Essential Tremor Associated With Focal Nonnigral Lewy Bodies

A Clinicopathologic Study

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Background: Essential tremor is one of the most common neurological diseases. Its links with Parkinson disease (PD) are often debated. There have been few published postmortem studies.

Objective: To study our first case of essential tremor through the recently established Essential Tremor Centralized Brain Repository.


Results: On postmortem examination, gross brain sections showed no abnormalities. Results of microscopic examination of hematoxylin-eosin–stained sections revealed that the locus coeruleus contained multiple Lewy bodies (LBs), although none were found in the substantia nigra, dorsal vagal nuclei, thalamus, substantia innominata, inferior olivary nucleus, or cerebellum. Immunohistochemical staining using antibodies directed against α-synuclein confirmed the presence of many LBs in the locus ceruleus and showed rare LBs in the substantia innominata and dorsal vagal nuclei. There were no LBs in the substantia nigra.

Conclusions: Our patient had a very focal presence of LBs in the locus ceruleus, an anatomically restricted form of LB disease. This study provides support for the link between essential tremor and LB disease and raises the question as to what proportion of patients with essential tremor might have unusual forms of LB disease.

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ESSENTIAL TREMOR (ET) IS A highly prevalent, progressive neurological disorder.1 There is growing evidence that it may represent a family of diseases rather than a single entity; evidence of clinical2 and genetic3 heterogeneity and variable response to medications4 supports this view. Essential tremor may be pathologically heterogeneous as well. The pathology of ET (ie, the structural manifestations of ET) is not well studied. Despite its high prevalence, there have been only 25 published postmortem studies, many of which were published 50 to 100 years ago, and the diagnosis is questionable in 6 of these.5-7 In the 4 cases in which potentially relevant brainstem structures (eg, the substantia nigra [SN] and locus coeruleus [LC]) were described, α-synuclein immunohistochemistry findings were not reported. The Essential Tremor Centralized Brain Repository at Columbia University Medical Center, New York, NY, was recently established to focus attention on the pathology of ET. Through this mechanism, we studied our first case of ET without concomitant clinical neurological disorders. The postmortem examination revealed an anatomically restricted manifestation of Lewy body (LB) disease. The unusual nature of the LB focality is striking, especially in the face of the paucity of postmortem examinations in ET. The implications of these findings are discussed, as the link between ET and LB disease has been debated for some time.8

REPORT OF A CASE

Clinical Evaluation

The patient, a right-handed woman, was initially seen at 75 years of age at the Center for Parkinson Disease and Other Movement Disorders at Columbia University Medical Center, New York, NY. She had been referred by a general neurologist, who had diagnosed severe ET that required further management. The tremor had begun at 45 years of age; she noted that her right hand shook while holding a cup of coffee. The action tremor gradually worsened, and
by 60 years of age it interfered with handwriting. By 63 years of age she had mild head tremor, and by 67 years of age, difficulty with multiple daily activities (eg, eating and writing) due to action tremor. She was initially treated with propranolol hydrochloride (maximal daily dosage, 320 mg), with mild improvement in tremor. Several ounces of vodka before a meal lessened the tremor, allowing her to eat independently. Her mother had had action tremor that began in her fifth decade of life, as did her mother’s sister and her mother’s aunt. There was no family history of parkinsonism. Her medical history was notable for chronic progressive hearing loss, arthritis, and a left mastectomy at 71 years of age for breast cancer.

When she first underwent evaluation at our center at 75 years of age, she reported that the tremor interfered with many daily activities, including handwriting, artwork, brushing her teeth, feeding herself, and putting on makeup. Results of the examination showed mild, intermittent head tremor and no tremor of her hands while they rested in her lap or when she walked or was lying down. There was a moderate to severe bilateral postural tremor and kinetic tremor, which were tested while she performed the finger-to-nose maneuver and wrote. There was no tremor of the tongue, lips, jaw, or voice and no axial or limb bradykinesia, rigidity, or postural instability. There was normal stride length and arm swing but mild difficulty with tandem gait. Results of the neurological examination were otherwise normal. She started therapy consisting of primidone, 125 mg/d, and then did not return for follow-up. She was seen again at 85 years of age by a second neurologist at our center. She reported worsened arm tremor. She was unable to pour water without spilling, cook food, or write because of tremor. She was taking propranolol hydrochloride, 40 mg/d, and primidone, 600 mg/d, which were moderately effective. Results of the examination showed no tremor at rest (while seated, standing, walking, or lying down). Facial expression was normal. There was an intermittent side-to-side head tremor of moderate amplitude. We noted severe bilateral postural and kinetic tremors. It was necessary for her to hold a cup when she brushed her teeth, fed herself, and put on makeup. She exhibited good arm swing and no flexed position. She was unable to pour water without spilling, cook food, or write because of tremor. She was taking propranolol hydrochloride (maximal daily dosage, 320 mg), and then did not return for follow-up. She was noted to have severe bilateral postural and kinetic tremors. It was necessary for her to hold a cup with 2 hands to avoid spilling and a pen with 2 hands while writing. She exhibited good arm swing and no flexed posture. Her performance of rapid alternating movements and the tone in her arms and legs were normal, as were memory and cognition. There were no complaints referable to dysautonomia. She continued follow-up with no significant change in examination results. She died at home at 91 years of age. Her last complete neurological examination was 4 months before death, during which no signs of parkinsonism were noted. She had undergone evaluation by her internist within 1 month of death, with no note of any resting tremor or reduction in facial expression.

POSTMORTEM EVALUATION

The brain was obtained 10.5 hours after death. On external examination, the dura and brain appeared to be normal. Cut surfaces of the brainstem revealed a well-pigmented SN and LC. Blocks were taken from the middle frontal, superior and middle temporal, precentral, and anterior gyri; striate cortex; inferior parietal lobule; hippocampus; amygdala; basal ganglia; thalamus; hypothalamus; midbrain with SN (including the rostral, middle, and caudal levels); pons with LC; medulla with inferior olivary nuclei; and cerebellar hemisphere with dentate nucleus. These samples from the right hemibrain were embedded in paraffin, and 7-µm-thick sections were stained with hematoxylin-eosin. In addition, sections from selected blocks were stained with thioflavine S and modified Bielschowsky silver stain. Formalin-fixed and paraffin-embedded sections were deparaffinized in xylene. The slides were immersed in 0.01M citrate buffer (pH, 6.0), microwave (2 times in 5-minute cycles) at 100°C, and cooled overnight. Sections from the following blocks were subjected to antibodies directed against α-synuclein, hyperphosphorylated tau (AT8), and ubiquitininated proteins: neocortex, calcineur cortex, cingulate gyrus, hippocampal formation, amygdala, lenticular nucleus, globus pallidum, substantia innominata, thalamus (level of lateral geniculate body), subthalamic nucleus, SN (3 levels), LC (2 levels), medulla (including the right and left dorsal vagal nuclei and the right inferior olivary nucleus), and cerebellar hemisphere (including the cortex and dentate nucleus). Enhancement of tissue epitopes was performed using heat-induced epitope retrieval methods.

On hematoxylin-eosin–stained sections, there were no LBs and no neuronal loss or macrophages in the dorsal vagal nuclei, substantia innominata, SN pars compacta (3 levels), thalamus, inferior olivary nucleus, or cerebellum (Table). Many neurons of the LC contained 1 or more LBs (Figure, A and B). At a magnification of ×200, 135 pigmented LC neurons were counted (including 2 levels). Of these neurons, 2 (1.5%) had 4 LBs, 2 (1.5%) had 3 LBs, 3 (2.2%) had 2 LBs, 15 (11.1%) had 1 LB, and 113 (83.7%) had no LBs. Lewy neurites were numerous and neuronal density was mildly decreased in the LC. We found no segmental loss of Purkinje cells, torpedoes (fusiform swellings of Purkinje cell axons), or Bergmann gliosis.

On sections subjected to immunohistochemistry for ubiquitin, there were LBs in the LC but nowhere else (Table). Sections subjected to antibodies directed against α-synuclein showed rare LBs in the substantia innominata (4 LBs in 1 section) and scant Lewy neurites, a few LBs in the dorsal vagal nuclei (6 LBs total, including the right and left), and numerous LBs and Lewy neurites in the LC at both levels examined. No LBs were found elsewhere, including the SN pars compacta (3 levels) (Table and Figure, C and D).

<table>
<thead>
<tr>
<th>LB Location</th>
<th>Hematoxylin-Eosin</th>
<th>Ubiquitin</th>
<th>α-Synuclein</th>
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<tbody>
<tr>
<td>LC</td>
<td>Many</td>
<td>Many</td>
<td>Many</td>
</tr>
<tr>
<td>SN</td>
<td>-</td>
<td>-</td>
<td>Rare</td>
</tr>
<tr>
<td>Dorsal vagal nuclei</td>
<td>-</td>
<td>-</td>
<td>Rare</td>
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<tr>
<td>Substantia innominata</td>
<td>-</td>
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<td>Rare</td>
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<tr>
<td>Thalamus</td>
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<td>Inferior olivary nucleus</td>
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<td>Cerebellum</td>
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Abbreviations: LB, Lewy body; LC, locus coeruleus; SN, substantia nigra pars compacta; minus sign, no LBs.
There were mild changes of the Alzheimer type (neurofibrillary tangles and neuritic plaques) in the hippocampal CA1 subfield, subiculum, entorhinal cortex, and transentorhinal cortex (Braak stage II). The amygdala was normal. The nucleus basalis of Meynert showed normal neuronal density and was free of neuronal tangles. Focal, mild amyloid angiopathy was seen in sections from the frontal, temporal, and parietal lobes.

**COMMENT**

Our patient had progressive, severe, alcohol-responsive action tremor. There was a history of action tremor in 3 maternal relatives. There was no clinically detectible parkinsonism on examination. The clinical diagnosis by 3 neurologists, including 2 neurologists specializing in movement disorders and 1 general neurologist, was ET. The pathological finding of major interest was an anatomically restricted form of LB disease characterized by the presence of numerous LBs in the LC, no LBs in the SN pars compacta, and LBs in other pigmented nuclei to a minimal degree only evident with anti-α-synuclein staining.

In patients with ET for many years, clinical PD can eventually develop, with the pathology showing LBs in the SN.9 Our patient had signs of ET for 46 years, but none of the hallmark clinical features of PD were present. Could our patient have had a subclinical form of PD? The hallmark pathological feature of PD is LBs in the SN,10 but growing evidence suggests that the formation of LBs in other pigmented brainstem nuclei (the dorsal vagal nucleus and LC) may precede the formation of LBs in the SN.11 In a recent study, postmortem examinations were performed on 41 individuals with clinical diagnoses of PD and 69 individuals who had not carried a clinical diagnosis of PD but had LBs and or Lewy neurites pathologically (ie, possible early subclinical PD). The pathological findings in these 110 individuals were ordered in a staging scheme. In stage 1 of PD, only the dorsal vagal nucleus exhibited LBs. In stage 2, there was greater involvement of the dorsal vagal nucleus and initial involvement of the LC. By stage 3, LB deposition began in the SN. The topographic pattern of LB in our patient (severe involvement of the LC predominantly) was not seen in any of the 110 individuals.11 Thus, although others have

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**Figure.** Staining results in our patient with essential tremor. A, Hematoxylin-eosin (H&E) staining of the locus coeruleus (LC) shows Lewy bodies (LBs) seen as pale, circular, eosinophilic structures within pigmented neurons. One neuron (upper right) has 1 LB and another neuron (lower left) has what appear to be 4 LBs, although a single multilobulated LB cannot be excluded (original magnification ×400). B, Hematoxylin-eosin staining of the substantia nigra (SN) pars compacta shows many pigmented neurons but no LBs or Lewy neurites (original magnification ×200). C, α-Synuclein staining shows numerous LBs in the LC (arrows). These appear as typical rounded bodies that are distinct from the punctate neuromelanin granules. One neuron (lower left) has 3 LBs. The inset shows LBs containing neurons (arrows) (original magnification ×200; inset, original magnification ×520). D, α-Synuclein staining shows no LBs or Lewy neurites in the SN pars compacta (original magnification ×200).
found LBs restricted to the brainstem dorsal vagal nucleus, to our knowledge the particular topographic pattern seen in our patient has not been reported in subclinical or clinically diagnosed PD.

Lewy body disease most notably includes PD and diffuse LB disease. Anatomically restricted forms of LB disease are also found in patients who, like our patient, did not have any motor features of PD and were not thought to have PD. In one report, a patient with brainstem-type LB pathology had no parkinsonism but had progressive lethargy and autonomic failure. Lewy bodies were evident in the brainstem nuclei and the intermediolateral columns of the spinal cord. There were no LBs in the SN. Three patients with progressive dysphasia but no parkinsonism demonstrated severe degeneration with LBs only in the dorsal vagal nucleus.

The pathology of ET is not well understood. No pathological abnormalities have been identified, but few studies have documented a pathological examination of the LC. Although we report only 1 case of ET, which was clinically entirely typical, the pathological findings included a very unusual, heretofore unreported distribution of focal, nonnigral, anatomically restricted form of LB disease. This raises questions of whether some cases of ET might represent a restricted form of LB disease and what proportion of patients with ET might have this type of pathology. This issue is critical in understanding disease mechanisms and ultimately the treatment of this disorder. The LC is the principal source of central nervous system norepinephrine. Its efferent connections are widespread, including Purkinje cells. Norepinephrine enhances cerebellar y-aminobutyric acid (GABA)ergic inhibition. The cerebellum and GABAergic mechanisms have been implicated in ET. It could be speculated that some cases of ET might result from LC lesions that change cerebellar activation.

Could the LBs in our patient’s LC have been the result of normal aging? Tomonaga assessed the prevalence of LBs in the LC in healthy elderly individuals. Lewy bodies were present in 16 (19.3%) of 83 individuals who were 80 years or older at the time of death. However, among these 16, only a very small proportion (<0.07%) of the LC neurons had LBs compared with the LC neurons in a similarly aged patient who had had PD. In that patient, 32.1% of the LC neurons had LBs.

The link between ET and PD has been debated for years. Studies suggest an increased risk of co-occurrence of the 2 disorders and increased risk of action tremor in family members of patients with PD. The possibility that a proportion of patients with ET could manifest LB pathology might explain some of these findings. Also, the present study raises the question as to whether action tremor, which is common in PD, arises from abnormalities in the LC.

CONCLUSIONS

We herein report the findings from a patient with ET during life whose postmortem examination results revealed an anatomically restricted form of LB disease. This study provides support for the link between ET and LB disease and raises the question as to what proportion of ET cases might have this form of LB disease. Additional studies that include an examination of the LC are warranted.

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