure of linear density of Purkinje cells and suggests that torpedoes and Purkinje cell loss may be concomitant features of cerebellar degeneration.

As in our previous study, ET cases could be divided into groups based on the presence or absence of Lewy bodies. Essential tremor patients with Lewy bodies have them (Lewy bodies) in the locus ceruleus and have a relatively low number of torpedoes, whereas ET patients without Lewy bodies have increased numbers of torpedoes.
and, as we have now demonstrated, a reduction in Purkinje cell number. Essential tremor patients with Lewy bodies had a similar Purkinje cell linear density as controls, further supporting the notion that there are pathologic subtypes of ET.14 This pathologic subdivision of ET cases seems to indicate, as has been suggested recently,29,30 that ET may be a family of diseases unified by the presence of action tremor that is further characterized by etiological, clinical, and pathologic heterogeneity. The clinical features that distinguish ET cases with Lewy bodies vs without are not established and are currently under investigation. That some cases of ET have Lewy bodies as their primary pathologic manifestation converges with a wealth of clinical data that center on the apparent links between ET and Parkinson disease.31-38 The development of Parkinson disease has often been described in ET patients,31,32,38 and ET-like action tremor is more common in Parkinson disease families than in control families,34 again, further demonstrating the links between ET and Lewy body disease. Whether ET patients with Lewy bodies are more prone to develop Parkinson disease than their counterparts without Lewy bodies is currently unknown.

The mean Purkinje cell linear density that we report for our controls was 3.46 (SD, 1.27) cells/mm. A range of mean linear Purkinje cell densities has been reported among healthy controls, with some studies reporting results as low as 1.6 cells/mm39 and others in the range of 2 to 3 cells/mm (2.36 cells/mm40 and 2.5-3 cells/mm41), 4 to 5 cells/mm (4.49 cells/mm41, 4.6 cells/mm42 and 4.6 cells/mm43), 6 to 7 cells/mm (6.9 cells/mm44 and 7.1 cells/mm45), and 10 to 11 cells/mm.46 This variability is likely caused by a variety of issues, including technical factors, such as fixation shrinkage, staining techniques, and section thickness, but also by demographic differences including age. Our numbers are within the reported range.

This study had limitations. First, we sampled only one region of the cerebellar hemisphere. This does not di-

Figure 2. Representative photographs (original magnification × 40) of calbindin immunohistochemistry on similar cerebellar folia sections from 2 individuals: an 84-year-old healthy control (A and B) and a 90-year-old patient with essential tremor (C and D). It is evident that whereas 12 Purkinje cells are seen in the Purkinje layer of the control (A, 4 denoted by arrows), only 2 are seen in the patient with essential tremor (C, arrows). Numerous Purkinje cell bodies are densely stained in the control (B), whereas there are only 2 evident in the patient with essential tremor (D). The Purkinje cell linear density was 4.29 cells/mm in the control and 1.27 cells/mm in the patient with essential tremor.
minish the validity of our findings. However, it remains to be demonstrated that these findings can be generaliz-
ed to other regions of the ET cerebellum (eg, vermis).

Second, a stereological assessment of Purkinje cell num-
ber would have allowed for greater precision as well as a randomized assessment. Such a study is currently un-
der way. Third, while the number of participants seems relatively small, this actually represents the second larg-
est series of reported ET cases, with all except one previous study\(^1\) reporting the results of only 1 or 2 cases. With our sample size, statistically significant findings were demonstrable. The strengths of this study include its use of a standardised, blinded, quantitative assessment of Purkinje cells and control brains for comparison. In addition, we could adjust for a number of important poten-
tial confounders (eg, age and PMI). Finally, we were able to examine the associations between linear density of Pur-
kinje cells and other pathologic changes in the cerebel-
lab (ie, torpedoes).

In summary, we demonstrated a reduction in Purk-
inje cell number in ET patients without Lewy bodies. These data further support the view that the cerebellum is functionally and structurally abnormal in these ET cases.

Accepted for Publication: March 29, 2007.
Correspondence: Elan Louis, MD, MSc, Unit 198, Neu-
rological Institute, 710 W 168th St, New York, NY 10032 (edl2@columbia.edu).

Author Contributions: Study concept and design: Ax-
elrad, Louis, and Honig. Acquisition of data: Axelrad, Louis, Honig, Flores, Ross, Pahwa, Lyons, Faust, and Vonsattel. Analysis and interpretation of data: Axelrad, Louis, Honig, and Vonsattel. Drafting of the manuscript: Axelrad, Louis, and Honig. Critical revision of the manuscript for important intellectual content: Louis, Honig, Flores, Ross, Pahwa, Lyons, Faust, and Vonsattel. Statistical analysis: Axelrad, Louis, and Honig. Obtained funding: Louis and Ross.

Administrative, technical, and material support: Louis, Honig, Flores, Lyons, Faust, and Vonsattel. Study supervision: Louis and Honig.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grants R01 NS42859, 5R01 AG017155, P50 AG08702, and P01 AG07232 from the National Institutes of Health, Bethesda, Maryland; by the International Essential Tremor Found-
dation, Lenexa, Kansas; and by the Parkinson’s Disease Foundation, New York, New York.

REFERENCES


door neurological exams in Mersin Province, Turkey. Neurology. 2003;61(12):
1804-1807.


4. Hassler R. Zur pathologischen Anatomie des senilen und des parkinsonisti-

5. Myle G, Van Bogaert L. Etudes anato-mo-cliniques de syndromes hypermimet-
1940;103:28-43.

6. Myle G, van Bogaert L. Du tremblement essentiel non-familial. Monatschr Psy-
chiatr Neurol. 1948;115:80-90.


8. Rajput AH, Rozdilsky B, Ang L, Rajput A. Clinicopathological observations in es-

9. Rajput A, Robinson GA, Rajput AH. Essential tremor course and disability: a clini-

2000;123:1568-1580.

tial tremor may indicate cerebellar dysfunction. Brain. 2003;126(pt 6):1319-1332.


14. Louis ED, Vonsattel JGP, Honig LS, Ross GW, Lyons KE, Pahwa R. Neuropatho-

15. Bress K, Braak E. Diagnostic criteria for neuropsychopathologic assessment of Alzhei-

16. Mirra SS. The CERAD neuropsychology protocol and consensus recommenda-
tions for the postmortem diagnosis of Alzheimer’s disease: a commentary. Neu-


18. Louis ED, Borden S, Moskowitz CB. Essential tremor centralized brain reposi-

19. Fahn S, Elton RL; UPDRS Development Committee. Recent Developments in Par-

2000;247(2):205-211.

21. Harasymiw JW, Bean P. Identification of heavy drinkers by using the early detec-

22. Louis ED, Shungu D, Chan S, Mao X, Jurewicz EC, Water D. Metabolic abnor-
malities in patients with essential tremor: a proton magnetic resonance spectro-


