

Essential Tremor: A Neurodegenerative Disease?

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Abstract

Background: Essential tremor (ET) is one of the most common neurological disorders among adults, and is the most common of the many tremor disorders. It has classically been viewed as a benign monosymptomatic condition, yet over the past decade, a growing body of evidence indicates that ET is a progressive condition that is clinically heterogeneous, as it may be associated with a spectrum of clinical features, with both motor and non-motor elements. In this review, I will describe the most significant emerging milestones in research which, when taken together, suggest that ET is a neurodegenerative condition.

Methods: A PubMed search conducted in June 2014 crossing the terms “essential tremor” (ET) and “neurodegenerative” yielded 122 entries, 20 of which included the term “neurodegenerative” in the article title. This was supplemented by articles in the author’s files that pertained to this topic.

Results/Discussion: There is an open and active dialogue in the medical community as to whether ET is a neurodegenerative disease, with considerable evidence in favor of this. Specifically, ET is a progressive disorder of aging associated with neuronal loss (reduction in Purkinje cells) as well as other post-mortem changes that occur in traditional neurodegenerative disorders. Along with this, advanced neuroimaging techniques are now demonstrating distinct structural changes, several of which are consistent with neuronal loss, in patients with ET. However, further longitudinal clinical and neuroimaging longitudinal studies to assess progression are required.

Keywords: Essential tremor, neurodegenerative, clinical, pathology, review

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Introduction

Neurodegenerative diseases are chronic, progressive disorders of the nervous system, often of long duration, with loss of specific vulnerable neuronal populations in the central and peripheral nervous system due to intrinsic processes rather than an identifiable outside influence (e.g., vascular, autoimmune), and they are often associated with gliosis and typical cytoskeletal protein aggregates.¹

Essential tremor (ET) is one of the most common neurological disorders among adults, and is the most common of the many tremor disorders.^{2,3} ET is a widespread condition, affecting people of all races and cultures, from the remote Eastern Highlands of Papua, New Guinea, to the urban area of Madrid, Spain (NEDICES study, a population-based study).^{4–6} Its most recognizable clinical feature is an 8–12 Hz kinetic tremor of the arms (i.e., tremor during voluntary

movement), which often is later accompanied by head and voice tremors.^{7–10} The traditional view of ET as a monosymptomatic condition is being replaced as a spectrum of clinical features, with both motor and non-motor elements, including ataxia, parkinsonism, cognitive impairment, dementia, personality disturbances, depressive symptoms, sensory abnormalities (e.g., mild olfactory dysfunction and hearing impairment), dysfunction of the upper respiratory airways, voice disturbances, and sleep disorders increasingly being documented.^{11–25} Furthermore, recent histopathological and neuroimaging studies in ET have demonstrated several distinctive structural changes, including neuronal loss.^{26–28}

With increasing data emerging from these new clinical, neuroimaging, and pathological studies, a crucial question arises. Is ET

neurodegenerative? The idea that ET could be neurodegenerative is not novel. In the landmark paper by Critchley and Greenfield, published in 1948, the authors wrote: “Although anatomical proof is as yet lacking, there are at least a number of clinical points to make question whether “essential tremor” may not, at times any rate, represent an incomplete or a premature variant of one of the cerebellar atrophies.”²⁹ Although not further elaborated on by those authors, these clinical characteristics include its insidious onset, association with advanced aging (i.e., both prevalence and incidence rates increase with age), gradually progressive nature, and the presence of “cerebellar” features (e.g., intention tremor and ataxia) on examination.²⁹ Indeed, these are many clinical features typical of neurodegenerative diseases of the cerebellum.

In this review, I will discuss the most significant milestones in ET research, which, when taken together, suggest that ET is a neurodegenerative condition.

Methods

A PubMed search conducted in June 2014 crossing the terms “essential tremor” (ET) and “neurodegenerative” yielded 122 entries, 20 of which included the term “neurodegenerative” in the article title. This was supplemented by articles in the author’s files that pertained to this topic. Of note is that a recent review of the 100 most cited papers on ET revealed that none dealt with issues related to neurodegeneration.³⁰

Alternative hypothesis on central oscillating pacemakers

The traditional hypothesis about pathogenesis of ET, since the early 1970s, posited the existence of a central tremor pacemaker or oscillator (the olivary model).³¹ A theoretical disturbance in the inferior olivary nucleus, an anatomic structure with inherent oscillatory pacemaking properties, was thought to be the possible origin of ET.³² This hypothesis was based on three observations. First, the original post-mortem examinations in ET erroneously concluded that there were no relevant pathological changes.²⁸ Many of these examinations were published 50–100 years ago, and few described relevant brain structures in detail.⁹ A further problem was the absence of any age-matched control brains for comparison.⁹ Second, there is an animal model of tremor using the neurotoxin harmaline, a potent tremor-producing chemical that is present in the human diet, especially in animal proteins (meats) that are cooked at high temperatures for extended periods.^{33–35} This neurotoxin causes non-specific action tremor in laboratory animals and post-mortem changes in the olivocerebellar pathway in these laboratory animals.^{33–35} Harmaline may excite inferior olivary neurons, causing marked Purkinje cell destruction.³⁶ However, action tremor is a non-specific sign.^{7–10} Further, the harmaline model is not a model of the human disease but an animal toxin model of acute tremor,³⁷ since it causes tremor, which tends to resolve after a few hours.³⁷ Third, in the inferior olivary nucleus there are cells with pacemaking properties;^{35,38} in other words, they can fire in a coordinated and rhythmical fashion.³⁷ However, the model is merely conjectural;³⁷ there is no empiric evidence that the

olivary model is an accurate reflection of what is occurring in human beings with ET.³⁷ In addition, the inferior olivary nucleus is not the only anatomic region in the central nervous system with pacemaker properties; there are many more examples of pacemakers in the central nervous system, including those in the locus ceruleus,³⁹ the dorsal raphe nucleus,⁴⁰ the thalamus,⁴¹ and the Purkinje cells from the cerebellum.⁴² Thus, one wonders why the inferior olivary nucleus and not any of the above pacemakers has been postulated to be pathologically relevant in ET.³⁷ Finally, imaging studies have not demonstrated any consistent changes in the inferior olivary nucleus and post-mortem studies have not found any structural changes either.^{26,43,44}

In closing, the lack of empiric evidence as well as the new emerging data on the neurodegenerative model of ET (as discussed next) have now called the olivary model into question.⁴⁵

The neurodegenerative model

Clinical studies

As with other neurodegenerative diseases, such as Parkinson’s disease (PD) or Alzheimer’s disease (AD),^{46–49} the incidence of ET increases with age.⁵⁰ In a study of a multiethnic community in northern Manhattan, New York, more than one in five individuals in the oldest age group (≥ 95 years of age) had this disease.⁵¹

ET is a progressive disorder, which worsens over time in most patients.^{7–9} Several processes could contribute in the progression of symptoms in ET, including the inherent worsening of the underlying disease with increasing disease duration and the effects of aging on the nervous system, yet there are few prospective studies on ET that have attempted to identify the variables that influence progression of ET.^{52–56} Interestingly, disease duration and age are independently associated with tremor severity in ET.⁵⁷ This suggests that the reported increase in tremor severity in ET may be related to the inherent worsening of the disease with increasing duration, and that this is independent of age and age-related processes like neuronal attrition and change in tremor frequency.⁵⁷ In a large clinical sample, older age of onset was associated with more rapid tremor progression.⁵⁸ In a brain bank, older age of onset was associated with more degenerative pathology in the cerebellum.⁵⁸

Only a few longitudinal studies have actually attempted to quantify the rate of actual tremor progression.^{52–56} An increase in tremor amplitude of about 30% in a period of 4 years and a decrease of frequency by approximately 0.06 to 0.08 Hz/year together with a reduction in tremor frequencies has been observed by accelerometry and surface electromyography.⁵⁵ A few longitudinal data^{53,56} have described a small, but significant, increase in tremor severity in ET patients, estimated as 12% per year from baseline evaluation in one clinical series,²⁹ and an average annual increase in tremor severity from baseline between 3.1% and 5.3% in another recent series followed for ≥ 5 years.⁵⁶

In addition, disease progression is not only characterized by spreading of tremor to the head (neck), which eventually occurs in approximately 40% of patients,⁵⁹ but also by the occurrence of

abnormalities of cerebellar function in ET.⁷⁻⁹ The wide spectrum of cerebellar symptoms that may be observed in ET, include the presence of intentional tremor,^{7-9,60} gait ataxia,^{11,38-40} dysarthria,⁶¹ oculomotor abnormalities,⁶² as well as deficits in hand-eye coordination.⁶³ Specifically, gait disturbances (i.e., ataxia) are seen more frequently in ET patients with longer disease duration who are at an advanced stage of ET and among those cases with midline (e.g., cranial) tremors.^{11,64-67} Of further interest is the observation that gait abnormalities in ET can temporarily improve with ethanol intake.⁶⁸ In one study, the ingestion of ethanol to a mean blood level of 0.45% led to a transient but significant improvement of ataxia in ET patients yet produced a worsening of gait parameters in controls.⁶⁸ Ethanol binds to the gamma-aminobutyric acid (GABA) receptor, thereby facilitating GABAergic neurotransmission.⁷⁻⁹ One should bear in mind that the neurochemical deficit involving ataxia and tremor could be the same, that is a deficit in GABA cerebellar neurotransmission.⁷⁻⁹ Therefore, tremor and ataxia could respond to an enhancement of GABAergic neurotransmission.⁷⁻⁹

Rest tremor of the arms is observed in one in five ET patients and also it may be an early sign of ET.⁶⁹ In one tertiary referral center, the patients with rest tremor had kinetic tremor that was more severe, more disseminated, and of longer duration than ET patients without rest tremor.⁶⁹ Although the pathogenesis of rest tremor in ET is unknown,⁷⁰ it could be related to pathologic spreading to extracerebellar circuits in patients with severe, long-standing, and disseminated disease. Alternatively, it may result from a pathological interaction between the basal ganglia and the cerebello-thalamo-cortical circuits.⁷¹

As the heterogeneity of ET becomes more evident, researchers have expressed increased interest in exploring the possibility that there are associated findings (e.g., motor and non-motor manifestations) associated with this disorder, and that it may be associated with other neurodegenerative diseases (e.g., PD or AD).^{7-9,72}

The weight of emerging evidence is indicating that ET is also associated with a series of non-motor manifestations, including cognitive deficits,^{14,15,73-76} mild cognitive impairment,¹³ dementia,^{16,17,77} personality changes,¹⁸ depressive symptoms,¹⁹ possible mild olfactory dysfunction,^{20,78,79} hearing impairment,^{21,22} and sleep disorders.^{80,81} Several of these non-motor manifestations are also seen in many other neurodegenerative conditions, such as PD and Huntington's disease, among others.^{82,83}

As in other neurodegenerative diseases,^{84,85} cognitive deficits, mainly in frontal-executive function and memory, have been reported to occur in ET patients in a range of independent studies,^{14,15,73-76} including a population-based case-control study of largely treatment-naïve ET patients nested in the NEDICES study.¹⁵ Taken together, these studies indicate that a frontosubcortical-type dysfunction occurs in some ET patients.^{14,15,73-76} Overall, the degree of cognitive impairment in ET is mild and is thought to be due to a dysfunction in the dorsolateral prefrontal cortex and in the inferior parietal cortex, including the cerebral-cerebellar loop.⁸⁶ In the NEDICES study, baseline cognitive test scores were lower in non-demented ET cases than non-demented controls;⁷⁶ moreover, during the 3-year follow-up

period, these scores declined at a rate that was seven-times faster in ET cases.⁷⁶

The NEDICES study also provided evidence that cognitive deficits in premotor ET (that is, ET cases who underwent neuropsychological evaluations at a baseline visit prior to the onset of their tremor) are not static, and that they appear to be progressing at a faster rate than in elders who do not develop this disease.⁸⁷ In addition, an association between elderly-onset ET and prevalent mild cognitive impairment was demonstrated in the NEDICES study.¹³ In line with this, in the NEDICES study, elderly-onset ET was found to be associated with prevalent dementia.¹⁶ ET cases with tremor onset after 65 years of age were 70% more likely to have dementia than were similarly aged controls.¹⁶ In the follow-up of the same population, ET cases with tremor onset after age 65 years were twice as likely to develop incident dementia than were controls, whereas ET cases with tremor onset <65 years of age and controls were equally to develop incident dementia.¹⁷ In a second population-based study of elders in New York, ET was also associated with both increased odds of prevalent dementia and increased risk of incident dementia,⁷⁷ with odds ratios and relative risks similar to those reported in the NEDICES study.⁷⁷ In both studies, the large majority of subjects with dementia had AD.^{16,77} Although additional studies are needed, these two studies suggest that the presence of dementia in ET appears to be greater than expected for age and that there are links between ET and AD.^{16,77} In a recent study that included 40 ET patients who were free of dementia clinically and without AD on post-mortem examination and 32 age-matched controls, ET patients had a higher Braak neurofibrillary stage, but similar scores for neuritic plaques.⁸⁸ ET may predispose individuals to accumulate more widespread cellular tau aggregates, and thus tau could play a central role in the cognitive impairment that can accompany ET.⁸⁸

The relationship between ET and PD has been a subject of reviews and debate for a long time, but there is now growing evidence that the two disorders are related, at least in some patient populations.^{12,89-92} Clinical series, follow-up studies of ET patients, and case-control and genetic epidemiological studies indicate that ET is associated with increased risk for PD.⁸⁹ In addition, some neuroimaging studies and neuropathological reports suggest an association between the two diseases. Some ET patients may have a circumscribed form of Lewy body disease, and the secondary development of PD may represent a spread of those Lewy bodies in the brainstem.⁹¹ ET patients may have some degree of bradykinesia. In a recent study, ET patients showed impaired motor performance, at least in some tasks, such as rapid repetitive finger movements (finger tapping and frequency) and visual reaction time (impairment was not related with tremor severity).⁹³ The link between ET and PD has been formally quantified in the NEDICES study, which demonstrated that the risk of developing incident PD was 4.3 times higher in ET cases than in age-matched controls without ET.¹²

Depressive symptoms might be more prevalent in ET than in the population,¹⁹ as is seen in other neurodegenerative diseases, such as PD.⁹⁴ In the NEDICES study, prevalent ET cases were twice as likely

as controls to report depression and three times more likely to be taking antidepressant medications.¹⁹ In prospective analyses of this study, baseline self-reported depression was associated with incident ET.¹⁹ These prospective data suggest that the mood disorder in ET may be more than a secondary response to disease manifestations; this mood disorder may be a primary feature of the underlying disease.¹⁹

Mild olfactory dysfunction has been detected in ET patients in several studies,^{20,95} but not in others;^{78,96} when observed, this dysfunction is, on average, milder than that observed in patients with PD.^{20,95} As in PD, this possible dysfunction does not correlate with disease duration or severity, indicating that it occurs early in the disease process.²⁰

Hearing impairment in ET has been reported in two case-control studies.^{21,22} At a tertiary referral center, ET was associated with hearing impairment, as shown by both subjective and objective measures of hearing loss.²¹ Similarly, in the NEDICES study, ET patients reported more hearing impairment than did matched controls.²² The basis for this possible hearing impairment is unknown. However, both central and peripheral nervous system mechanisms have been suggested.²¹

Sleep dysregulation is often described in neurodegenerative diseases.^{97,98} The association between sleep dysregulation and ET has been assessed in several studies.^{80,99} Adler et al.⁹⁹ compared Epworth Sleepiness Scale scores (ESS) in 53 ET cases to 49 PD cases and 175 normal controls, and noted no ET case-control difference; in that study, ESS scores in ET were intermediate between normal controls and PD but far more similar to those of normal controls.⁹⁹ Chandran et al.⁸⁰ found a marked difference in Pittsburgh Sleep Quality Index (PSQI) scores in 50 ET cases as compared with 50 controls, yet no difference in ESS scores. Gerbin et al.⁸¹ compared the ESS and the PSQI scores in 120 ET cases, 120 normal controls, and 40 PD cases. The ET case-control difference was not significant, yet in a test for trend, PD cases had the highest PSQI score, followed by ET (intermediate), and lowest scores in controls. Finally, in NEDICES short sleep duration was associated with an increased risk of ET.²⁵

Similar to PD and AD, the two paradigmatic neurodegenerative diseases, there is a proportion of the ET patients with a clear family history of disease, which is lower in PD and AD, and higher in ET.¹⁰⁰ The risk of action tremor and ET is increased in the relatives of PD patients, particularly when they have tremor-dominant PD.^{101,102} These findings suggest that PD and ET may share familial susceptibility factors.⁹⁰

Pathological evidence

There is a marked and continued rise in ET prevalence and incidence in advanced ages.⁷⁻⁹ ET has an insidious onset and then follows a gradual yet progressive clinical course.⁷⁻⁹ The clinical constellation, discussed in the previous section, is somewhat compelling; however, none of the clinical features in isolation is specific to neurodegenerative diseases. On a tissue-based level, the evidence is more compelling.⁴⁴

A fundamental question about the neurodegenerative nature of a neurological disorder is whether there are histopathological changes in the brain. Selective involvement of an anatomically and physiologically related system of neurons (Purkinje cells), has been reported in ET cases in recent series.⁴⁴ Until several years ago, only 25 reported post-mortem examinations in ET were available, many of which were published 50–100 years ago, and few of which described relevant brain structures in detail.⁹ A further problem was the absence of any age-matched control brains for comparison. The Essential Tremor Centralized Brain Repository at Columbia University (New York, NY) was established in 2003 to prospectively collect and study in detail the brains of individuals with ET, and to compare them with matched control brains.¹⁰³ A preliminary analysis, including 10 ET cases and 12 controls, demonstrated that ET may be pathologically heterogeneous.¹⁰⁴ The number of torpedoes (a marker of axonal damage or regenerative process) and Bergmann glia was increased in ET cases;¹⁰⁴ six cases (60%) had Lewy bodies vs. two controls (16.7%); four of these six had an atypical distribution of brainstem Lewy bodies.¹⁰⁴ Overall, ET cases clustered into two groups: those with cerebellar degenerative changes ($n=4$) and those with brainstem Lewy bodies ('Lewy body variant of ET'; $n=6$), raising the possibility that some ET cases have a form of Lewy body disease.¹⁰⁴ Of note, the presence of torpedoes is not specific to ET, and is observed in other well-known neurodegenerative conditions, such as progressive supranuclear palsy, dentatorubropallidolusian atrophy,¹⁰⁵ and fragile X-associated tremor/ataxia.¹⁰⁶

A more relevant study by Axelrad et al.¹⁰⁷ demonstrated a reduction in Purkinje cell number in the brains of patients with ET who did not have Lewy bodies. These data further support the view that the cerebellum is anatomically, as well as functionally, abnormal in these ET cases.¹⁰⁷ Recently, an abundance of torpedoes has been shown in the cerebellar vermis of ET brains, mainly in patients with neck, voice, and jaw tremors.¹⁰⁸

In the Essential Tremor Centralized Brain Repository of New York, which compared 33 ET cases to 21 controls, the mean number of Purkinje cells per $100\times$ field was reduced in ET cases and there were approximately seven times as many torpedoes in ET cases as well.¹⁰⁹ Two cases also had degeneration of the dentate nucleus.¹⁰⁹ Other structural abnormalities in ET cases were Purkinje cell heterotopias and Purkinje cell dendrite swellings as well as hypertrophy of basket cell axonal processes.^{109,110} Eight (24.2%) of the 33 ET brains had Lewy bodies in the brainstem, mainly in the locus ceruleus, and normal cerebella.¹⁰⁹ By contrast, two recent studies reported no reduction in Purkinje cells in ET¹¹¹ or have concluded that there is no clear distinction between ET, PD, and normal control subjects in the number of Purkinje cells.¹¹² However, there are a number of significant methodological problems with the design of these studies, and these issues cast considerable doubt on the validity of the reported results.¹¹³

In summary, clearly identifiable structural changes (i.e., Purkinje cell loss, Lewy bodies) have been observed in the brains of ET patients.²⁸ These changes are not uniform and seem to follow several patterns, localizing to the cerebellum itself or to a collection of brainstem

neurons in the locus ceruleus that synapse directly with Purkinje cells.²⁸ Furthermore, these changes are similar to those seen in degenerative diseases.²⁸

Neuroimaging evidence

In contrast to post-mortem studies, neuroimaging studies provide a non-invasive method to examine structural changes in living patients who have not yet arrived at an end-stage of disease. A broad array of neuroimaging methods used in a rising tide of studies, including functional magnetic resonance imaging (MRI) studies,¹¹⁴ positron emission tomography studies,^{115,116} [¹H] magnetic resonance spectroscopic imaging studies,^{117–119} diffusion tensor imaging studies,^{120–122} voxel-based morphometry studies,^{26,123,124} and studies using other automated volumetric methods,¹²⁵ now indicate the presence not only of functional and metabolic abnormalities in the ET cerebellum, but of structural abnormalities in both the cerebellar gray and white matter as well.¹²⁶

A reduction in cerebellar cortical N-acetyl-L-aspartate (NAA) and total choline, relative to total creatine (tCR), indicates that there is neuronal damage or loss in ET, suggesting that ET may be a neurodegenerative disease.^{117–119} Voxel-based morphometry studies using 1.5 T MRI have led to contradictory results;^{123,124} however, by using 3 T MRI, structural white and gray abnormalities may be detected in ET patients in both the cerebellum and different cerebral areas. Specifically, Benito-León et al.²⁶ detected white matter changes in several areas (right cerebellum, left medulla, right parietal lobe, and right limbic lobe) and gray matter changes in several areas as well (bilateral cerebellum, bilateral parietal lobes, right frontal lobe, and right insula) in 19 ET patients vs. 20 controls. In line with these results,²⁶ another recent report of 20 ET patients and 20 controls showed widespread areas of atrophy in both the cerebellum and cerebral gray matter, as well as a relationship between gray matter atrophy and tremor severity score, which supports the current concept of the progressive and diffuse nature of ET.¹²⁷

Diffusion-weighted imaging is used to search for evidence of tissue integrity abnormalities; although a previous study did not detect any significant changes between 10 ET patients and 10 controls, another study involving 10 ET patients and eight controls¹²² showed a significantly reduced fractional anisotropy in the anterolateral portion of the right pons and decreased fractional anisotropy in the bilateral cerebellum, left retrorubral area of the midbrain, and bilateral deep white matter, including the orbitofrontal, lateral frontal, parietal, and temporal white matter. Further, by means of 3 T MRI, significant reduction of fractional anisotropy was reported in the dentate nucleus and superior cerebellar peduncle of patients with familial ET;¹²¹ additionally, among patients with familial ET, those with longer disease duration showed fractional anisotropy values in the dentate nucleus lower than those with shorter disease duration. Finally, Klein et al.,¹²⁰ by means of a whole-brain analysis with tract-based spatial statistic, confirmed by voxel-wise analysis, circumscribed pathology of the inferior cerebellar peduncles. Moreover, increased diffusivity in white matter structures of both hemispheres suggests widespread

alterations of fiber integrity in motor and non-motor networks in ET patients.¹²⁰

Finally, in a study using volumetric data obtained with automated segmentation of subcortical and cerebellar structures, reduction of cerebellar volume in patients was observed in patients with head tremor when compared with healthy controls, after controlling for intracranial volume was observed.¹²⁵

Conclusions

The neurodegenerative hypothesis of ET on the surface seems at odds with the early onset and clinically slow and heterogeneous progression of ET in some patients.¹²⁸ Indeed, some researchers have advocated for an alternative pathophysiological explanation for ET based on central oscillating pacemakers.¹²⁸ This hypothesis would not require structural changes in the anatomical organization or connectivity of the cerebello-thalamo-cortico-cerebellar loops.¹²⁸ However, the hypothesis is purely conjectural and based on little if any empiric evidence. ET is a progressive, aging-associated condition, associated with cell loss (reduction in Purkinje cell number in properly designed studies) and other types of changes (Lewy body formation) that traditionally occur in neurodegenerative disorders. Further, the overwhelming data from different independent study groups, including new pathological and MRI findings, as well as the constellation of non-motor findings, all present in the same disease, similar to other neurodegenerative diseases, suggest that ET is a neurodegenerative disease.^{129,130} In addition, the considerable evidence for an association between ET and PD and the fact that elderly-onset ET increases the risk of developing AD nearly twofold suggests that ET may share pathogenic mechanisms with these disorders. Finally, there are no reported cases of spontaneous remission of ET; a disease condition whose pathophysiology was based on a disorder of a central oscillating pacemaker might result in either a spontaneous improvement or disappearance of the same. However, further longitudinal clinical and neuroimaging longitudinal studies to assess progression are required.

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