

Essential Tremor Associated With Pathologic Changes in the Cerebellum

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Background: Although essential tremor (ET) is one of the most common neurologic disorders, there have been few postmortem studies. We recently reported postmortem changes (torpedoes and Bergmann gliosis) in the cerebellar cortex in a few ET cases.

Objective: To describe more extensive postmortem changes in the cerebellum in another ET case.

Design: Case report.

Results: A 90-year-old woman had a 30-year history of ET. At postmortem examination, there was segmental loss

of Purkinje cells, presence of torpedoes, and Bergmann gliosis in the cerebellar cortex. Moreover, there were extensive changes in the dentate nucleus, in the form of neuronal loss, neuronal atrophy, microglial clusters, and reduction in the number of efferent fibers (ie, pallor of the hilum).

Conclusions: The brain in the current case exhibited more marked cerebellar pathologic features than noted in previously reported ET cases and thereby extends the described cerebellar findings in this common, yet pathologically poorly characterized, neurologic disorder.

Arch Neurol. 2006;63:1189-1193

A FUNDAMENTAL QUESTION about the biology of essential tremor (ET) is whether there are histopathologic changes in the brain. Until recently, the number of postmortem examinations was only 25, and many of these were published 50 to 100 years ago and few described relevant brain structures in detail.¹ The pathologic characteristics were unclear, although mild to diffuse loss of Purkinje cells was reported in 4 isolated cases.² The Essential Tremor Centralized Brain Repository at Columbia University, New York, NY, was recently established to focus attention on the pathologic features of ET. An initial report (10 ET cases vs 12 control subjects) demonstrated that the pathologic findings in ET were heterogeneous.³ Essential tremor cases were clustered into 2 preliminary groups: those with brainstem Lewy bodies (n=6) and those with mild cerebellar changes (ie, torpedoes and Bergmann gliosis; n=4).³ We report the findings in a new ET case in which cerebellar involvement was more marked than that in our previously reported cases. This case further extends the cerebellar changes that have been

described in patients with this common, yet pathologically poorly characterized, neurologic disorder.

METHODS

PATIENT

In 1993, this 79-year-old right-handed woman was enrolled in the Washington Heights–Inwood Columbia Aging Project and prospective neurologic examinations were conducted by general neurologists at 1½-year intervals from 1993 to 2002. During each examination, action tremor of both arms and head tremor were noted, and ET was diagnosed. The patient had mild dementia. Tremor reportedly had begun at age 60 years, worsening gradually with time. There was no family history of tremor or ataxia in first- or second-degree relatives. She did not use ethanol or have a history of heavy ethanol consumption. There was no exposure to other agents (eg, lithium or diphenylhydantoin) known to cause cerebellar damage.^{4,6}

In 1996, the patient was enrolled in the Washington Heights–Inwood Genetic Study of Essential Tremor. Videotaped neurologic examinations at ages 82, 83, and 84 years included tests to elicit postural and kinetic tremors, and standardized assessments of facial expression, speech, tremor at rest,

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Table. Tremor Ratings at 3 Evaluations*

| Evaluation | Rating† | | |
|-----------------------------|-----------|-----------|-----------|
| | Age 82 y | Age 83 y | Age 84 y |
| Arm extension | | | |
| Right | 3 | 3 | 3 |
| Left | 3 | 3 | 2 |
| Pouring | | | |
| Right | 2 | 2 | 3 |
| Left | 3 | 2 | 3 |
| Using a spoon | | | |
| Right | 2 | 2 | 1 |
| Left | 3 | 3 | 3 |
| Drinking from a cup | | | |
| Right | 2 | 2 | 3 |
| Left | 2 | 3 | 3 |
| Finger-nose-finger maneuver | | | |
| Right | 2 | 2 | 2 |
| Left | 3 | 3 | 3 |
| Archimedes spiral | | | |
| Right | 2 | 2 | 1 |
| Left | 3 | 3 | 3 |
| Total Tremor Score | 30 | 30 | 30 |

*The videotaped examination included 6 tests (1 to elicit postural tremor and 5 to elicit kinetic tremor) performed with the dominant and nondominant arms. Each of the 12 tests was rated from 0 to 3, resulting in a total tremor score (range, 0-36). Ratings of 0 indicate no tremor; 1, mild tremor; 2 moderate tremor; and 3, severe tremor.

†Washington Heights–Inwood Genetic Study of Essential Tremor criteria.

rapid alternating movements in arms and legs, handwriting, walking, and balance.⁷ The videotaped examinations were reviewed by 3 neurologists specializing in movement disorders (E.D.L., B.F., and S.F.), who noted moderate to severe action tremor of the arms (**Table**) and mild tremor of the head but no dystonia or signs of parkinsonism or of cerebellar disorders (ie, dysarthria, dysidiadochokinesis, overshoot on finger-nose-finger maneuver, or gait ataxia). The neurologists independently diagnosed definite ET using Washington Heights–Inwood Genetic Study of Essential Tremor criteria.⁷

At age 88½ years, during an admission to Columbia University Medical Center for treatment of dehydration, the patient reported lower back and bilateral thigh and leg pain. She was taking a combination of primidone, 50 mg/d, and gabapentin, 100 mg twice daily, for tremor. During that admission, she was noted to have mild chronic renal insufficiency, hypertension, diabetes mellitus, congestive heart failure, and mild Alzheimer disease (clinical dementia rating, 1). When examined by a general neurologist, the patient exhibited voice tremor but no dysarthria, side-to-side (no-no) head tremor, and marked postural and kinetic tremors of both arms. Tone was normal in all limbs, and there was no cogwheeling. Rapid alternating movements were normal for age. There was no dysmetria of the upper limbs (finger-to-nose maneuver) or lower limbs (heel-to-shin maneuver) and no signs of parkinsonism. Deep tendon reflexes were diminished at the ankles but were otherwise normal. There was marked impairment of joint position sense in both lower limbs, which was attributed to diabetic neuropathy, and marked thoracic scoliosis. She walked with the assistance of a walker because of severe scoliosis and markedly impaired proprioception and radicular pain in the lower limbs, but her gait was not ataxic. Computed tomography of the brain without contrast medium

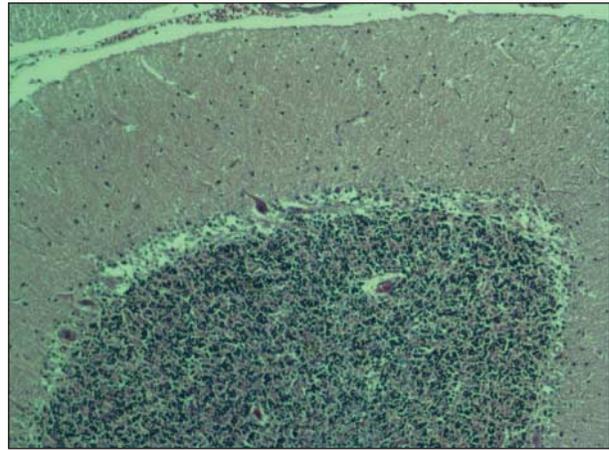


Figure 1. Section of a cerebellar folium shows segmental loss of Purkinje cells (Luxol fast blue and counterstained with hematoxylin-eosin, original magnification $\times 100$).

revealed moderate periventricular white matter microvascular changes; 2 isolated lacunar infarcts, in the thalamus and basal ganglia; and a normal cerebellum. In June 2005, at age 90 years, the patient died of congestive heart failure.

HISTOLOGIC STUDIES

The brain was received and frozen 6 hours 18 minutes after death. At external examination, the dura and brain were normal. Blocks were taken from standardized brain regions, as described previously.¹ Blocks from the midbrain included the substantia nigra, including 3 levels: rostral, middle, and caudal. Other blocks included the pons with locus ceruleus, at 2 levels; the medulla with inferior olivary nuclei; and the cerebellar hemisphere with dentate nucleus. These samples from the left hemibrain were embedded in paraffin, and sections 7- μ m thick were stained with Luxol fast blue and counterstained with hematoxylin-eosin (LHE). In addition, sections from selected blocks were stained with thioflavine S and modified Bielschowsky silver stain. As described,¹ sections from selected blocks were subjected to antibodies directed against α -synuclein, β -amyloid, hyperphosphorylated tau, glial fibrillary acidic protein, and ubiquitinated proteins. Cerebellar disease was assessed using a standard 20 \times 25-mm LHE-stained section that included portions of the cerebellar cortex, white matter, and dentate nucleus (standard cerebellar section). Using this standard LHE-stained cerebellar section, torpedoes (fusiform swellings of the proximal, unmyelinated segment of the Purkinje cell axon) in the entire section were counted. Bergmann cells (Golgi-type glial cells in the Purkinje layer) were assessed using a standard cerebellar section stained with glial fibrillary acidic protein.

RESULTS

The cerebellum showed segmental loss of Purkinje cells (**Figure 1**) with Bergmann gliosis. On the standard cerebellar section, there were 9 torpedoes (**Figure 2**). The dentate nucleus was strikingly abnormal; there was marked neuronal loss and the remaining neurons were atrophic (**Figure 3A**, from our patient; **Figure 3B**, from a comparison patient with Parkinson disease; and **Figure 3C**, from a healthy control) with numerous processes (**Figure 4**). Microglial clusters were apparent

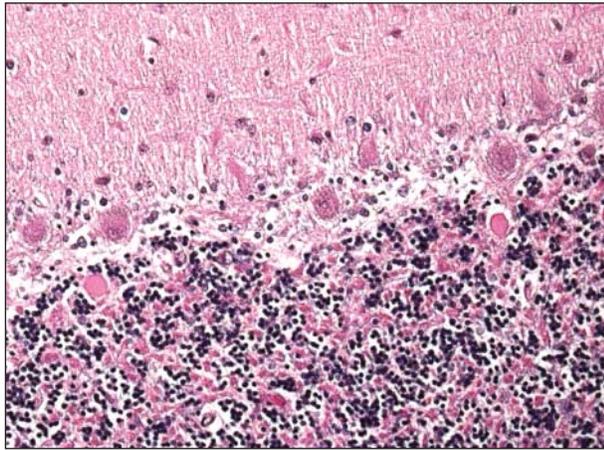


Figure 2. Section of a cerebellar folium shows 2 torpedoes in close proximity (Luxol fast blue and counterstained with hematoxylin-eosin, original magnification $\times 200$).

throughout the dentate nucleus. On LHE-stained sections, the dentate hilum was pale (**Figure 5**).

On LHE-stained and α -synuclein-stained sections, there were no Lewy bodies, Lewy neurites, neuronal loss, or macrophages in the dorsal vagal nuclei, inferior olivary nucleus, locus ceruleus (2 levels), substantia nigra pars compacta (3 levels), thalamus, substantia innominata, or cerebellum. There were mild changes of Alzheimer disease, including neuritic plaques in the prefrontal cerebral cortex and a few diffuse plaques in the prefrontal and parietal cortices. Scattered neuronal tangles were seen in the hippocampus (CA1, CA2, and CA4), subiculum, and entorhinal, parahippocampal, and occipitotemporal cortices. The nucleus basalis of Meynert was normal and without tangles. Mild cerebral amyloid angiopathy was present.

COMMENT

Our patient had a 30-year history of ET characterized by gradually worsening action tremor. The major findings at postmortem examination were mild degenerative changes in the cerebellar cortex, as described previously,³ and unreported changes in the dentate nucleus that were extensive and included marked neuronal loss, neuronal atrophy, microglial clusters, and pallor of the white matter (hilum).

One question is whether these changes in the dentate nucleus were due to age. This is unlikely. First, in our previously reported³ sample of 12 control subjects (mean \pm SD age, 83.4 ± 8.8 years), these changes in the dentate nucleus were absent (also, see Figure 3B and C for comparison). That sample³ included 3 control subjects who were older than 90 years and 3 who were aged 85 to 89 years. Second, to our knowledge, these changes in the dentate nucleus have not been described as age-associated changes in the literature.

Clinical, imaging, and electrophysiologic studies have consistently pointed to cerebellar changes in patients with ET.⁸⁻¹⁰ Pathologic studies are providing additional supporting evidence for cerebellar involvement in ET. Our patient had 9 torpedoes on the standard LHE-stained cer-

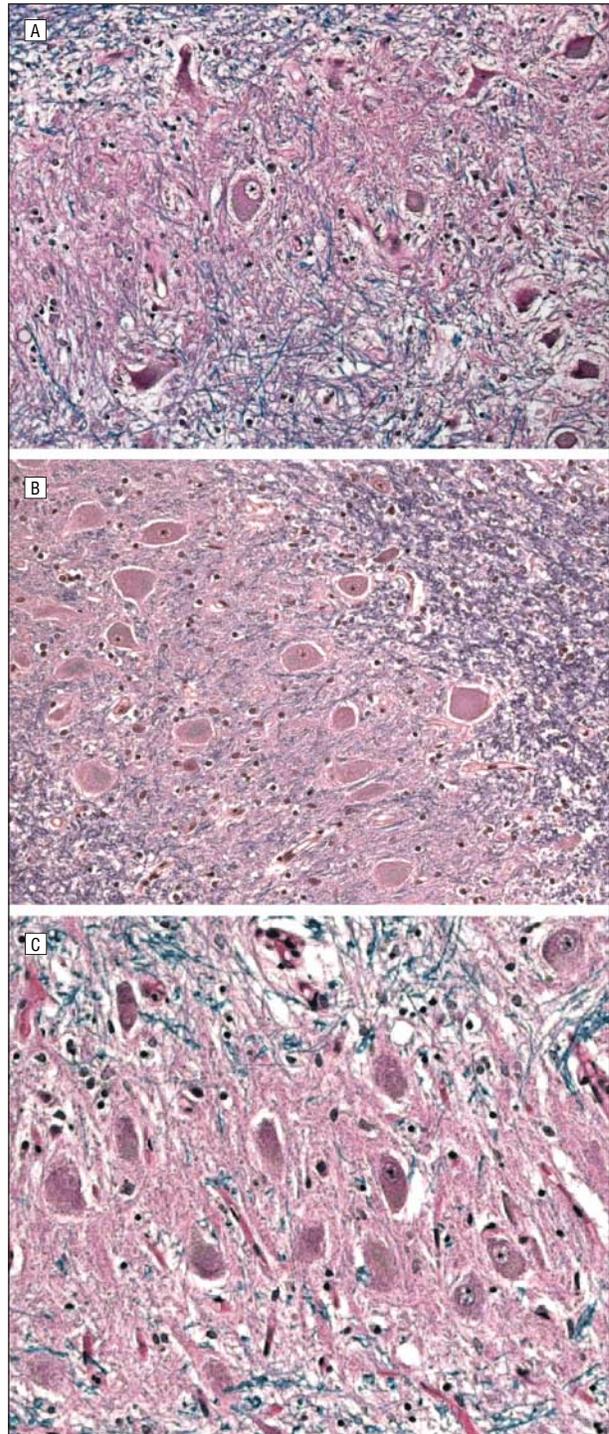


Figure 3. A, Section of the dentate nucleus shows neuronal loss. Those neurons that remain are small and angular. There is 1 normal, rounded dentate neuron in the center (Luxol fast blue and counterstained with hematoxylin-eosin [LHE], original magnification $\times 200$). B, Section of the dentate nucleus in a similarly aged comparison patient with Parkinson disease shows normal cellularity. The neurons in the dentate nucleus are rounded and plump (LHE, original magnification $\times 200$). C, Section of the dentate nucleus in a 92-year-old control subject shows normal cellularity. The neurons in the dentate nucleus are rounded and plump (LHE, original magnification $\times 200$).

ebellar section. In our recent study,³ the mean \pm SD number of torpedoes per section was 17.5 ± 6.1 (range, 9-22) in 4 ET cases with cerebellar pathology vs 1.6 ± 1.4 (range,

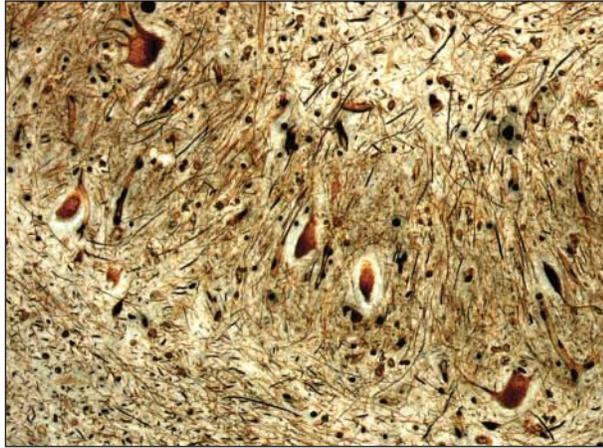


Figure 4. Section of the dentate nucleus shows atrophic, angular neurons with numerous processes (Bielschowsky, original magnification $\times 200$).

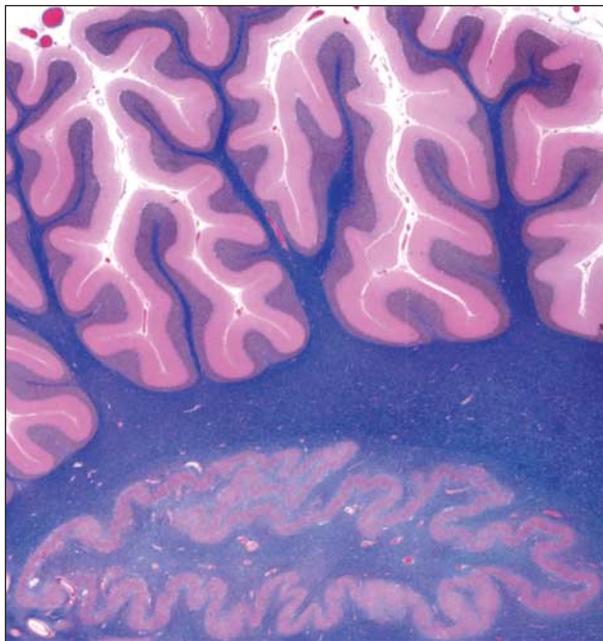


Figure 5. Standard 20 \times 25-mm section of the cerebellum shows atrophy of the dentate hilum (Luxol fast blue and counterstained with hematoxylin-eosin, original magnification $\times 1$).

0-4) in 12 control subjects, indicating that the number of torpedoes in the current case is in excess of that which we have described in similarly aged control subjects. Torpedoes, which consist of massive accumulations of disoriented neurofilaments, occur in degenerating and possibly regenerating Purkinje cells. They have also been described in other disease processes involving destruction of cerebellar tissue.¹¹⁻¹³

Our patient's dentate nucleus was not normal; there was neuronal loss and the remaining neurons were atrophic. There was a reduction in efferent fibers (ie, pallor of the hilum). The neurons of the dentate nucleus receive synaptic input from Purkinje cells, serving as a major relay center for the inhibitory Purkinje cell output from the cerebellum. Efferent fibers from the dentate nucleus leave the nucleus through the hilum, exiting the cerebellum through the superior cerebellar peduncle and

synapsing in the contralateral ventrolateral nucleus of the thalamus, from which they project to the motor cortex via the internal capsule.

Neuronal loss in the dentate nucleus may occur in a few other disorders, including some forms of spinocerebellar ataxia and in patients with progressive supranuclear palsy.^{14,15} Our patient was serially examined by general neurologists and movement disorder neurologists, all of whom diagnosed ET. A diagnosis of spinocerebellar ataxia is unlikely given the absence at examination of dysarthria, dysdiadochokinesis, overshoot on the finger-nose-finger maneuver, dysmetria on the heel-to-shin maneuver, and gait ataxia. The late age at onset and the absence of a family history of an ataxic disorder also argue against this, as does the normality of the cerebellum on computed tomographic scans. Progressive supranuclear palsy was unlikely clinically because of the absence of extraocular movement abnormalities, early postural instability, axial rigidity, or parkinsonism, and was not present at pathologic examination. Our patient had early Alzheimer disease. In end-stage Alzheimer disease, cerebellar plaques and mild dropout of cells in the Purkinje and granular layers have been reported; however, the changes we observed, especially, atrophy of the dentate nucleus, have not been described in that disorder.¹⁶

In summary, preliminary studies indicate that ET may be pathologically heterogeneous, with a proportion of patients exhibiting mild cerebellar pathologic findings.³ The brain in our patient, with particularly good serial premortem clinical data, exhibited more marked cerebellar pathologic features than were described in 4 previously reported cases. It thereby extends the described cerebellar pathologic features of ET. Future work in the Essential Tremor Centralized Brain Repository at Columbia University will focus on cataloging and describing the extent of cerebellar and other pathologic changes in this little-understood disorder.

Accepted for Publication: February 16, 2006.

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Author Contributions: Dr Louis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Louis, Vonsattel, and Honig. *Acquisition of data:* Vonsattel, Lawton, Moskowitz, Ford, and Frucht. *Analysis and interpretation of data:* Louis, Vonsattel, and Honig. *Drafting of the manuscript:* Louis, Vonsattel, Honig, Ford, and Frucht. *Critical revision of the manuscript for important intellectual content:* Louis, Vonsattel, Honig, Lawton, Moskowitz, Ford, and Frucht. *Statistical analysis:* Louis. *Obtained funding:* Louis. *Administrative, technical, and material support:* Vonsattel, Honig, Lawton, Moskowitz, Ford, and Frucht. *Study supervision:* Louis and Vonsattel.

Funding/Support: This study was supported in part by grants R01 NS42859, AG08702, and AG07232 from the National Institutes of Health and by the International Essential Tremor Foundation.

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