The Emerging Neuropathology of Essential Tremor

Elan D. Louis, MD, MSc[1,2,3,5] and **Jean Paul G. Vonsattel, MD**[3,4]

[1]GH Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[2]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[3]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[4]Department of Pathology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[5]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

Abstract

Essential tremor (ET) is one of the most prevalent neurological disorders. At the same time, it is among the most poorly-understood of these disorders. The underlying anatomic pathology of ET has been elusive until recently. Postmortem studies have begun to display some of the underlying brain changes in patients with this disease. These types of investigations are likely to lead the way to additional insights into the pathophysiology of ET and guide the development of therapies for this common movement disorder.

Keywords

essential tremor; pathology; cerebellum; Lewy body; neurodegeneration

Introduction

The time-honored view is that there are no identifiable pathological changes in the brains of patients with essential tremor (ET).[1] Consistent with this view, anatomic pathology is often not discussed in textbook chapters of this disorder.[2,3] In this sense, ET could be regarded as a functional-metabolic disorder without a structural brain correlate. Curiously, though, the number of postmortem examinations has been small, despite the high prevalence of this disorder.[4,5] In recent years, the number of such postmortem studies has increased and these studies have provided new insights. A systematic review of published reports on postmortem studies has not been undertaken. With this in mind, our purpose was to review the literature on the pathologic basis of ET.

Correspondence: Dr. Elan Louis, Unit 198, Neurological Institute, 710 West 168th Street, New York, NY, 10032, USA. Tel: (212) 305 - 9194, FAX: (212) 305 -1304, Email: EDL2@columbia.edu.

Clues about the ET Brain: Clinical, Neuroimaging, and Animal Studies

Converging evidence from clinical, neuroimaging, and animal studies suggests that the cerebellum is involved in the generation or propagation of ET. These studies provide an important framework from which one may view the postmortem studies.

First, clinical studies have suggested that cerebellar function is not normal in patients with ET. Cerebellar-like changes in tandem gait and balance have been described in several studies of ET patients; these signs exceed those observed in similarly-aged non-tremulous controls.[6,7] Intention tremor occurs commonly during arm movements in ET patients; Deuschl et al.[8] reported a moderate intention tremor of the arms in 25% of ET patients and a milder form of such tremor in 33% of patients. ET patients with intention tremor also have other cerebellar signs (e.g., dysdiadochokinesia, tandem gait difficulty, and ballistic arm movements).[9] Others have also observed intention tremor of the head[10] and oculomotor abnormalities in ET patients. [11] ET can abruptly disappear after an acute cerebellar infarct,[12] and, therapeutically, cerebellar outflow (dentato-rubrothalamic) pathways are the target of high frequency deep brain stimulation, which is effective in treating the tremor of ET.[13,14]

Over the past thirty years, neuroimaging studies have provided valuable clues about the underlying pathological anatomy of ET. A functional MRI (fMRI) study demonstrated bilateral cerebellar hemispheric activation[15] and positron emission tomography imaging studies have documented increased regional blood flow in the cerebellar hemispheres and, variably, in the red nuclei and inferior olivary nuclei of ET patients.[16-22] These studies suggest that involvement of cerebellar circuitry occurs during the initiation of tremor or as a by-product of tremor, and hence, blood flow to this brain region is enhanced. Using [^{1}H] magnetic resonance spectroscopic imaging (MRSI), reductions in N-acetylaspartate to total creatine ratio (NAA/tCR) have been demonstrated in the ET compared to the control cerebellum.[23,24] A common interpretation of such metabolic changes is that they are indicative of neuronal death, although these metabolic changes have occasionally been described in dying neurons, which then recover.[23]

Beta-carboline alkaloids, like harmaline, are neurotoxic chemicals that produce tremor; they have been used to produce an animal model of ET.[25] These neurotoxins damage olivary-cerebellar tracts, producing significant destruction of cerebellar climbing fibers and Purkinje cells.[26] Progressive ET-like action tremor has been occasionally observed in animals that have pathological changes in the cerebellum.[27]

In summary, these studies suggest that cerebellar function and, perhaps structure, are abnormal in patients with ET. Interestingly, from physiological studies, a central oscillator is also hypothesized to exist in patients with ET and, more specifically, tremor is hypothesized to arise from a perturbation in olivary-cerebellar pathways. However, the location of this oscillator has not been clearly established.

Postmortem Studies

The first published postmortem examination appeared in 1903.[28] Between then and 1990, there were only seven additional reports,[28-34] so that up to 17 years ago, there were fewer than 10 published pathological cases. A number of these cases exhibited unusual clinical features (e.g., choreiform movements) or evidence of other neurological disorders (e.g., marked dystonia), [30,31,34] which casts doubt upon the clinical diagnosis of ET (Table). None of these studies compared the ET brains to control brains and all predated the use of alpha-synuclein immunohistochemistry to identify Lewy bodies and Lewy neurites in the locus ceruleus (LC) and other brainstem structures. In the earlier literature, it was occasionally noted that Purkinje

cell loss was mild[33] or marked,[30-32] but these investigations did not quantify Purkinje cells or torpedoes, which are fusiform swellings of Purkinje cell axons.[35,36]

In 1991, Rajput et al.[37] published an important paper that nearly doubled the number of reported postmortem examinations, with six new cases (four with pure ET). It was the largest clinical-pathological study at that time, reflecting a concerted effort over 22-years to collect ET brains. The investigators found no abnormality that could be regarded as specific for ET. Another case report in 2000[38] of a post-surgical patient was also unremarkable (Table). In 2004, the Rajput et al.[39] published a series of 20 cases, which included 14 new cases and six from their initial published series. Two cases had pathological findings of progressive supranuclear palsy and one of Parkinson's disease (PD). In two cases, mild cerebellar Purkinje cell loss was noted. These series[37-39] did not include control brains and Purkinje cells and torpedoes were not quantified.

In 2004, Verghese et al.[40] reported ten demented persons with rest tremor; among these were five who had reported prior diagnoses of ET. All five had vascular disease with strokes and three had other features of parkinsonism (e.g., bradykinesia or gait changes). None had Lewy bodies; Purkinje cells and torpedoes were not quantified.

In 2004, Ross et al.[41] reported eleven individuals from the Honolulu-Asia Aging Study; each had had bilateral action tremor on at least one occasion during life and the presumed clinical diagnosis was ET, although that diagnosis had not been assigned during life. Unlike previous studies, the authors matched these 11 case brains to 11 control brains who had been free of neurological diagnoses during life. They noted that brainstem Lewy bodies and pale bodies were more common in ET cases than in controls and that ET cases had more changes in the cerebellum, however, the limited format (abstract) did not allow the investigators to provide further details.[41]

Beginning in 2003 and 2004, the Essential Tremor Centralized Brain Repository (ETCBR) was established, with the support of the National Institutes of Health, to serve as a facility for the collection, standardized processing, and study of ET brains.[42] Both archival and prospectively-collected brains were to be processed in a uniform manner and then examined alongside age-matched control brains, with the rigorous quantification of cerebellar and brainstem pathology. Data emerging from this study are presented chronologically below.

The first ETCBR brain was from a patient with severe, ethanol-responsive, familial ET for 46 years who had no signs of parkinsonism up to one month prior to death.[43] There was an abundance of Lewy bodies in the LC with sparing of the substantia nigra pars compacta and near sparing of the dorsal vagal nucleus. This anatomically-restricted pattern of Lewy body involvement was not observed with normal aging or in individuals with incidental Lewy body disease (pre-clinical PD).[43]

In a follow-up study, data on 10 ET and 12 control brains were presented.[44] Four ET brains (including one previously reported)[43] had a similar pattern of restricted Lewy body involvement (Figure 1). Four other cases exhibited cerebellar degenerative changes. First, the number of torpedoes was increased ten-fold compared to similarly-aged control brains (Figure 2) and, second, there was an increase in the number of Bergmann glial cells in these cases. Purkinje cell loss was similar in cases and controls, although this was not rigorously quantified. Based on these initial results, the ET cases formed two pathological subtypes: those with restricted LC Lewy bodies (referred to as the "Lewy body variant of ET" or LBVET) and those without such Lewy bodies but with cerebellar degenerative changes (referred to as "cerebellar ET").

In the same year, an eleventh ET case was reported separately.[45] The patient was 90 years old, with a 30 year history of ET. On postmortem examination, there was segmental loss of Purkinje cells and an increased number of torpedoes and Bergmann glial cells. In addition, there were extensive changes in the dentate nucleus: neuronal atrophy, neuronal loss, microglial clusters, and a reduction in efferent fibers (i.e., myelin loss involving the hilum). That case,[45] with more marked cerebellar degeneration than in those previously-reported,[44] further extended the range of pathological changes observed in cerebellar ET.

Because Purkinje cell loss was noted in the early literature,[30-33] and because segmental loss of Purkinje cells was observed in ETCBR cases,[45] the same investigators undertook a more rigorous quantitative study of Purkinje cell linear density, using calbindin immunohistochemistry in ET cases and control brains. In that study,[46] of 14 ETCBR ET cases and 11 controls, Purkinje cell linear density differed by diagnosis: controls (3.46 ± 1.27 cells/mm), LBVET (3.33 ± 1.06 cells/mm), and cerebellar ET (2.14 ± 0.82 cells/mm), $p = 0.04$, with the main difference being between cerebellar ET cases and controls, where the reduction in Purkinje cells was 38.2% ($p = 0.04$)(Figure 3).[46] Lower Purkinje cell linear density was also associated with greater numbers of torpedoes ($r = -0.42$, $p = 0.04$), suggesting that torpedoes and Purkinje cell loss may be concomitant features of cerebellar degeneration in this form of ET.

At present, data are available for 33 ETCBR ET brains. Three-quarters of these exhibit degenerative changes of the cerebellar variant of ET while one-quarter have LBVET. Of additional note is that there are no detectable changes in the inferior olivary nucleus, red nucleus, thalamus, caudate, putamen, globus pallidum, or motor cortex in these brains. Among those with cerebellar ET, besides the degenerative cerebellar changes noted above (loss of Purkinje cells and marked increase in torpedoes), a number of other changes are becoming apparent. These include the presence of heterotopic Purkinje cells (i.e., Purkinje cells that are slightly displaced into molecular layer) as well as abnormal dendritic swellings (Figure 4). Each of these features has been described in degenerative cerebellar disorders,[47] where they correlate with early degeneration of Purkinje cell dendrites. Investigators at the ETCBR are currently studying whether they can correlate the clinical features of ET cases with postmortem brain changes.

Recently, an additional series of 26 ET cases enrolled in the Sun Health Research Institute Brain Donation Program was reported in preliminary form.[48] As in the ETCBR, postmortem changes were heterogeneous, with the largest number of patients exhibiting degenerative changes in the cerebellum (e.g., segmental Purkinje cell loss), while others exhibited brain stem Lewy bodies and depletion of neurons in the locus ceruleus.

Biological Implications of Postmortem Data

The data emerging from postmortem studies have a number of biological ramifications.

Pathological Changes are Identifiable in the ET Brain

In the previous section, pathological changes were described in ET brains in recent brain bank series from Hawaii,[41] New York,[43-46] and Arizona.[48] Two of these were case-control series. [41,44] To date, the findings in New York have been published in the most detail. In each of these ET cases studied at the ETCBR, including five previously reported by others,[40] there have been identifiable structural changes in the brain, with three-quarters of the cases having cerebellar degenerative changes and the remainder showing a restricted pattern of brainstem Lewy bodies. The view that ET is a disease with no identifiable brain pathology does not hold up to rigorous studies that use immunohistochemistry, quantitative methods, and control brains for comparison.

ET is Pathologically Heterogeneous

Recent studies demonstrate two different types of changes: patients with degenerative changes in the cerebellum (cerebellar ET) and patients with brainstem Lewy bodies and with relatively preserved cerebellum (LBVET).

That the main pathological subtype of ET (i.e., approximately three of four ETCBR cases) is characterized by subtle but discrete cerebellar degenerative changes is consistent with clinical and neuroimaging evidence linking cerebellar dysfunction with ET.[8-12,15-24] A smaller proportion of ET brains have Lewy bodies confined especially within their LC. The mechanism whereby LC Lewy bodies result in action tremor is not clear. The LC is the principal source of central nervous system norepinephrine. Among the main efferent connections of the LC are those to Purkinje cells.[49] It has been suggested that noradrenergic LC-cerebellar connections are important for the normal function of Purkinje cells and their inhibitory output.[50-52] LC-cerebellar connections may modulate Purkinje cell responses to climbing fiber afferent input.[50]

The presence of pathological heterogeneity in ET is consistent with evidence demonstrating that this disorder is clinically heterogeneous.[53] There is an increasing appreciation that patients may exhibit other motor features, apart from action tremor (i.e., rest tremor, intention tremor, changes in tandem gait and balance).[6-8,10,54] In addition, non-motor features occur in some ET patients,[55,56] including specific personality traits,[57,58] anxiety,[59] social phobia,[60] cognitive changes,[61-66] and dementia.[67,68]

ET Is Neurodegenerative

Cerebellar ET is characterized by the presence of a marked increase in the number of torpedoes compared to their occurrence in normal aging. On electron microscopy, these fusiform swellings consist of massive proliferations and accumulations of disoriented neurofilaments, which displace normal neuronal structures.[69,70] These swellings occur in degenerating Purkinje cells, and, possibly, regenerating Purkinje cells.[71,72] They have been described in disease processes that are characterized by destruction of cerebellar tissue, including cerebellar ataxias,[73] cerebellar damage from mercury toxicity,[36] and paraneoplastic cerebellar ataxia.[74] In addition to the increased number of torpedoes in cerebellar ET, there is a reduction in the number of Purkinje cells, indicating neuronal death. This reduction is modest (approximately 40%), which may explain why gross atrophy of the cerebellum is not a readily visible feature of ET in the limited neuroimaging studies.[15,75] Whether more subtle and widespread changes are present in the ET cerebellum is not clear and more detailed studies of dendritic arborization have not been performed. In LBVET, the main feature is the Lewy body, a microscopic abnormality associated with other degenerative diseases like PD and diffuse Lewy body disease. Hence, the changes observed in both pathological subtypes of ET are consistent with a degenerative process. That this is the case is not surprising given other knowledge about ET, including epidemiological observations that its incidence and prevalence are associated with age,[4,5,76] recent data demonstrating a modest increased risk of mortality in ET,[77] and the clinical observation that the disorder is often progressive.[78,79]

Neuroimaging studies have consistently demonstrated increased regional blood flow (i.e., activation) in the cerebellar hemispheres in ET[16-22] while postmortem studies are now revealing neurodegeneration. Although on the surface, these results could appear to be disparate, they are not. First, diseased neurons may be metabolically active, resulting in regional hyperperfusion.[80-83] Second, in certain degenerative diseases, regional hyperperfusion is commonly observed as a compensatory response.[84] Third, imaging studies tend to sample patients at an earlier point in their illness than autopsy studies, whose sampling is by nature, a terminal event. Fourth, the Purkinje cells are inhibitory; their death likely results

in decreased modulation (i.e., increased activation) of the cerebellum, with resultant increased blood flow and tremor.

One Form of ET is a Lewy Body Disease

The very focal finding of Lewy bodies in the LC in LBVET is not typical of normal aging (i.e., the numbers of LC Lewy bodies observed in ET is far in excess of that reported with normal aging[85-88] and, indeed, far in excess of that observed in any of the ETCBR age-matched controls[44]). Nor is this pattern typical of "incidental Lewy body disease" (the pattern of Lewy bodies in LBVET has not been described in hundreds of autopsies of individuals thought to have emerging PD) or of PD itself (in the recent Braak pathological staging scheme for PD, Lewy body pathology begins in the dorsal vagal nucleus and only then spreads to the LC, which first becomes markedly involved in Stages II - III).[89,90] Hence, one can not easily ascribe these findings to normal aging or emerging PD.

The spectrum of Lewy body disease includes entities other than PD,[91-93] such as diffuse Lewy body disease or Alzheimer's disease with Lewy bodies, both of which are associated with dementia. With the description of Lewy bodies in the LC in ET brains, Lewy body diseases would now also seem to include some cases of ET. A possible association between ET and PD has long been debated in the literature.[94-100] The development of PD has been described among ET patients, as has the co-occurrence of the two disorders in the same patient.[94,100] It is possible that patients with the LBVET are at increased risk of developing PD/ET, although this remains to be proven.[101]

Summary

Although for many years it has been noted that there is no consistent pattern of pathology in ET, this view was neither based on the postmortem examination of very many brains nor the rigorous, quantitative study of those few brains. Over recent years, clear degenerative pathologies have been shown in ET and, moreover, these pathologies are heterogeneous.

Future directions

An understanding of the mechanisms of ET will further advance with imaging studies (e.g., functional neuroimaging and voxel based studies) as well as pathological studies. The advantage of the latter is that they provide direct access to brain tissue. The postmortem study of ET remains in its infancy. At this time, several basic changes have been described in the ET brain. These establish an identifiable pathology in this disease. Using these initial findings as a foundation, it is important to expand our knowledge of the postmortem changes in ET. It will be important to determine whether one can move beyond the gross anatomic findings in cerebellar ET (e.g., torpedoes and Purkinje cell loss) to determine whether earlier yet more widespread changes in the health of Purkinje cells in the ET brain (e.g., changes in Purkinje cell dendritic arborization and synaptic density) can be identified. Ultimately, the goal of these anatomic-pathologic investigations is to provide the mechanistic framework for the development of disease-modifying and symptomatic therapies. Finally, it would be useful for clinicians to be able to predict in clinical settings which patients have cerebellar degenerative changes and which have LBVET.

Acknowledgments

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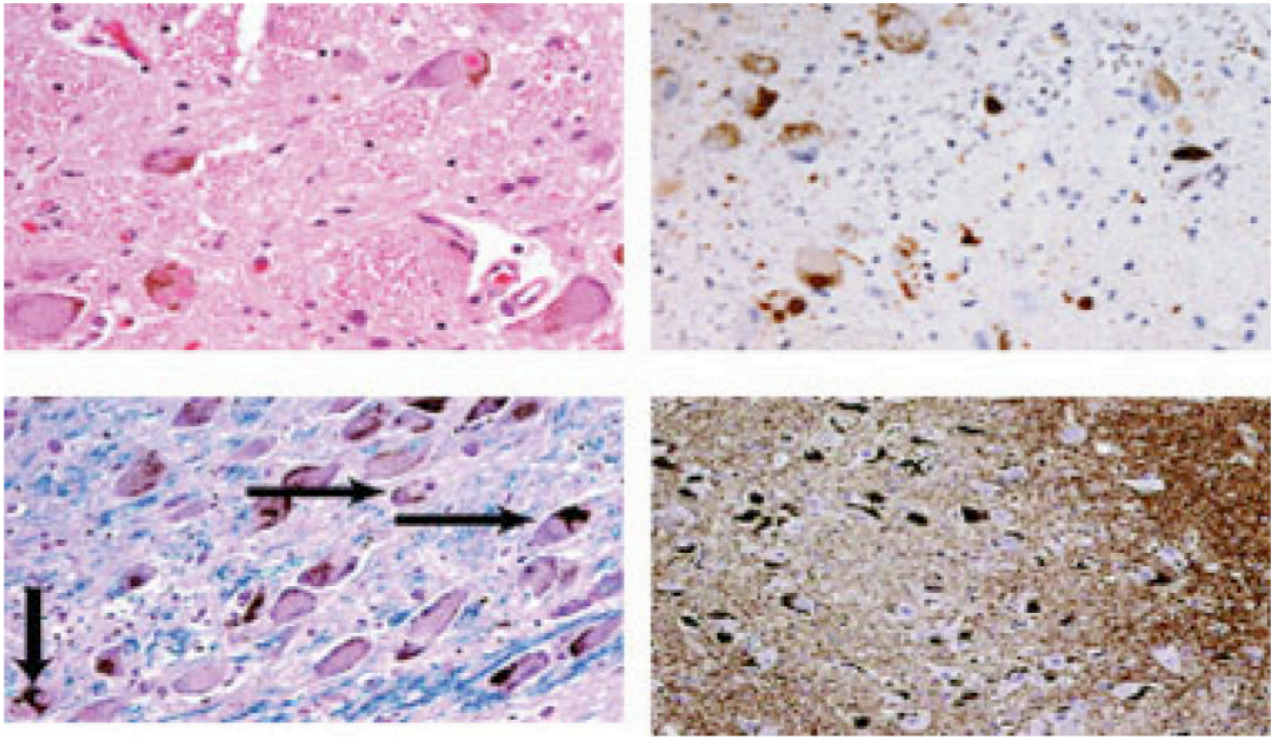
FIG. 1.
Two LBVET cases. Two panels on left are Hematoxylin and Eosin (H&E) or Luxol Fast Blue and H&E (LH&E) stained sections of the LC in a first ET case (top, 400×) and a second ET case (bottom, 200×) showing multiple Lewy bodies (arrows). The top right panel (200×) shows an alpha-synuclein-stained section of numerous Lewy bodies in the LC of one of these ET cases. The bottom right panel is an alpha-synuclein-stained section of the substantia nigra pars compacta (100×) showing normal pigmentation and cellularity, and complete absence of Lewy bodies or Lewy neurites in one of these ET cases. (Permissions for Figure 1 as follows: Figure 1, top left and top right: Archives of Neurology, 2005, volume 62, page 1006, Copyright © 2005, American Medical Association. All rights reserved. Figure 1, bottom left and bottom right: Louis et al. Neuropathologic findings in essential tremor. Neurology, 2006;66:1756–1759.)
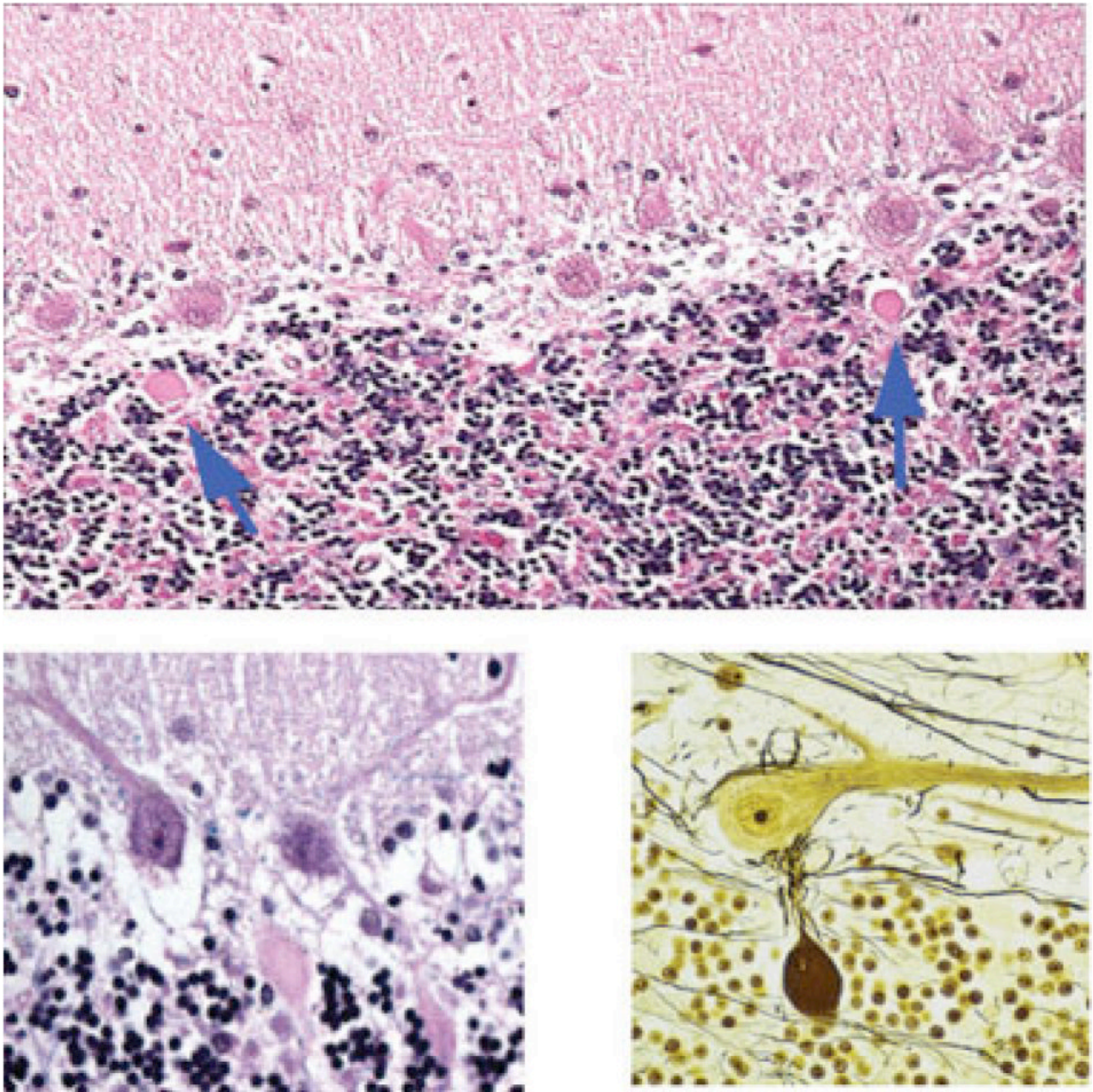
FIG. 2.
Cerebellar tissue from several ET cases showing two torpedoes in close proximity (top, LH and E 200× magnification), (bottom left, LH and E 400× magnification), and one torpedo (bottom right, Bielschowsky-stained, 400× magnification). (Permissions for Figure 2 as follows: Figure 2, top: Archives of Neurology, 2006, volume 63, page 1191, Copyright © 2006, American Medical Association. All rights reserved. Figure 2, bottom left: Louis et al. Neuropathologic findings in essential tremor. Neurology, 2006;66:1756–1759.)
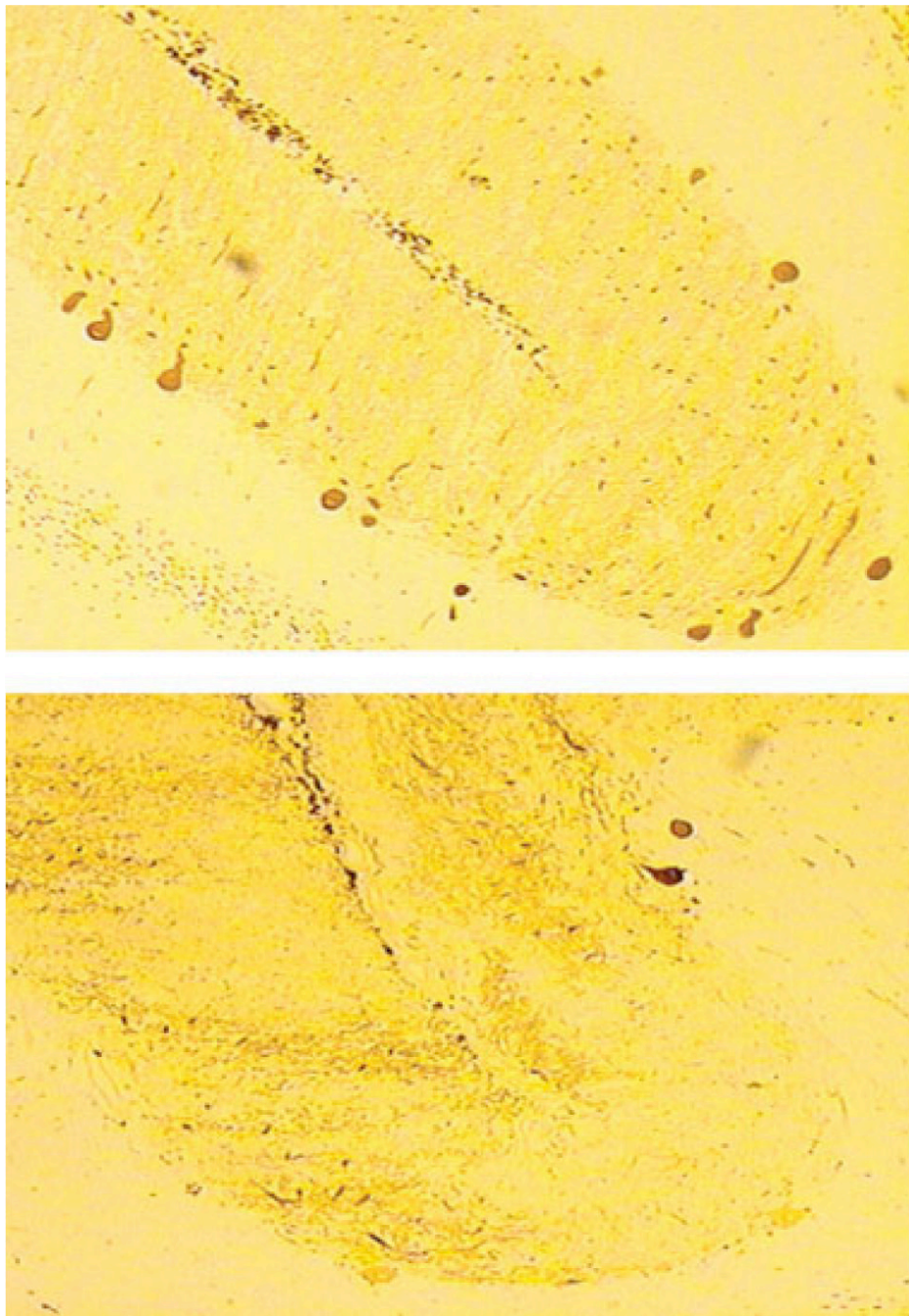
FIG. 3.
Top panel shows a cerebellar cortical section of a control at 40× magnification immunostained with rabbit anti-calbindin D28k antibody. In age-matched ET case (bottom panel), Purkinje cells occur sparsely and Purkinje cell linear density was greatly reduced.
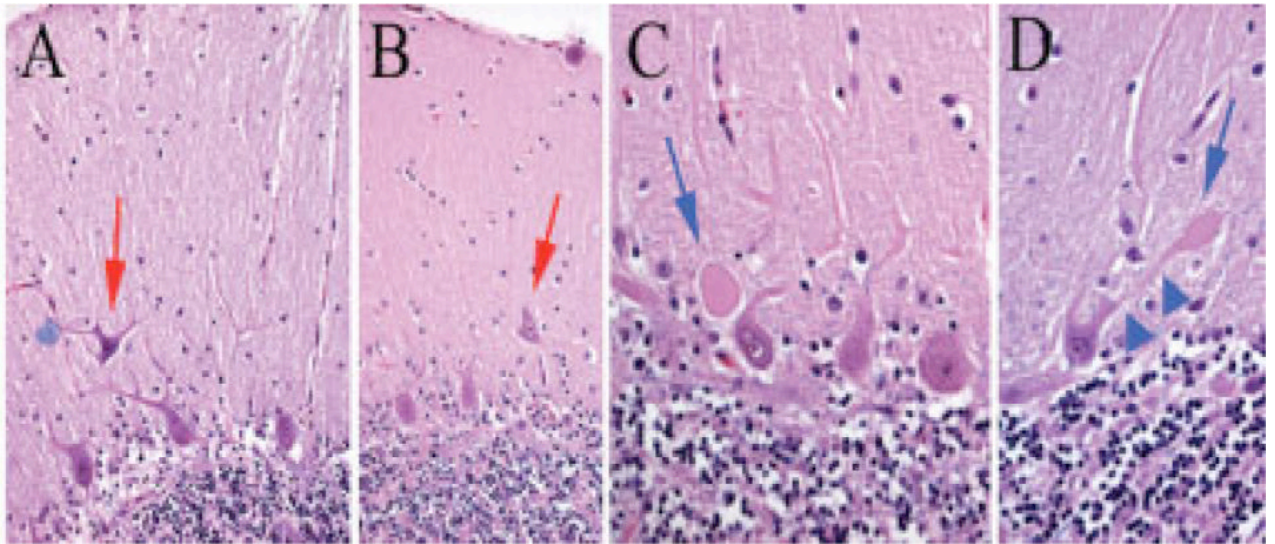
FIG. 4.
(**A** and **B**): LH and E stained cerebellar cortical sections (200× magnification). Purkinje cell heterotopias and dendrite swellings in cerebellum from an ET case. The cell bodies of occasional Purkinje cells are displaced upward into the molecular layer (red arrows). (**C** and **D**): LH and E stained cerebellar cortical sections (400× magnification). Eosinophilic swellings in the molecular layer adjacent to Purkinje cell bodies (blue arrows). Their connection to a Purkinje cell dendrite (blue arrowheads in D) identifies this as a dendrite swelling. (Figure provided by Phyllis Faust MD, PhD).