Recent Advances in Essential Tremor
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Abstract
In this review recent advance in essential tremor is discussed in terms of clinical, pathophysiological features as well as treatment options.

Keywords: Essential tremor; Tremor disorder; Neurodegenerative disease; Kinetic tremor

Essential tremor (ET) is the most prevalent tremor disorder. It is characterized by 8–12 Hz action tremor of the arms; head tremor and other cranial tremors may also occur, as well as limb and gait ataxia and subtle eye motion abnormalities [1-5]. The prevalence and incidence increase with age, so that more than 20% of individuals over 90 years have ET [1,6].

In recent years neuroepidemiological, clinical and pathological studies have substantially contributed to the changing of view of ET. The traditional view of ET as a monosymptomatic condition is being replaced by an appreciation of the spectrum of clinical features and clinical associations, with both motor and non-motor features [7-11]. It is even possible that ET might be a family of diseases, unified by the presence of kinetic tremor, but further characterized by etiological, clinical and pathological heterogeneity [10].

Both genetic and environmental factors play a role in ET, but the underlying causes are far from fully elaborated. Recent studies have reported a genome-wide significant association between leucine-rich repeat and Ig domain containing 1 gene (LINGO1) and risk for essential tremor [12-15]. Further studies also confirmed this finding in populations of European and Asian descent, showing LINGO1 is likely a risk factor for essential tremor with widespread distribution [14,15]. Parkinson's disease (PD) and ET are regarded as distinct entities, but clinical evidence suggest that there is a considerable overlap. For instance, in some cases action tremor can precede the onset of PD symptoms and there is a fourfold increased risk of developing PD in patients with ET [16]. Moreover, in a number of ET cases Lewy bodies have been identified in the brain stem and imaging studies have found signs of dopaminergic deficits in some patients with ET [17]. Given these overlapping features and the association of LINGO1 with ET, Villarino-Guell et al. [14] investigated the role of LINGO1 in PD and their results revealed an association between LINGO1 and risk of PD. Although these results are not confirmed by other reports, further studies of larger populations are required to investigate the role of LINGO1 in PD [18]. From the pathophysiological perspective, traditionally ET is considered as a primary electrical/ectrophysiological entity. It is the result of pacemaking neurons in the inferior olivary nucleus that fire in a coupled manner, and produce tremor through an abnormal olivocerebellar output. But this olivary model of ET suffers from a number of critical problems, such as lack of evidence that this process is occurring in human ET as well. Another major problem of this model is that there are numerous pacemakers in the central nervous system which are also connected with the cerebellum [19-21]. Therefore, olivary pacemakers are not unique. Moreover, the main empiric support of olivary model comes from the harmaline model which is not a model of human disease [22]. Over the past decade an alternative model, cerebellar degenerative model of ET, is based on the notion that ET is a neurodegenerative disease and the focal point of degeneration is cerebellum itself [23]. Clinical evidences imply that ET is neurodegenerative is based on its insidious onset, gradually progressive course, lack of spontaneous remission and age-associated increase in disease prevalence [23,24]. Furthermore, emerging neuroimaging studies also showed that there are structural degenerative changes in the ET cerebellum [25,26]. Finally recent clinical and epidemiological studies are pointing to the links between ET and PD, ET and Alzheimer's disease, and ET and progressive supranuclear palsy [16,27,28]. Recent postmortem studies in ET also support cerebellar degeneration, especially in Purkinje cell morphology in both axonal and dendritic compartment [29]. To conclude, cerebellar degenerative model is relatively new, based on tissue based studies and offers an alternative view of pathophysiology of ET.

Depending on the patient's needs treatment may not be necessary or it may be highly challenging [30]. Nearly half of the patients either cannot tolerate medications or have refractory, disabling tremor despite medication [31]. Unfortunately there has been no breakthrough development in medical treatment of ET since 4 years, only a few off-label medications, such as beta blockers or antiepileptics are available for ET. However, there are new treatments coming up like, octanoic acid. Patients with ET frequently report a significant recovery of postural tremor after consuming alcohol. Octanoic acid is the active metabolite of a long chain alcohol 1-octanol and has been demonstrated to alleviate tremor in both harmaline induced animal model of ET and ET patients without causing sedation or intoxication [32-34]. Nevertheless, future trials should examine the long term effects of octanoic acid and explore the safety of chronic intake. In cases who do not benefit or tolerate medical treatment surgery can be an option which includes lesional therapies, deep brain stimulation (DBS) and superficial brain stimulation.

In lesional therapies thermocoagulation of ventral intermediate nucleus (Vim) was of choice since 1950. After introduction of DBS, this approach is largely diminished, but still it can be performed unilaterally when DBS fails or not available. During the last decades, lesioning with gamma knife surgery has re-emerged lesional procedures. However this technique has some limitations such as delayed clinical improvement and possibility of extending lesion beyond the initially targeted region over time, which may lead to permanent neurological deficits [35]. MRI guided focused ultrasound (MRgFUS) technique is another novel and promising treatment in lesioning deep brain structures. In this incision...
free technique, thermal tissue ablation is performed by applying a series of low power sonications (150-250 W) producing 40–45°C temperature which is stereotactically concentrated on a specific brain target. Targeting and monitoring of the lesioning process is achieved by high precision MRI and real time MR thermal imaging [36,37]. In spite of causing transient neurological abnormalities, recent pilot studies confirm that MRgFUS is a safe and effective technique [36]. MRgFUS is certainly an interesting and promising treatment to be considered as a non-invasive approach to be possibly applied when the risk/benefit profile is in favor of lesioning rather than DBS. However, larger studies are required to better establish its safety and efficacy, specifically in comparison to DBS.

Vim-DBS is considered the preferred treatment for drug refractory patients with disabling ET [38]. Continuous high frequency stimulation of Vim can reduce tremor with both unilateral and bilateral procedures [39,40]. Although DBS is a safe and effective method, stimulation induced side effects, including dysarthria, paresthesia and ataxia can be challenging the programming of patients with bilateral implants. In spite of stimulation induced side effects, bilateral Vim DBS is required to treat midline tremor and bilateral upper limb tremor. With the advent of new directional electrodes that are capable of interleaving stimulation it is possible to reduce the stimulation induced side effects [41]. Although Vim DBS is effective in tremor control, recent retrospective studies have reported a loss of benefit in as high as 70% of the patients which is possibly related with tremor progression rather than stimulation tolerance [42,43].

Recent studies focusing on the potential role for primary motor cortex (M1) within the central oscillatory network in ET demonstrated that unilateral continuous theta burst stimulation (cTBS) of M1 cortex improves tremor in ET patients [44]. When compared to DBS, superficial cortical stimulation is less complex to perform and has a lower incidence of cerebral haemorrhage. However, adverse events such as sensory effects, contraction of the contralateral fingers and seizures can limit its clinical use [45].

In parallel with the evolution of DBS as a therapeutic and research tool for movement disorders, advances in targeting, electrode and implanted pulse generator (IPG) technology are promising for a better presurgical planning and postoperative management of ET patients. Diffusion tensor imaging (DTI) and tractography can help in fine targeting during preoperative planning. Specific parts of the nucleus or possibly a part of a complex network can be targeted by using these techniques. Moreover, development of new electrodes based on directional electrode design can allow shaping the electrical current field in the target of interest and avoiding potential side effects due to the spread of electrical current to structures surrounding the target [46,47]. Developments in IPG technology also allows independent and alternated stimulation of 2 contacts with different voltage, pulse width and frequencies, thus providing more alternatives in postoperative programming, a better control of tremor and avoiding side effects [48]. Patients with ET may require stimulation with higher voltages and frequencies over time, which in turn leads to frequent battery replacements. Rechargeable IPG technology is available and reduces the number of battery replacements. In addition to this new generation IPGs offer current controlled stimulation that dynamically adjusts the current to adapt to impedance changes in tissue/electrode interface [48]. Current FDA approved IPGs deliver continuous stimulation however, next generation IPGs that are designed to sense and respond to physiological signal (closed loop stimulation) will provide feedback modulation of stimulation. In clinical practice the application of adaptive stimulation will be a real breakthrough, but at this point it is crucial to determine a reliable biomarker that can guide automatic adjustment of stimulation. An understanding of the relationship between patient's clinical state and a neuronal signal under the influence of external stimulation is fundamental to any future application of these systems. Strategy development for interpreting neuronal signals in closed loop neurostimulation applications is underway. Recent advances in the DBS technology aside, further studies need to focus on some particular topics including, the heterogeneity of pathological processes in ET ensuing the heterogeneity of treatment response and development of good animal models.

References


