Is Essential Tremor Predictive of Parkinson’s Disease?

Yes

—Elan D. Louis MD, MSc, Professor of Neurology and Epidemiology, Columbia University, New York, NY, USA

The possible link between essential tremor (ET) and Parkinson’s disease (PD) has been a subject of interest and debate for some time. Dating back to the first comprehensive clinical review of ET in 1949,1 there has been discussion regarding the possibility of a relationship between these two tremor disorders, with clinicians observing that ET patients have a tendency over time to develop PD.23 Interestingly, the converse does not seem to occur (i.e., PD patients developing ET).23 The co-occurrence of the two tremor disorders within the same families is also well-documented.4

Three epidemiological studies, including two case-control studies and one population-based prospective study, each provide measures of association that support the notion that there is a link between ET and PD, and, furthermore, that the presence of baseline ET increases the risk of developing incident PD during follow-up.5-6 The magnitude of the increased odds/risks reported in the three epidemiological studies is on the order of 3 to 13.3 Most important of these was the 2010 prospective, population-based study that was conducted to estimate the incidence of PD in ET patients vs. normal controls.5 The study sample was comprised of 3,813 elderly persons (age ≥65 years) residing in three communities in central Spain. The baseline evaluation consisted of an initial screening questionnaire followed by an in-person neurological examination; a follow-up examination was performed after a median time interval of 3.3 years. During that time interval, 6 of 201 (3.0%) ET cases vs. 24 of 3,574 (0.7%) controls developed incident PD (adjusted relative risk [RR] = 4.27, 95% confidence interval [CI] = 1.72 – 10.61, p = 0.002).5 Presently, there are no contrary data, either from case-control or prospective studies, to refute the model that ET is a risk factor for PD.5 Moreover, the evidence from three genetic epidemiological studies is that ET and PD seem to co-occur in families to an extent ET and PD. Both may have rest, postural and kinetic tremor as well as some degree of bradykinesia and rigidity. However, these clinical findings do not guarantee a diagnosis of PD as it is clear that patients with all three cardinal features of PD can have normal dopaminergic imaging (so called Scans Without Evidence of Dopamine Deficiency) and no evidence of Lewy bodies neuropathologically. From a clinical-pathological standpoint there are two ways one can approach determining whether ET and PD are related: 1) Is there an increased occurrence of α-synuclein staining or Lewy bodies in cases of ET, and 2) Is there an increase in ET in subjects with Lewy body pathology. The number of autopsied cases of ET has been small. In the first few series there was no evidence of Lewy body pathology, even to the point of some cases with ET and parkinsonian features actually not having Lewy bodies and thus any linking of the two disorders would have been erroneous. More recently multiple pathologic series from a single group of investigators have proposed a link between ET and Lewy bodies. They have published a number of papers building on their case series and while initially the percentage of ET cases with Lewy bodies was greater than in the controls, their more recent papers have shown that there is no difference in Lewy body

No

—Charles H. Adler, MD, PhD, Professor of Neurology, Mayo Clinic College of Medicine, Mayo Clinic, Scottsdale, AZ, USA, Co-Principal Investigator, Arizona Parkinson’s Disease Consortium

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. A major confounding factor for linking the two is our limited knowledge regarding their etiology. Both PD and ET appear to be syndromes and not diseases with a single cause so a link is difficult to prove. 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 is the main focus of this presentation. Clinically there is overlap between ET and PD. Both may have rest, postural and kinetic tremor as well as some degree of bradykinesia and rigidity. However, these clinical findings do not guarantee a diagnosis of PD as it is clear that patients with all three cardinal features of PD can have normal dopaminergic imaging (so called Scans Without Evidence of Dopamine Deficiency) and no evidence of Lewy bodies neuropathologically. From a clinical-pathological standpoint there are two ways one can approach determining whether ET and PD are related: 1) Is there an increased occurrence of α-synuclein staining or Lewy bodies in cases of ET, and 2) Is there an increase in ET in subjects with Lewy body pathology. The number of autopsied cases of ET has been small. In the first few series there was no evidence of Lewy body pathology, even to the point of some cases with ET and parkinsonian features actually not having Lewy bodies and thus any linking of the two disorders would have been erroneous. More recently multiple pathologic series from a single group of investigators have proposed a link between ET and Lewy bodies. They have published a number of papers building on their case series and while initially the percentage of ET cases with Lewy bodies was greater than in the controls, their more recent papers have shown that there is no difference in Lewy body...
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Yes

greater than expected by chance alone, with PD patients being more likely than controls to have first-degree relatives with ET. The epidemiological and genetic epidemiological data are consistent with biological evidence, which further supports the possibility of common disease mechanisms and pathogenesis. Thus, several imaging studies have suggested that there may be some degree of overlap between ET and PD. These findings are further supported by genetic studies, which demonstrate that some of the same genetic variants are associated with both ET and PD. More recently, large post-mortem series have demonstrated the presence of more brainstem Lewy bodies in ET cases than in similarly-aged controls, suggesting that there is the presence of Lewy body variant of ET, and raising the possibility that these cases might be at increased risk for developing a more complete Lewy body syndrome (i.e., PD).

The composite data are difficult to ignore. Indeed, a recent editorial on the putative relationship between ET and PD remarked as follows: "Perhaps there are not enough studies to completely end the discussion, but the consistency of the results and the biological plausibility of the association are very strong."

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References


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occurrence in prospectively ascertained ET cases (2/32, 6.3%) than in controls (2/21, 9.5%). Therefore, the conclusion that ET has a "Lewy body variant" was not supported as their number of ET cases grew. Our group has published one of the largest series to date of prospectively ascertained and examined ET cases and we found no difference in Lewy body occurrence between ET case (3/24, 12.5%) and Controls (2/21, 9.5%).

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. Studies have found that up to 50% of autopsied individuals over age 65 have ILBD so both ET and ILBD are extremely common. Unfortunately, most ILBD studies do not detail the clinical findings in ILBD. We have recently published the finding that there was no difference in the occurrence of ET in ILBD cases (6/13, 46%) compared to Controls (22/55, 40%). There was also no difference in the occurrence of ≥ 2+ postural or kinetic tremor of the hands: 4/13 (31%) ILBD and 14/55 (25%) Controls.

A third way to assess association would be neurochemically. It is well-proven that striatal tyrosine hydroxylase levels are low in both PD and ILBD. If ET was a risk factor for PD then we might expect TH levels to be low in ET, or at least in a subgroup of ET cases, but this is not what we found as we recently published.

Epidemiologic studies suggesting ET is a risk factor for ET have many flaws. In one retrospective paper, the occurrence of ET in PD cases was greater than in Parkinson-Plus cases, but this does not link ET to PD as there was no control group for comparison. A second study found a 4x higher incidence of PD in ET cases ≥65 year old when compared to controls, but the number of incident cases during 3.3 years of follow-up was very small (6/201 ET and 24/3574 Controls) and produced an absolute increased risk of only 2.3%. Also, these cases did not require dopaminergic response for the diagnosis of PD, and had no imaging or pathology to support the diagnosis of PD.

The genetic association between ET and PD has been debated. Currently there is no clear cut evidence that the genes associated with PD, LRRK2, SNCA variants, glucocerebrosidase, LING01, or LINGO2, have an association with ET. There is no clear neuroimaging data linking ET to PD and there is no therapeutic evidence that currently links ET to PD.

In conclusion, to date the overwhelming evidence supports a lack of a link between ET and PD. ET is very common and its occurrence in PD may well be coincidental. Certainly, if there is a biological link then it may be for a subset of ET patients. To move this controversy forward, we need clear diagnostic markers for both disorders along with prospective, controlled studies utilizing longitudinal, standardized assessments for tremor and parkinsonism in subjects.
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with and without ET along with either neuroimaging (a surrogate marker) or autopsy, the only gold-standard marker, for PD.

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