Essential tremor: a disorder of cerebellar degeneration?

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Essential tremor (ET) is a chronic brain disease whose most recognizable feature is a 4-12 Hz kinetic tremor (i.e., tremor occurring during volitional movement) of the arms; head tremor may also occur [1]. The disease is present in 4.0% of individuals who are ≥ 40 years of age [2], and perhaps as many as 20% of the oldest old (age ≥ 95 years) [3]. The incidence increases with age [4,5]. Hence, as the population ages, the number of people with ET is expected to rise markedly. Although the condition is sometimes labeled 'benign', this term is misleading. The tremor is usually progressive [6], producing disabilities with basic daily activities such as eating, writing, body care, and driving [7].

Studies that explore the pathological anatomy and improve our understanding of the pathophysiology of ET are critically important as there is no cure for ET and first-line medications, of which there are only two, are estimated to be ineffective in as many as 50% of patients [8,9]. There is a wealth of clinical data that suggests that ET is a disorder of cerebellar dysfunction. Intention (i.e., 'cerebellar') tremor of the hands (in addition to the more typical kinetic tremor of ET) occurs in approximately 44% of ET patients [10] and, in 10% of ET patients, intention tremor also involves the head [11]. Cerebellar-like problems, with abnormalities in tandem gait and balance, have been repeatedly described in ET patients [12-14], and ET patients with intention tremor may also have other cerebellar signs (e.g., disdiadochokinesia) [15]. Eye movement abnormalities, indicating cerebellar dysfunction, have been described in ET; these include an impaired smooth pursuit initiation and pathological suppression of the vestibulo-ocular reflex time constant by head tilts [16]. Unilateral cerebellar stroke has been reported to abruptly terminate ipsilateral arm tremor in ET [17] and cerebellar outflow (dentato-rubro-thalamic) pathways are the target of deep brain stimulation surgery, which is effective in treating ET [18,19]. Numerous neuroimaging studies have provided evidence that the cerebellum is functionally, as well as structurally, not normal in ET. These studies have used a variety of techniques including functional magnetic resonance imaging [20], positron emission tomography [21,22], magnetic resonance spectroscopic imaging [23,24], diffusion-tensor imaging [25], and voxel-based morphometry [26].

These clinical and neuroimaging data, which all implicate a disorder of the cerebellum, are consistent with findings from more recent postmortem studies, which will be reviewed below. Historically, the first published ET autopsy was in 1903 [27]. Over the next 100 year period, only 15 additional postmortem examinations were published [28] and, in many of these, the clinical diagnosis was ambiguous (e.g., patients had chorea or other atypical features) [28]. In 2004, a study of 14 additional brains was published [29]; however that study, along with earlier studies did not quantify cerebellar pathology (numbers of torpedoes or Purkinje cells) or include control brains for comparison. Although in four cases in this earlier literature, qualitative remarks about 'mild' to 'marked' Purkinje cell loss were made, there were no control brains for comparison, so this statement was difficult to interpret [28]. Since 2004, results from two larger case-control series have been published. The first series is from the Essential Tremor Centralized Brain Repository at Columbia University [30-35]; data on 33 ET brains have been reported. In that series, there are degenerative changes in all brains studied to date [28,31]. While a modest proportion (approximately 25%) of brains exhibited an abundance of Lewy bodies, mainly confined to the locus ceruleus, the large majority of brains exhibited clear structural changes in the cerebellum [28,31]. These changes have been of several types. First, there is a 6-7 fold increase in the number of torpedoes in the ET brains compared to age-matched control brains [28,31,34]. Torpedoes are swellings of the proximal portion of the Purkinje cell axon and they are thought to represent a cellular response to injury. On electron microscopy, these fusiform swellings consist of massive accumulations of disoriented neuro-

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filaments, displacing normal neuronal structures [35]. Torpedoes occur in degenerating Purkinje cells; they also may be a feature of Purkinje cell recovery in response to injury [35]. They have been described in disease processes characterized by degeneration of cerebellar tissue, including cerebellar ataxias, cerebellar damage from mercury toxicity, and paraneoplastic cerebellar ataxia [34,35]. Along with this relative abundance of torpedoes, there is a modest yet significant reduction in the number of Purkinje cells in ET (approximately 40% reduction compared to age-matched control brains), indicating neuronal death [30,31]. In two brains, more extensive cerebellar destruction was described (marked changes in the dentate nucleus with neuronal loss, microglial clusters and reduction in efferent fibers) [33]. Other changes in this series of brains were Purkinje cell heterotopias and Purkinje cell dendrite swellings [31], further structural indications that the cerebellum is not normal in ET. In a second series, from Arizona [36], 24 ET brains were compared with control brains. Seven brains had evidence of cerebellar pathology (Purkinje cell loss, cerebellar cortical sclerosis, and proliferation of Bergmann glia), however, Purkinje cell number, along with torpedoes were not quantified in these or the remaining ET or control brains [36].

As noted above, structural changes have been noted in the brains of ET cases in more modern case-control series, with these changes seeming to be of a degenerative nature (e.g., Purkinje cell loss) [28]. In general, neurodegenerative diseases traditionally have been defined as diseases that begin insidiously, pursue a gradually progressive course over many years, and are characterized by the selective involvement of anatomically and physiologically related systems of neurons due to intrinsic processes rather than an identifiable outside influence (e.g., vascular, auto-immune). Neuronal loss is also considered by many to be a prominent feature of these diseases [37]. Furthermore, their occurrence often increases markedly with advancing age. Many of these characteristics are features of ET. Indeed, the idea that ET could be neurodegenerative is not new. In 1948, Critchley and Greenfield wrote as follows: 'Although anatomical proof is as yet lacking, there are at least a number of clinical points to make question whether ET may not, at times any rate, represent an incomplete or a premature variant of one of the cerebellar atrophies' [38]. With the past as a backdrop, it is hoped that in the coming years, our understanding of the pathological mechanisms that underlie this common neurological condition will continue to be elucidated through clinical studies as well as tissue-based studies. Work over the recent years suggests that these tissue-based studies should focus further attention on the degenerative changes described thus far in the cerebellum.

References

1. Louis ED. Essential tremor. Lancet Neurol 2005; 4: 100-10.
2. Dogu O, Sevim S, Camdeviren H, Sasmaz T, Bugdayci R, Aral M, et al. Prevalence of essential tremor: door-to-door neurologic exams in Mersin Province, Turkey. Neurology 2003; 61: 1804-6.
3. Louis ED, Thawani SP, Andrews HF. Prevalence of essential tremor in a multiethnic, community-based study in northern Manhattan, New York, NY. Neuroepidemiology 2009; 32: 208-14.
4. Benito-León J, Bermejo-Pareja F, Louis ED. Incidence of essential tremor in three elderly populations of central Spain. Neurology 2005; 64: 1721-5.
5. Rajput AH, Offord KP, Beard CM, Kurland LT. Essential tremor in Rochester, Minnesota: a 45-year study. J Neurol Neurosurg Psychiatry 1984; 47: 466-70.
6. Critchley M. Observations on essentia (heredofamilial) tremor. Brain 1949; 72: 113-39.
7. Busenbark KL, Nash J, Nash S, Hubble JP, Koller WC. Is essential tremor benign? Neurology 1991; 41: 1982-3.
8. Hubble JP, Busenbark KL, Koller WC. Essential tremor. Clin Neuropharmacol 1989; 12: 453-82.
9. Findley LJ, Koller WC. Essential tremor: a review. Neurology 1987; 37: 1194-7.
10. Louis ED, Frucht SJ, Rios E. Intention tremor in essential tremor: prevalence and association with disease duration. Mov Disord 2009; 24: 626-7.
11. Leegwater-Kim J, Louis ED, Pullman SL, Floyd AG, Borden S, Moskowitz CB, et al. Intention tremor of the head in patients with essential tremor. Mov Disord 2006; 21: 2001-5.
12. Singer C, Sánchez-Ramos J, Weiner WJ. Gait abnormality in essential tremor. Mov Disord 1994; 9: 193-6.
13. Stolze H, Petersen G, Raethjen J, Wenzelburger R, Deuschl G. The gait disorder of advanced essential tremor. Brain 2001; 124: 2278-86.
14. Parisi SL, Heroux ME, Culham EG, Norman KE. Functional mobility and postural control in essential tremor. Arch Phys Med Rehabil 2006; 87: 1357-64.
15. Koster B, Deuschl G, Lauk M, Timmer J, Guschlbauer B, Lucking CH. Essential tremor and cerebellar dysfunction: abnormal ballistic movements. J Neurol Neurosurg Psychiatry 2002; 73: 400-5.
16. Helmchen C, Hagenow A, Miesner J, Sprenger A, Rambold H, Wenzelburger R, et al. Eye movement abnormalities in essential tremor may indicate cerebellar dysfunction. Brain 2003; 126: 1319-32.
17. Dupuis MJ, Delwaide PJ, Boucquey D, Gonsette RE. Homolateral disappearance of essential tremor after cerebellar stroke. Mov Disord 1989; 4: 183-7.
18. Schuurman PR, Bosch DA, Bossuyt PM, Bonsel GJ, Van Someren EJ, De Bie RM, et al. A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor. N Engl J Med 2000; 342: 461-8.
19. Benabid AL, Pollak P, Seigneuret E, Hoffmann D, Gay E, Perret J. Chronic VIM thalamic stimulation in Parkinson's disease, essential tremor and extra-pyramidal dyskinesias. Acta Neurochir Suppl (Wien) 1993; 58: 39-44.
20. Bucher SF, Seelos KC, Dodel RC, Reiser M, Oertel WH. Activation mapping in essential tremor with functional magnetic resonance imaging. Ann Neurol 1997; 41: 32-40.
21. Colebatch JG, Findley LJ, Frackowiak RS, Marsden CD, Brooks DJ. Preliminary report: activation of the cerebellum in essential tremor. Lancet 1990; 336: 1028-30.
22. Jenkins IH, Bain PG, Colebatch JG, Thompson PD, Findley

LJ, Frackowiak RS, et al. A positron emission tomography study of essential tremor: evidence for overactivity of cerebellar connections. Ann Neurol 1993; 34: 82-90.
23. Louis ED, Shungu DC, Chan S, Mao X, Jurewicz EC, Watner D. Metabolic abnormality in the cerebellum in patients with essential tremor: a proton magnetic resonance spectroscopic imaging study. Neurosci Lett 2002; 333: 17-20.
24. Pagan FL, Butman JA, Dambrosia JM, Hallett M. Evaluation of essential tremor with multi-voxel magnetic resonance spectroscopy. Neurology 2003; 60: 1344-7.
25. Shin DH, Han BS, Kim HS, Lee PH. Diffusion tensor imaging in patients with essential tremor. AJNR Am J Neuroradiol 2008; 29: 151-3.
26. Cerasa A, Messina D, Nicoletti G, Novellino F, Lanza P, Condino F, et al. Cerebellar atrophy in essential tremor using an automated segmentation method. AJNR Am J Neuroradiol 2009; 30 : 1240-3.
27. Frankl-Hochwart. La degenerescence hepato-lenticulaire (maladie de Wilson, pseudo-sclerose). Paris: Masson; 1903.
28. Louis ED, Vonsattel JP. The emerging neuropathology of essential tremor. Mov Disord 2007; 23: 174-82.
29. Rajput A, Robinson CA, Rajput AH. Essential tremor course and disability: a clinicopathologic study of 20 cases. Neurology 2004; 62: 932-6.
30. Axelrad JE, Louis ED, Honig LS, Flores I, Ross GW, Pahwa R, et al. Reduced purkinje cell number in essential tremor: a postmortem study. Arch Neurol 2008; 65: 101-7.
31. Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain 2007; 130: 3297-07.
32. Louis ED, Honig LS, Vonsattel JP, Maraganore DM, Borden S, Moskowitz CB. Essential tremor associated with focal nonnigral Lewy bodies: a clinicopathologic study. Arch Neurol 2005; 62: 1004-7.
33. Louis ED, Vonsattel JP, Honig LS, Lawton A, Moskowitz C, Ford B, et al. Essential tremor associated with pathologic changes in the cerebellum. Arch Neurol 2006; 63: 1189-93.
34. Louis ED, Vonsattel JP, Honig LS, Ross GW, Lyons KE, Pahwa R. Neuropathologic findings in essential tremor. Neurology 2006; 66: 1756-9.
35. Louis ED, Yi H, Erickson-Davis C, Vonsattel JP, Faust PL. Structural study of Purkinje cell axonal torpedoes in essential tremor. Neurosci Lett 2009; 450: 287-91.
36. Shill HA, Adler CH, Sabbagh MN, Connor DJ, Caviness JN, Hentz JG, et al. Pathologic findings in prospectively ascertained essential tremor subjects. Neurology 2008; 70: 1452-5.
37. Adams RD, Victor M. Principles of neurology. 4 ed. New York: McGraw-Hill; 1989.
38. Critchley M, Greenfield J.G. Olivo-pontocerebellar atrophy. Brain 1948; 71: 343-64.