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The etiology of essential tremor: Genes versus environment

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ABSTRACT

Introduction: Essential tremor (ET) is characterized by bilateral upper limb action tremor. Here we review the pathophysiology (cerebral mechanisms) and etiology (genetic and environmental risk factors) of ET.

Methods: We reviewed the literature (until June 2017) by searching PubMed for relevant papers.

Results: The pathophysiology of ET involves oscillatory activity in the cortico-olivo-cerebello-thalamic circuit, evidenced by electrophysiological and metabolic imaging. Possible underlying mechanisms include GABA-ergic dysfunction, cerebellar neurodegeneration, olivary dysfunction, or a combination. Genetic studies have examined affected ET families (linkage studies and whole-exome sequencing studies). These studies revealed several chromosomal regions and genes associated with ET, but the findings have not been replicated across different ET families. Genetic studies also assessed the sporadic occurrence of ET using genome wide genotyping of single nucleotide polymorphisms (SNP's) and candidate gene studies. Several SNP's are associated with ET, and this has been replicated across different cohorts. Interestingly, some of the involved genes are linked to the cerebellum and inferior olive. Environmental studies point to an association between ET and beta-carboline alkaloids (such as harmane), which have been found in the cerebellum.

Conclusion: Genetic and environmental risk factors may influence cerebellar and/or olivary function, resulting in abnormal cortico-olivo-cerebello-thalamic activity, and ultimately ET.

1. Introduction

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part. The most prevalent tremor is a bilateral action tremor of the arms, which is often diagnosed as essential tremor (ET). Recently there has been discussion about whether or not ET is a specific disease (or a syndrome), and some authors have proposed to abandon this term altogether. Important challenges are the lack of stringent diagnostic criteria and the lack of biomarkers. This has probably resulted in the inclusion of rather diverse patient populations with heterogeneous etiologies into genetic and pathophysiological studies, which in turn has hampered the identification of specific ET genes and specific ET mechanisms [1]. Here we discuss how genetic and environmental factors (etiology) may cause cerebral changes (pathophysiology) that ultimately result in a clinical ET syndrome. We define environmental factors as substances (e.g. toxins) that are associated with ET, and refrain from other acquired causes for tremor, such as transient tremorogenic effects of medication, central nervous system infections, and structural abnormalities – since these are associated with other tremor syndromes than ET.

2. The clinical definition of ET

This year the new consensus statement on the classification of tremors from the Task Force on Tremor of the International Parkinson and Movement Disorder Society will be released (Bhatia et al., in press). According to this consensus statement, tremor is defined along two main axes: clinical features (Axis 1) and etiology (Axis 2). The two axes are independent, meaning that a clinical tremor syndrome may have multiple etiologies, and a particular etiology may produce multiple tremor syndromes. The ET syndrome (on Axis 1) is defined as an isolated tremor syndrome of bilateral upper limb action tremor, with a duration>3 years, with or

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without tremor on other locations (e.g. head, voice, lower limbs), and without other neurological signs (e.g. dystonia, ataxia, and parkinsonism). The Task Force also defined an "ET plus syndrome", where patients have an ET syndrome with additional "soft" neurological and systemic symptoms with unclear meaning. Exclusion criteria for both ET syndromes are isolated focal tremors (voice, head), orthostatic tremor with a frequency >12 Hz, task- and position-specific tremors, and sudden onset and stepwise deterioration.

These clinical inclusion and exclusion criteria do not clearly separate the ET syndrome from its most common differential diagnosis (which is another tremor syndrome on Axis 1): enhanced physiological tremor. Electrophysiology may help to distinguish these tremor syndromes, by identifying tremor characteristics that are not immediately visible to the clinical eye, such as tremor frequency and the change of tremor frequency after weighing of the limb. Specifically, enhanced physiological tremor often has a slightly higher frequency (typically 6–12 Hz) than ET (typically 4–8 Hz), the frequency is often more variable than that of ET, and enhanced physiological tremor is most often of peripheral origin (which is visible in a frequency drop of >1 Hz after loading of the limb) [2].

ET is often associated with a positive family history, suggestive of an autosomal dominant inheritance pattern. Estimates of the proportion of ET patients with a positive family history vary between 20% and 90% [1]. The onset of ET varies widely between childhood and old age. Interestingly, it has been shown that the age at onset has a bimodal distribution (early-onset <24 years of age and late-onset >46 years of age), suggesting two distinct phenotypes [3]. The early-onset group more often reported a positive family history than the late-onset group, as well as a better response of tremor to alcohol. Taken together, it is clear that ET is a clinically diverse syndrome, and probably there is no one-to-one mapping between clinical features and etiological factors.

3. The pathophysiology of ET

Tremor may involve both central oscillators (single-site or network), peripheral mechanisms (mechanical oscillations or mechanical-reflex oscillations), or both. In ET, there is clear evidence that central mechanisms are involved. Specifically, using electroencephalography (EEG) as well as magnetoencephalography (MEG), it was found that neural activity in a network consisting of frontal cortex, cerebellum, diencephalon (putatively thalamus) and the brainstem (putatively the olivary region) is coherent with the ongoing tremor oscillation (as assessed using electromyography, EMG) [4,5]. Functional magnetic resonance imaging (fMRI) studies showed that ET is associated with increased cerebellar activity compared to mimicked tremor in healthy subjects [6]. Furthermore, cerebral activity associated with 3–8 Hz force oscillations was increased in the primary motor cortex in ET patients compared to healthy subjects [7]. Other fMRI studies focusing on inter-regional connectivity found that ET patients have increased thalamo-cortical functional connectivity at rest [8] and altered effective connectivity in the cerebello-dentato-thalamic tract [9]. Taken together, these studies suggest that ET is associated with increased, tremor-related activity in a cortico-olivo-cerebello-thalamic circuit [10].

It is unclear what drives this circuit into tremor. Theoretically, tremor may occur either because an oscillator sends tremor oscillations through the circuit, or because deficient feedforward/feedback loops render the circuit unstable (causing it to oscillate). The latter option is supported by the fact that the tremor in ET is activated during voluntary movements, and by the finding that the timing of agonist bursts during voluntary movements is abnormal in ET [11]. A possible oscillator within the cortico-olivo-cerebello-thalamic circuit is the inferior olive, which has pacemaker properties. The inferior olive is associated with tremor in the harmaline animal model of ET [10] and shows high expression of EAAT2, the major glutamate reuptake transporter that has been associated with the ET phenotype in a genome-wide association study [12]. Another possible oscillator is the dentate nucleus [10]. What argues against the idea that there is a single oscillator (or pacemaker) is that ET can be entrained by rhythmic stimulation over multiple sites (thalamus and cerebellum) [13]. This underlines that the oscillation results from the entire network. Taken together, ET likely results from a dysfunctional network rather than a single brain region, but the nature of the network dysfunction (oscillator, instability, or both) is not clear. Besides the olivary pacemaker hypothesis, there are two prominent theories that may explain the cortico-olivo-cerebello-thalamic network dysfunction in ET: the GABA hypothesis and the cerebellar degeneration hypothesis [10].

The hypothesis that ET results from GABA-ergic dysfunction is supported by nuclear imaging, which showed abnormal 11C-flumazenil binding to GABA-A receptors in the ventrolateral thalamus, cerebellar dentate nucleus, and premotor cortex [14]. Furthermore, a postmortem study showed decreased levels of GABA-A (35% reduction) and GABA-B (22–31% reduction) receptors in the dentate nucleus in ET [15]. Post-mortem markers of GABA-ergic dysfunction have also been found in other brain areas in ET, for example the locus coeruleus and pons, but these findings are less established [10]. GABA-ergic dysfunction has been hypothesized to cause disinhibition of the dentate nucleus, inducing pacemaker-like activity that then spreads through the cortico-olivo-cerebello-thalamic circuit [15].

Evidence for the cerebellar degeneration hypothesis mainly comes from the work by Louis and colleagues, who observed structural changes in Purkinje cells and neighboring neurons, reduced Purkinje cell linear density with "empty baskets", and Purkinje cell heterotopias [16]. Furthermore, changes in the distribution of climbing fiber-Purkinje cell synapses have been found [17]. Not all findings have been replicated by other groups, possibly due to varied approaches to examination (including differences in sampling protocols, staining and assessment methods, and subject/control definitions) [1]. Cerebellar Purkinje cell dysfunction may lead to cortico-olivo-cerebello-thalamic network dysfunction through impaired inhibition of the dentate nucleus (contributing to pacemaker activity), impaired coordination of voluntary movements (causing instabilities in cortico-olivo-cerebello-thalamic processing), or both. Genetic and environmental risk factors that may potentially cause these pathophysiological changes are reviewed below.

4. The genetics of ET

Since the early days of ET research in 1940's, a positive family history has been considered as a major phenotypic feature of ET, with many families showing an autosomal dominant inheritance pattern [18]. Beside this familial clustering, a sporadic incidence of ET had been reported too. At the turn of the millennium, several epidemiological twin studies have been performed, assessing heritability in monozygotic and dizygotic twins. One study in the United States found pairwise concordance of 0.60 (for clinically "definite" ET) for monozygotic twins and 0.27 for dizygotic twins [19]. Another Danish/German study showed pairwise concordance of 0.93 for monozygotic twins and 0.29 for dizygotic twins [20]. These results suggest a high heritability in ET on a genetic level. In the following decades, the prevalence and heritability of ET has been examined in large population based studies. Due to differences in data collection, reports about the estimated rate of

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