Essential tremor and ageing

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Abstract

Essential Tremor (ET) is a very common neurological condition that increases with age. Tremor progresses in severity and body distribution with aging. Patients with ET may develop clinical signs of cerebellar dysfunction. Other neurological signs may be seen as well, but their association with ET has not been fully solidified. Pathological changes in the cerebellum are seen with ET, although describing ET as a neurodegenerative disease is still premature. Links to other neurodegenerative disorders such as Alzheimer’s and Parkinson’s disease can be seen but may simply reflect co-incidental co-morbidities of aging.

Keywords: Cerebellum, dementia, parkinsonism, pathology

INTRODUCTION

Essential Tremor (ET) is a very common neurological condition whose prevalence increases with age. This paper will first review the clinical features across age including differences based on age of onset for topographic spread, rate of progression, and familial segregation. Other neurological signs will be discussed, including the concept of ET-Plus. Cerebellar pathological findings will be reviewed. Finally, the relationship between ET with dementia and parkinsonism will be reviewed [Figure 1].
Figure 1. Venn diagram demonstrating the relationship between essential tremor and ageing with respect to clinical features, cerebellar pathology, parkinsonism, and dementia. Older age is both associated with a more severe phenotype of essential tremor (likely due to a combination of progression with time as well as age and age-related processes), higher prevalence, higher chance of meeting criteria for essential tremor plus, and a higher rate of co-morbid parkinsonism/Parkinson’s disease and dementia. However, there is limited evidence that essential tremor increases the risk of degenerative disorders (e.g., dementia, Parkinson’s disease) in carefully controlled populations. Pathological features of essential tremor do not seem to correlate with tremor severity or duration.

CLINICAL SIGNS ACROSS AGE
ET exhibits a progressive natural history[4-3]. In one study, which included 44 ET patients enrolled in an epidemiological study and 39 ET patients in a brain donation program, the average (median) annual increase in total tremor score (TTS, range 0-36) was 5.3% (1.8%) and 3.1% (2.0%) from baseline, respectively[2]. In another longitudinal study of 116 ET patients, the Bain and Findley spiral score increased at an annual rate (SD) of 0.12 (0.23)[3]. Notably, 10% of patients experienced faster progression with ≥ 0.4 point/year increase. Disease severity may increase not only as a consequence of cumulative pathology with longer disease duration, but potentially also as a factor of age. As an example, in a community-based study of 55 ET patients (mean disease duration 13.2 years), the total tremor score independently correlated not only with ET duration ($P=0.02$) but also with age ($P=0.02$) in a regression analysis[4]. The study included a clinic-based cohort of 79 ET cases from which similar results were obtained. Most patients experience subjective worsening of their tremors as time progresses[5]. Tremor progression is typically gradual and consistent[6]. However, some individuals (up to 1/3 to 1/2 in this longitudinal study with a mean follow-up of 10.2 years) demonstrate nonlinear progression, i.e., marked increases or even decreases between consecutive assessments. This occurs more commonly in women than in men; other variables such as alcohol and medication use do not represent the reason for these fluctuations in tremor severity.

Early-onset versus late-onset
The majority of patients with ET reliably report their age of onset[9]. This is of strict importance when comparing groups of individuals according to their age at the time of tremor onset.

Topographic spread
Over time, the typical kinetic and postural hand tremor, hallmarks of ET, may show topographical spread with the involvement of other body segments such as head, neck, and legs[8]. However, the age of the individual may be more important than the ET duration. In a cross-sectional study of 363 patients, older (> 60 years) vs. younger (< 40 years) patients with disease duration greater than 10 years experienced head tremor in 42.8% (121/283) vs. 7.4% (2/27) of cases, respectively[9]. A multivariate logistic regression analysis revealed that only age ($P < 0.001$), but not duration ($P = 0.26$) or family history ($P = 0.35$), was
independently associated with head tremor. Although this study did not specifically evaluate the correlation between the age of onset of ET and the presence of head tremor, the clustering of head tremor in older patients at least suggests that head tremor would be more common in late-onset ET. Another study, although limited by its retrospective design, did find that tremors of the head and voice were more often the initial symptoms in late-onset ET patients compared to early-onset patients\textsuperscript{[10]}. The presence of head tremor is also more commonly seen in women\textsuperscript{[11]}.

Leg tremor was evaluated in a case-control study of 63 cases with ET and 63 controls\textsuperscript{[12]}. Action tremor of the legs occurred in 44.4% of cases and 14.3% of controls ($P < 0.001$). No clinical correlates, including age of onset, were found between ET patients with or without leg tremor. However, leg tremor severity was associated with both ET duration ($P = 0.02$), younger age of onset ($P = 0.03$), and presence of voice tremor ($P = 0.008$). In another epidemiological study, ET patients with (27.3%) and without intention tremor of the legs showed no significant differences in terms of demographics and clinical characteristics, although there were non-significant trends towards association with longer disease duration\textsuperscript{[13]}.

**Rate of progression**

The age of onset appears to play a major role in the rate of progression of ET. A few studies have estimated the rate of tremor progression by dividing the specific tremor score with duration as reported by the patient, and all found faster progression in late- vs. early-onset ET\textsuperscript{[14-17]}. As an example, 978 patients with ET were recruited through a cross-sectional study and population-based study and underwent a standardized interview and examination\textsuperscript{[15]}. Although late-onset ($\geq 46$ years) patients had a mean disease duration more than 25 years shorter than early-onset patients ($\leq 24$ years), tremor scores were similar in both groups. This suggests that the rate of progression was much faster in the late-onset group. Similarly, in an earlier cross-sectional study, 115 patients (60 from a community and 55 from a clinic) underwent detailed clinical assessments and videotaping of their examination\textsuperscript{[14]}. The rate of progression among the patients who recalled their tremor onset (36 from the community and 54 from the clinic) correlated only with age of onset ($P < 0.001$), but not with any other independent variable. Those with onset after age 60 years progressed markedly faster than those with onset before age 60 years (4.6 vs. 1.2 tremor score points per year, $P < 0.001$).

Higher spiral scores may also correlate with worse physical and cognitive functioning, as well as a higher mortality rate\textsuperscript{[18]}. There are conflicting studies on life expectancy in ET, with studies supporting both greater longevity and reduced life expectancy\textsuperscript{[19,20]}.

**Family history**

Onset of ET occurs on average at least 10 years earlier in familial compared to sporadic ET cases (from $\sim 40$ to $\sim 50-60$ years of age)\textsuperscript{[21-22]}. One genetic study conducted at a tertiary referral center reported that 86.6% of childhood-onset cases were familial rather than sporadic\textsuperscript{[22]}. Furthermore, while ET onset was after age 40 in most cases, 53.9% of familial cases and 81.9% of sporadic cases occurred after age 40. Underscoring the genetic basis of ET, individuals with ET within the same family often have an onset of tremor at a similar age and do not show any evidence of anticipation\textsuperscript{[23]}.

**Alcohol responsiveness**

Alcohol effectively controls tremor in at least 45%-50% of ET patients\textsuperscript{[24-26]}. In one study, familial ET (76% vs. 45%, $P < 0.0001$) and alcohol responsiveness (75% vs. 59%, $P < 0.0001$) were both more common in early-onset ET compared to late-onset ET\textsuperscript{[13]}. However, the nature of the correlation between early age of onset, family history, and alcohol responsiveness is uncertain.
ET-plus
To clarify diagnostic criteria for tremor disorders, a task force of the International Parkinson and Movement Disorder Society in 2018 proposed a new classification system based on two axes: clinical features (Axis 1) and etiology (Axis 2)\cite{27}. ET was defined as an “isolated tremor syndrome of bilateral upper limb action tremor” of “at least 3 years’ duration”, “with or without tremor in other locations” and “absence of other neurological signs, such as dystonia, ataxia, or parkinsonism”. ET-plus was defined as a distinct tremor syndrome (i.e., not a subtype of ET), characterized by a “tremor with the characteristics of ET and additional neurological signs of uncertain significance such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurologic signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis”. The arguments for\cite{28-29} and against\cite{30-31} ET-plus have been extensively reviewed elsewhere.

A clinical pathological study of 241 ET patients included 105 with younger (< 40 years) onset ET and 132 with older onset ET\cite{32}. In both younger and older onset cases, age correlated significantly (\(P < 0.05\)) with missteps on tandem gait, cognitive test scores (MMSE, MoCA), and cognitive diagnosis; only in younger onset cases was there a significant correlation between tremor duration and rest tremor while seated/standing, tandem missteps, cognitive test score (MoCA), and cognitive diagnosis. These findings suggest that many patients with an initial diagnosis of ET could eventually be re-classified as ET-plus if followed prospectively. Two longitudinal studies illustrate this. In one study (\(n = 201\)), the proportion of ET-plus patients shifted in favor of ET-plus from 58.7% to 72.1% over 54 months, most commonly due to impairment of tandem gait, intention tremor, and memory impairment\cite{33}. Similarly, in the other study (\(n = 37\)), ET-plus diagnoses increased from 81.08% to 97.3% over 39 months, primarily due to an increase in rest tremor, bradykinesia, and impaired tandem gait\cite{34}. Prior cross-sectional studies have shown that ET-plus is more common than ET\cite{26,29-31}. According to these studies, ET-plus patients are generally characterized by older age, older age of onset, longer disease duration, higher tremor scores, and faster progression compared to “pure” ET.

Regardless of whether or not ET-plus should simply be considered an advanced stage of ET or a separate diagnostic entity, when ET is diagnosed based on the 2018 MDS criteria, it is far less common than previously considered. Younger patients with tremor are generally more likely than older patients to have isolated action tremor consistent with ET, whereas older patients (late-onset or early-onset/long-duration tremor) are more likely to have ET-plus because of accrual of additional soft signs with time/aging. Does this mean that they have a disease entity different from ET? ET-plus can be evaluated probabilistically using a Bayesian analysis of soft signs to determine the likelihood that they have ET versus a combined tremor syndrome, such as dystonic tremor or Parkinson’s disease\cite{29,38}. This might directly impact clinical practice and underscore the importance of detailed phenotyping of tremor patients.

EPIDEMIOLOGY
The prevalence in many population studies supports that ET is very much a disorder of aging (for review, see Louis et al.\cite{39}). Across all ages, the pooled prevalence is just over 1%. However, when one looks at people over the age of 65, this percentage rises above 5%\cite{40}. In people over the age of 80, the rates may be as high as 10%-20%. Men and women are equally affected, although there may be differences in clinical manifestations as noted above. Many of those with ET do not receive a formal clinical diagnosis. This is seen when formal population studies are done and often uncover a more than doubling in the proportion of ET\cite{41-42}. In a study done using a limited data set of US Medicare claims data, the total number of diagnosed ET in the US would be just over 500,000\cite{44}. Compared with the total number of Medicare beneficiaries in the US, this represents only 1% of the aged population with ET, suggesting that about 80% of ET in the outpatient setting are never
formally diagnosed by their physicians. In our own US-based brain bank studies, 5% of individuals who come into the Arizona Study of Aging and Neurodegenerative Disorders as neurological controls receive a diagnosis of ET based on a more than 3-year history of action tremor without secondary cause\[65]. The average age of these individuals at the time of entry into the program is 80 years old. These types of studies underscore the vast unre cognition and/or under-reporting of this common and often disabling condition.

The accurate determination of the rate of ET within different racial/ethnic populations presents a challenge due to differences in study methodology across studies. These differences include how ET is defined (duration/severity) and how it is ascertained. For the latter, screening questionnaires are less sensitive than in-person examinations.\[39,60,67\]. Neurologists, and more specifically, movement disorder neurologists, may be more likely to screen for and recognize ET, resulting in higher prevalence estimates.\[41-43,64\]. With this in mind, there are a few studies that have directly compared the rate of ET in similarly studied yet differing racial and ethnic populations. Studies in the US suggest that whites are more likely to have ET than blacks\[69,50\]; however, there may have been methodological differences in the responses to the screening questions amongst these populations as a follow-up study found opposite results\[51\]. Studies in New Guinea and Singapore also report different rates in the various populations studied\[62,53\]. Lastly, studies done in North Israel Arabic villages showed that ET is less common than PD\[64,55\]. This may suggest differences in genetic predisposition to this often hereditary disorder, but more research is clearly needed.

Overall, the epidemiology of ET suggests that it is a common disorder of aging across the world with increased prevalence with age. Furthermore, ET is often not diagnosed in the clinical setting.

**ET AND THE CEREBELLM**

The cerebellum has been examined in ET for more than 3 decades. The clinical features that suggest cerebellar involvement are gait impairment as noted above and an increase in cerebellar-like limb ataxia\[54\]. This led to imaging studies supporting that the cerebellum is overactive in ET, and this over-activity dampens with treatment, suggesting the cerebellum is directly involved in the pathogenesis of tremor production or suppression\[57-60\]. Physiological studies suggest that ET patients have abnormalities in motor learning, a task thought to be mediated through the cerebellum, with this abnormality improving with deep brain stimulation\[61,62\]. Clinical features such as cerebellar gait disorder also respond to treatment with alcohol\[60\]. Given the involvement of the cerebellum, attention then focused on whether there were discernible pathological changes. Early pathological studies in a small number of patients suggest no lesions associated with ET\[64\]. In a larger series of 10 cases with ET, there were increased cerebellar torpedoes and Bergmann glia, both indicative of injury to the cerebellum\[60\]. Purkinje cells are the main neuronal outflow pathway from the cerebellum and torpedoes are proximal swelling of the Purkinje cell axon, filled with neurofilaments and organelles\[66\]. Similar findings in ET were seen by another group\[67\]. These studies led to further quantification of Purkinje cells as well as other cerebellar features. A series of 33 ET cases were compared with 21 controls\[48\]. The ET cases were relatively severe, with at least 5 years of tremor, interference with ADLs and most requiring treatment for ET. Controls were drawn from an aging study and were matched by age and were free from AD and PD clinically as well as had a lower rate of incidental pathology typical of age, such as Lewy bodies and mild AD changes (Braak AD stage more than double in ET over controls) although these differences in age-related pathologies were adjusted for in the analysis. In the 25/33 ET brains that did not have Lewy pathology, there was a 31% reduction in Purkinje cell count and a 6-7-fold increase in cerebellar torpedoes. Further study went on to examine the relationship of torpedoes in ET, PD and AD, demonstrating that ET has higher numbers of torpedoes than either of these degenerative disorders, although all groups were higher than controls\[69\].
More quantitative measures were then used to count Purkinje cells using a method called linear cell density. The early studies showed a reduction in Purkinje cell linear density in those 8/14 ET cases without Lewy bodies compared with 11 controls and no reduction in those with Lewy bodies\textsuperscript{70}. These findings were confirmed in a larger series of 32 cases compared with 16 controls, although again, there were higher rates of AD pathology in the ET cases, although this was controlled for in the analysis, and the percent with Lewy bodies was not reported\textsuperscript{70}.

Other researchers have not found evidence for Purkinje cell loss in ET. In a small study of 7 ET, 6 tremor dominant PD and 2 controls using three different counting methods, there were no differences between groups\textsuperscript{72}. There was no correlation with Purkinje cell counts and tremor severity, but there was a correlation with age. One could argue that the number of cases was too underpowered to demonstrate significance; however, the number of cases is comparable to the 8 “cerebellar ET” cases reported previously where there was a reported difference from controls\textsuperscript{70}. A subsequently published larger series found the same\textsuperscript{73}. In 2014, a large series of 56 ET cases were compared to 62 controls\textsuperscript{74}. All had been prospectively followed in the Arizona Study for Aging and Neurodegenerative Disorders (AZSAND). Subjects were selected according to clinical criteria (ET vs. control), excluding those with dementia, Parkinsonism, or exposure to cerebellar toxins. There was no need to match individuals as there were no differences in the two populations in terms of age, post-mortem interval, and incidental pathologies such as Lewy bodies or Braak AD stage.

In this very well-matched cohort, with the only difference being ET action tremor, the Purkinje cell linear density was nearly identical with no outliers. There has been controversy about the findings of this study\textsuperscript{75} and this has been addressed in the literature\textsuperscript{76}. In this same population of ET subjects, carefully quantifying cerebellar volume also shows no differences between ET and controls, whereas there was a demonstrable reduction seen in multiple system atrophy\textsuperscript{77}.

In addition to the work in Purkinje cells, other abnormalities have been described in the ET cerebellum. ET subjects have 3 times as many heterotopic Purkinje cells, displaced into the molecular layer\textsuperscript{78}. GABAergic basket cells, which synapse on the Purkinje cells, are unusually dense and are speculated to reflect drop out of other nearby Purkinje cells with resulting overgrowth of synapses as compensation, leading to a “hairy” appearance\textsuperscript{79}. Climbing fibers to Purkinje cell density is lower in ET and this correlates with Purkinje cell counts and torpedoes\textsuperscript{80}. These findings have not been independently studied by other groups.

In addition to the positive studies, there is also an important negative one. The inferior olive was examined in 14 ET cases and compared with 15 controls with no difference in neuronal density or gliosis, making it unlikely that this pacemaking nucleus is contributing to any purported degeneration in ET\textsuperscript{81}.

The reasons for the differences in the results of these pathological studies are not clear. There may be differences in the ET population studied with varying definitions of ET. For instance, if one defines ET based on tremor in a handwriting sample\textsuperscript{82}, this may result in more ET patients with a more ataxic tremor and therefore more likely to have cerebellar changes. There may be differences in the severity of the population studied, although to date, most of the pathological features of ET do not correlate with tremor severity or disease duration. Exposure to medication and alcohol (a known cerebellar toxin) may be different in the groups and difficult to fully control in studies. Finally, there may be differences in the control population, as noted above. Therefore, given the large carefully controlled studies suggesting a lack of Purkinje cell loss combined with the lack of confirmatory studies by other investigators on the many other cerebellar findings seen in the last 10 years, it is premature to consider ET as a degenerative disorder.
of the cerebellum. More work needs to be done on this.

ASSOCIATION BETWEEN ET AND DEMENTIA

ET has been labeled "benign essential tremor" due to the fact that ET has not been associated with an increased risk of additional neurological co-morbidity or early mortality. Over the last 2 decades, there have been studies examining additional neurological features including cognitive aspects of ET. In one of the earliest studies, a series of advanced ET patients being referred for neurosurgical treatment of tremor was examined using neuropsychological testing. In this study, 27 patients with ET were studied, with the pattern of change being similar to PD. The authors speculated that ET may be due to problems in the dopaminergic pathway, a conclusion that has not been substantiated. In another study, 13 subjects with advanced ET were compared to 13 PD patients being similarly assessed. In this study, 12/13 subjects demonstrated at least mild impairment on one or more of the cognitive measures, with half of the patients having impairment on 50% or more of the measures. The pattern of change suggested dysfunction of the frontal subcortical system (cognitive flexibility, verbal fluency and complex attention) and was similar to that seen with PD (albeit PD was more severe). The authors proposed that the results were typical of cerebellar disorders and may reflect dysfunction in thalamocortical-projections. Similar conclusions were made in another study of 18 advanced ET patients referred to surgical treatment for tremor. In one of the largest case series reported, 101 pre-surgical DBS patients with ET were studied with comprehensive neuropsychological testing. Thirty-four to 60% of patients had deficits on select tests of attention, verbal fluency, semantic encoding, and facial matching. The authors concluded that this pattern was again consistent with dysfunction in the cerebello-thalamo-cortical loop. Therefore, taken together, it seems that cross-sectional studies of advanced ET support at least mild cognitive deficits in the frontal lobe circuitry. Confounds of these types of studies include the more severe patient population and the fact that many were currently or previously treated with years of ET medication (primidone, for example, is a barbiturate-type medication), although the study by Lombardi et al. did not find a relationship between tremor treatment and neuropsychological test results.

More population-based studies began to examine cognitive function in ET as well. In a large aging study of central Spain (NEDICES), elderly participants were asked the question "have you ever had tremor of the head, hands or legs that has lasted longer than several days?" This question was previously validated to yield no false negatives. Those who screened positive were invited for a neurological examination performed by senior neurologists, which contained an assessment for postural and kinetic tremor of the arm, including spiral drawings. Those who did not have an in-person examination done had their medical records reviewed. Those who had an action tremor of the hands lasting for at least 1 year (or had a family history of ET), positive tremor in their spirals, and without secondary causes were diagnosed as ET. This methodology was repeated about 3 years later to identify both prevalent and incident ET. This yielded 232 ET cases, which were compared 1:3 to matching controls. A limited cognitive battery was performed in these individuals and included 37 item MMSE, Trails A, category fluency tests, 6 object naming and memory tests, and story recall. In this study, the median tremor duration was 3 years, with only 6% of this population taking medications for ET, thus representing a much milder tremor population than the surgical studies. Results of this study showed poorer performance on the MMSE, trails, fruit fluency (but not animals), and naming/memory. More patients with ET reported subjective forgetfulness (50.4% vs. 43.1%). Confounds of this study included that subjects with ET were significantly more likely to suffer from depression (which could affect cognition) and the short duration of tremor (where early PD/LBD might not be able to be excluded), although both of these concerns are addressed in the discussion. Further, in the same population, there was a higher rate of baseline alcohol consumption correlating with incident ET, which, while speculative, might play a role in cognitive impairment. These same authors then turned to
examine cognitive function prior to the development of ET in this large Spanish cohort\(^9\). Of the 56 incident ET cases, MMSE declined faster during the 3.4-year period between assessments, leading the authors to conclude there is a premotor phase of ET such as has been described for PD. Confounds of this study are similar to the previous studies and also include that the ET cases were more likely to be illiterate (17.8% vs. 9.6%) and come from a predominantly working-class area of Spain, which they demonstrated were factors that correlated with MMSE results.

The reasons for these findings of milder cognitive impairment in both early and advanced ET are not clear, as there are no neuropathological studies specifically examining this due to the inherent difficulties of cross-sectional autopsy studies. However, many of the authors of these papers propose that the findings are due to the involvement of the of the cerebello-thalamo-cortical loop.

Given the cross-sectional nature of many of these studies, it was not clear whether the cognitive features of ET were static, and potentially related to the tremor circuitry, or whether these findings were progressive. More recent studies have examined this. The same Spanish study reported that those with ET onset after the age of 65 were more likely to have cognitive decline (RR for dementia 1.98) and prevalent dementia\(^{90,91}\). In a second population-based study in New York, USA, there was also approximately double the risk of prevalent and incident dementia\(^92\). In this aging study, ET was defined based on analysis of handwriting samples done during the neuropsychological testing. Dementia was defined by a consensus conference of clinical examinations conducted by neurologists and a neuropsychology assessment battery. Of 2285 participants, 124 were identified with ET. Thirty-one of 124 ET (25%) cases had prevalent dementia versus 198 controls (9.2%). Most were felt to have Alzheimer’s disease. ET cases were older than controls and had fewer years of education, although, after adjustment, they were still nearly twice (OR 1.84) as likely to have dementia. They then followed the participants for a mean follow-up of 3.8 +/- 2.2 years. After that time, those 93 ET subjects without baseline dementia had an adjusted rate of incident dementia of 1.64 (\(P = 0.055\)). All were felt to have AD as a cause for the dementia.

A third study has different findings\(^{93}\). This study was performed in the USA at the AZSAND. In the study, subjects were examined prospectively by movement disorder neurologists examining for both PD and ET. ET was diagnosed according to established criteria. Subjects also received cognitive assessment similar to the New York studies and the diagnosis of MCI and dementia based on consensus conferencing. There were 83 subjects with ET that were compared to 424 controls. The mean duration of tremor was 14 years at study entry and follow-up was a median of 5.4 years. The incidence of dementia within 5 years of study entry was 6% for ET and 8% for controls. This resulted in a hazard ratio of 0.79 (\(P = 0.58\)); therefore, ET was at a non-significantly lower risk for dementia in this well-categorized prospectively followed older cohort. Further, in pathological work by the same group, there was no increased rate of AD pathology compared with controls\(^{74}\).

A proposed mechanism by which ET might increase the risk for Alzheimer’s dementia is not clear. Therefore, given the conflicting studies and the lack of a defined mechanism by which tremor may predispose to AD, it is premature to link the two and more research is needed.

Studies have also examined cognitive response to treatment for ET. There is no adverse effect on cognition 1 year out from unilateral thalamic deep brain stimulation, although those with pre-existing verbal fluency problems may worsen\(^94\). Interestingly, turning the stimulator off may alter cognition with increased subjective distress and declines in verbal fluency\(^95\). Medication such as topiramate, while effective, has known adverse effects on cognition and this should be taken into account when assessing the patient for
cognitive issues\cite{96,97}. Primidone is also an efficacious ET medication that is a barbiturate with known side effects of sedation, particularly at higher dosing\cite{98}. Cognitive side effects have not been well studied with this therapy.

In summary, the studies on ET and cognitive decline support that there are cognitive issues in more advanced ET and that, overall, patients with ET may be at higher risks for dementia, although there are conflicting studies on this concept.

**LINK BETWEEN ET AND PARKINSONISM**

The link between ET and PD has been debated for years\cite{99,100}. In highly selected patients in a tertiary movement disorder clinic, there appears to be a greater risk (as high as 24 times) of conversion from ET to PD\cite{101-103}. In the large Spanish population study, with the caveats noted above regarding this study, there was a 3.47 times relative risk of developing incident parkinsonism in the 207 ET cases followed over a median of 3.3 years for an absolute percentage of 5.8% developing parkinsonism\cite{104}. Of these, 6/201 (3.0%) were felt to have idiopathic PD with an adjusted relative risk of 4.27 ($P = 0.002$) compared with the control population without ET. Taken together, this would suggest that ET is at fairly high risk for conversion to PD, although the absolute numbers are quite low in this study. However, it is also clear that patients with ET may develop features of parkinsonism without the concomitant presence of neuropathological features of PD. Rest tremor (jaw/hand) in ET is not associated with an increased risk of Lewy body (LB) pathology\cite{105,106}. Bradykinesia can be seen in aging ET patients and is not always associated with LB pathology\cite{107,108}. In a recent large series of ET patients followed to autopsy, the rate of LB pathology was 25.1% (58/231)\cite{109}. This was felt to be significant, although there was no similarly followed control group; instead, a comparison was made to historical controls. In the AZSAND study, where there were well-categorized, well-matched and similarly followed controls, the rate of Lewy bodies was the same. Of the 237 autopsied ET subjects, the rate of LB pathology is 22.1%, with an average age of 88.6\cite{110}. This study supports that LBs are incidental in ET. Similarly, while there are studies suggesting Progressive Supranuclear Palsy (PSP) might be more common in ET\cite{111}, when studies are appropriately controlled, the PSP pathology appears to be incidental as well\cite{74}. Whether a small percentage of ET will go on to develop PD is not clear, but it is clear that there should be some caution in interpreting clinical features of PD in those with longstanding ET without pathological confirmation.

**CONCLUSION**

ET has a progressive clinical course with increasing amplitude of tremor over time and spread to other body parts. This suggests the potential for a neurodegenerative cause of ET. However, when one examines the literature on cerebellar pathology in ET, it is clear that more work needs to be done. There is a lack of independent validation of some of the key findings in the cerebellum and in cases where multiple groups are working on this topic (Parkinje cell counting), there are conflicting results and conclusions. There is a need for studies using independent oversight of patient and control selection with independent and blinded neuropathological assessment using the most unbiased methods for cell counting. Links between ET and other neurodegenerative disorders can similarly be questioned. When ET patients are carefully matched to control populations, links between dementia and parkinsonism disappear. Further, there is little plausible defined pathophysiology linking ET to subsequent development of dementia and PD/PSP. Additional large population studies might be a way to get at this issue, but these studies are fraught with concerns about how best to even ascertain a diagnosis of ET, given the controversy of such topics as “ET-plus”. The ET community needs to better define ET and its potential subtypes so that these types of studies might be reliably conducted.
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Authors’ contributions
Made substantial contributions to the conception and design of the manuscript, helped draft the first version, and provided critical review of the final version: Niemann N, Shill HA

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