Review

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Essential Tremor: A Focused Literature Review on Its Pathophysiology, Neurophysiology, Etiology, and Management

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Abstract: Essential Tremor (ET) is among the most common neurological movement disorders, with incidence rates increasing with age. The disorder is characterized by a bilateral action tremor of the upper limbs, enduring for a minimum of three years in duration, and shows early signs of onset with progression over time. Recent terminology has categorized a subcategory of ET, known as Essential-Tremor Plus (ET-Plus), which consists of a combination of symptoms that include tremors at rest and additional neurological signs. This includes memory impairment, gait disturbances, or various other neurological symptoms that do not have full clinical significance for diagnosis and suggest a more complex underlying neurological condition. Abnormalities located primarily in the cerebellum, including the loss and damage to Purkinje Cells (PC), were core pathological features of cerebellar damage in postmortem ET. Given the complexity and uncertainty of the pathophysiological aspects of tremor generation, treatment options are still limited, and current therapeutic measures lack the capacity to fully alleviate symptoms. In consideration, there are current pharmaceutical, stimulation, and genetic studies being conducted to characterize the etiology and pathophysiology of ET and aid in the reduction of progression and symptoms. In this review, we will discuss various aspects of ET including neurophysiology, pathophysiology, genetic factors and etiology, treatment options and future directions of advancements for ET management.

Keywords: Deep Brain Stimulation (DBS); Essential Tremor Plus (ET-Plus); Genome Wide Association Studies (GWAS); Magnetic Resonance Imaging (MRI); Mechanism of Action (MOA); Parkinson's disease (PD); Purkinje cells (PC); Tremor stability index (TSI); Next Generation Sequencing (NGS); Long-read sequencing (LRS); Huntington's disease (HD), Spinocerebellar Ataxias (SCAs)

Introduction

Essential Tremor (ET) is a prevalent neurological movement disorder that remains widely recognized, but not fully understood. Despite limitations and complexities, ET was first used by Pietro Burresi in 1874 (1). It is characterized as an involuntary, rhythmic shaking that can occur in the arms, legs, head, and torso (2,3,4,5). ET is often recognized as a hereditary condition, inherited as an autosomal dominant trait, and typically occurs without any other associated neurological condition (1,6). According to the Tremor Task Force of the International Parkinson's and Movement Disorders Society, ET is defined as an isolated tremor syndrome involving tremors of both upper limbs that persists within three years, independent of movement in lower limbs (7-11). ET can be classified into various subtypes such as Action, Postural, and Kinetic Tremor based on the affected body region, and the type of tremor being displayed, which could be constant or periodic overtime (3,12,13,14). The region of the brain affected by ET is the cerebellum, responsible for movement and coordination (3). Research, although limited to clinical studies, neuroimaging and postmortem analysis, (15) has revealed cerebellar abnormalities associated with ET that includes changes to Purkinje cell (PC) axons

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and dendrites, displacement and loss of PCs, changes to basket cell axonal processes, abnormal distribution of climbing fiber connections to PCs and changes in GABA receptors in the dentate nucleus (15,16). In addition, ET has been linked to causing subtle morphologic changes also to the brain stem, basal ganglia, frontal lobes, inferior olivary nucleus and thalamus (9,17). Despite these detailed findings, which are crucial in understanding the structural-functional changes of the cerebellum region associated with ET, the exact cause of ET still remains unknown (2,6,18-20). In the United States, ET has affected approximately 10 million individuals (2,19,21). This benign, progressive disorder affects both men and women of all ages but may slightly influence more men than women (4,8). There have been clinical manifestations in the elderly, but ET also appears in children and adolescents (17). Currently, ET diagnosis is based on the manifestation of the patient, excluding any other disease through laboratory tests. Although there is no evidence of life-threatening effects of ET, it can substantially impact individuals' quality of life and increase the risk of developing other neurological disorders (22).

The understanding of ET is still evolving due to limited studies (16), substantial uncertainties and ongoing debates concerning its genetic makeup, neurophysiology, pathophysiology, and etiology. One area of ongoing discussion is the concept of the term Essential Tremor Plus (ET-Plus) (15). According to the Consensus classification of Tremor 2018, ET-Plus is deemed essentially a subcategory of ET. It is characterized as individuals with ET, but they also present other neurological signs, not just action and postural tremors. These other neurological conditions include Parkinsonism, ataxia, cognitive changes, and dystonia (15,22-25). The proposal of this term was brought about to better categorize patients and to distinguish ET cases from those with additional neurological signs and determine whether there are currently any underlying pathological differences (15). The controversy raises questions as to whether ET is its own separate entity, or if there could be a broad spectrum of subcategories related to the disorder. The uncertainty surrounding ET, along with the importance of each study, demonstrates the need for further research to create a better understanding of the disorder's complexity; with the aim to explore its causes, clarify diagnostic criteria, propose more future studies, investigate more treatment options/therapies and possible related conditions (26).

Methods

Peer reviewed literature research on ET was identified using key terms including neurophysiology, treatment, pathophysiology, Parkinsonism, and genetics. Articles used in this literature review were obtained from PubMed, Google Scholar, and Science Direct and compiled into a detailed summary describing the etiology and pathophysiology of ET, as well as potential connections between Parkinson's Disease (PD) and ET. Our literature research was limited to only the English language.

Etiology

Although the exact origin of ET remains unknown, it is suggested that a combination of genetic, non-penetrance, and non-autosomal dominant factors play a role in ET development (6,7). While studies on monozygotic twins have provided insight (7,27-29), and other researchers have observed an autosomal-dominant pattern of inheritance (6,7,29,26), it is still unknown how individuals can be affected since the variability in how ET manifests between generations and person is still not fully recognized (6,29). The cardinal symptom of ET is defined as kinetic tremor, which manifests when moving one's hands but is less noticeable when resting (6-7). While kinetic tremor worsens as patients age, medicine or stress can exacerbate symptoms (7). Genetic or environmental factors contribute to the etiology of the disease. First degree relatives have a higher likelihood of developing ET than the general population (6-7). Typically, symptoms increase appreciably if the disease starts at an early age. A cohort study sought to identify the gene that could cause ET (30). Results revealed that out of sixteen family members, ten had the disease while six were unaffected (30). A TUB p.V431I variant (rs75594955) was consistent with autosomal-dominant inheritance (30). Exome resequencing of TUB in 820 unrelated patients with sporadic ET and a control group of 620 patients demonstrated

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nonsynonymous TUB variants (e.g. rs75594955: p.V431I, rs1241709665: p.Ile20Phe, rs55648406: p.Arg49Gln.) were directly involved in the pathogenesis of this disease (30). TUB, a member of the Tubby family of transcription factors, are primarily expressed in neurons in the cerebellum and, via thyroid signaling and G-protein coupled receptor signaling, regulates the pathways responsible for neuron function during development and post-differentiation (30-31). Moreover, TUB protein modulates dopaminergic and cholinergic pathways, two pathways associated with the tremor phenotype (30).

Pathophysiology and Neurophysiology

ET is believed to originate in the brainstem or cerebellum and is known to worsen under stressful situations. ET is also considered a risk factor of PD with physical symptoms becoming more prominent when patients extend both arms in front of themselves (15,18). Recent postmortem studies have confirmed the involvement of several brain structures in the development of ET: olive nuclei, cerebellum, red nucleus, thalamus, and cerebral cortex (7,9,15,18,32). Furthermore, three main hypotheses are proposed as key contributors in the pathogenesis of ET: 1) Neurodegenerative hypothesis, 2) Central oscillatory network hypothesis and 3) The GABAergic hypothesis (33). Underlying mechanisms that may relate to oscillatory activity in the cortico-olivo-cerebello-thalamic circuit and its relationship with ET, may be a result of disruption in GABA-ergic neurotransmission causing dysfunction and the neurodegeneration of cerebellar structures (34). Additionally, neurological damage and dysfunction in the cerebellum, a critical region in movement control, ultimately results in involuntary shaking and tremors.

There are two major pathologies of ET: one involving brainstem Lewy bodies that are restricted to the locus coeruleus, and the other, more frequent pathology consisting of either the loss of PCs, or a presence of ovoid enlargement of the proximal part of PC axons and heterotopias (33). As more research is published, due to the observed projection of locus coeruleus noradrenergic neurons into the cerebellum and synapsing with PCs along with the apparent outflow from the cerebellum being the final common pathway of the disease, it is likely that the neurodegeneration of the cerebellum is the cause of ET (32,33).

The tremor stability index (TSI) is a quantitative measure taken by accelerometry (35). Accelerometry differentiates ET from other tremor syndromes with a 95% sensitivity and a 90% accuracy. The criteria includes: 1) tremor frequency of 5-15 Hz, 2. a peak dispersion equals or below 2.5 Hz, 3. spectral coherence higher than 80%, 4. no unilateral tremor, and 5. action amplitude greater than resting amplitude. Another way to differentiate ET from PD according to the TSI index is higher in patients with ET meanwhile according to the study PD-tremor index is lower (36).

Biomarkers

Uric acid, a metabolite known to be a natural antioxidant believed to have a protective role in neurodegenerative disease, was lower in patients with ET in comparison to control patients (28,37-38). Studies have demonstrated low levels of uric acid in patients with PD, Alzheimer's disease and Amyotrophic Lateral Sclerosis (28,37-38). However, the levels found were not high enough to serve a protective role in neurodegeneration. Interestingly, sporadic cases showed a correlation between lower levels of uric acid and higher age (37-38). Thus, uric acid can serve as a potential indicator of neurodegeneration.

Brain Imaging

Magnetic Resonance Imaging (MRI) has been proposed as a means of identifying the neuromelanin inside the neuron of the substantia nigra in ET (37). While this signal remains the same in ET patients, the neuromelanin-sensitive MRI does identify a decrease in PD patients. Other sources state that with a specificity of 96.2% and a sensitivity of 84.4%, Dopamine Transporter (DAT) has been shown to be a useful protein in differentiating ET from tremor dominant PD (37,39). However, Position Emission Tomography is expensive and uses radiation. Therefore, MRI is viewed as the

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preferred neuroimaging procedure for distinguishing the two motor diseases (37). Neuromelanin has noticeable paramagnetic properties on the MRI called neuromelanin-sensitive MRI (NM-MRI) (11,37). This has demonstrated a decrease in PD patients while remaining the same in ET patients (11,37).

Misdiagnosis

There is a high risk of misdiagnosis between ET and PD due to overlapping symptoms, such as tremors. A 2006 study examined misdiagnosis of PD and ET. The research found that 37% of ET patients, twenty six out of seventy-one, were initially misdiagnosed (false ET). Many later received a correct diagnosis of PD's or other conditions (40). PD and ET are often misdiagnosed because both conditions display similar tremors that may appear in the early stages; however, there were found to be some noteworthy differences (41-42). ET typically involves bilateral action tremors unlike PD which typically features unilateral resting tremors with bradykinesia and rigidity (10,15,43-44). With some cases, ET and PD may coexist within a single case, thus adding to the complexity (42). Specific tremor features (frequency, pattern, etc.) may help distinguish patients with these two conditions if they are compared to associated neurological findings in the laboratory. Misdiagnosis can lead to inappropriate treatment, as antiparkinsonian medications may be prescribed incorrectly (45). Differentiation is crucial to achieving the best possible outcomes.

Treatments: Deep Brain Stimulation, Pharmaceutical, and Therapeutic Measures

Current treatments of ET include pharmaceutical interventions, physical and occupational therapy, and Deep Brain Stimulation alleviate the severity of tremor amplitudes and frequency (9,18,35-36,41,46-53). Beta-adrenergic antagonists such as propranolol have evidence of weakening tremors through peripheral sites; however, beta-2 affinity agents may show higher benefits in reducing symptoms (48). Commonly used medications such as propranolol, primidone, and topiramate are useful oral medications to reduce tremors; although, given their mechanism of action (MOA), these medications do not fully attenuate ET symptoms (48). Propranolol is a cardiac medication used to slow heart rate and reduce high blood pressure, yet it has been found to reduce unrelated symptoms such as shaking and sweating, making it an accepted treatment option for mild tremors (48-49). While propranolol reduces shaking, more effective and successful options for tremor reduction include GABA inhibitors and calcium channel blockers. Drugs such as clonazepam (a benzodiazepine) and flunarizine (slow channel calcium blocker) could be far more beneficial (48-49). Benzodiazepines increase inhibitory GABA effects, ultimately resulting in muscle relaxation which, with further evaluation and research, has the potential to be a more targeted medication option for ET symptoms (48). Additionally, calcium channel blockers have been suggested as alternative treatment as they work by blocking calcium channels through the control of calcium ions into cells (initiating and regulating biological processes), a key contributor in the role of muscle control and nerve function (48-49). Calcium channel blockers have the potential to mitigate overactive signaling that is a contributor to tremors (48-49). Flunarizine, as previously mentioned, is a calcium channel blocker that has the ability to cross the blood-brain barrier, affecting the neurons in the brain directly, making for an efficient tremor medication (49). Furthermore, GABA inhibitors and calcium channel blockers are currently only used in research and additional studies need to be done to approve the drugs for clinical use (49).

DBS is one of the most used treatments for movement disorders that is approved by the United States as a treatment for PD, dystonia and tremors (18,35,50-53). DBS uses electrical stimulation through surgical implantation of electrodes. Electrodes are implanted bilaterally into deep structures of the brain, most commonly in the thalamus, which are connected to a pulse generator through wires. The pulse generator is placed in the chest wall, sending continuous electrical impulses to the electrodes implanted in the ventral intermediate nucleus of the thalamus (35, 50-51). Essentially, DBS works to deliver targeted electrical impulses to motor control regions, modulating abnormal neural activity and reducing tremors. DBS is more suitable for patients with more severe tremors who typically do not respond well to oral medications, with ventral intermediate thalamic DBS relieving

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tremors within seconds (51). While DBS is considered a safe procedure (51), side effects such as intracranial hemorrhage, infections, and problems with implanted hardware devices should be considered prior to treating the patient. DBS does not cure movement disorders but can alleviate symptoms. Recent studies have shown a 50%-90% decrease in tremors and improvement in mobility and functionality in patients who have undergone DBS (18,53).

A more non-invasive route to treating ET involves therapeutic exercises used to moderate symptoms involving occupational therapy, speech therapy, or psychotherapy (26). Various therapy options allow for the assessment needed to determine specific daily tasks that are typically difficult for patients on a case-by-case basis. By determining an individualized care plan, occupational therapy can be incorporated to provide the skills needed to manage tremors and learn to function more comfortably. Occupational therapy utilizes interventions such as weighted utensils, hands free electronic devices, and dressing options such as velcro sneakers (26,47). Psychotherapy aids in the overall improvement of an individual's mental health with individuals that are impacted by the disorder (26). Overall, while there are no clinically approved cures for ET, there is a wide variety of treatment and symptom management options available to reduce the struggles of living with tremors. Furthermore, Et is an active research area which will insure further advancements in pharmaceutical and therapeutic treatments for ET (26).

Conclusions

ET is a chronic, autosomal dominant progressive neurological disorder that primarily impacts the basal ganglia (1,2,6). However, recent research indicates involvement of the cerebellum and inferior olivary nucleus as well (3-4,7,9,14-15). The condition is characterized by involuntary, rhythmic tremors, which often worsen with age and are exacerbated by actions like lifting against gravity. This disorder is most observed in older adults (10,12,18,41). Recent advancements in neurophysiology, genetics, and imaging have illuminated ET's potential relationship to cerebellar degeneration and its connections to other neurodegenerative diseases, such as PD (11,14,30,51). The broader implications of ET and its various presentations have spurred ongoing debate and research. The broader implications of ET and its different forms continue to be debated and studied. The "ET-plus" classification, which categorizes ET patients with extra neurological symptoms, is controversial. (15,22,32). A better understanding of ET's pathogenesis and links to other neurodegenerative conditions, like PD, could be gained by identifying biomarkers, like uric acid, and genetic variants associated with them (4,28,30,38). To enhance diagnostic accuracy and differentiate ET from other tremor-related disorders, including Parkinson's disease, advances in imaging techniques, such as neuromelanin-sensitive MRI, should be explored more (40). Furthermore, it is imperative that future research explores the efficacy of treatments such as DBS and new pharmacological approaches, especially in patients with ET and overlapping PD features (16,18,29,51-53). Developing more effective and personalized treatment strategies will depend on understanding how ET progresses, especially when it evolves into PD or other neurological disorders (17-18,42,47). Interdisciplinary collaborations are essential to understanding ET's complex relationship with other neurodegenerative processes.

For accurate diagnosis of genetic disorders, targeted sequencing remains essential despite advancements in long-read sequencing (LRS), next-generation sequencing (NGS), and gene editing technologies. While these cutting-edge technologies have improved our understanding of genetic mutations, precise targeting is still necessary to identify disease-causing variants in ET and similar conditions (54). In addition to its potential to correct genetic defects related to ET, CRISPR-Cas9, a powerful DNA editing tool, is currently in the preclinical phase. It has not yet been used clinically in treatment with amplification-free approaches (No-Amp) or next generation sequencing platforms (55-56). CRISPR has been extensively researched for genetic disorders with clearer causes, such as Huntington's disease (HD) and Spinocerebellar Ataxias (SCAs), but further investigations are needed before it can be used in ET (56). As opposed to HD or SCA, ET involves multiple genes and environmental factors, making it more difficult to target. Further studies are required to better understand ET's genetic basis, refine diagnostics, and develop more effective treatments beyond

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current options like DBS and symptom management. (26,52). The development of biomarkers for the early detection of ET needs to be a priority area of further research. In addition, a better understanding of how environmental factors impact ET outside of genetics could allow preventative measures to be developed to reduce its risk.

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