Published in final edited form as:
Eur J Neurol. 2013 November ; 20(11): 1440–1444. doi:10.1111/ene.12256.

Is There a One Way Street from Essential Tremor to Parkinson's Disease? Possible Biological Ramifications

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Abstract

There is considerable evidence for an association between essential tremor (ET) and Parkinson's disease (PD), although the topic remains somewhat controversial. An important issue, not previously addressed, is what seems to be the uni-directional nature of the relationship (ET→ET+PD and not PD→PD+ET). The aims of this review are (1) to discuss the evidence for and against a uni-directional relationship and (2) to discuss the implications of such a uni-directional relationship, if it exists, for disease mechanisms. Evidence "for" a uni-directional relationship includes: (1) abundant clinical anecdotal observation, (2) clinical and epidemiological studies. Evidence "against" is theoretic rather than empiric. Overall, the evidence "for" is stronger, though additional studies are needed in order to be certain; for the time being, it might be best to leave this as an open question. The biological ramifications/extensions of such a unidirectional relationship include: (1) that the association is causal (i.e., some aspect of ET pathophysiology predisposes an individual to develop PD), (2) that some ET cases may have a circumscribed form of Lewy body disease, and the secondary development of PD may represent a spread of those Lewy bodies in the brainstem. The presence and nature of the links between ET and PD are controversial. Further primary data (epidemiological and pathological) are needed to improve understanding of the relationship and its implications for the pathogenesis of both disorders.

Keywords

essential tremor; Parkinson's disease; epidemiology; biology; neurodegeneration

INTRODUCTION

There is considerable evidence for an association between essential tremor (ET) and Parkinson's disease (PD), although the topic remains somewhat controversial [1–7]. Interestingly, a conspicuous issue, which has not been formally addressed in the literature, is what seems to be the *uni-directional* nature of the relationship, that is, that ET patients seem prone to develop PD (ET→ET+PD) but the converse is not often observed (PD→PD+ET).

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Disclosure: There are no conflicts of interest and no competing financial interests.

The aims of this review are (1) to discuss the evidence both for and against a true *uni-directional* relationship and (2) to discuss the implications of such a uni-directional relationship, if it exists, for disease mechanisms.

METHODS

The authors used Pubmed (1966 to May 2013) to cross search the terms "essential tremor" with "Parkinson disease." Additional search terms that were included, one by one, were "association", "risk", "odds", "epidemiology," and "cause". All English language papers were reviewed. The authors supplemented this review with published peer-reviewed papers in their files.

EVIDENCE FOR A UNI-DIRECTIONAL RELATIONSHIP

The evidence "for" a uni-directional relationship is derived from two main sources: (1) abundant anecdotal clinical observation and commentary [1, 8–15], (2) cross-sectional [16, 17], case-control [3], and prospective epidemiological studies [18].

Though anecdotal observation is potentially problematic for a number of reasons, including the absence of a control group and the possibilities of selection bias (e.g., a greater likelihood of seeking medical attention for a neurological condition that has worsened or changed markedly in character, such as from ET to PD, rather than the converse) and recall bias (a greater likelihood of recalling action tremor than tremor at rest), clinical observation often forms the initial foundation for the formulation of new hypotheses to be tested in rigorous clinical research. In some scenarios in medicine, evidence from clinical observation may even be sufficiently strong that controlled data are deemed unnecessary. For example, in the discovery of the link between exposure to a synthetic heroin contaminant (MPTP) and parkinsonism, initially in only four persons in California, the strength of the data in this small number of cases was deemed to be sufficient to establish a link [19]. A clinical connection, particularly if observed repeatedly in a range of different settings, may at a minimum be viewed as reproducible. In numerous clinical series of ET cases spanning many years, clinicians have commented on the occurrence of ET→ET+PD (i.e., the superimposition of PD onto ET)[8–15]; curiously, though, the converse (PD→PD+ET) has not been documented or discussed. Hence, the weight of evidence from clinical observation clearly supports a unidirectional increase in risk.

In terms of the epidemiological evidence, a number of cross-sectional [16, 17], case-control [3] and prospective epidemiological studies [18], have demonstrated an association between ET and PD [20]. Moreover, there are no case-control or prospective epidemiological studies that have documented the absence of an association. In epidemiological studies [3, 16–18], the direction of the relationship has been ET→ET+PD, though some caveats must be considered. These studies will be reviewed below.

A case-control study at a tertiary referral center in Singapore included 204 outpatients with PD, 206 diseased controls (i.e., neurological outpatients with hemifacial spasm) and 190 healthy controls (i.e., medical and technical staff from the hospital as well as volunteers) [3]. Twelve (5.9%) PD patients also carried a prior diagnosis of ET, compared to 2 (1.7%) diseased controls (odds ratio [OR] = 6.4, 95% confidence interval [CI] = 1.5 – 27.7, p = 0.006) and 1 (0.5%) healthy control (OR = 11.8, 95% CI = 1.9 – 71.3, p = 0.003) (presumably this healthy control was found to have ET after enrollment, as ET was an exclusion criterion for controls) [3]. In 2010, a prospective, population-based study was conducted to estimate the incidence of PD in ET patients versus normal controls [18]. The study sample comprised 3,813 elderly persons (age ≥65 years) living in three communities in central Spain. During the study interval (approximately 3 years), 6 of 201 (3.0%) ET

cases versus 24 of 3,574 (0.7%) controls developed incident PD (adjusted relative risk [RR] = 4.27, 95% CI 1.72 – 10.61, p = 0.002). The investigators estimated that the lifetime risk of developing PD was 8.5% in men with ET and 5.6% in women with ET, compared to 2% in men and 1.3% in woman without ET [18].

In both of these studies, the design necessitated that the diagnosis of ET precede that of PD [3, 18]. Thus, while these studies both provide evidence for an increased risk of PD in individuals with a previous diagnosis of ET, they do not address whether or not the converse also occurs.

There are no case-control studies, to our knowledge, in which ET patients were compared to controls without ET (without specifying that other neurological diagnoses were absent) to determine whether a prior diagnosis of PD was more prevalent in the ET cases. Nor are there any studies in which PD patients and controls were followed prospectively, and in which an increased risk of ET was noted in the PD vs. control group. The likely reason is that the weight of the clinical anecdotal evidence, as noted above, supports a unidirectional relationship, and there is little index of suspicion among clinicians that prevalent PD increases the risk of developing incident ET.

Two studies selected individuals from movement disorders centers who carried both diagnoses (ET+PD) (i.e., without requiring that one diagnosis preceded the other) [16, 17]. In the first of those, 53 ET+PD cases were identified from a computerized billing database at the Center for Parkinson's Disease and Other Movement Disorders at the Neurological Institute of New York, Columbia University Medical Center [17]. Interestingly, all of the ET +PD cases had first had a diagnosis of ET and then a diagnosis of PD, rather than the reverse [17]. Although the latency from onset of ET to PD was brief (<5 years) in 38.5% of cases, yet in a sizable proportion (30.8%) of cases, it was very long (>20 years) [17]. In the second study 18 ET+PD cases were identified from the Movement Disorder Program of University of Louisville, Kentucky [16]. As in the first study, all of the ET+PD cases had first had a diagnosis of ET and then a diagnosis of PD, rather than the converse [16]. The mean duration of ET prior to the diagnosis of PD was 19.3±15.7 years [16].

In summary, only a few epidemiological studies have addressed this question, and additional studies are needed. Interestingly, the sheer strength of the clinical anecdotal evidence has provided far more motivation for investigators to examine whether ET is a risk factor for PD rather than the converse. Thus, there are no clinical or epidemiological data supporting the notion that PD increases the risk of ET whereas there are data supporting the notion that ET is a risk factor for PD. In the clinical studies that have not pre-specified whether ET must precede PD or vice versa, it has been the ET that has preceded the PD.

EVIDENCE AGAINST A UNI-DIRECTIONAL RELATIONSHIP

Several issues raise doubt about the previous evidence for a unidirectional relationship. First, there is the issue of diagnostic validity - there is a possibility that ET diagnoses and PD diagnoses in previous studies may have been invalid. Some prevalent "ET" cases may have actually been forme frustes of PD [17, 21]. There is no doubt that isolated action tremor *with unusual features* (e.g., strictly unilateral postural tremor without kinetic tremor) may represent early PD rather than ET [15]. ET is often misdiagnosed: in approximately 30–50% of cases diagnosed as ET, the true diagnosis is another neurological disorder [21, 22]. Misdiagnosis often results from the failure to distinguish between typical and unusual features of ET. However, evidence is lacking that isolated action tremor *that is typical of ET* is a forme fruste of PD. Furthermore, in the study by Minen et al. [17] a sizable proportion (30.8%) of ET+PD cases had had ET for more than 20 years before onset of PD; PD is unlikely to manifest as isolated action tremor for >20 years.

There are also concerns about the validity of PD diagnoses. Rest tremor is a feature of advanced ET [23]; ET cases with rest tremor may be misdiagnosed as ET+PD rather than just ET, leading to inflated estimates of incident "PD" in ET. However, in the epidemiological studies [3, 16–18], PD was diagnosed only when two or more hallmark features of PD were present; hence in these studies, ET patients with isolated rest tremor (without at least one other hallmark feature of PD) would not have been diagnosed with PD.

Additionally, diagnosing ET in a patient with PD is inherently difficult because action tremor is present in many PD patients. Although rest tremor is a hallmark feature of PD, the prevalence of action tremor in PD is very high (> 90% by some estimates) [24, 25]; if this action tremor of PD were to mask that of ET, it would be difficult for clinicians to appreciate the onset or presence of ET in a patient with PD. However, postural tremor in ET differs from that in PD with regard to the joints typically affected (distal [metacarpal-phalangeal] joints vs. proximal [wrist] joints in hand), tremor quality (e.g., wrist flexion-extension in ET vs. wrist pronation-supination in PD) [26], and sometimes, the timing of the tremor (re-emergent tremor in PD vs. immediately-emerging tremor in ET) [27]. Furthermore, the finger-nose-finger tremor of PD tends not to have an intention component, whereas this a feature of approximately one-half of ET cases [28]. Finally, the action tremor of ET does worsen with time, and it can become quite severe; in older individuals, rate of progression can be marked [29, 30]. By contrast, there is no evidence that the action tremor of PD worsens with time. Hence, even if the action tremor of ET were initially masked in a PD patient, its presence would become clearer with time. Nonetheless, it may be difficult to appreciate all of these subtle differences in tremor characteristics, and there are no diagnostic tests (e.g., imaging) to establish an ET diagnosis, as there are for PD. That an ET diagnosis might not usually be applied to a PD case remains a valid concern.

Second, a truly bidirectional relationship could have failed to be appreciated because of differences in the typical age at onset of ET and PD. ET often has an onset before age 40 years [31] whereas PD typically has an onset >60 years [32], so ET→ET+PD would be expected to be more common than the converse (PD→PD+ET). On the other hand, a study of the incidence of ET indicated that 144 (54.1%) of 266 cases arose at or after age 60 years, which is the typical age of onset of PD [33]. Given the high prevalence of ET relative to that of PD (by some estimates as much as twenty times higher) [34], there is ample opportunity for ET to develop in PD patients.

Third, clinicians might overlook the onset of ET in patients with PD because they are focused on other more pressing therapeutic issues (gait and balance impairment, increasingly profound bradykinesia, dementia, psychosis). Although this could be occurring, action tremor can become quite severe and disabling in ET [35, 36], especially in older patients [30], and it is unlikely that this would be totally and completely overlooked and unappreciated in all clinical settings.

Fourth, the duration of illness in ET may be far longer than that of PD. This means that prevalent ET cases have more time to develop other illnesses (including PD) whereas prevalent PD cases have less time to do develop these illnesses (including ET). Nonetheless, the incidence of ET is far higher than that of PD [37], making it more likely that a prevalent a PD case would develop incident ET than that a prevalent ET case would develop incident PD; these issues likely counter-balance one another.

WEIGHING IN – MORE FOR "FOR" OR MORE FOR "AGAINST"?

There is empirical evidence for a unidirectional association between ET and PD and no empirical evidence of the converse; this point should not be under-appreciated. While several issues (discussed above) might have obscured a true bidirectional association, each

appears unlikely to account fully for the observation of a unidirectional relationship between ET and PD. Yet, additional studies are needed in order to be certain; for the time being, it might be best to leave this as an open question.

BIOLOGICAL RAMIFICATIONS

If the relationship of ET to PD is unidirectional, there are several biological ramifications. The first possibility is that ET is a risk factor for and possibly a cause of PD whereas, conversely, PD is not a cause of ET. The mechanism whereby this could occur is not clear, but the implication is that some aspect of the clinical manifestation or pathophysiology of ET predisposes an individual to develop PD.

The second possibility is that in a subset of ET patients, ET and PD are part of a spectrum (i.e., Lewy body diseases), with PD being more advanced. Lewy bodies have been reported in several ET brain bank series [38–40], though not in others [41]. Differences between studies could merely reflect sampling issues. In the largest of these series, the Lewy bodies were mainly located in the locus ceruleus rather than the dorsal vagal nucleus or substantia nigra pars compacta [42]. These findings raise the possibility that a subgroup of ET cases have a circumscribed form of Lewy body disease, and the secondary development of PD represents a spread of those Lewy bodies upwards through the brainstem to involve the substantia nigra pars compacta [43]. The notion that Lewy body disease comprises several disease entities rather than a single entity (e.g., PD, diffuse Lewy body disease, to name two) is already well-ingrained in the literature, as is the notion that PD is the result of an upward spreading of Lewy bodies within the brainstem over time and that diffuse Lewy body disease may also be the result of cortical spread of Lewy bodies [44]. The notion that ET is not a single disease but a family of related diseases has also been raised in the literature [45] and is supported by the clear presence of genetic heterogeneity [46, 47] and well as pathological heterogeneity (i.e., the presence of changes in the cerebellum in some patients and Lewy bodies in others) [41, 42]. Interestingly, the observation that ET does not follow PD could be explained in part by the fact that, according to the Braak staging scheme for PD [44], when the disease manifests clinically as parkinsonism (Braak stage 3), Lewy bodies are already present in the locus ceruleus (this occurs earlier during Braak stage 2) as well as the dorsal vagal nucleus (stage 1). Given this widespread distribution of Lewy bodies in the brainstem in PD, a patient with PD (i.e., with Lewy-bodies distributed in multiple places in the brainstem) could not, by definition, later develop a Lewy body-associated ET, in which Lewy bodies appear to be confined to one region of the brainstem (i.e., the locus ceruleus). Furthermore, the presence of Lewy bodies in the locus ceruleus in PD could explain the high prevalence of mild action tremor in PD patients.

CONCLUSIONS

The presence and nature of the links between ET and PD are controversial. While the current evidence supports a unidirectional association, further primary data (epidemiological and pathological) are needed to help sort out the nature of the relationship. These data will likely contribute to our understanding of the biology of both disorders. The resolution of this issue will have several potentially important biological ramifications.

Acknowledgments

Funding: National Institutes of Health Grant R01 NS039422 (Dr. Louis).

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