Review paper

Folia Neuropathologica

Neuropathological findings in essential tremor

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Folia Neuropathol 2024; 62: 1-8 *DOI: https://doi.org/10.5114/fn.2024.140569*

Abstract

Essential tremor (ET) is one of the most common neurological conditions and the most common movement disorder. The pathophysiological mechanisms that underlie this entity have not yet been described. However, recent post-mortem brain studies have provided useful insight into the underlying pathology of ET. Two brain areas have been consistently found to present neuropathological alterations in patients with ET: the brainstem, for presence of Lewy bodies or neuronal depletion, and the cerebellum, regarding Purkinje cells' morphology and density. In the present study we aim to review the literature on the main neuropathological findings in ET brains.

Key words: *essential tremor, neuropathology, Purkinje cells, locus coeruleus, Lewy bodies.*

Introduction

Essential tremor (ET) is a chronic, progressive neurological syndrome encompassing a diverse array of clinical phenotypes. It is primarily characterized by involuntary tremors affecting the hands or arms, and as it advances, it may also manifest in the head, jaw, and voice [14,48]. There is a subset of patients who exhibit a broader spectrum of intricate deficits [5,7,38].

The prevalence of ET is about 1 percent in the global population, rising to 5 percent in adults over 60 years [4,14,36]. While ET's incidence escalates with age, it is not confined to the elderly, with early adulthood and childhood cases, particularly in familial contexts [19]. The gender distribution is relatively even, but a slight male predominance has been noted in some studies [36].

The roots of ET remain elusive. Its diverse phenotypes and genetic makeup indicate that ET might be a collection of related disorders rather than one singular condition [18,43]. A robust genetic foundation is evident as 30-70 percent of ET patients report a family history of the condition. This number swells to 80 percent in cases with onset before 40 years [11,33]. Research suggests an autosomal dominant inheritance pattern with a nuanced expression [3,11,16,17,25,59]. The genetic realm of ET is intricate; the genetic variants linked with the disorder are numerous, and their interactions complex [21,24,51,52,63,64,66-68]. Nevertheless, the exact neuroanatomical foundation remains controversial, with the cerebellum and brainstem frequently implicated [30,35].

Tremor is predominantly an action tremor, and primarily affects hands and arms. Although usually bilateral, it can be slightly asymmetric. It is notable during voluntary movement or when limbs counteract gravity. Activities like drinking or finger-to-nose testing often intensify it [20,35]. While tremor should ideally be the only manifestation of ET, some patients display difficulty with tandem gait, cognitive deficits, or tremor overflow [7,31]. Preliminary research indicates possible cognitive impairments in ET patients compared to their counterparts [5,6,15,28].

Distinguishing ET from other tremor syndromes is crucial. Factors that can exacerbate a physiological tremor, such as stress, differ from those influencing ET. The differentiation between parkinsonian tremor and

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Received: 3.07.2023, **Accepted:** 1.10.2023, **Online publication:** 2024

ET is notably common, with Parkinson disease (PD) primarily manifesting as a rest tremor [54]. Other conditions like dystonic head tremor and spasmodic dysphonia also enter the diagnostic equation [1].

One of the first steps in managing ET is identifying and mitigating any exacerbating factors. Common culprits include medications and stimulants like caffeine. In certain instances, merely discontinuing these agents can control the tremor temporarily. Interestingly, alcohol, in modest amounts such as a half to one glass of wine, can reduce tremor in many patients, proving useful in social situations [56].

The decision to commence drug treatment is based on the intensity and frequency of the tremor, and its impact on the patient's daily life. It is vital to underscore the need for personalized care [70]. While some patients might be indifferent to a minor tremor, others might find even a slight shake cosmetically bothersome or psychologically distressing. Patients reporting frequent symptoms, resulting in functional or psychological impairments like embarrassment or anxiety, generally need daily medications.

Propranolol, a nonselective beta-adrenergic blocker, and primidone, an antiseizure medication, are regarded as the first-line therapies for ET. Their choice is determined by factors like side effect profiles, existing medications, and underlying health conditions. When monotherapy does not suffice, a combination or an alternative might be recommended. Notably, gabapentin, topiramate, and benzodiazepines serve as potential second-line agents [70].

Patients experiencing situational exacerbations, such as tremor spikes during stressful events or public appearances, might benefit from intermittent drug treatment [70]. An individualized approach is pivotal here. Propranolol, for instance, is commonly used in low doses for such patients. Primidone, though effective, may not be as feasible due to its slow onset. In specific social settings, a controlled consumption of alcohol or low-dose short-acting benzodiazepines may be beneficial [56].

Among the treatment options available for ET, propranolol and primidone stand out due to the robust evidence supporting their efficacy. Clinical trials have revealed a comparable effectiveness between them, with each potentially reducing tremor amplitude by approximately 50% [70]. Yet, they are not universal remedies. For instance, in a study with 50 patients, propranolol lacked therapeutic effect in 30% of them, and a similar percentage was noted for primidone. Side effects, too, play a role in drug choice. Acute reactions with primidone and chronic effects of propranolol could limit their usage. However, a slow titration approach with primidone might mitigate some side effects [56].

Histological and cellular examinations of postmortem brain samples from individuals afflicted with ET have uncovered a range of alterations within the cerebrum, brainstem, and cerebellum. The principal neuropathological findings in ET can be classified into two primary categories: alterations in the Purkinje cells and the presence of Lewy bodies within the locus coeruleus [49].

These findings have been instrumental in enriching the understanding of ET's neurobiology and hold the potential to facilitate a more comprehensive grasp of the clinical-pathological interrelationships associated with this disorder [13,59].

The objective of the current study is to conduct a review of the extant literature concerning the cardinal neuropathological findings observed in ET.

Methodology

Search strategy

A comprehensive literature search was conducted using the PubMed database. The search was tailored to encompass articles published from 1 January 1990, through 28 May 2023. The search strategy employed four Medical Subject Headings (MeSH) terms: ["ET" OR "essential tremor"] AND ["neuropathology" OR "histopathology" OR "neuropathological findings"], with additional filters for English language and human studies.

Inclusion and exclusion criteria

To qualify for inclusion in this review, studies were required to meet the following criteria: (1) be an original research article; (2) involve human subjects; (3) be written in the English language; and (4) discuss neuropathological findings in the brains of individuals with ET, in comparison to either healthy controls or individuals with other neurodegenerative conditions. The exclusion criteria included: (1) review articles, meta-analyses, letters to the editor, book chapters, and editorials; (2) studies involving animal subjects. The selection process adhered to the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines".

Selection of studies

The search query in PubMed yielded a total of 604 articles. Upon application of the exclusion criteria, 550 articles were eliminated due to reviews, meta-analyses, animal studies, editorials, or case reports. Of the remaining 54 articles that fulfilled the inclusion criteria, further scrutiny of the full text and data extraction led to the final selection of 26 studies for inclusion in this review.

Results

Purkinje cells' pathology

Purkinje cell counts

Pathological changes of Purkinje cells are amongst the main findings described in the majority of studies. Axelrad *et al.* studied Purkinje cells using calbindin immunohistochemistry on 14 ET cases and they reported a significant reduction in Purkinje cell number (38.2%, $p = 0.04$) in the ET brains who did not have Lewy bodies, and they additionally found an inverse correlation between the Purkinje cell linear density and the age and number of axonal torpedoes [2]. Louis *et al.* examined 33 ET brains compared to 21 controls and they reported a significant decrease of the mean Purkinje cell number per 100× fields in ET cases without LB (6.6 ±2.4 vs. 9.6 ±3.4, $p < 0.01$), and seven times more Purkinje cells axonal torpedoes per section (12.6 ±7.9 vs. 1.7 ±1.4, $p < 0.001$) compared to controls [32]. The same group on a later study of theirs, using calbindin antibodies, quantified Purkinje cells per mm in the Purkinje cell layer on 32 ET cases compared to 16 controls, and found significantly lower Purkinje cells density in ET cases (1.14 ±0.32 vs. 1.35 ±0.31 per mm^{-1}, $p = 0.03$) [35]. In a more recent study coming from the same group investigated Purkinje cell counts on 50 ET brain compared to 25 age-matched controls. They used a random sampling approach to quantify the density of Purkinje cells along the Purkinje cell layer with a mean of 217 sites in each of the specimens and using a nearest neighbour analysis to estimate the distance between Purkinje cell bodies reported significantly lower Purkinje cell density, and greater mean distance from one Purkinje cell body to another, in ET cases [10]. In the most recent study on 156 brains with ET, spinocerebellar ataxias, multiple system atrophy, Parkinson's disease, dystonia and controls, Louis *et al.* investigated the numbers of Purkinje cells, heterotopic Purkinje cells, Purkinje cells' dendritic and axonal changes, basket cell axonal changes, and climbing fibre to Purkinje cells synaptic changes between the groups of the study. They found that ET brains showed significant changes in most of the parameters compared to normal controls [39].

Different studies, however, failed to reproduce the above findings. Rajput *et al.* studied 20 ET brains and found PC loss in only two of them [55], and in an attempt to replicate the observations in previous reports, Rajput et al. repeated the measurements on additional 15 ET and control brains and found no evidence that PC loss was the pathological basis of ET [58]. In another study on a total of 59 cases including ET patients, PD controls and normal controls [60], they used three different markers for PC identification, and they found no significant differences between the groups of the study (Table I).

Purkinje cell heterotopias

Purkinje cells' heterotopias with their cell's bodies mislocated in the molecular layer have also been reported by other studies, as a disease-associated feature of ET [26,39,40], and are also considered as markers of neurodegeneration. Kuo *et al.* on a post-mortem study

Table I. Studies which investigated the Purkinje cells counts in essential tremor (ET), and their main findings

Study	Sample size (ET cases/controls)	Main findings	References
Axelrad *et al.*	14 ET cases	38.2% reduction in Purkinje cell number in ET brains without Lewy bodies ($p = 0.04$)	9
Louis *et al.* (a)	33 ET cases/21 controls	Significant decrease of mean Purkinje cell number in ET cases without LB (6.6 ±2.4 vs. 9.6 ±3.4), seven times more axonal torpedoes per section in ET cases (12.6 ±7.9 vs. 1.7 ±1.4)	10
Louis *et al.* (b)	32 ET cases / 16 controls	Significantly lower Purkinje cell density in ET cases (1.14 ± 0.32 vs. 1.35 ± 0.31 per mm^{-1}, $p = 0.03$)	11
Louis *et al.* (c)	50 ET cases/25 controls	Significantly lower Purkinje cell density and greater mean distance between Purkinje cell bodies in ET cases	12
Louis *et al.* (d)	156 brains (various conditions)	ET brains showed significant changes in the number of Purkinje cells, heterotopic Purkinje cells, dendritic and axonal changes compared to normal controls	13
Rajput *et al.* (a)	20 ET cases	Found Purkinje cell loss in only 2 cases, suggesting PC loss might not be the pathological basis of ET	14
Rajput *et al.* (b)	15 ET cases and controls	Found no evidence that Purkinje cell loss was the pathological basis of ET	15
Rajput *et al.* (c)	59 cases (ET, PD, normal)	No significant difference in Purkinje cell counts between the groups	16

Table II. Summary of findings on heterotopic Purkinje cells in essential tremor (ET) brains

Study aspect	**Kuo *et al.* study details**
Study type	post-mortem study
Number of ET brains	35
Number of control brains	32 (21 non-disease, 11 PSP)
Method used	Modified Bielschowsky method
Finding: heterotopic Purkinje cells in ET brains (average per section)	3.8 ±3.6
Heterotopic Purkinje cells in control brains (average per section)	1.6 ±1.7
Statistical significance	$p = 0.007$
Comparison with PSP brains	Significant difference
Relation to total Purkinje cell counts	Inverse relation between the number of heterotopic cells and total Purkinje cell counts

Table III. Studies on dendritic changes in Purkinje cells in essential tremor (ET) patients

Study	Number of participants	Method	Main findings
Louis *et al.*	27 ET cases, 27 age-matched controls	Golgi-Kopsch method, quantitative estimation of Purkinje cell dendritic anatomy	Significant reduction in dendritic complexity in ET cases, including: – Decreased total dendritic length – Decreased mean branch length – Decreased maximum branch order – Decreased number of terminal branches – Decreased dendritic spine density
Mavroudis *et al.*	12 patients with ET (7 males and 5 females), 15 normal controls (8 males and 7 females)	Golgi silver staining method, 3D neuronal reconstruction	Significant morphological changes in Purkinje cells of patients with ET, including: – Decrease in dendritic length and field density – Overall loss of terminal branches – Decrease in the density of dendritic spines Specifically, in the ET-h group from the cerebellar vermis: – Significantly lower total dendritic length compared to ET-a, ET-plus, and normal controls – Significantly lower total number of terminal branches compared to other groups – Reduced dendritic spine density compared to other groups

on 35 ET brains vs 32 controls, including 21 non-diseases controls and 11 PSP brains, and using a modified Bielschowsky method, demonstrated three times higher number of heterotopic Purkinje cells per section in ET brains (3.8 ±3.6 vs. 1.6 ±1.7, $p = 0.007$). They also described a significant difference between ET and PSP brains, and an inverse relation between the number of heterotopic cells and the total Purkinje cell counts [26] (Table II).

Purkinje cell dendritic and spinal changes

Purkinje cells' dendrites is another potential target for degeneration in patients with ET [39,41]. A study on cerebellar cortical tissue from 27 ET cases and 27 age-matched controls using Golgi-Kopsch method, and quantitative estimation of Purkinje cell dendritic anatomy revealed a significant reduction in dendritic complexity in ET cases. Authors found decreased total dendritic length, mean branch length, maximum branch order, number of terminal branches and dendritic spine density, providing additional evidence of a pervasive abnormality of Purkinje cells in ET [68]. Mavroudis *et al*. investigated the changes in Purkinje cells in patients with ET and ET-plus compared to normal controls [48]. The study was conducted on 12 patients with ET (7 males and 5 females) and 15 normal controls (8 males and 7 females). The patients with ET were further divided into three groups: ET with head and arm tremor (ET-h; $n = 5$); ET with arms tremor only (ET-a; $n = 4$); and ET-plus ($n = 3$). The researchers used the Golgi silver staining method and 3D neuronal reconstruction to perform a morphometric analysis of Purkinje cells. They found significant morphological changes in the Purkinje cells of patients with ET compared

to normal controls. These changes included a decrease in dendritic length and field density, an overall loss of terminal branches, and a decrease in the density of dendritic spines. In terms of specific findings, the total dendritic length of Purkinje cells from the cerebellar vermis was significantly lower in the ET-h group compared to the ET-a, ET-plus, and normal control groups. The total number of terminal branches of Purkinje cells from the cerebellar vermis was also significantly lower in the ET-h group compared to the other groups. Furthermore, the dendritic spine density was reduced in the ET-h group compared to the other groups (Table III).

Purkinje cell axonal changes

Focal swellings of the proximal portion of the Purkinje cell axons, known as axonal torpedoes, are one of the common findings in ET brains. These ovoid axonal swellings contain an accumulation of hyperphosphorylated neurofilaments and disrupted organelles [35,42]. Axonal torpedoes are not specific for ET since they can be present in other neurodegenerative conditions, such as spinocerebellar ataxias, and to a less extent even in normal controls [42] (Table IV).

Basket cells and olivocerebellar climbing fibres

In addition to Purkinje cells changes, Basket cells, γ-aminobutyric acid (GABA)-ergic inhibitory interneurons found in the molecular layer around the Purkinje cell bodies, exhibit dense and tangled, "hairy" appearances of their axonal plexuses in ET cases [39].

Certain changes at the expression of membrane glutamate transporters, which are of critical importance for the recycling of glutamate and can be related to a failure of glutamate reuptake by astrocytes, and therefore accumulation in the synaptic cleft, and overstimulation of glutamate receptors, which leads to overexcitation of glutaminergic olivocerebellar climbing fibres and alterations on the normal cerebellar circuitry and output have been described in ET [27,39].

The dentate nucleus

Severe neuronal loss and atrophy, microglial clusters, and reduction in the number of efferent fibres [61], along with reduced GABA-A and GABA-B receptors, have been reported [54]. However, further evidence is needed to support these findings due to the relatively small number of observations.

Lewy bodies and locus coeruleus pathology

Lewy bodies have been extensively described in the locus coeruleus of ET brains [8,22,35,50]. The locus coeruleus is the main norepinephrine centre of the central nervous system, and one of the main inputs to the Purkinje cells, and of high importance for the modulation of responses to climbing fibres and to normal function and inhibitory output of Purkinje cells [54].

Lewy bodies are found in the locus coeruleus of about one in four ET cases, but interestingly they have not been described in cases with extensive cerebellar gliosis [27]. Lewy bodies are thought to be incidental and/or related to normal aging or emerging Parkinson's disease or Lewy body dementia, and not to the pathophysiology of ET [35].

Shill *et al*. have described another pattern of pathology of the locus coeruleus in patients with ET, which involves a loss of pigmented neurons in the locus coeruleus without the presence of Lewy bodies [60,61].

Discussion

Most of our understanding so far has been possible through analysing neuroimaging studies and the findings from post-mortem studies of ET brains [35,44].

Table IV. Purkinje cells axonal changes, basket cells and climbing fibres pathology in essential tremor (ET)

Finding	Description	Study reference
Purkinje cell axonal changes	Focal swelling of the proximal portion of the Purkinje cell axons, known as axonal torpedoes. These swellings contain an accumulation of hyperphosphorylated neurofilaments and disrupted organelles. Axonal torpedoes are not specific to essential tremor and can be found in other conditions such as spinocerebellar ataxias	[10,22]
Basket cell changes	In essential tremor cases, Basket cells (GABA-ergic inhibitory interneurons found around Purkinje cell bodies) show dense and tangled appearances of their axonal plexuses, termed „hairy" appearances	[13]
Changes in glutamate transporter expression	Changes in the expression of membrane glutamate transporters are observed. This could be related to a failure of glutamate reuptake by astrocytes, leading to accumulation in the synaptic cleft and overstimulation of glutamate receptors. This overstimulation can affect the olivocerebellar climbing fibres and alter normal cerebellar circuitry and output	[13,23]

The main neuropathological findings can be divided into two main axons, the presence of Lewy bodies in the locus coeruleus and the morphological and morphometric changes of Purkinje cells.

The main findings include a decrease in number [2,10,35] or heterotopias of cerebellar Purkinje cells [26, 40], changes of their dendritic fields, ovoid swellings of their axons known as axonal torpedoes, and changes at the chemical levels regarding the olivocerebellar climbing fibres. It is evident that ET neuropathological findings are heterogeneous, as is the clinical presentation. Louis et al., based on the neuropathological findings, have suggested that ET can be divided into "LB ET" and "Cerebellar ET", and these are related to different clinical manifestations [45].

Although the aforementioned findings have been extensively described, many studies failed to reproduce them and reported no significant pathology in ET brains, despite the typical clinical presentation.

Dendritic and spinal changes have been described in other conditions as well, including Alzheimer's disease [49]. In addition to that, none of the studies so far, have shown strong correlation between the severity of the tremor and the significance of Purkinje cells' loss.

Although loss of Purkinje cells is commonly found in ET brains, it is not pathognomonic, and whether it is directly linked to the pathophysiology of the disease remains unclear [55].

The degeneration of Purkinje cells may interrupt the cerebellar inhibitory output, amplifying the cerebellar-thalamo-cortical circuit's activity, resulting in tremors. This perspective is deepened by the cerebellum's responsibility in orchestrating precise motor activities; any functional or structural aberration can therefore translate to tremorous movements. Altered connectivity patterns between the cerebellum and other brain areas in ET patients, suggesting these changes might contribute to the disease's motor symptoms. Moreover, the cerebellum's potential influence on neurotransmitter balance, specifically GABA and glutamate, presents another possible layer to the symptomatic manifestation of ET, since these neurotransmitters play pivotal roles in governing motor pathways' excitatory and inhibitory signals.

Lewy bodies are found in the locus coeruleus of about one in four ET cases, and it has been proposed that they are incidental and/or related to normal aging or emerging Parkinson's disease. Lewy bodies pathology in Parkinson's disease is different, while it begins in the dorsal vagal nucleus and then spreads to the locus coeruleus in Braak stage II-III. In ET cases, Lewy bodies are solely found in the locus coeruleus and its pathology is also thought to be linked to the pathophysiology of ET, but again it is not pathognomonic and it is not clear if it precedes the tremor, and if it is related to the severity of the symptoms.

Further studies on the pathological anatomy and pathophysiology of ET would improve our understanding of the disease and could pave the way for the discovery of targeted treatments for this common neurological disorder.

Limitations

The observed heterogeneity in results across various studies could likely be attributed to differences in methodologies employed and inherent limitations within each study. Methodological variations, such as sample selection criteria, data collection tools, analysis techniques, and the duration or setting of the study, can introduce variability in outcomes. Additionally, each study might possess its unique set of limitations, be it in terms of sample size, potential biases, control measures, or the precision of instruments used, further contributing to the disparity in results. It is essential to consider these methodological differences and limitations when comparing and interpreting findings from different studies.

Conclusions

Essential tremor is a heterogenous neurological condition, with a wide spectrum of pathological changes; however additional studies which will consider the new classification of tremor are required, on larger series of patients, to define the clinical manifestations of patients with different neuropathological backgrounds. The different pathological patterns may correlate and explain the variety of neurological signs that may present together with the tremor and have been described as ET plus syndromes.

Funding

Financial support and sponsorship: none.

Disclosures

Approval of the Bioethics Committee was not required.

The authors report no conflict of interest.

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