Published in final edited form as:
Mov Disord. 2011 February 15; 26(3): 372–377. doi:10.1002/mds.23509.

Essential Tremor and Parkinson's Disease: Lack of a Link

C. H. Adler, M.D., Ph.D.[1], **H. A. Shill, M.D.**[2], and **T.G. Beach, M.D., Ph.D.**[2]
[1]Parkinson's Disease and Movement Disorders Center, Mayo Clinic, Scottsdale, AZ
[2]Sun Health Research Institute, Sun City, AZ

Abstract

Essential tremor (ET) is a very common disorder and proving that there is a relationship to another common movement disorder, Parkinson's disease, has been debated for years. While some published reports suggest a link between ET and Lewy bodies, the primary aim of this review is to discuss the lack a link based on analysis of neuropathologic and neurochemical studies.

The relationship between essential tremor (ET) and Parkinson's disease (PD) has been debated for years. Whether ET is actually a risk factor for developing PD, or whether the relationship is merely coincidental remains unclear. In this issue of *Movement Disorders* Fekete and Jankovic discuss clinical, epidemiological, genetic, neuroimaging, pathological, and therapeutic evidence which they interpret as proving a causal relationship between these disorders. This paper will discuss mainly the pathological data and the lack of clear evidence that the disorders are causally related.

A major confounding factor when trying to determine whether ET and PD are related is the fact that currently we have limited knowledge regarding the cause of these two disorders. It is very likely that these are syndromes and not diseases with a single cause and therefore if a link exists it may well be in a subgroup of these individuals. As there is no diagnostic test for either ET or PD, and the only definitive diagnostic finding for either is the presence of Lewy bodies and neuronal loss in the substantia nigra (SN) of subjects with PD, neuropathologic studies will be the focus of this review.

Clinically there appears to be clear overlap between ET and PD. Postural and kinetic tremor are common in PD while the presence of rest tremor is common in ET. Bradykinesia and rigidity can occur in ET and at what point patients with these findings become clinically classified as PD is unclear. Finally, it is clear that there are patients with long-standing ET who go on to develop PD, but whether this is greater than the general population, as

Correspondence: Charles H. Adler, M.D., Ph.D., Parkinson's Disease and Movement Disorders Center, Mayo Clinic Arizona, 13400 E. Shea Blvd., Scottsdale, AZ 85259, Phone: 480-301-6328; Fax: 480-301-8451; cadler@mayo.edu.

Financial disclosure related to research covered in this article: The authors have reported no conflicts of interest

Documentation of Author Roles: 1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript: A. Writing of the first draft, B. Review and Critique; Adler 1A, 1B, 1C, 3A, 3B. Shill 1A, 1B, 1C, 3B. Beach 1A, 1B, 1C, 3B.

Financial Disclosure for previous 12 months:
Adler- Consulting fees for advisory boards from Biogen Idec, Eli Lilly, Ipsen, Medtronic, Merck Serono. Research funding from the Arizona Biomedical Research Commission (ABRC), Avid Radiopharmaceuticals, Bayer, Michael J. Fox Foundation (MJFF), Parkinson Study Group, Department of Defense, National Parkinson Foundation (NPF), and the NIH.
Shill- Consulting fees from Medtronic and Ipsen. Honoraria from Allergan and Teva. Research funding from the ABRC, Boehringer-Ingleheim, Chelsea, MJFF, Schering-Plough, International Essential Tremor Foundation, and Nexalin.
Beach- Research funding from the ABRC, MJFF, NIH, National Cancer Institute, NPF, NIA, GlaxoSmithKline, University of Arizona, Science Foundation Arizona, Avid Radiopharmaceuticals, and Bayer.

suggested in some studies,[1] and even if it is, whether the actual cause of PD in these cases relates to ET or other factors, has not been established. Until the cause(s) of these disorders are delineated, linking the two may be impossible. In our opinion all of these issues very much require well designed longitudinal cohort studies that have pathologic confirmation as the gold standard outcome measure.

From a clinico-pathological standpoint there are two ways one can approach determining whether ET and PD are related: 1) Is there an increased occurrence of Lewy bodies in cases of ET, and 2) Is there an increase in ET in subjects with Lewy body pathology. We will first address published reports of Lewy bodies in ET.

Lewy Body Pathology in Essential Tremor

For decades the literature has suggested that there is no clear pathology that underlies ET. In 1969 Herskovits and Blackwood[2] published a case report and review of the literature regarding the pathology of ET. They noted two cases from Hassler in 1939,[3] one who had ET and was an alcoholic had decreased small nerve cells in the striatum. The other had ET of the hands, chorea of the legs, and evidence of infarcts, small nerve cells in the striatum, and diffuse Purkinje cell loss. The other two cases they summarized were from Mylle and van Bogaert in 1948[4] both having pallidum changes and one having fibrillar gliosis in the cerebellar peduncles and loss of Purkinje cells. The case of Herskovits and Blackwood however had no significant findings other than softenings in the putamen.[2]

One of the first published series on the pathology of ET was by Rajput et al.[5] and was a series of six cases. They found no neuropathologic lesions to explain ET and specifically they stated that there was no abnormality in the substantia nigra consistent with PD.[5] In 2004 Rajput et al. reported on the largest series of cases to date, 20 cases of ET.[6] The onset age averaged 46.5 yrs with the oldest onset being age 68. The authors clearly stated that only 14 of the cases were tremor only and that the rest had parkinsonism, including one case of idiopathic PD.[6] Two cases had cerebellar ataxia. The only case with Lewy body pathology was the case that had PD, no other case was reported to have Lewy bodies (LBs). The authors also point out that while the other 5 ET cases with parkinsonism could have been clinically diagnosed as PD, this would have erroneously overestimated the possible relationship between ET and PD as none had Lewy bodies. Rather their parkinsonism was due to progressive supranuclear palsy, neuroleptics, and basal ganglia status cribrosus. Lewy body determination was made by hematoxylin-eosin (H&E) staining. Clearly the value of pathologic confirmation of PD and Lewy bodies was needed in this study and emphasizes its importance for all studies trying to link the disorders.

In 2004 Ross et al.[7] published an abstract of 11 autopsied ET cases. They reported finding no consistent pathology to explain ET. Unfortunately a full paper has never been published.

More recently multiple pathologic series from a single group of investigators has implicated the cerebellum in the pathology of ET, and they also have proposed a link between ET and Lewy bodies saying some cases have a Lewy body variant of ET. Their first publication was of a single 91 yo woman with ET and no parkinsonism at the time of death.[8] They found Lewy bodies in the locus ceruleus (LC) using both H&E and ubiquitin stains, and with alpha-synuclein stains found LBs in the LC as well as the dorsal vagal nuclei (DVN) and substantia inominata. In our opinion this case would appear to represent a case of incidental Lewy body disease, see discussion below. As this was only a single case with no controls the authors concluded that a link between ET and Lewy body disease would appear to be premature.[8]

In 2006 this group published pathologic findings from 10 ET and 12 control cases.[9] The cases were ascertained from multiple investigators at multiple sites including cases that may have been published in the series discussed above.[6, 7] One of the ET cases had developed clinical PD with dementia prior to death and one had some parkinsonian features. Some cases in the ET group had been retrospectively diagnosed with ET based on tremor being found on UPDRS rating scales, however the cases were not actually examined for ET nor had they been diagnosed during life as having ET.[9] Controls were free of clinical signs of PD, AD, or ET and also did not meet neuropathologic criteria for AD or PD. Using alpha-synuclein staining 6/10 (60%) ET cases and 2/12 (16.7%) control cases had brainstem Lewy bodies (p=0.035). Two of these ET cases met neuropathological criteria for PD, yet the methods state that controls who met neuropathologic criteria for PD were excluded. Four of the cases had a greater density of LBs in the LC than in the DVN or the SN. An argument was made for ET possibly being secondary to a higher density of Lewy bodies in the LC than in the DVN or the SN. While the density may have been greater in the LC, the other regions were involved. Some study limitations included the small number of cases, end-of-life clinical evaluations were not complete on many cases, different exclusion criteria for ET cases and controls (controls but not ET cases with signs of PD were excluded).[9]

As a follow-up to the 2006 study, Louis et al.[10] reported on 33 ET cases and 21 controls. As with their previous reports, controls that met neuropathological criteria for AD or PD were excluded, as were controls with signs of PD, potentially biasing against the presence of Lewy bodies in the control group. It is unclear how many controls were excluded based on these criteria. In this study 8/33 (24.2%) ET cases had Lewy bodies, and as in the previous report[9] two of the ET cases met neuropathologic criteria for PD and likely should have been excluded as PD was excluded from the control group. This new report actually added only two new cases with Lewy bodies as the other six cases were previously reported in 2006.[9] Therefore, of the subsequent 23 cases of ET prospectively collected, only two (8.7%) actually had LBs. Of these two new cases (Table 2[10]) one had LBs with alpha-synuclein staining in the LC, SN, and DVN, and with H&E staining in the LC, while the other did not have the DVN assessed and had LBs with H&E in the LC but not SN. If the ET cases that met criteria for PD are removed then 6/31 (19.4%) ET cases had Lewy bodies, very similar to published reports of ILBD. While this series found that only 2/21 (9.5%) of controls had Lewy bodies, both being mild and limited to the LC, they had excluded control cases that met neuropathologic criteria for PD.

A third follow-up study by this group was reported in 2009.[11] Their series had grown to include 40 ET cases (27 prospectively obtained and 13 from other sites), 6 (15%) of whom had Lewy bodies. In this report the investigators excluded the two cases who met pathological criteria for PD that were previously reported. If we remove these PD cases from the previous reports as well, then the number of ET cases with LBs went from their 2006 report[9] of 4/8 (50%), to the 2007 report[10] showing 6/31 (19.4%), to the current 2009 update now finding only 6/40 (15%) ET cases had Lewy bodies. As a number of the cases with Lewy bodies were retrospectively obtained, of their prospectively ascertained ET cases only 2/32 (6.3%) had Lewy bodies. Therefore, the conclusion that ET has a “Lewy body variant” is not supported as the number of ET cases collected has grown.

The most recent series of cases from Louis et al.[12] further calls into question a link between ET and Lewy bodies. In a non-controlled study they report nine cases of ET who had not only postural or kinetic tremor but also had unilateral (n=2) or bilateral (n=7) rest tremor. Using H&E and alpha-synuclein staining, none of these cases had Lewy bodies or Lewy neurites in the SN, nor any basal ganglia changes. Two cases had rare LBs with alpha-synuclein staining in the DVN and LC. They concluded that isolated rest tremor, which actually was not “isolated” in that the cases also had postural and kinetic tremor, was not an

expression of underlying Lewy body pathology in the SN or of evolving PD.[12] These nine rest tremor in ET cases when added to the six rest tremor cases of Rajput et al.[6] now reveal no cases with Lewy bodies in the SN or basal ganglia. Thus, no link between rest tremor without other signs of PD and Lewy bodies has been shown.

In our own series[13] of 24 ET and 21 control subjects, subjects with a clinical diagnosis of PD or dementia were excluded from both groups. No neuropathological exclusions were used. Of the 24 ET cases only 11 had been clinically diagnosed, the others met research criteria for ET.[13] Using alpha-synuclein staining 3/24 (12.5%) ET cases had LBs, one had LBs isolated to the LC, one had neocortical LBs only, and one had neocortical, LC, and SN LBs. In the control group 2/21 (9.5%) had LBs, both being neocortical. Additionally, 4 ET and 1 Control case had moderate to severe depletion of LC pigmented neurons. Thus, the occurrence of LBs in this series was no different than controls and was similar to the number seen in the prospectively collected cases of Louis et al.[11] as described above.

Essential Tremor in Subjects with Lewy Body Pathology

From the opposite angle, if ET were a Lewy body disorder then studies of incidental Lewy body disease (ILBD) might aid in establishing this link. ILBD is a term used to define subjects that during life do no have Parkinson's disease or dementia yet at autopsy have Lewy bodies present. Studies have found that up to 30% of autopsied individuals over age 65 have ILBD.[14-20]

Most studies do not detail the clinical findings in ILBD rather they discuss distribution of Lewy bodies. As discussed above, Louis et al.[9] hypothesized that Lewy bodies in the locus ceruleus may be a cause of ET. Saito et al.[16] found that 149/1,241 (12%) of their autopsied cases had incidental Lewy bodies. One case had Lewy bodies isolated to the LC while the others were classified as Braak Stage 1 which indicated more involvement of the dorsal vagal nucleus.[16] No mention is made of whether cases may have had ET or tremor.

Another report found that 34/235 (14.5%) autopsies had ILBD and found the distribution of Lewy bodies varied widely.[21] Twelve had a widespread distribution including the neocortex and were considered Braak Stage 5 or 6,[22] two were Stage 1, nine were stage 2 or 3, and nine were stage 4. One case had Lewy neurites in the LC and superior temporal cortex only and another had them in the nucleus basalis of Meynert only. Again, no mention is made about the clinical findings in these cases. While these subjects did not have PD or dementia, the occurrence of tremor is not noted.

As ILBD has been associated with substantia nigra neuron degeneration,[23, 24] decreased tyrosine hydroxylase immunoreactivity[25, 26] and reduced levels of vesicular monamine transporter 2 (VMAT2)[24] our group investigated the clinical findings, including tremor and essential tremor, comparing ILBD and controls.[20] There was no difference in the occurrence of ET in the two groups: 6/13 (46%) ILBD cases and 22/55 (40%) controls. There was also no difference in the occurrence of at least a 2+ postural or kinetic tremor of the hands: 4/13 (31%) ILBD and 14/55 (25%) Controls.[20]

If ET was an early stage of PD or a risk factor for PD then one might argue that if the hypothesis of Lewy body pathology mainly progressing in a caudal to rostral pattern were true[22, 27] then there should be an increased occurrence of ET in ILBD cases that have olfactory bulb, DVN, or LC involvement without SN or limbic region involvement. To date that has not been shown. Additionally, the prevalence of ILBD is much greater (up to 30% of autopsied cases > age 65) than that of PD. Thus, the ILBD literature would not appear to support a link between ET and PD.

Neurochemical findings in ET

While examining for Lewy bodies is one way to assess a relationship between ET and PD, neurochemical analysis of brain regions in ET and PD is also revealing. There have been very few studies of neurochemical markers in ET. In a study published in abstract form only, Rajput et al.[28] found higher levels of norepinephrine in three ET cases compared to controls, the opposite of what is seen in PD. Shill et al.,[29] also in abstract form only, have shown that mean striatal tyrosine hydroxylase (TH) levels did not differ between 23 ET cases, 90.3 ± 113.0 ng/mg, and 37 Controls, 98.0 ± 101.8. As our group[25] and others[24, 26] have previously shown, ILBD and PD are associated with decreased levels of TH, then if ET were a risk factor for ET we would have expected TH levels to be reduced.

Other evidence

As regards the epidemiologic studies suggesting ET is a risk factor for ET, Deuschl and Elble[30] discuss this in detail in *Movement Disorders* and therefore this paper will not repeat the discussion as nothing new has been published. Despite Benito-Leon et al.[1] finding a 4× higher incidence of PD in ET cases ≥65 yo when compared to controls, the number of incident cases during 3.3 yrs of follow-up was very small (6/201 ET and 24/3574 Controls) and produced an absolute increased risk of only 2.3%. Additionally while Fekete and Jankovic discuss their own unpublished data showing a higher of occurrence of ET >5 years prior to the development of PD and not PSP or CBD, this does not link the disorders. There was no control group presented, and the overall incidence of PD is much higher than either PSP or CBD, so a causal relationship is not clear. It is also unclear how data showing that 37% of 71 patients with ET had been misdiagnosed as PD or dystonia in anyway links ET with PD.[31]

The genetic association between ET and PD has been debated. One paper by Yahr et al.[32] described a family of 36 individuals 11 of whom had ET, and 2 of whom were twin boys who eventually developed PD. Pathology from one of these cases revealed Lewy bodies and confirmed the pathologic diagnosis of PD. It is unclear how this case demonstrates a causal relationship between ET and PD, rather it demonstrates that an ET case who eventually develops clinical PD can have pathologically confirmed PD. What certainly would be of interest would be the pathologic findings of the cases of ET that did not have PD clinically, and literature review did not reveal any further publications from this group.

As regards non-motor signs of PD and how these may relate to ET, one of the key findings in PD is hyposmia. There are many papers demonstrating the loss of olfaction in PD but not ET.[33-37] One report compared olfactory function in 59 ET, 64 tremor-predominant PD, and 245 controls.[35] They found PD but not ET cases to be hyposmic, and even found that ET cases with a family history of tremor had better olfactory function than controls. In another comparison paper hyposmia was found in PD (n=191) but not ET (n=26) compared to controls (n=136).[36] A report from our group found hyposmia when comparing 19 PD cases with 37 ET and 207 controls.[37] There have only been two reports[38, 39] from the same group finding a very slight decrease in UPSIT scores first comparing 37 ET and 37 controls, [38] then 87 ET and 92 controls.[39] The difference in mean score was only 2.1 points and was not in the hyposmic range. When comparing the percentage of cases that were hyposmic (UPSIT score <25) there was a non-significant difference between the ET (19.8%) and Control (9.8%) groups.[39] As hyposmia appears to precede the onset of motor findings in PD by years, the lack of a clear difference between ET and controls would not support a link between the disorders. Follow-up of hyposmic ET cases, and even hyposmic controls, to determine the incidence of PD might eventually aid in answering this question.

A full discussion of the neuroimaging data comparing ET and PD is beyond the scope of this review. One of the cited papers, Ceravolo et al.,[40] evaluated β-CIT SPECT in subjects with unilateral tremor, none of whom were diagnosed with ET. Eventual conversion to PD was not shown to be a link between ET and PD, rather it was evidence that an abnormal scan may predict eventual development of PD. While SN hyperechogenicity has been found in PD, it is a nonspecific finding as it is also seen in 9% of healthy controls,[41] as well as in corticobasal degeneration,[42] multiple sclerosis,[43] and restless legs syndrome.[44] Additionally, there is no progression of as PD progresses making its diagnostic value unclear. While Fekete and Jankovic cite Budisic et al.[45] as showing hyperechogenicity in ET that is not what they actually reported. Rather they reported 91% of 80 PD cases, 13% of 30 ET cases, and 10% of 80 controls had hyperechogenicity. They concluded that it might be possible that there is an increased risk of PD in these ET and Control cases but they definitively showed that ET as a group did not have an abnormality.[45] Finally, as the neuroimaging data has not been confirmed by pathological studies, and since there are multiple conflicting reports of radioligand uptake studies and even diffusion tensor imaging,[46] in addition to what is discussed above, no clear link between PD and ET has yet been proven by neuroimaging.

Lastly, Fekete and Jankovic make it clear that there is no therapeutic evidence that currently link ET to PD.

Conclusion

While there is some data to suggest that ET may in some way be linked to PD, to date the overwhelming amount of evidence continues to suggest that this may well be coincidence and not a biological link. Without clear diagnostic markers for either ET or PD the answer to this question will require prospective studies utilizing longitudinal, standardized assessments for tremor and parkinsonism in subjects with and without ET. While neuroimaging may provide a surrogate marker for PD, the only gold-standard marker is neuropathologic evaluation. Clearly defining the populations and establishing criteria for inclusion and exclusion remains critical.

Acknowledgments

This work was funded by the Arizona Biomedical Research Commission (contracts 4001, 05-901, 0011, and 1001), the Michael J. Fox Foundation for Parkinson's Research, the Arizona Department of Health Services (contract 211002), and the National Institute on Aging (P30 AG19610).

References

1. Benito-Leon J, Louis ED, Bermejo-Pareja F. Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population based study. Journal of neurology, neurosurgery, and psychiatry. 2009; 80(4):423–425.
2. Herskovits E, Blackwood W. Essential (familial, hereditary) tremor: a case report. Journal of neurology, neurosurgery, and psychiatry. 1969; 32(6):509–511.
3. Hassler R. Zur pathologischen Anatomie des senilen und des parkinsonistischen Tremor. J Psychol Neurol (Lpz). 1939; 49:193–230.
4. Mylle G, van Bogaert L. Etudes anatomo-cliniques de syndromes hypercinetiques complexes. Mschr Psychiat Neurol. 1940; 103:28–43.
5. Rajput AH, Rozdilsky B, Ang L, Rajput A. Clinicopathologic observations in essential tremor: report of six cases. Neurology. 1991; 41(9):1422–1424. [PubMed: 1891091]
6. Rajput A, Robinson CA, Rajput AH. Essential tremor course and disability: A clinicopathologic study of 20 cases. Neurology. 2004; 62(6):932–936. [PubMed: 15037695]
7. Ross GW, Dickson D, Cersosimo M, Tsuboi Y, Katsuse O, Petrovitch H. Pathological investigation of essential tremor. Neurology. 2004; 62(5):A537–538.

8. Louis ED, Honig LS, Vonsattel JP, Maraganore DM, Borden S, Moskowitz CB. Essential tremor associated with focal nonnigral Lewy bodies: a clinicopathologic study. Archives of neurology. 2005; 62(6):1004–1007. [PubMed: 15956174]
9. Louis ED, Vonsattel JP, Honig LS, Ross GW, Lyons KE, Pahwa R. Neuropathologic findings in essential tremor. Neurology. 2006; 66(11):1756–1759. [PubMed: 16769958]
10. Louis ED, Faust PL, Vonsattel JP, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain. 2007; 130(Pt 12):3297–3307. [PubMed: 18025031]
11. Louis ED, Faust PL, Vonsattel JP, et al. Torpedoes in Parkinson's disease, Alzheimer's disease, essential tremor, and control brains. Mov Disord. 2009; 24:1600–1605. [PubMed: 19526585]
12. Louis ED, Asabere N, Agnew A, et al. Rest tremor in advanced essential tremor: a post-mortem study of nine cases. Journal of neurology, neurosurgery, and psychiatry. 2010
13. Shill HA, Adler CH, Sabbagh MN, et al. Pathologic findings in prospectively ascertained essential tremor subjects. Neurology. 2008; 70(16 Pt 2):1452–1455. [PubMed: 18413570]
14. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. Journal of neurology, neurosurgery, and psychiatry. 1988; 51(6):745–752.
15. Mayeux R, Marder K, Cote LJ, et al. The frequency of idiopathic Parkinson's disease by age, ethnic group, and sex in northern Manhattan, 1988-1993. American journal of epidemiology. 1995; 142(8):820–827. [PubMed: 7572958]
16. Saito Y, Ruberu NN, Sawabe M, et al. Lewy body-related alpha-synucleinopathy in aging. Journal of neuropathology and experimental neurology. 2004; 63(7):742–749. [PubMed: 15290899]
17. Bloch A, Probst A, Bissig H, Adams H, Tolnay M. Alpha-synuclein pathology of the spinal and peripheral autonomic nervous system in neurologically unimpaired elderly subjects. Neuropathology and applied neurobiology. 2006; 32(3):284–295. [PubMed: 16640647]
18. Minguez-Castellanos A, Chamorro CE, Escamilla-Sevilla F, et al. Do {alpha}-synuclein aggregates in autonomic plexuses predate Lewy body disorders?: A cohort study. Neurology. 2007; 68(23):2012–2018. [PubMed: 17548551]
19. Jellinger KA. Lewy body-related alpha-synucleinopathy in the aged human brain. J Neural Transm. 2004; 111(10-11):1219–1235. [PubMed: 15480835]
20. Adler CH, Connor DJ, Hentz JG, et al. Incidental Lewy body disease: clinical comparison to a control cohort. Mov Disord. 2010; 25(5):642–646. [PubMed: 20175211]
21. Frigerio R, Fujishiro H, Ahn TB, et al. Incidental Lewy body disease: Do some cases represent a preclinical stage of dementia with Lewy bodies? Neurobiology of aging. 2009
22. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 2004; 318(1):121–134. [PubMed: 15338272]
23. Ross GW, Petrovitch H, Abbott RD, et al. Parkinsonian signs and substantia nigra neuron density in decendents elders without PD. Annals of neurology. 2004; 56(4):532–539. [PubMed: 15389895]
24. DelleDonne A, Klos KJ, Fujishiro H, et al. Incidental Lewy body disease and preclinical Parkinson disease. Archives of neurology. 2008; 65(8):1074–1080. [PubMed: 18695057]
25. Beach TG, Adler CH, Sue LI, et al. Reduced striatal tyrosine hydroxylase in incidental Lewy body disease. Acta neuropathologica. 2008; 115(4):445–451. [PubMed: 17985144]
26. Dickson DW, Fujishiro H, DelleDonne A, et al. Evidence that incidental Lewy body disease is pre-symptomatic Parkinson's disease. Acta neuropathologica. 2008; 115(4):437–444. [PubMed: 18264713]
27. Beach TG, Adler CH, Lue L, et al. Unified staging system for Lewy body disorders: correlation with nigrostriatal degeneration, cognitive impairment and motor dysfunction. Acta neuropathologica. 2009; 117(6):613–634. [PubMed: 19399512]
28. Rajput A, Hornykiewicz O, Deng Y, Birdi S, Miyashita H, Macaulay R. Increased noradrenaline levels in essential tremor brain. Neurology. 2001; 56(3):A302.
29. Shill HA, Adler CH, Beach TG, et al. Striatal tyrosine hydroxylase in autopsied patients with essential tremor. Neurology. 2009; 72(3):A100.

30. Deuschl G, Elble R. Essential tremor--neurodegenerative or nondegenerative disease towards a working definition of ET. Mov Disord. 2009; 24(14):2033–2041. [PubMed: 19750493]
31. Jain S, Lo SE, Louis ED. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? Archives of neurology. 2006; 63(8):1100–1104. [PubMed: 16908735]
32. Yahr MD, Orosz D, Purohit DP. Co-occurrence of essential tremor and Parkinson's disease: clinical study of a large kindred with autopsy findings. Parkinsonism & related disorders. 2003; 9(4):225–231. [PubMed: 12618058]
33. Busenbark KL, Huber SJ, Greer G, Pahwa R, Koller WC. Olfactory function in essential tremor. Neurology. 1992; 42:1631–1632. [PubMed: 1641163]
34. Djaldetti R, Nageris BI, Lorberboym M, Treves TA, Melamed E, Yaniv E. [(123)I]-FP-CIT SPECT and olfaction test in patients with combined postural and rest tremor. J Neural Transm. 2008; 115(3):469–472. [PubMed: 18250955]
35. Shah M, Muhammed N, Findley LJ, Hawkes CH. Olfactory tests in the diagnosis of essential tremor. Parkinsonism & related disorders. 2008; 14:563–568. [PubMed: 18321760]
36. Silveira-Moriyama L, Schwingenschuh P, O'Donnell A, et al. Olfaction in patients with suspected parkinsonism and scans without evidence of dopaminergic deficit (SWEDDs). Journal of neurology, neurosurgery, and psychiatry. 2009; 80(7):744–748.
37. McKinnon J, Evidente V, Driver-Dunckley E, et al. Olfaction in the elderly: A cross-sectional analysis comparing Parkinson's disease with controls and other disorders. Int J Neurosci. 2010; 120:36–39. [PubMed: 20128670]
38. Louis ED, Bromley SM, Jurewicz EC, Watner D. Olfactory dysfunction in essential tremor: a deficit unrelated to disease duration or severity. Neurology. 2002; 59(10):1631–1633. [PubMed: 12451211]
39. Applegate LM, Louis ED. Essential tremor: Mild olfactory dysfunction in a cerebellar disorder. Parkinsonism & related disorders. 2005; 11(6):399–402. [PubMed: 16102998]
40. Ceravolo R, Antonini A, Volterrani D, et al. Predictive value of nigrostriatal dysfunction in isolated tremor: a clinical and SPECT study. Mov Disord. 2008; 23(14):2049–2054. [PubMed: 18759337]
41. Walter U. Transcranial brain sonography findings in Parkinson's disease: implications for pathogenesis, early diagnosis and therapy. Expert review of neurotherapeutics. 2009; 9(6):835–846. [PubMed: 19496687]
42. Walter U, Dressler D, Wolters A, Probst T, Grossmann A, Benecke R. Sonographic discrimination of corticobasal degeneration vs progressive supranuclear palsy. Neurology. 2004; 63(3):504–509. [PubMed: 15304582]
43. Walter U, Wagner S, Horowski S, Benecke R, Zettl UK. Transcranial brain sonography findings predict disease progression in multiple sclerosis. Neurology. 2009; 73(13):1010–1017. [PubMed: 19657105]
44. Godau J, Schweitzer KJ, Liepelt I, Gerloff C, Berg D. Substantia nigra hypoechogenicity: definition and findings in restless legs syndrome. Mov Disord. 2007; 22(2):187–192. [PubMed: 17133515]
45. Budisic M, Trkanjec Z, Bosnjak J, Lovrencic-Huzjan A, Vukovic V, Demarin V. Distinguishing Parkinson's disease and essential tremor with transcranial sonography. Acta Neurol Scand. 2009; 119(1):17–21. [PubMed: 18549415]
46. Nicoletti G, Manners D, Novellino F, et al. Diffusion tensor MRI changes in cerebellar structures of patients with familial essential tremor. Neurology. 2010; 74(12):988–994. [PubMed: 20308683]