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Review article

Knowledge gaps and research recommendations for essential tremor

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ABSTRACT

Essential tremor (ET) is a common cause of significant disability, but its etiologies and pathogenesis are poorly understood. Research has been hampered by the variable definition of ET and by non-standardized research approaches. The National Institute of Neurological Disorders and Stroke (USA) invited experts in ET and related fields to discuss current knowledge, controversies, and gaps in our understanding of ET and to develop recommendations for future research. Discussion focused on phenomenology and phenotypes, therapies and clinical trials, pathophysiology, pathology, and genetics. Across all areas, the need for collaborative and coordinated research on a multinational level was expressed. Standardized data collection using common data elements for genetic, clinical, neurophysiological, and pathological studies was recommended. Large cohorts of patients should be studied prospectively to collect bio-samples, characterize the natural history of the clinical syndrome including patient-oriented outcomes, investigate potential etiologies of various phenotypes, and identify pathophysiological mechanisms. In particular, cellular and system-level mechanisms of tremor oscillations should be elucidated because they may yield effective therapeutic targets and biomarkers. A neuropathology consortium was recommended to standardize postmortem analysis and further characterize

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neuropathological observations in the cerebellum and elsewhere. Furthermore, genome-wide association studies on large patient cohorts (>10,000 patients) may allow the identification of common genes contributing to risk, and whole exome or genome sequencing may enable the identification of genetic risk and causal mutations in cohorts and well-characterized families.

1. Introduction

Essential tremor (ET) affects approximately 1% of the general population and 5% of the population over 65 years of age [1]. Despite this high prevalence, there is no satisfactory pharmacologic treatment, the pathological findings are debated, the underlying genes have been elusive, the mechanisms of neural network oscillation are unknown, and the clinical definition of ET has been inconsistent. There are several tangible reasons that may account for the lack of a breakthrough in ET research. ET remains poorly defined and can be diagnosed only on clinical grounds. The main challenges are the lack of stringent diagnostic criteria and the lack of biomarkers. Efforts in ET genetics have been impeded by "phenocopies" that share the phenotype but not the genetic cause, and by genetically heterogeneous changes that present as a syndrome similar to ET. The importance of an accurate diagnosis to study the underlying disease mechanism also applies to the investigation of the pathophysiology and pathology in ET.

In May 2015, the National Institute of Neurological Disorders and Stroke, National Institutes of Health, USA held a workshop to discuss current knowledge gaps in ET and to identify research opportunities regarding ET phenomenology and phenotypes, clinical trials, mechanisms of tremorogenic oscillation, pathology, and genetics. The goal was to develop consensus recommendations for future research, which are presented herein along with a summary discussion for the following topic areas: phenomenology and phenotypes, therapies and clinical trials, physiology, pathology, genetics (Table 1).

2. Phenomenology and phenotypes

The 1998 MDS consensus criteria define "classic ET" as a monosymptomatic disorder with bilateral, largely symmetric postural or kinetic tremor involving the hands and forearms that is visible and persistent, or as isolated head tremor in the absence of dystonic posturing [2]. However, many have challenged this narrow definition and have expanded the phenotype of ET to include subtle cerebellar abnormalities [3], cognitive dysfunction [4], hearing abnormalities [5,6], and dystonia [7]. Furthermore, it is common for investigators to deviate from the MDS criteria, and patients fulfilling the MDS criteria subsequently may develop signs of Parkinson disease (PD), dystonia and other disorders [8]. As published prevalence estimates of ET vary and genetic risks likely are multiple [9], it is probable that the term ET encompasses multiple disorders [10]. Although the MDS criteria exclude abnormal neurological signs other than tremor, delineating the core phenotypic features of ET is challenging and somewhat arbitrary because there is no diagnostic marker for ET. Furthermore, the common occurrence of subtle or questionable dystonia, parkinsonism, or ataxia creates additional diagnostic uncertainty, regardless of how ET is defined. Moreover, the clinical significance of incident tremor in the upper limbs depends on age of onset; the development of monosymptomatic upper extremity tremor after age 65 is associated with higher risk of incident PD, incident dementia, and mortality [11–14].

While tremor is a common feature of dystonia, the relationship of tremor in one area (e.g., head, voice, upper limb) to dystonia elsewhere is uncertain and frequently debated. It is unclear to what extent task-specific and focal tremors are forms of ET, dystonia, or separate disorders. Dystonic disorders with known genetic causes, such as DYT24, may present with isolated postural and action tremor suggesting that the phenotypic heterogeneity of dystonia may include presentations with isolated tremor [15].

There was general agreement that ET is a common clinical syndrome, not a specific disease, and that this syndrome should be defined and used consistently among clinicians and researchers. Other isolated tremors and isolated tremor syndromes (e.g., isolated head tremor, isolated task-specific writing tremor, and isolated voice tremor) should not be referred to as ET or variants of ET. Over time, some patients may convert to an alternate phenotype, resulting in a change in diagnosis years after the initial syndromic diagnosis of ET. By defining ET as a clinical syndrome, no inference can be made regarding etiologies. To establish a link between clinical presentation and potential etiologies, phenotypic data should be documented to the fullest extent possible, including signs of uncertain significance.

3. Recommendations

- Regard ET as a specific, common isolated tremor syndrome, not a specific disease. Other monosymptomatic tremors should be referred to as isolated tremor syndromes, not essential tremors.
- Define ET as an isolated tremor syndrome of unknown etiology in which there is bi-brachial action tremor (i.e., postural and/or kinetic tremor) with a duration of at least three years, with or without head tremor or tremor in other regions. A duration of three years is usually sufficient time to rule out alternate diagnoses. There should be no other diagnostic neurologic signs, such as overt dystonia or parkinsonism, or evidence of endogenous (e.g., autoimmune disease) or exogenous (e.g., toxins) disturbances that could cause tremor. Difficulty with tandem walking is permissible, but there should be no abnormality of gait.
- Apply the definition of ET consistently in clinical and research settings.
- Prospectively study large multi-national cohorts of individuals with ET and other isolated tremor syndromes (e.g., isolated head tremor, isolated voice tremor, and other focal and task-specific tremors), using validated assessment tools and standardized terminology (i.e., common data elements) [16]. Such studies will improve our understanding of the phenotype and natural history of ET and its relationship to other isolated tremor syndromes.
- Collect biospecimens using standardized protocols to aid in elucidating underlying etiologies, pathophysiology, therapeutic targets, and biomarkers. Broad subject consent is important to allow for data and sample sharing.
- Capture neurologic signs and symptoms to the fullest extent possible to ensure unbiased and careful phenotyping. Tremulous people in ET pedigrees and population studies will frequently have neurologic signs and symptoms of uncertain significance.