

The cerebellar involvement in essential tremor: the connecting roads

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Abstract

Keywords

- Essential Tremor
- Cerebellum
- Purkinje Cells
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- Cholinergic Antagonists

Essential tremor (ET) is the most prevalent movement disorder globally, affecting about 1% of the general population and 5% of those aged over 65 years. Characterized by involuntary, rhythmic oscillations, it primarily manifests as postural and kinetic tremors, predominantly in the upper limbs. Genetic studies, neuropathological examinations, neurophysiological assessments, and various neuroimaging techniques have demonstrated functional, neurotransmitter-related, and structural abnormalities within the cerebello-thalamo-cortical circuit. These findings collectively portray ET as a neurodegenerative syndrome with diverse etiologies and clinical manifestations, highlighting the involvement of the cerebellum.

INTRODUCTION

Essential tremor (ET) is the most prevalent movement disorder globally, affecting about 1% of the general population and 5% of those over 65.¹ Characterized by involuntary, rhythmic oscillations, ET primarily manifests as postural and kinetic tremors, predominantly in the upper limbs, with a frequency ranging from 4 to 12 Hz. While it traditionally affects the hands, in approximately 95% of the cases, other areas can also be involved, such as the head, tongue, legs, voice, face, chin, and torso.²

Historically, ET was first differentiated from Parkinson's disease (PD) by James Parkinson in 1817, a distinction

published posthumously in 1872 by Jean-Martin Charcot.^{3–5} The term *essential tremor* (initially from the Italian “tremore semplice essenziale”) was coined by Pietro Buresi in 1874 and, over the years, the understanding of ET has evolved significantly.⁶ Once considered a monosymptomatic condition, recent studies have challenged this view, documenting additional motor signs and a range of nonmotor features, thus recognizing it as a complex neurodegenerative syndrome with diverse causes and manifestations.^{7,8}

Neuroimaging and functional studies have played a crucial role in enhancing our understanding of ET, particularly highlighting the cerebellum's involvement. These studies have demonstrated structural and functional abnormalities

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in this area, associated with altered connectivity within the cerebello-thalamo-cortical circuit. This disrupted connectivity is evident in reduced links between the primary motor cortex and the cerebellum, as well as heightened connectivity between the thalamus and the cerebellum, suggesting the its central role in tremor generation through the modulation of central oscillators.^{9–11}

The aim of this narrative review is to synthesize and organize the findings from various studies concerning the pathophysiology, neuropathology, genetics, clinical manifestations, neuroimaging, and treatment approaches that highlight the cerebellum's crucial role in the genesis of ET.

METHODS

The current narrative review encompassed original research articles, including observational, cohort, cross-sectional, and case-control studies, as well as case series, clinical cases, metaanalysis, and reviews that contribute to connecting genetics, clinical findings, neurophysiology, neuroimaging, and the pathophysiology of ET with the cerebellum.

A thorough three-step search strategy was employed to gather relevant literature:

- Initial search: A preliminary exploration was conducted in key databases such as PubMed, Embase, and CINAHL using terms like *essential tremor* and *cerebellum*. This step involved retrieving and identifying index terms, Medical Subject Headings (MeSH), and keywords from the title and abstract of relevant papers;
- Full search: This subsequent, more extensive search incorporated all the identified keywords and index terms across the aforementioned databases;
- Hand search: The reference lists of all located studies were manually searched to uncover additional ones that might not have been included in the database searches.

The references from the articles were also thoroughly searched for additional articles.

Two reviewers independently screened the literature for each topic: pathophysiology, pathology, neurophysiology (CHFC and GLF), as well as clinical alterations and neuroimaging (LEBMZ and LC). Any discrepancies between reviewers were resolved through discussion.

PATHOPHYSIOLOGY

Recent advancements in ET's genetics, environmental factors, animal models, pathology, and physiology emphasize the cerebellum's crucial role and connections within the cerebello-thalamo-cortical circuit (► **Figure 1**). These insights pinpoint significant therapeutic targets for ET and enhance our understanding of how cerebellar dysfunction contributes to the rhythmic, involuntary movements associated with this disorder.¹

Cerebellum and pathophysiology of ET

There is no question that the cerebellum plays a crucial role in the pathways implicated in the pathophysiology of ET.

What remains to be fully elucidated are the cellular and molecular dynamics within the cerebellum that disrupt normal movement modulation enough to contribute to tremor development.¹

Complex inputs from peripheral sources enter the cerebellum via the inferior cerebellar peduncle. These originate from the inferior olivary nucleus through climbing fibers, as well as from the vestibular nuclei, the accessory cuneate nucleus, and Clarke's dorsal nucleus via mossy fibers to the cerebellar cortex. Commands from the cerebral cortex reach the cerebellum through the middle cerebellar peduncle, consisting of mossy fibers from the pontine nuclei to the cerebellar cortex. The cerebellum's outputs are mediated by its deep nuclei (dentate, interposed, and fastigial), which receive projections from Purkinje cells.

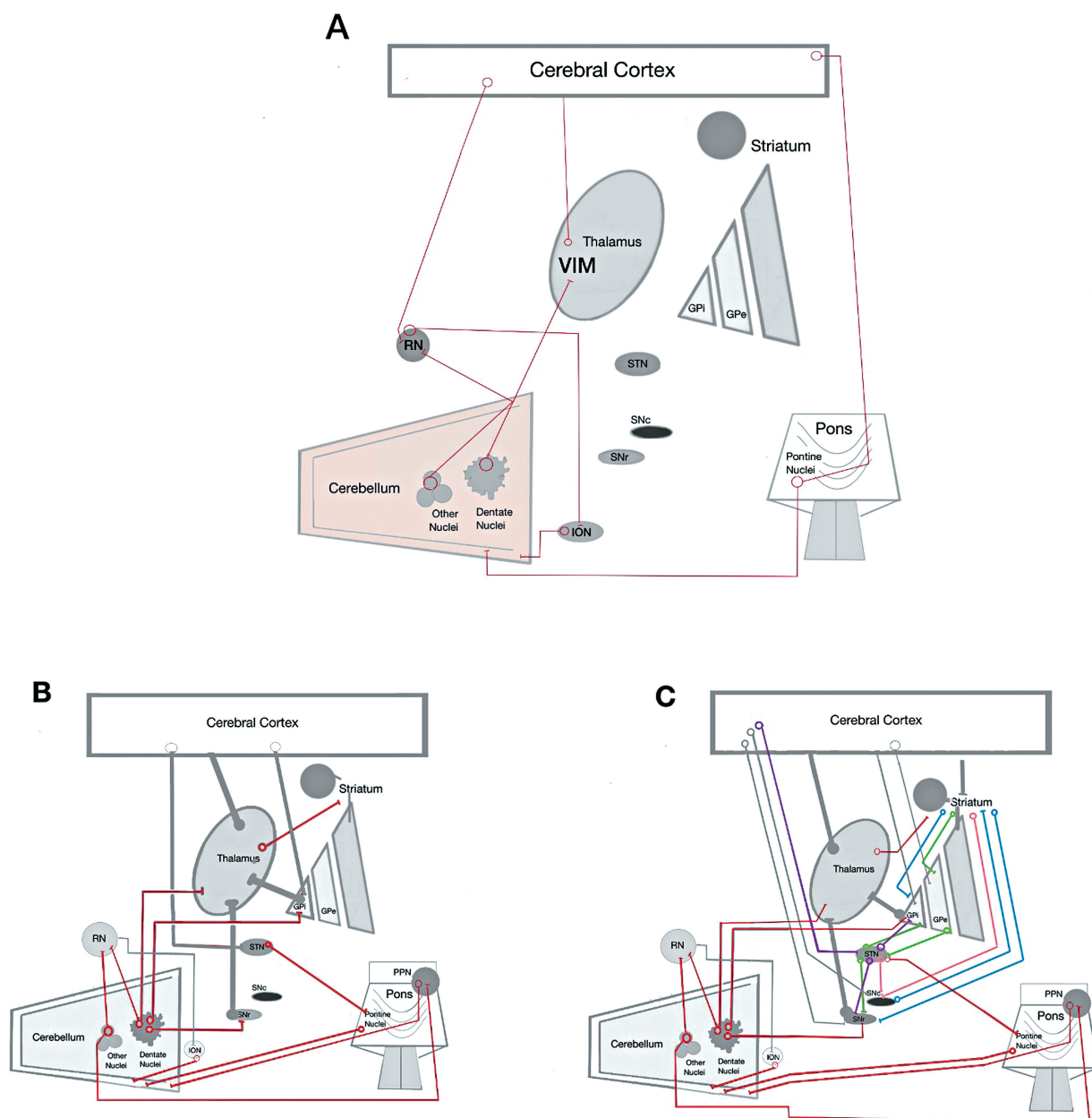
These cells, the sole efferent neurons of the cerebellar cortex, are GABAergic and inhibitory. Furthermore, they are characterized by strong pacemaking activity, rigorously regulated by GABAergic neurotransmission from various interneurons, including stellate and basket cells. Basket cells exert inhibitory control over the soma of Purkinje cells, while stellate ones receive inputs from parallel fibers and provide inhibitory feedback to the dendrites of Purkinje cells.

Golgi cells, also receiving inputs from parallel fibers, furnish inhibitory feedback to the granule cells that form the parallel fibers (► **Figure 2**).^{12–14} Studies indicate that pathological changes in the cerebellum of patients with ET may occur in the cells comprising the input system, Purkinje, or even in those that modulate the system.^{1,15–18}

Regarding the efferent system, several pathological features centered around Purkinje cells have been identified in the cerebellum of patients with ET. These include a modest loss, swelling of axons known as torpedoes, displacement of cell bodies from their typical layer, and dendritic spine loss.^{15–17,19–21}

A study suggests that axonal swelling in Purkinje cells can enhance action potential fidelity, which may influence tremor dynamics.²² While these morphological changes in the ET cerebellar cortex are evident, it raises the question of whether the downstream deep cerebellar nuclei are similarly affected. Research indicates no change in neuronal density within the dentate nucleus in this condition, suggesting that this region does not experience neuronal loss.²³ Furthermore, detailed postmortem analysis of GABA type A (GABA-A) and B (GABA-B) receptor binding in the dentate nucleus of ET patients shows a reduction in both, highlighting significant alterations in neurotransmitter receptor dynamics.²⁴

Numerous morphological changes in the ET cerebellum indicate degenerative alterations, primarily in Purkinje cells, although other associated cells also exhibit abnormalities. Notably, basket cells exhibit denser and more elongated plexuses surrounding the initial segment of Purkinje cell axons.^{15,18} Furthermore, climbing fibers in ET form atypical synaptic connections with Purkinje cells within the parallel fiber synaptic territory. Among the various pathological features identified, the synaptic pathology of climbing fibers



Abbreviations: ET, essential tremor; GPi, globus pallidus internus; GPe, globus pallidus externus; ION, inferior olivary nucleus; MLR, mesencephalic locomotor region; PPN, pedunculopontine nucleus; RN, red nucleus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nucleus.

Figure 1 Simplified diagrams illustrating the principal interrelationships among brain structures involved in essential tremor (ET) and other movement disorders. Connections belonging to various pathways are depicted in grey. (A) Cerebello-thalamo-cortical loop. (B) Main cerebellar connections associated with ET (red). (C) Superimposed representation of major motor pathways. Classic cortico-basal ganglia-thalamo-cortical circuits are shown as follows: direct pathway (blue), indirect pathway (green), and hyperdirect pathway (purple). Additional interconnections among the basal ganglia are illustrated in salmon, and the main cerebellar connections in red. **Adapted from:** Camargo et al.³⁴

is particular to ET, suggesting a unique and distinctive mechanism underlying the disorder.¹

Compared to other degenerative cerebellar diseases such as spinocerebellar ataxias and multiple system atrophy, the cerebellum in ET exhibits an expansion of the climbing fiber synaptic territory, extending into the parallel fiber synaptic territory. In contrast, in ataxic cerebellums, there is a regression of climbing fiber synaptic territory.^{15,25,26} This synaptic pathology of climbing fibers is consistently ob-

served across ET patients with varying clinical characteristics, suggesting a direct correlation. In this condition, climbing fibers extend into the parallel fiber synaptic territory and form lateral connections to innervate multiple Purkinje cells. This specific pathological feature correlates with tremor severity. Originating from the inferior olive, which possesses intrinsic oscillatory properties, the extensive reach and multiple Purkinje cell innervation by climbing fibers could influence their pacemaking activity and

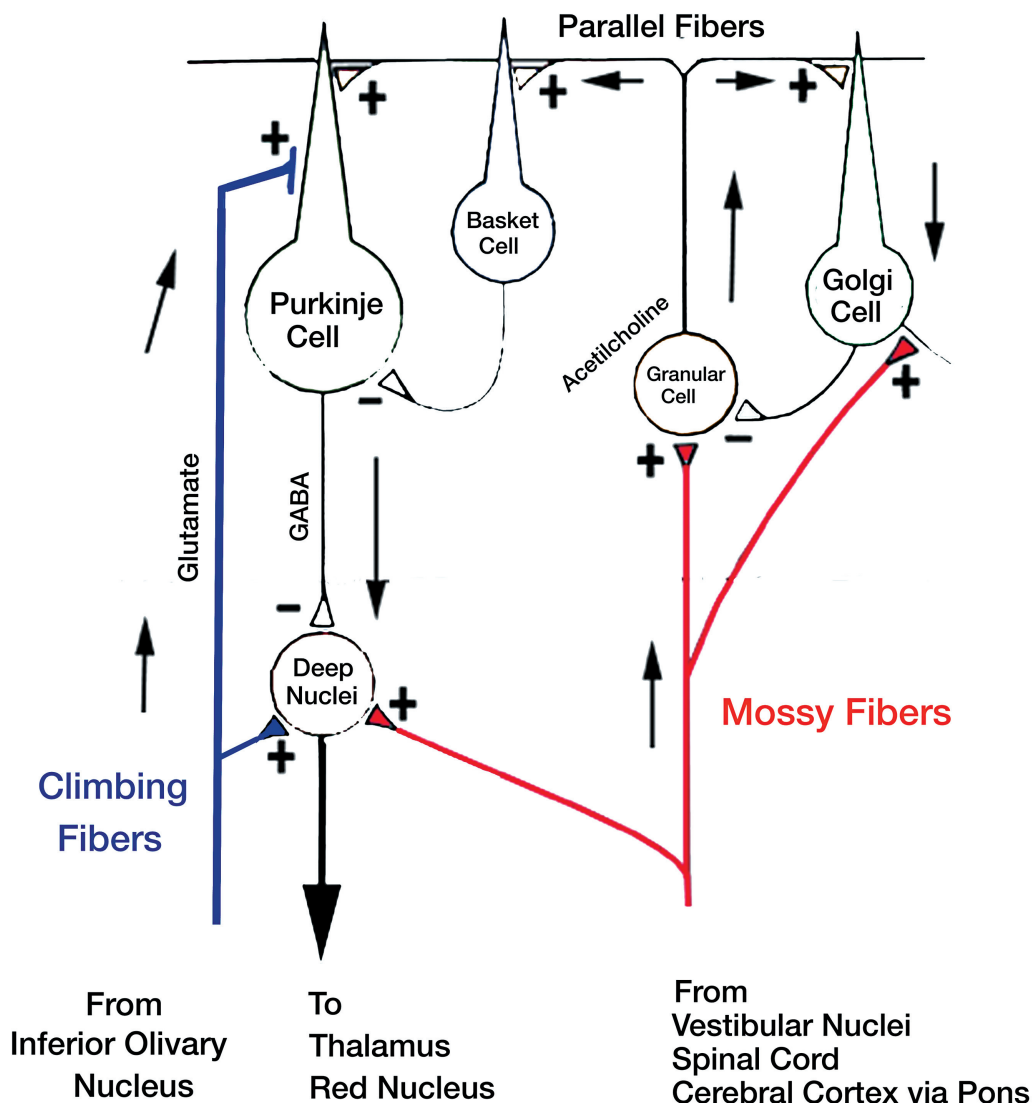


Figure 2 Simplified diagram illustrating the principal interrelationships among cerebellum cells in ET.

alter cerebellar physiology, contributing to the manifestation of tremors.¹

Moreover, deficiencies in the synaptic pruning of climbing fibers to Purkinje cells, often linked to insufficient levels of the glutamate receptor $\delta 2$ subunit (GluR $\delta 2$) protein, lead to excessive cerebellar oscillatory activity. The protein acts as a master synaptic organizer, strictly regulating the territories innervated by climbing and parallel fibers on Purkinje cell dendrites, which may potentially suppress tremors. A deficiency in GluR $\delta 2$ can cause abnormal expansion of the climbing fiber synaptic territory in mice. Correspondingly, the cerebellum in ET shows reduced levels of this protein, which is associated with climbing fiber synaptic pathology. These findings suggest that GluR $\delta 2$ -mediated climbing fiber synaptic pathology may be present in ET patients, impacting the development and severity of tremor symptoms.^{1,27,28}

Despite the logically sound and widely accepted hypothesis of the inferior olive nucleus's role as a pacemaker,

modulating the action of Purkinje cells via climbing fibers glutamatergic action and potentially contributing to their degenerative process, it faces challenges in validation.^{29,30}

First, there is an apparent absence of functional and structural changes in the inferior olive nucleus in neuroimaging studies of patients with ET. The lack of morphological changes in postmortem examinations also supports this.^{16,17,31}

Secondly, while the inferior olive nucleus is undoubtedly capable of generating rhythmic burst activity, Purkinje cells, cerebellar nuclei, globus pallidus, thalamus, and sensorimotor cortex also possess this capability. These neurons with pacemaker properties are part of the cerebello-thalamo-cortical loop and other motor pathways, suggesting that the role of the inferior olive nucleus may be auxiliary within a more complex system.²⁹

Thirdly, animal models using harmaline or ibogaine may not be suitable models for simulating ET in humans. These work by inducing potentiation of the low-threshold voltage-gated calcium channels (CaV3.1) in the inferior olive nucleus

crucial for the genesis of 4 to 10 Hz tremor-related rhythms.^{29,32}

Cerebellum and brain circuits in ET patients

Given surface electromyography (EMG) and accelerometer findings point to a central origin of the tremor generator in ET, researchers have employed tremor frequency as a marker to investigate oscillatory activity and pinpoint the tremor source. Imaging techniques such as electroencephalogram (EEG) and magnetoencephalogram (MEG) have been used to assess functional connectivity and conduct frequency analysis in ET patients, revealing insights into the central mechanisms involved.^{1,33} The major findings of these techniques indicate the role of the cerebello-thalamo-cortical loop in ET.¹

Recent studies, such as the one by Pan et al.,²⁸ have demonstrated that enhanced cerebellar oscillatory activity can be directly recorded via cerebellar EEG in ET patients, underscoring the cerebellum's critical role. This activity is also significant in Parkinsonian tremors, as the cerebello-thalamo-cortical loop is vital for both conditions.¹ Interestingly, it has been suggested that the pathological mechanisms underlying ET and tremor in PD partially overlap.^{1,34} Symptoms of both diseases appear simultaneously quite often, in up to 20% of cases.³⁵

The cerebellum's role in ET involves oscillatory activity that flows primarily towards the sensorimotor cortex, indicating a cerebellar origin of tremor oscillations. This is supported by findings of reduced cerebellocortical functional connectivity in ET, which correlates with tremor severity.^{36,37}

Schnitzler et al.³⁸ utilized MEG to identify a core structure consistently linked to the brainstem and cerebellar activities in ET, providing direct evidence of altered communication within a network that includes the cerebellum. The inferior olivary nucleus also plays a pivotal role by encoding tremor frequency. Research in both animal models and human patients indicates that the temporal coherence of neuronal firing in the olivocerebellum is closely linked to frequency-dependent cerebellar oscillations. Some EEG studies have shown that such oscillations persist even when tremor symptoms are suppressed by thalamic deep brain stimulation, suggesting that they do not depend on reciprocal interactions with the thalamus, highlighting the cerebellum's autonomous role in tremor generation.³⁹

Intrathalamic recordings indicate that the highest concentration of neurons with oscillatory characteristics is found within the ventral intermediate nucleus (VIM) of the thalamus, as noted by Hua et al.⁴⁰ This strong neuroanatomical link between the cerebellar nuclei and Vim neurons serves as indirect evidence of cerebellar pathology.

Buijink et al.⁴¹ employed a combination of EMG and functional magnetic resonance imaging (fMRI) to simultaneously record the peripheral manifestations of tremor and the underlying brain activity. They reported that variations in tremor during a motor task exert an excitatory influence on both the extrinsic connectivity from cerebellar lobule V to the thalamus and the intrinsic activity within these regions. They also found that the motor network is notably compromised in ET, characterized by decreased connectivity between cortical and

cerebellar motor regions during motor tasks, which correlates with an increase in clinical tremor severity. Furthermore, they noted that enhanced functional connectivity between right cerebellar lobules I to IV and the left thalamus is associated with more severe tremor symptoms.⁴¹

Extending these findings, Contarino et al.⁴² explored the neurological underpinnings of tremors using an EMG regressor. They established that voluntary movements activate the contralateral motor cortex, supplementary motor area, and ipsilateral cerebellum. Additionally, their analysis using a tremor frequency-tuned EMG regressor highlighted connections between tremor activity and activation in both the ipsilateral cerebellum and contralateral thalamus. Intriguingly, the specific sites of thalamic activation varied among patients and were not localized to the VIM, suggesting a complex, patient-specific pathophysiology underpinning tremors.⁴²

INSIGHTS FROM GENETICS

The intricate role of genetics in the etiology of ET is underscored by the high prevalence of positive family history in patients, ranging from 20 to 90%, and the phenomenon of genetic anticipation, where tremor manifests at an earlier age in successive generations.^{43,44} Genome-wide association studies (GWAS) have identified several genetic variants in genes such as *LINGO1*, *SLC1A2*, *STK32B*, *PPARGC1A*, and *CTNNA3* linked to ET, though these findings have yet to be replicated consistently. Additionally, exome studies have pinpointed genes associated with familial ET—such as *FUS*, *HTRA2*, *TENM4*, *FUS*, *SORT1*, *SCN11A*, *NOTCH2NLC*, *NOS3*, *KCNS2*, *HAPLN4*, *USP46*, *CACNA1G*, *SLIT3*, *CCDC183*, *MMP10*, and *GPR151*—although these appear to represent private polymorphisms unique to specific families, highlighting the need for further research to identify the genes responsible for ET.⁴⁴

Dysfunctions in the *LINGO1* gene may contribute to the loss of Purkinje cells and axonal damage, potentially leading to ET. Notably, the rs9652490 and rs11856808 variants within intron 3 of the *LINGO1* gene were identified as potential risk factors in the first GWAS on ET patients.⁴⁵ Furthermore, dysfunction in the *SLC1A2* gene, which regulates glutamate uptake, could lead to elevated levels, increasing the risk of neurotoxicity. This is particularly significant given that increased expression of *SLC1A2* has been observed in the inferior olive—a key area involved in generating the oscillations thought to underlie tremor.^{46,47}

Complementing genomic studies, transcriptomic research provides insights into differentially expressed genes (DEGs) that reflect changes in the molecular environment induced by the disease rather than the genetic mutations causing it. This approach bridges the gap between genomics and proteomics, offering a dynamic perspective on how genetic and environmental changes interact and contribute to the pathophysiology of ET.⁴⁸ For instance, a pioneering study by Liao et al.⁴⁹ utilized RNA sequencing to analyze postmortem tissue from the cerebellar cortex and dentate nucleus of ET patients, revealing significant transcriptomic

variability that suggests different brain regions may uniquely contribute to the disorder's pathology.

Further, the study highlighted several underexpressed genes in the cerebellar cortex, such as *SHF* and *CACNA1A*. The latter is critical for the function of CaV2.1 voltage-gated calcium channels in Purkinje cells and is linked to familial hemiplegic migraine—a disorder that also features tremors. This suggests a possible mechanistic link between the dysregulation of calcium channels and tremor manifestation in ET.⁴⁹ Moreover, genes like *CACNA1A* and *CACNA1C*, which are involved in calcium channel functioning within the olivocerebellar circuitry, were found to be differentially expressed, aligning with findings from animal models that demonstrated enhanced neuronal synchrony and rhythmicity.^{50,51}

In 2023, Martuscello et al.⁵² advanced this line of inquiry by focusing on the transcriptomic profiles of Purkinje cells—the cell type thought to degenerate in ET. Using laser capture microdissection, they analyzed the transcriptomes of such cells from ET patients and healthy controls, identifying key genes that differed in expression. This cell-type-specific analysis is critical for understanding the underlying mechanisms of the condition and could pave the way for targeted therapeutic interventions. This study not only reinforces the importance of the cerebellum in ET but also highlights the potential for transcriptomic approaches to uncover novel insights into the disease's molecular underpinnings.⁵²

INSIGHTS FROM CLINICAL FINDINGS

In 2018, the International Parkinson and Movement Disorders Society (MDS) consensus standardized the ET definition and diagnostic criteria. These criteria include an isolated syndrome of bilateral upper limb action tremors with or without occurrences in other locations (such as the head, voice, or lower limbs), in the absence of other neurological signs such as dystonia, ataxia, or parkinsonism. This clinical entity must present a time course of at least 3 years, and all exclusion criteria must be absent (►Table 1).⁸

In the last two decades, several advances in clinical and pathophysiological characterization of ET challenged its definition as a homogeneous condition. In the 2018 MDS

consensus, these studies were taken into consideration, and an essential tremor-plus (ET-Plus) definition was designed as a “placeholder” classification to group patients with prototypical findings associated with mild neurological signs of uncertain significance, insufficient to establish an alternative diagnosis. These neurological signs include motor symptoms, such as tandem gait ataxia and dystonia, and non-motor symptoms like cognitive impairment (►Table 1).^{2,8,53–59}

ET-Plus and tandem gait ataxia/cerebellar findings

Since 1949, with the seminal paper by Critchley,⁶⁰ cerebellar findings have been described in ET.⁶¹ Gait ataxia is one of its underestimated nontremulous features. A recent systematic review on the subject, including 23 studies, demonstrated an odds ratio of 7.03 for tandem gait ataxia compared to healthy controls and estimated that balance problems occurred in 42% of ET cases. It is also noteworthy that the qualitative gait analysis reported a pattern of impairment similar to the observed in cerebellar disorders, apart from a wide base of support, which was not shared among these pathologies.⁶²

A prospective longitudinal study in a population of 149 elderly patients with ET showed that those presenting with ataxia experienced gradual worsening of the gait disorder, with more missteps in examination, fewer seconds in tandem stance, and a cumulative number of falls and near-falls. This study, however, did not include age-matched healthy controls.⁶³

Other cerebellar findings, such as slower smooth pursuit, some forms of nystagmus, saccadic dysmetria, and reduced performance in predictive motor timing tasks, might be present in ET and are well documented. On the other hand, scanning or dysarthric speech, dysmetria, and dysdiadochokinesis are not expected and should prompt an alternative diagnosis.^{53,64}

Although the conception of the ET-Plus entity was an opportunity to establish the heterogeneity of clinical findings in the condition, it also raised several criticisms from experts worldwide.^{53–57} One of the main points of criticism is the fact that several movement disorders, such as spinocerebellar ataxias, dystonia, and PD, present a high degree of clinical heterogeneity. Frequently, different clinical phenotypes exist

Table 1 Diagnostic criteria of essential tremor and ET-plus⁸

2018 MDS consensus statement on the classification of tremor diagnostic criteria for essential tremor
• Isolated tremor syndrome of bilateral upper limb action tremor. • At least 3 years of duration. • With or without tremor in other locations (e.g., the head, voice, or lower limbs). • Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism.
Definition of ET-Plus: 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 neurologic signs of unknown significance that do not suffice to make an additional syndrome classification or diagnosis. Cases of ET with tremor at rest should be classified here.
Exclusion criteria for ET and ET-Plus: • Isolated focal tremors (voice, head). • Orthostatic tremor with a frequency > 12 Hz. • Task- and position-specific tremors. • Sudden onset and step-wise deterioration.

Abbreviations: ET, essential tremor; MDS, Movement Disorders Society.

within the same genotype, and these different presentations do not represent another entity but rather subsets of the same disease. This should be the case for ET, thus rendering the concept of another clinical entity named ET-Plus unnecessary.^{53–57}

NEUROIMAGING INSIGHTS

Cerebellar abnormalities have been increasingly recognized in ET pathophysiology through neuroimaging studies. Current knowledge of the related cerebello-thalamo-cortical circuit dysfunction can be summarized in two theories. The first is an increased cerebellar oscillatory activity, and the second is cerebellar disconnection, or “decoupling”.⁶⁵ They are supported by different modalities of neuroimaging studies, which can be divided into gray and white matter structural abnormalities observed in diffusion tensor imaging (DTI) and voxel-based morphometry (VBM) analysis. Additionally, there are more advanced methods, including molecular imaging, which comprises single-photon emission computed tomography (SPECT), positron-emission tomography (PET), and MRI spectroscopy studies focusing on metabolic and neurotransmitter abnormalities. Lastly, functional imaging studies use fMRI to observe resting-state activated territories and EMG-fMRI changes during tasks.⁶⁵

Structural abnormalities

Subtle and variable structural abnormalities of cerebellar gray and white matter are the most frequent findings in MRI studies.⁶⁶ However, there is significant heterogeneity in the results of structural imaging studies. Most have reported cerebellar mild gray matter (GM) atrophy in varying locations, including the vermis, lobules IV and V, and the posterior and anterior lobes.^{66–71} In contrast, other studies reported no significant differences and even found subtle cortical abnormalities, including increased volume of the supplementary motor area.^{9,10,72} Additionally, white matter (WM) changes may be seen in the cerebellar peduncles, right cerebellum, left medulla, right parietal lobe, and right limbic lobe, contributing to the cerebellar decoupling hypothesis.^{73,74}

Somatotopic organization of the cerebellum should be considered, as exemplified by a study of ET patients with hand and head tremor, which found abnormal vermis and lobule IV volume. Meanwhile, ET patients with only hand tremor had no significant difference compared to healthy controls.^{67,71}

Molecular neuroimaging abnormalities

The MRI spectroscopy studies have largely supported the role of ET as a neurodegenerative disorder. The main findings involve N-acetyl aspartate/choline (NAA/Cho) ratio reduction, reflecting neuronal loss, with one study reporting an inverse correlation with arm tremor severity.^{75,76}

Neurotransmitter abnormalities can be assessed with specific radioligands, with the most impactful being the ¹¹C-flumazenil PET. This radioligand is designed to reflect GABA-A receptor function, and one study demonstrated

increased binding in the cerebellum (dentate nucleus), ventrolateral thalamus, and lateral premotor cortex. These findings suggest GABAergic dysfunction, though it remains unclear whether this is due to a reactive receptor upregulation or neuronal loss, but it is possibly related to overactivity in the tremor network.⁷⁷

Functional abnormalities

The first functional studies utilized SPECT and PET to evaluate cerebral blood flow (CBF) or glucose metabolism, reflecting neuronal activation. Increased bilateral cerebellar CBF was found in ET patients,^{78,79} mitigated by ethanol consumption.⁸⁰ One study revealed that PET imaging with 2-([18F] fluoro-2-deoxy-D-glucose (FDG) hypermetabolism in the left thalamus and right cerebellar posterior lobe in 42 ET patients who underwent the Gamma Knife VIM procedure, which may be reversible after treatment. Additionally, there was a decrease in metabolic consumption in cortical areas, including the left temporal, bilateral middle, and inferior frontal gyri. Also, hypometabolism in the right temporo-occipital area, right retrosplenium, and posterior cingulate area, in addition to high connectivity between temporo-occipital and thalamic areas, were predictive of nonresponse to treatment.⁸¹

Currently, most functional imaging studies use fMRI with blood oxygenation level-dependent (BOLD) sequences to assess neuronal activation and its association with motor symptoms during a resting state or a postural/kinetic task. Several fMRI studies have shown abnormal activity in the cerebellar hemispheres. There has been association between ET and hyper- and hypoactivity in numerous cerebellar segments, with the most consistent involvement in lobules IV to VI and increased activity in the contralateral sensorimotor cortex. Resting-state fMRI has more frequently reported hypoactivity, while studies during action and postural tasks have more commonly shown cerebellar hyperactivity.^{10,36,41,42,82–91} However, some ET patients may have decreased dentate nucleus connectivity with the SMA, the primary sensorimotor cortex, and the prefrontal cortex, showing an inverse correlation with tremor severity and disease duration.⁹² Hence, in some cases, there may be an excess of activity in central oscillators in the cerebello-thalamo-cortical network, while, in others it may be related to a functional disconnection of cerebellar output.^{65,66,93–95}

The functional abnormalities in ET patients can be modulated with deep brain stimulation (DBS) treatment, as shown in a study with 16 participants, where fMRI abnormalities were compared with ON/OFF DBS caudal zona incerta. The postural tremor was associated with increased activity in the contralateral primary sensorimotor and premotor cortices, SMA, thalamus, and bilateral cerebellum (right lobules IV, V, VI, vermis, VIII, and left VI). When the treatment began, the activity decreased in the primary sensorimotor cortex and cerebellar lobule VIII during postural tasks. In contrast, resting tremors improved with this treatment, which was related to the increased activity in the SMA and cerebellar lobule V.⁹⁶

TREATMENT INSIGHTS

Pharmacological treatments

The clinical pharmacology of ET strongly implicates cerebellar involvement, mainly through alterations in GABAergic transmission. Commonly prescribed medications for ET, such as primidone, phenobarbital, benzodiazepines, gabapentin, and topiramate, all work primarily by enhancing this transmission, underscoring the hypothesis of reduced GABAergic tone in ET.⁹⁷ The central role of Purkinje cells, the primary GABAergic output of the cerebellum, suggests that a reduction in the cells' functionality could lead to decreased GABAergic tone, contributing to the pathology.⁷

Research has mainly focused on the structure and functionality of GABA-A receptors, which are predominantly composed of 2 α (6 types), 2 β (3 types), and 1 δ or γ subunit. Genetic and pharmacological studies underline the importance of these receptors in managing ET symptoms. For instance, GABA-A receptor $\alpha 1$ knockout mice display postural and kinetic tremors, emphasizing the critical role of specific receptor subunits in the symptoms.⁹⁸ Further, positive allosteric modulators of the $\alpha 6$ subunit of GABA-A receptors have been shown to improve tremor in animal models.⁹⁹

The SAGE-324/BIIB124 is a neuroactive steroid-positive allosteric modulator of GABA-A receptors with a particular affinity for $\alpha 4\beta 3\delta$ subtypes. In a recent phase-2 study involving 67 ET patients (NCT04305275), this modulator demonstrated a significant decrease in tremor severity. Despite these encouraging results, the trial also reported significant adverse effects: a 62% rate of dose reductions and a 38% discontinuation rate among participants, underscoring the challenges in balancing efficacy with tolerability.¹⁰⁰

The use of anticholinergic agents to treat tremor dates back to Charcot and Gowers.⁴ The traditional understanding has been that anticholinergics alleviate tremors by correcting a striatal neurotransmitter imbalance, characterized by reduced dopaminergic and increased cholinergic activity.¹⁰¹ However, recent studies have expanded this view, suggesting that the anticholinergic effects on tremors may also involve modulation of cerebellar circuits.^{102,103}

Acetylcholine (ACh) plays a critical role in cerebellar function, with dense cholinergic projections terminating in the granule cell layer. These anatomical findings suggest that ACh significantly influences cerebellar processing and associated behaviors.

Fore et al.¹⁰⁴ demonstrated *in vitro* that ACh exerts a prolonged inhibitory effect on Golgi cells via muscarinic receptor activation, leading to reduced synaptic inhibition onto granule cells. Additionally, muscarinic receptor activation on mossy fibers diminishes the excitatory input to granule cells. This concurrent reduction in excitation and inhibition alters spike probability in a heterogeneous manner, enhancing excitability in some granule cells while suppressing it in others. Notably, ACh preferentially increases the excitability of granule cells that are strongly inhibited, supporting the idea that this mechanism is stimulus-specific and may be essential for cerebellar learning.

These findings imply that cholinergic neuromodulation could selectively enhance learning for specific mossy fiber inputs, depending on behavioral context or stimulus salience. Thus, ACh may play a key role in tuning cerebellar plasticity and modulating the gain of cerebellar signal processing. Nevertheless, the *in vivo* mechanisms regulating its release and precise impact on synaptic and network dynamics have yet to be fully elucidated.¹⁰⁴

Neurosurgical treatment

The cerebellum exerts significant influence through glutamatergic inputs to the VIM nucleus via deep cerebellar nuclei (dentate, interposed, and fastigial).¹⁰⁵ This connection is fundamental to the efficacy of DBS targeting the VIM and its afferent fibers, the dentato-rubro-thalamic tract (DRRT), particularly in alleviating tremor across various disorders, including ET.¹⁰⁶

The VIM nucleus is a principal target for DBS and thalamotomy aimed at tremor management. The DRRT fibers from the cerebellum traverse the brachium conjunctivum, pass anterior to the red nucleus, and ascend into the VIM. The latter then projects to the ipsilateral motor cortex (M1) and associated cortical areas such as the premotor cortex, supplementary motor area, and presupplementary motor area.¹⁰⁶

Clinical outcomes from VIM stimulation are highly significant for tremor reduction, particularly in ET. A thorough review of 40 studies reported that unilateral VIM DBS resulted in a tremor reduction of 53.4 to 62.8% in this cohort after 12 months, with action tremors showing the best response, with improvements up to 78.9%. Additionally, bilateral stimulation has been shown to be both safe and effective, providing greater tremor relief (range: 66–78%) and better management of axial and voice tremors.¹⁰⁷

In conclusion, the existing body of scientific literature emphasizes the intricate interactions among cerebellar dysfunction, disrupted neuronal signaling, and compromised feedback mechanisms that contribute to the pathophysiology of ET. These insights affirm the central role of the cerebellum in this condition, mainly through abnormal oscillations and impaired cerebello-cortical connectivity. This understanding supports the notion that therapies targeting cerebellar activity could effectively mitigate tremor symptoms.

To date, a combination of genetic studies, neuropathological examinations, neurophysiological assessments, and various neuroimaging techniques have demonstrated functional, neurotransmitter-related, and structural abnormalities within the cerebello-thalamo-cortical circuit. These findings collectively suggest ET as a neurodegenerative syndrome with diverse etiologies and clinical manifestations.

However, caution must be exercised in interpreting these findings due to the limitations of most studies, which typically involve small sample sizes and are restricted to cross-sectional analyses. These limitations hinder our ability to draw definitive conclusions about causality and the precise relationship between the cerebellum and ET. Ongoing and future longitudinal studies are essential to provide a more robust understanding of these associations and to confirm the cerebellum's definitive role in this condition.

Authors' Contributions

Conceptualization: HAGT; Methodology: CHFC; Project administration: CHFC, HAGT; Supervision: CHFC, GLF, HAGT; Validation: CHFC, LC, LEBMZ, GLF, HAGT; Visualization: CHFC, LC, LEBMZ, GLF, HAGT; Writing – original draft: CHFC, LC, LEBMZ, GLF; Writing – review & editing: CHFC, HAGT.

Conflict of Interest

The authors have no conflict of interest to declare.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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