

Viewpoints

Isolated Voice Tremor: A Clinical Variant of Essential Tremor or a Distinct Clinical Phenotype?

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Abstract

Background: The consensus statement by the Task Force on Tremor of the International Parkinson and Movement Disorder Society excludes individuals with “isolated voice tremor” as a clinical variant of essential tremor (ET). This clinical viewpoint presents a rationale for reconsideration of “isolated voice tremor” as a clinical variant of ET.

Methods: Evidence from the literature was extracted to characterize the clinical phenotype of “isolated voice tremor,” or essential vocal tremor (EVT). Clinical features were extracted from relevant literature available at pubmed.gov using the terms “EVT,” “essential voice tremor,” “primary voice tremor,” and “organic voice tremor.”

Results: The average age of onset in those with EVT was older than 60 years (range 19–84 years), with 75–93% being female. The typical duration of vocal tremor ranged from 1 to 13 years (average 6 years). The distribution of structures exhibiting tremor included the larynx, soft palate, pharynx, and base of tongue in the majority of patients, with some exhibiting tremor of the head and respiratory musculature. The condition of tremor occurred during speech and quiet respiration in 74% of individuals. Rate of tremor ranged from 4 to 10 Hz. Nearly 70% reported onset of vocal tremor prior to upper limb involvement. Family history of tremor was reported in 38–42% of individuals.

Discussion: Those previously classified with EVT demonstrate a similar familial history, rate, tremor classification, and body distribution of ET. EVT is proposed as a clinical variant of ET in the pattern of onset and progression of body distribution from the midline cranial to spinal neural pathways.

Keywords: Essential tremor, essential vocal tremor, essential voice tremor, primary vocal tremor, isolated voice tremor

Citation: JM. Barkmeier-Kraemer. Isolated Voice Tremor: A Clinical Variant of Essential Tremor or a Distinct Clinical Phenotype? Tremor Other Hyperkinet Mov. 2020; 10. doi: 10.7916/tohm.v0.738

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Editor: Elan D. Louis, Yale University, USA

Received: October 07, 2019; **Accepted:** November 26, 2019; **Published:** January 23, 2020

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Funding: This work is funded by the NIDCD to conduct research on those with essential tremor and vocal tremor (R01DC016838, Physiologic correlates of vocal tremor affecting those with essential tremor, PI: Barkmeier-Kraemer).

Financial Disclosures: None.

Conflict of Interest: The author conducts funded and unfunded research on individuals with vocal tremor relevant to the topic of this viewpoint.

Ethics Statement: Not applicable for this category of article.

Introduction

“What’s in a name? That which we call a rose, by any other name would smell as sweet.” This famous quote spoken by Juliet in William Shakespeare’s play, *Romeo and Juliet*, asserts that an individual’s name does not adequately capture his or her essence or characteristics. Yet, medical and scientific nomenclature aim to systematically define terms and classification systems that accurately capture the essence and characteristics of individuals, including the presence or absence of familial patterns. Consistent and accurate use of clinical terminologies by healthcare

professionals and researchers is critical for purposes of characterizing, classifying, and determining the nature and optimal care of individuals diagnosed with a disease.¹ As such, classification systems and clinical terminology are periodically re-evaluated for the purpose of integrating advancements in our understanding of diseases that translate into improved research approaches and healthcare practices. Unfortunately, classification systems that define specific medical terms or classification systems by one medical discipline may not always be adopted or accurately implemented by others. In some cases, discipline-specific consensus

publications offer criteria for classification of disorders that reflect each particular discipline's body of literature and clinical practice standards with differing perspectives. This is the case with essential vocal (or voice) tremor, also known as "isolated voice tremor." The purpose of this viewpoint is to propose essential vocal tremor (EVT) as a clinical variant of essential tremor (ET) as opposed to a distinct clinical phenotype of "isolated voice tremor."

Discipline-specific consensus

A recent consensus statement on classification of tremors was published by the Task Force on Tremor by the International Parkinson and Movement Disorder Society (IPMDS).² This task force clinically defined ET as an "isolated tremor syndrome of bilateral upper limb action tremor with or without tremor in other locations (e.g., head, voice, lower limbs) and in the absence of other neurological signs like dystonia, ataxia, or parkinsonism for at least 3 years duration."² A period of 3 years was selected as the minimum criterion based on the consensus that this time frame allows elucidation of progression of disease associated with eventual onset of other neurological signs such as ataxia, parkinsonism, or dystonia.^{2 (p.17)} For individuals describing duration of symptoms for less than 3 years, the term "indeterminate tremor" is recommended until the criterion of 3 years duration of symptoms is met.^{2 (p.6)} Isolated focal tremors involving the voice, head, orthostatic tremor (frequency > 12 Hz), task- and position-specific tremors, and report of sudden onset or step-wise deterioration are considered exclusion criteria for ET and ET plus. "ET plus" was proposed as a separate or extended classification to include those meeting the definition of ET exhibiting additional soft clinical signs of unclear significance possibly indicative of potential subgroupings.² As such, those with isolated onset of vocal tremor are no longer classified as a variant of ET unless they develop signs and symptoms commensurate with the new definition.

The most recent consensus related to movement disorders affecting the larynx was published in 2005 by a committee representing the Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS).³ Although an earlier publication, the statement by this committee drives current standards of practice in the field of otolaryngology for evaluating and treating those with movement disorders affecting the larynx and other head and neck structures. Within this document, a description of clinical features of ET and variants affecting the larynx and other speech and respiratory structures involved in speech production were provided. This committee used the term, "laryngeal essential tremor," rather than EVT since the larynx is the primary structure associated with voice production during speech. However, clinical features associated with laryngeal ET included observation of vertical oscillation of the larynx (i.e., tremor affecting strap musculature influencing the vertical position of the larynx) as well as tremor affecting articulators (e.g., pharyngeal constrictors, intrinsic laryngeal muscles, tongue, soft palate, jaw, and lips) and respiratory system musculature. This committee also highlighted the fact that tremor affecting the larynx would not be classified as "rest" tremor given that the laryngeal musculature is actively involved in respiratory posturing when it is not otherwise engaged in the activities of

phonation and swallowing.⁴⁻¹⁰ Differentiation between laryngeal tremor of the essential versus dystonic type was reliant on the task specificity of laryngeal behavior during volitional speech tasks compared to nonvolitional respiration (i.e., tidal breathing). Individuals with essential laryngeal tremor were described to exhibit oscillation of speech structures during both respiration and speech tasks (i.e., non-task specific). Those with a dystonic type of laryngeal tremor would demonstrate oscillation of speech structures during volitional tasks such as sustained phonation or speech production, and potentially exhibit improved signs/symptoms in response to sensory tricks, including placement of the nasoendoscope or application of topical anesthesia.

Unfortunately, no group publishing expert consensus-based documents integrated multi-disciplinary expertise on their panels. Representation of salient expertise across related disciplines beyond the primary sponsoring entity would improve generalizability and accuracy of the final classification system. Consequently, both consensus documents offer limited generalizability and accuracy related to the "isolated voice tremor" phenotype. The AAO-HNS group introduced a term, laryngeal ET that does not sufficiently represent involvement of the extra-laryngeal articulators. Although their intent was to link ET manifesting in the larynx, associated clinical features demonstrate that tremor is not typically restricted to the larynx and can involve the respiratory musculature. As such, reference to laryngeal ET is misleading. The IPMDS relied heavily on a systematic review of the literature to inform their updated classification system distinguishing between clinical phenomenology and etiologies (i.e., Axis I versus Axis II criteria). The new classification system accommodates change in the clinical phenotype of individuals diagnosed with ET. In this way, the new tremor classification system may provide new insights regarding the pathophysiology of focal or isolated forms of tremor that may be distinct from ET or ET plus forms. However, the current classification system of tremor referred to "isolated voice tremor" as a focal tremor in the same way as tremor affecting individual structures such as the jaw or head. However, voice production requires coordination across multiple structures innervated by cranial and spinal nerves. The idea that vocal tremor is focal, or "isolated," may stem from the focus on acoustic measures as a surrogate to tremor patterns affecting speech structures. The voice is a radiating quasiperiodic and modulated airstream resulting from the coordinated contribution of respiratory and articulatory structures. However, studies of individuals with vocal tremor have not yet linked the affected speech apparatus kinematics to associated voice signal patterns. Although tremor has been observed in respiratory and articulatory structures, the larynx as the sound generator is typically the focus of study in those with vocal tremor. Yet, the literature demonstrates that those with EVT distinctly exhibit tremor across multiple structures coordinated and innervated through bilateral cranial and spinal nerve output.

Clinical features of vocal tremor and EVT

In contrast to the vast literature describing the clinical features and phenotypes of ET and other classifications of tremor, the literature describing vocal tremor does not offer comparable information

regarding kinematic measures of speech structure tremor rate, or detailed characteristics of onset and progression of the disorder. More typically, studies describing those with EVT confirm that there is either an associated diagnosis of ET, or no other associated neurological diagnoses with onset of voice symptoms. The systematic description of participant's duration of disease, family history, duration of vocal tremor, age of onset, activation condition(s), body distribution, and other important information for clinical phenotyping is absent in the majority of literature describing those affected with EVT. Alternatively, these individuals are commonly studied among the same cohort with those exhibiting vocal tremor associated with other neurological disorders, including spasmodic dysphonia. As such, it can be difficult to extract clinical features and phenotypes for those with EVT that distinguish them from other clinical phenotypes of vocal tremor.

Vocal tremor is generally considered a neurogenic voice disorder characterized by modulation of pitch and loudness.¹¹⁻¹⁶ Individuals with this disorder report increased effort during speaking and worsening of their vocal tremor during stressful activities that promote anxiety or require more concentration and effort.^{3,17,18} Most individuals believe vocal tremor to be typical of age-related changes in the voice.^{19,20} As such, many individuals with vocal tremor may not seek treatment, as suggested by community-based studies of ET²¹ and general population estimates of those with voice disorders.^{22,23} Those seeking treatment for vocal tremor frequently have co-occurring neurological diagnoses with the majority having ET followed by dystonia (e.g., spasmodic dysphonia) and other neurodegenerative diseases (e.g., Parkinson's disease, cerebellar degeneration, and myasthenia gravis).²⁴⁻²⁶

Literature characterizing vocal tremor, in general, describes clinical features of tremor affecting the respiratory system,^{4,27-29} tongue,^{11,13,29,30} jaw,^{29,31,32} soft palate,^{10,29,33,34} and larynx.^{12,13,15-17,29,30,35} Clinical characteristics of vocal tremor are best identified and characterized during sustained phonation of a vowel.^{11,17,36-38} However, judgment of the severity of the vocal tremor should consider the degree of impact on connected speech rather than judgment limited to the sustained phonation condition.^{11,38} Nasoendoscopic examination enables direct observation of upper airway structures such as the soft palate, base of the tongue, larynx, and pharyngeal walls during respiratory activity as well as during sustained phonation and connected speech-related tasks.^{29,30} Additional direct observation of the face, lips, jaw, and palpation of the respiratory system can be used to identify other structures of the speech apparatus contributing to the perceived vocal tremor.²⁹ A thorough evaluation enables accurate documentation regarding the presence/absence of tremor across speech structures to determine whether tremor appears postural, kinetic, or dystonic (i.e., task specific).

Methods

To determine clinical characteristics aligned with the recommended classification of tremor for this viewpoint, relevant literature was identified through the pubmed.gov search engine using the terms "essential vocal tremor," "essential voice tremor," "primary vocal tremor," or "organic voice tremor." Literature published in the English language was reviewed to identify information regarding family history, duration

of vocal tremor, age of onset, representation of males and females, body distribution, activation condition(s), frequency of vocal tremor, and associated neurological disorders in those classified as affected with EVT. If available, EVT symptomatology response to alcohol intake was also documented. Publications without clinical phenotype information used to classify participants with EVT were excluded from final descriptive analysis. In addition, clinical phenotype information reported for EVT participants also documented with co-morbidities of dystonia or parkinsonism was excluded from the final descriptive analysis.

Results

Figure 1 illustrates the process of the literature review resulting in the identification of three published studies that met inclusion criteria. A total of 53 references were identified across all four search phrases with 30 unique references describing EVT patient populations. Of the 30 publications on EVT, only three provided clinical phenotype information meeting criteria for characterizing isolated vocal tremor. Table 1 shows the 30 total references reviewed for clinical phenotype characteristics. Table 2 shows the descriptive analysis findings for each of the three studies meeting inclusion criteria. That is, only three out of the total of 30 studies studying EVT-affected populations provided clinical phenotype information including participant family history, duration of vocal tremor, age of onset, male to female representation, body distribution, activation condition(s), vocal tremor frequency rate, alcohol responsiveness, and neurological co-morbidities.³⁹⁻⁴¹

The average age of onset in those affected with EVT was older than 60 years,^{39,40} with a larger proportion of those affected being females.³⁹⁻⁴¹ The typical duration of vocal tremor symptoms reported at the time of evaluation ranged between 1 and 12.7 years (see Table 1). The distribution of anatomical structures observed with tremor typically involved

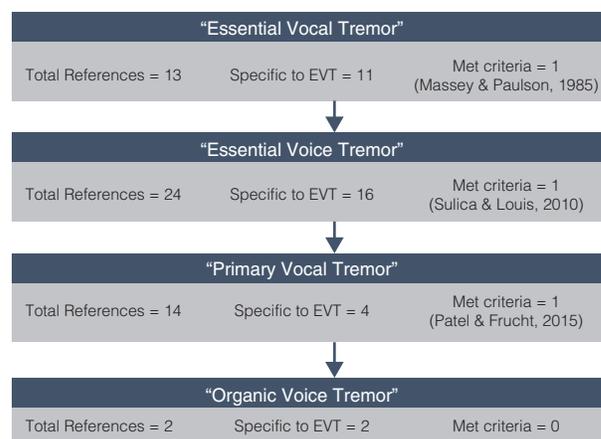


Figure 1. Total Number of References Identified during the PubMed Search Using Each of the Specific Search Phrases. References specific to EVT and those providing adequate clinical phenotype information to meet inclusion criteria for final descriptive analysis are indicated. A total of 30 unique references addressing EVT were evaluated for clinical phenotype characteristics and three references provided the target clinical phenotype information for descriptive analyses.

Table 1. Total Unique References Reporting on EVT Populations for Review

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Table 1. (Continued) **Total Unique References Reporting on EVT Populations for Review**

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the larynx in two studies; the study by Massey and Paulson⁴¹ utilized an indirect method of viewing the larynx such that identification of upper airway involvement was difficult to accurately determine. In addition, palatal, pharyngeal, and base of tongue involvement was documented in the majority of patients.^{39,40} The condition of tremor was noted to occur in all individuals during speech context and in 74% of individuals during quiet respiration.⁴⁰ Measures of rate were reported from acoustic modulation or laryngeal electromyographic measurements and ranged from 4 to 10 Hz for two studies^{40,41} and 4 to 8 Hz for one study.³⁹ None of these studies directly evaluated respiratory involvement. One study reported that 68% of those diagnosed with EVT reported onset of their vocal tremor prior to upper limb involvement.⁴⁰ The other two studies solely described those with isolated voice tremor, although a small proportion of those seen also exhibited tremor involving the head (N = 6) and upper extremities (N = 3) as shown in the study conducted by Patel and Frucht.³⁹ A family history of tremor was reported in approximately 38–42%.^{39,40} Two studies reported improved vocal tremor symptoms in 100% of participants who consumed alcohol,^{39,41} whereas approximately 43% reported similar benefit among those who consume alcohol in the third study.⁴⁰

One study that was not included in Table 1 reported outcomes of a thorough prospective assessment of tremor affecting the structures of the speech apparatus in 20 adults diagnosed with mild, moderate, and severe vocal tremor and two adult controls.²⁹ This study did not use the term, EVT, and six individuals from among the cohort were also diagnosed with spasmodic dysphonia. None of the participants were diagnosed with parkinsonism or cerebellar dysfunction. This study was one of the first studies to systematically document the severity level of vocal tremor and associated involvement of speech apparatus structures during sustained phonation. The outcomes of this study showed a pattern of greater perceived severity of vocal tremor associated with wider spread of tremor across oral, pharyngeal (including laryngeal), and respiratory structures. The only speech condition tested in this study was sustained phonation of the vowel, “ee,” such that the condition of

tremor during respiratory patterns was not determined. The latter condition would help distinguish between those individuals with dystonic (i.e., task specific) tremor and those with tremor patterns across volitional and nonvolitional conditions. Nonetheless, the findings of this study support the fact that those with vocal tremor do not generally exhibit an isolated laryngeal tremor as those with EVT. Rather, those meeting diagnostic criteria for EVT exhibit greater spread of tremor across the speech apparatus, including the respiratory structures. This was particularly true as the severity of the vocal tremor was rated as worse.

Discussion

In general, the clinical features of EVT include classification as an action tremor involving multiple oral, pharyngeal (including laryngeal), and respiratory structures across volitional (i.e., speech) and nonvolitional (i.e., tidal breathing) conditions. Given that the larynx is neurologically regulated by nonvolitional as well as volitional respiratory functions, it is not surprising that tremor affecting the larynx might also be found in other respiratory structures.⁴² Overall, both “isolated” and ET-associated forms of vocal tremor demonstrate spread of tremor through the speech apparatus innervated by cranial nerves, although respiratory and strap musculature may also be involved.

EVT as a clinical variant of ET

The revised classification of tremors requires careful documentation of distinct clinical phenotypes. Based on a limited review of literature describing those classified as EVT, improved documentation of clinical phenotyping is needed. Only three of 30 published studies specific to EVT offered adequate clinical characterization to assure accurate classification. Based on the small number of carefully conducted studies documenting characteristics of those with EVT, the majority of affected individuals reported onset of vocal tremor prior to onset of tremor in the upper extremities required for classification as ET. Interestingly, the current classification criteria for ET include those exhibiting spread of

Table 2. Literature Describing Clinical Characteristics of those with EVT, or Isolated Voice Tremor

Reference	Population Size	Family History	Duration of Vocal Tremor	Age of Onset	Male and Female Representation	Body Distribution	Activation Condition (Rest vs. Action)	Rate	Alcohol Responsiveness	Other Associated Neurologic Disorders
Patel and Frucht ³⁹	19	8 (42%) with family h/o ET and 5 (26%) with vocal tremor specifically	6 years (+/- 4 years)	64 years (+/- 8 years)	89% female	Larynx, palatal, and pharyngeal musculature during sustained phonation (no mention of respiratory observations); Head tremor (N = 6), N = 3 had slight action tremor of upper extremities; N = 2 had both head and limb tremor	Action (based on presence during phonation)	4-8 Hz via acoustic measures	100% of those who consumed alcohol (N = 11)	“Patients were subsequently followed for as little as 6 months and as long as 10 years without the development of dystonia or parkinsonism.” (p 2)
Sulica and Louis ⁴⁰	34	38.2% had a familial history and 58.8% did not	12.7 years (+/-13.4 years) Range of 0.5-20 years	62.9 years (+/- 15 years) Range of 19-84 years	92.6% female	68% experienced onset of vocal tremor prior to upper limb involvement; 74% exhibited laryngeal oscillation during respiration, palate, pharyngeal wall in majority, with 24% exhibiting base of tongue oscillation	Action, Kinetic and postural (based on presence during phonation and quiet breathing)	4-10 Hz via laryngeal Electro-myography (EMG)	42.9% of those who consumed alcohol	essential tremor
Massey and Paulson ⁴¹	4 of 131	Of the four patients with isolated vocal tremor, all reported a family history for tremor (one exhibited family history only of vocal tremor)	0.67-6 years	not reported, although the age range was 37-59 years at time of evaluation	75% female	respiratory; indirect laryngeal examination only was conducted, making body distribution difficult to determine	Action (based on presence during phonation)	4-10 Hz via acoustic measures	100% (N = 4)	26 of 131 exhibited vocal tremor with 4 of these as the initial sign; all others met inclusion criteria for essential tremor. From the 26 with vocal tremor, 2 exhibited head, hands, and voice; 5 exhibited head and voice; 14 exhibited hands and voice; 1 exhibited head, voice, and chin

Abbreviations: EVT, Essential Vocal Tremor; ET, Essential Tremor.

tremor along the motor somatotopy of the body from the upper extremities to the neck (i.e., head) and respiratory/articulatory structures. This represents a spread from spinal to cranial (or midline) structures as a more common clinical phenotype. However, nearly 70% of those with EVT were reported by one study to exhibit the opposite spread of tremor beginning in the midline structures (i.e., cranial) to the upper extremities. This suggests a reverse clinical phenotype of tremor in ~1/3 of individuals eventually meeting inclusion criteria for ET originally classified as “isolated voice tremor.” Although further systematic work is needed regarding clinical characteristics of those with EVT, current evidence suggests an action tremor at a rate between 4 and 10 Hz and a similar family history rate as expected for those with ET. The primary distinction of individuals with EVT is the disproportionate representation of females and the direction of tremor spread from cranial to spinal motor somatotopy. Another topic for future consideration is to compare treatment responses between those classified with “isolated voice tremor” and those with ET and vocal tremor. Several published studies that did not meet inclusion criteria for this article provide evidence that those with vocal tremor due to EVT or ET may exhibit similar improvement in voice symptomatology as those with bilateral limb tremor classified as ET in response to pharmaceutical treatment^{43–48} and deep brain stimulation (DBS).^{49–52}

Although “isolated voice tremor” may offer a unique clinical phenotype in onset and progression, it appears to be a variant of ET rather than a distinct clinical phenotype. Eventually, ET and EVT may be considered clinical phenotypic variants of tremor in the same way regional variants of amyotrophic lateral sclerosis (ALS) inform disease prognosis and pathophysiology.⁵³

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